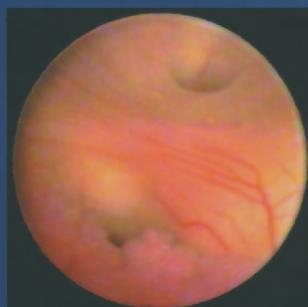
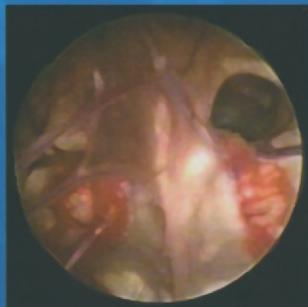
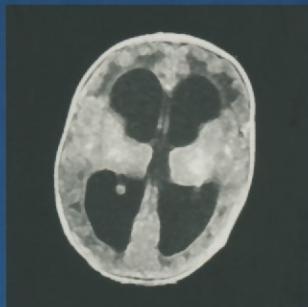


**G. Cinalli
W. J. Maixner
C. Sainte-Rose
(Eds.)**

Pediatric Hydrocephalus



Springer

*To Fabrizia, Francesco, and Maria Allegra,
the most beautiful gifts of my life,
to thank them for their patience and support
in all the moments that this book has stolen from us*

*To my Mother, who loved and supported me all my life,
and to my Father, who accompanied me at every step
but allowed me to find the way*

GC

*To my parents and Harriott, who is inspiration
for me in all things*

WM

To Federica, Elise, and George

CSR

Springer-Verlag Italia Srl.

G. Cinalli · W.J. Maixner · C. Sainte-Rose (Eds)

Pediatric Hydrocephalus



Springer

GIUSEPPE CINALLI, MD
Pediatric Neurosurgery
Santobono-Pausilipon Children's Hospital
Naples, Italy

WIRGINIA JUNE MAIXNER, MD
Pediatric Neurosurgery
Royal Children's Hospital
Melbourne, Australia

CHRISTIAN SAINTE-ROSE, MD
Pediatric Neurosurgery
Hôpital Necker-Enfants Malades
Paris, France

springeronline.com

© Springer-Verlag Italia 2005

Originally published by Springer-Verlag Italia, Milano in 2005

ISBN 978-88-470-2173-0 ISBN 978-88-470-2121-1 (eBook)
DOI 10.1007/978-88-470-2121-1

Library of Congress Cataloging-in-Publication Data:
Pediatric hydrocephalus / [edited by] G. Cinalli, W.J. Maixner, C. Sainte-Rose.
p. ; cm.

Includes bibliographical references and index.
(softcover : alk. paper)

1. Hydrocephalus in children. 2. Pediatric neurology. 3. Brain--Diseases. I. Cinalli, G. (Giuseppe), 1961- II. Maixner, W. J. (Virginia June), 1963- III. Sainte-Rose, Christian. [DNLM: 1. Hydrocephalus--Child. 2. Hydrocephalus--Infant. WL 350 P371 2003]
RJ496.H9P43 2003
618.91'858843--dc22

2003064076

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, re-use of illustrations, recitation, broadcasting, reproduction on microfilms or in other ways, and storage in data banks. Duplication of this publication or parts thereof is only permitted under the provisions of the Italian Copyright Law in its current version, and permission for use must always be obtained from Springer-Verlag. Violations are liable for prosecution under the Italian Copyright Law.

The use of registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statementm that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: the publisher cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Typesetting: Color Point Srl (Milan)

Cover design: Simona Colombo

SPIN: 10969809

Preface

This book was conceived as a result of the weekly staff meetings and daily clinical rounds at the Department of Neurosurgery, Hôpital Necker-Enfants Malades in Paris. The understanding and management of pediatric hydrocephalus has been part of our routine work for years. As so often happens to those who are thus preoccupied, the first proposition for the book came not from the neurosurgical unit, but from our colleagues, in this instance Jean Aicardi in 1994. He understood that it was a period of "revolution" for pediatric hydrocephalus particularly as it pertained to neuroendoscopy. He therefore petitioned Christian Sainte-Rose to write a book on pediatric hydrocephalus addressed to pediatric neurosurgeons, pediatric neurologists, and pediatricians.

The gestational phase was long, but serendipitous for the project. This phase witnessed the publication of the final results of the shunt trial (1998 and 2000) and the evolution and definition of neuroendoscopy. In 1999, the time finally became ripe to look back and try to define the real impact of these two events in the treatment of pediatric hydrocephalus. Thus, the book was born.

We are deeply indebted to Springer-Verlag Italia, who agreed to publish the book, and we are particularly grateful to Dr. Donatella Rizza and to the whole editorial team for their patience, their professionalism and for the quality of their work.

It is necessary also to thank in this page all the people who have directly or indirectly contributed to the ideas that are included within – to all the permanent and temporary neurosurgical staff at Necker-Enfants Malades, the residents, the chefs de clinique, the students, and the consultants whose questions, criticisms, and comments have molded our thoughts. We are and always will be grateful to Jean-François Hirsch for his curiosity, his teaching, and his support. We thank our nurses for their care of our patients. Most of all, we thank our little patients, all of them, for bearing the consequences of our decisions.

January 14, 2004

*Giuseppe Cinalli
Virginia Maixner
Christian Sainte-Rose*

Foreword

by Maurice Choux

Yet another book on hydrocephalus! That was my first thought when I received a copy of the manuscript of the present book. It is true that the problems related to hydrocephalus and their importance seem more limited now than they were a few years ago. The reason for this apparently reduced interest is the belief that hydrocephalic patients have become significantly fewer in recent years. The development of prenatal diagnosis and the drop in the birth rate in developed countries may explain this.

I believe this impression needs to be corrected. As pointed out by Hanlo et al. in Chap. 7, "The actual importance of hydrocephalus as a neurological disorder is severely underestimated. The incidence of congenital and infantile hydrocephalus is reported to be 0.48 to 0.81 per 1000 live births and stillbirths Cases of secondary hydrocephalus are seldom included in the incidence and prevalence figures". That is true in developed countries and, moreover, in developing countries where prenatal diagnosis is not widespread and where shunt costs significantly limit the number of shunt implantations. In developing countries, the total number of hydrocephalus cases has not only not diminished, but is increasing with the higher birth rate. Consequently, the questions raised by its management remain fundamental.

The main recent changes in the field of hydrocephalus relate to modern radiological investigations and modern ways of management, since shunts are no longer the exclusive treatment for a child with hydrocephalus. We are in need of a new approach to hydrocephalus, and that is why this book, edited by highly esteemed experts in hydrocephalus, is so welcome and promises to be such a great success.

This is a modern and new presentation of an old disease. Thus, it is significant that the opening chapter is devoted to genetics, and that the chapters dedicated to endoscopy are longer than those on shunts. Some aspects of hydrocephalus that were ignored in most previous books on the topic are extensively developed here: examples are growth and puberty in hydrocephalus, and hydrocephalus and epilepsy. Classical concepts, such as the development of the cerebrospinal fluid (CSF) pathways, CSF hydrodynamics, the pathophysiology of hydrocephalus, or the classification and definition of hydrocephalus, are covered in a new way and will change our previous certainties.

The perfect or ideal shunt is not described in this book, but we may dream with Ginsberg and Drake when they say, in Chap. 20, "We envision a future where a patient receives only one shunt in his/her lifetime, which is sophisticated enough to control intracranial pressure within normal physiological limits, can be adjusted and monitored noninvasively, and treated minimally invasively for shunt obstruction".

Another aspect of hydrocephalus which is of central importance at present and is not commonly discussed is the cost of the different treatments. Garton and Steinbok treat of this crucial question in Chap. 31, in a cost analysis of shunt surgery versus endoscopic surgery.

This book on pediatric hydrocephalus is indispensable not only for neurosurgeons but also for those interested in all aspects of hydrocephalus: pediatricians, radiologists, endocrinologists, pathologists, and geneticists. They will all discover that the best management of hydrocephalus is definitely not shunting, and alternatives to shunts, such as external drainage, endoscopic procedures, and management of the causes, are always preferable. Interestingly, four chapters of this book are dedicated to tumoral hydrocephalus, underlining how managing the mass lesion first, without inserting a shunt, will avoid a definitive shunt in most cases. Faced with a hydrocephalic patient, the first question will no longer be "What type of shunt is needed", but, "Does the child need a shunt?" This book also devotes space to the question of shunt malfunctions, with special attention to their management – which is not always shunt revision. Alternatives to shunt revisions also exist, and endoscopic techniques may not only avoid shunt replacement, but also allow shunt

removal. I am pleased to see that Dr. Hammer's old motto, "once a shunt, always a shunt", is no longer valid in 2004.

I am glad to congratulate the editors and all the contributors to this excellent book, and to deeply thank Giuseppe Cinalli, Virginia Maixner, and Christian Sainte-Rose for giving me the great honour and pleasure of recommending this major modern contribution in the field of hydrocephalus to its public.

January 2004

Foreword

by Giuseppe Maggi

A book published at the beginning of the third millennium offering a thorough review of the diagnosis and treatment of pediatric hydrocephalus has been long awaited by many neurosurgeons. This is by far the most commonly observed pathology in the everyday clinical practice of pediatric neurosurgeons. Its prognosis has changed dramatically since the introduction of the devices for the diversion of cerebrospinal fluid, and the last ten years have witnessed a very significant breakthrough in treatment with the advent of neuroendoscopy. Pediatricians and pediatric neurologists and neurosurgeons nowadays need to be aware of the existence of two alternative and sometimes complementary treatments, with different indications, diagnostic and therapeutic implications, and different follow-up schedules. The main objective of putting them in this position is well achieved in this book, all the chapters of which are by experts recognized as among the best in the world in the various fields of hydrodynamics, pathophysiology, diagnosis, and treatment.

But I think that the most important quality of this book is its clear, detailed, and attentive guide for the reader in the choice of the best surgical strategy for the treatment of the most challenging forms of hydrocephalus, such as the post-meningitic, loculated, tumoral, and Dandy-Walker-related forms. This is probably the first, real organic attempt at a valid organization of the knowledge in this field of neurosurgery.

Neuroendoscopic techniques are critically described and their effectiveness thoroughly evaluated. The complications, and their avoidance and management are depicted in detail and are illustrated progressively, following the single individual steps of every procedure, with wonderful pictures that powerfully support the text.

In conclusion, I am very grateful to the editors for the high quality of their work, for this titanic attempt to share their knowledge with their colleagues all over the world, and for giving me the opportunity to introduce this very unique book in the crowded ballroom of the international neurosurgical library.

January 2004

Acknowledgements

This volume has been published thanks to the generous contributions of:

Association pour le Recherche en Neurochirurgie Pédiatrique (ARNP), Paris, France

Codman-Johnson & Johnson, Raynham, Boston, USA

Integra, Sophia Antipolis, France

Medtronic Italia, Sesto San Giovanni, Milan, Italy

Promedical, Naples, Italy

Karl Storz, Tuttlingen, Germany

Tekmed Instruments, Rozzano, Milan, Italy

Table of Contents

CHAPTER 1	
Genetics of Hydrocephalus	1
PETER B. DIRKS	
CHAPTER 2	
Development of the Cerebrospinal Fluid Pathways During Embryonic and Fetal Life in Humans	19
MARTIN CATALA	
CHAPTER 3	
Cerebrospinal Fluid Dynamics	47
MAREK CZOSNYKA, ZOFIA H. CZOSNYKA, PETER C. WHITFIELD AND JOHN D. PICKARD	
CHAPTER 4	
Pathophysiology of Hydrocephalus	65
MÁRCIA C. DA SILVA	
CHAPTER 5	
Modern Imaging of Pediatric Hydrocephalus	79
FRANCIS BRUNELLE	
CHAPTER 6	
Classification and Definition of Hydrocephalus: Origin, Controversy, and Assignment of the Terminology	95
SHIZUO OI	
CHAPTER 7	
Hydrocephalus: Intracranial Pressure, Myelination, and Neurodevelopment	113
PATRICK W. HANLO, ROB H.J.M. GOOKSENS AND PETER W. VANDERTOP	
CHAPTER 8	
Posthemorrhagic Hydrocephalus of Prematurity	121
FREDERICK A. BOOP	
CHAPTER 9	
Hydrocephalus with Myelomeningocele	133
SPYROS SGOUROS	

CHAPTER 10	
Benign Pericerebral Collections in Children	145
SPYROS SGOUROS AND CHRISTOS TOLIAS	
CHAPTER 11	
Hydrocephalus in Pediatric Patients with Posterior Fossa Tumours	155
CHRISTIAN SAINTE-ROSE	
CHAPTER 12	
Treatment of Hydrocephalus in Suprasellar Lesions	163
VITALY SIOMIN AND SHLOMI CONSTANTINI	
CHAPTER 13	
Hydrocephalus and Colloid Cysts	171
PHILIPPE DECQ, CAROLINE LE GUERINEL, LAURENT SAKKA, CHRISTO CHRISTOV, PIERRE BRUGIÈRES, STÉPHANE PALFI, ELIANE MELON AND JEAN-PAUL NGUYEN	
CHAPTER 14	
Hydrocephalus and Spinal Tumors	187
HELEN MAROULIS, WIRGINIA MAIXNER, ENRICO LEONE AND GIUSEPPE CINALI	
CHAPTER 15	
Postinfectious Hydrocephalus in Children	201
ALEXANDER V. CIUREA, TEODORA C. COMAN AND DAN MIRCEA	
CHAPTER 16	
Multiloculated Hydrocephalus	219
PIETRO SPENNATO, GIUSEPPE CINALI, GIUSEPPE CARANNANTE, CLAUDIO RUGGIERO AND MARIA LAURA DEL BASSO DE CARO	
CHAPTER 17	
Hydrocephalus in Neurocysticercosis and Other Parasitic and Infectious Diseases	245
SERGIO CAVALHEIRO, SAMUEL T. ZYMBERG AND MÁRCIA C. DA SILVA	
CHAPTER 18	
Hydrocephalus and the Dandy-Walker Malformation	259
GIUSEPPE CINALI, PIETRO SPENNATO, MARIA LAURA DEL BASSO DE CARO AND MARIA CONSIGLIO BUONOCORE	
CHAPTER 19	
Hydrocephalus and Aqueductal Stenosis	279
GIUSEPPE CINALI, PIETRO SPENNATO, EMILIO CIANCIULLI AND MARIA D'ARMIENTO	
CHAPTER 20	
Shunt Hardware and Surgical Technique	295
HOWARD J. GINSBERG AND JAMES M. DRAKE	

CHAPTER 21	
Abdominal Complications of Peritoneal Shunts	315
MATTHIEU VINCHON AND PATRICK DHELEMMESES	
CHAPTER 22	
Patterns of Shunt Failure According to the Hydrodynamic Features of the Valve: Lessons from the Shunt Design Trial	329
JOHN R.W. KESTLE AND JAMES M. DRAKE	
CHAPTER 23	
Slit Ventricle Syndrome or Syndromes: Diagnosis and Management	335
HAROLD L. REKATE	
CHAPTER 24	
Endoscopic Anatomy of the Ventrices	351
PHILIPPE DECQ	
CHAPTER 25	
Endoscopic Third Ventriculostomy	361
GIUSEPPE CINALLI	
CHAPTER 26	
Third Ventriculostomy in Shunt Malfunction	389
JONATHAN PUNT	
CHAPTER 27	
Dynamic MRI of Cerebrospinal Fluid in Children	397
FRANCIS BRUNELLE	
CHAPTER 28	
The CISS Sequence in the Preoperative MRI Assessment of Neuroendoscopic Third Ventriculostomy	405
NORMAN S. McCONACHIE	
CHAPTER 29	
Complications of Endoscopic Third Ventriculostomy	411
CHARLES TEO	
CHAPTER 30	
Repeat Third Ventriculostomy	421
VITALY SIOMIN AND SHLOMI CONSTANTINI	
CHAPTER 31	
Economic Analysis of Endoscopic Third Ventriculostomy and Ventricular Shunts	425
HUGH GARTON AND PAUL STEINBOK	

CHAPTER 32	
Growth and Puberty in Hydrocephalus	435
RAJA BRAUNER, FLORENCE CHOLLEY AND CHRISTINE TRIVIN	
CHAPTER 33	
Epilepsy in Childhood Shunted Hydrocephalus	443
MARIE BOURGEOIS, CHRISTIAN SAINTE-ROSE, GIUSEPPE CINALLI, WIRGINIA MAIXNER AND JEAN AICARDI	
Subject Index	455

List of Contributors

- AICARDI, Jean 443
BOOP, Frederick A. 121
BOURGEOIS, Marie 443
BRAUNER, Rasa 435
BRUGIÈRES, Pierre 171
BRUNELLE, Francis 79, 397
BUONOCORE, Maria Consiglio 259
CARANNANTE, Giuseppe 219
CATALA, Martin 19
CAVALHEIRO, Sergio 245
CHOLLEY, Florence 435
CHRISTOV, Christo 171
CIANCIULLI, Emilio 279
CINALLI, Giuseppe 187, 219, 259, 279, 361, 443
CIUREA, Alexander V. 201
COMAN, Teodora C. 201
CONSTANTINI, Shlomi 163, 421
CZOSNYKA, Marek 47
CZOSNYKA, Zofia H. 47
D'ARMIENTO, Maria 279
DA SILVA, Márcia C. 65, 245
DECQ, Philippe 171, 351
DEL BASSO DE CARO, Maria Laura 219, 259
DHELEMMESES, Patrick 315
DIRKS, Peter B. 1
DRAKE, James M. 295, 329
GARTON, Hugh 425
GINSBERG, Howard J. 295
GOOSKENS, Rob H.J.M., 113
HANLO, Patrick W. 113
KESTLE, John R. W. 329
LE GUERINEL, Caroline 171
LEONE, Enrico 187
MAIXNER, Wirginia 187, 443
MAROULIS, Helen 187
McCONACHIE, Norman S. 405
MELON, Eliane 171
MIRCEA, Dan 201
NGUYEN, Jean-Paul 171
OI, Shizuo 95
PALFI, Stéphane 171
PICKARD, John D. 47
PUNT, Jonathan 389
REKATE, Harold L. 335
RUGGIERO, Claudio 219
SAINTE-ROSE, Christian 155, 443
SAKKA, Laurent 171
SGOUROS, Spyros 133, 145
SIOMIN, Vitaly 163, 421
SPENNATO, Pietro 219, 259, 279
STEINBOK, Paul 425
TEO, Charles 411
TOLIAS, Christos 145
TRIVIN, Christine 435
VANDERTOP, Peter W., 113
VINCHON, Matthieu 315
WHITFIELD, Peter C. 47
ZYMBERG, Samuel T. 245

Genetics of Hydrocephalus

PETER B. DIRKS

Introduction

Due to the complexity of organization and function of the human brain, a large proportion (estimates are >50%) of the 40 000 or so genes in the human genome are expected to be involved in the formation and function of the brain [20]. As hydrocephalus is a frequent manifestation of a variety of human neurological diseases, we are at a threshold for improved understanding of the molecular pathogenesis of hydrocephalus and its associated diseases. This review discusses the genetics of CNS disorders associated with hydrocephalus. In these disorders hydrocephalus is usually not the only clinical manifestation of a genetic defect, but is seen in the context of a more broad CNS malformation or syndrome. In this chapter I intend to focus on disorders with hydrocephalus that have been significantly characterized from studies of human subjects and from studies of animal models. These animal studies, mainly using mice, have led to exciting discoveries that will prove to be breakthroughs for understanding the molecular pathogenesis of many disorders with hydrocephalus. This chapter covers vast ground and a complete discussion of all the literature is not possible, but important other reviews from the literature are cited to allow the reader to explore the area in more detail.

ered, even though these diseases or the response to the primary insult may have an important genetic component. Excluding these etiologies, hydrocephalus may occur as a primary malformation or associated with other complex brain malformations such as neural tube defects, X-linked hydrocephalus (part of the clinical spectrum of CRASH syndrome), or Dandy-Walker syndrome. Hydrocephalus also occurs as a feature of genetic syndromes with multiple systemic malformations (such as occurring with chromosomal abnormalities or other mendelian disorders). Chromosomal abnormalities associated with congenital hydrocephalus are most commonly trisomy 13, trisomy 18, and trisomy 9. The number of genetic conditions where hydrocephalus is described as a clinical feature is enormous; this review will focus on human conditions with hydrocephalus with known genetic association.

Determining the genetic cause for hydrocephalus is critically important in determining outcome and plays an important role in genetic counseling. The recurrence risk of congenital hydrocephalus varies widely depending on the etiology. For non-NTD and non-X-linked hydrocephalus, the recurrence risk has been estimated at 1-4% for subsequent children [115]. These risks will be modified with increasing understanding of genetic causes of hydrocephalus and improved genetic testing. The clinical presence of additional congenital malformations or cytogenetic abnormalities adversely affects prognosis for intellectual development in hydrocephalus patients despite treatment with shunting.

Genetics of Hydrocephalus: Overview

Congenital hydrocephalus has an incidence of 0.5-2.5:1000 total births [54, 115]. Congenital hydrocephalus is a heterogeneous group of developmental disorders. For the purposes of this chapter hydrocephalus secondary to intracranial infection, hemorrhage, vascular malformations (such as vein of Galen malformation), and neoplasms will not be consid-

X-Linked Hydrocephalus

X-linked hydrocephalus is a neurological disorder characterized by hydrocephalus due to aqueductal stenosis (see Table 1). Male preponderance in congenital hydrocephalus is due in part to this condition. X-

Table 1. Features of X-linked hydrocephalus

	Clinical genetics	Key clinical features	Gene	Gene mutations in disease
X-linked hydrocephalus	1:30 000 male births About 25% of males with definite aqueductal stenosis have this disease Chromosome Xq28	Spectrum of abnormalities part of the “CRASH” syndrome Aqueductal stenosis with hydrocephalus Spasticity and hypoplasia of corticospinal tracts Adducted thumbs	L1CAM A neural cell surface adhesion molecule	Large variety of different mutations Mutations involving cytoplasmic portion of the molecule may have less severe hydrocephalus

linked hydrocephalus is thought to represent about 2–5% of all nonsyndromal congenital hydrocephalus [115]. This condition has been recognized since the early 1960s [32, 33]. X-linked hydrocephalus is the most common genetic form of congenital hydrocephalus and occurs in about 1:30 000 male births. Transmission of the disease gene is from mothers to sons. The neurological abnormalities can be variable, and in addition to a varying severity of hydrocephalus, there may be hypoplasia of the corticospinal tracts (characterized by absence of medullary pyramids), corpus callosal agenesis, hypoplasia of the anterior cerebellar vermis and fusion of the thalami [132]. Other neurological abnormalities can occur. Patients present with hydrocephalus, mental retardation, spastic paraparesis, and a characteristic adduction deformity of the thumbs (“clasped” thumbs are present in about 50% of cases) [52]. There is a generally poor intellectual outcome in children despite adequate treatment of hydrocephalus related to the intrinsic brain abnormalities [52]. Non-X-linked hydrocephalus has a better intellectual prognosis.

It has been estimated that about 25% of males with definite aqueductal stenosis have X-linked hydrocephalus [8, 52]. This information is critically important in counseling parents of a male fetus with hydrocephalus. Knowing the sex of the fetus with hydrocephalus is obviously essential. X-linked hydrocephalus should be strongly considered if there is a maternal history of spontaneous abortion or early death of previous males in the family. However, these historical features are frequently not present as two-thirds of cases of X-linked hydrocephalus are sporadic. Female carriers can be mildly affected [54]. The risk for a male child for the condition is 50% if the mother is a carrier. Identification of associated clinical features in the suspected fetus is also important to consider in determining risk. In a male with obstructive hydrocephalus without the clinical findings of adducted thumbs and without hypoplasia of medullary pyramids, the estimated risk for a subsequent male is 4% and that for a female is 2% [52].

In the early 1990s linkage analysis studies of families with X-linked hydrocephalus established that the disease gene was located at chromosomal region Xq28 [65, 133]. Another syndrome known as the MASA syndrome (mental retardation, adducted thumbs, spasticity, and aphasia) was also localized to this region, suggesting that it may be caused by the same disease gene and that the two syndromes could be variations of the same disorder. It has now been established that mutations in the neural cell adhesion molecule known as L1 (also called L1CAM) causes both disorders [38, 39, 106, 124]. In fact, it is apparent that spastic paraplegia type 1 and X-linked agenesis of the corpus callosum are also caused by L1 alterations. Because of overlap and similarity between these disorders and common molecular genetic etiology, these groups of conditions have been grouped as the CRASH syndrome (corpus callosal hypoplasia, mental retardation, adducted thumbs, spastic paraplegia, and hydrocephalus) [38].

L1 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily of cell adhesion molecules that mediate cell-cell adhesion [39, 68]. The protein has a large extracellular domain, a single transmembrane domain, and short cytoplasmic tail [5]. L1 is predominantly expressed in the nervous system and is thought to play a role in neuron-neuron adhesion, axonal elongation, and axonal pathfinding [71]. It has been functionally implicated in learning and memory. The molecular mechanism of activation and signaling of L1 is poorly understood. Many different molecules bind to the extracellular domain of L1, including L1 itself, and the significance of these different ligands is unclear. The intracellular signaling pathways have not yet been completely defined, but the cytoplasmic domain interacts with components of the sub-plasma membrane cytoskeleton [71]. L1-L1 interactions have been shown to activate fibroblast growth factor receptors leading to activation of calcium channels at the sites of axonal elongation, called growth cones [71].

The gene for L1 is large, having 28 exons over 15 KB of genomic DNA. A large number of different mutations have been described with each family having their own unique mutation. The mutations reported including missense, splicing, frameshift, nonsense, duplication, and deletion, meaning that they can have extremely variable effects on L1 genotype and possibly phenotype [41]. Mutations causing severe extracellular domain truncation or absence of protein seem to have more severe clinical phenotypes [41]. Mutations involving the cytoplasmic domain seem to cause less severe phenotypes, particularly less severe hydrocephalus [71, 137]. It has been speculated that these cytoplasmic mutations cause less severe phenotypes because they do not disrupt L1 extracellular adhesive function [71].

Mouse models have been generated to understand the function of L1 and to understand the pathogenesis of the CRASH syndrome. Complete loss of L1 in transgenic mice causes abnormalities in the brain similar to those of patients with the disease [16, 40, 68]. Homozygous L1 deletion ($L1/-/-$) in mice leads to hydrocephalus, abnormal cortical pyramidal neurite extension, small hippocampi, small corpus callosum due to failure of crossing of axons, corticospinal tract hypoplasia, and cerebellar vermis aplasia – features strikingly similar to those seen in humans with L1 mutations. Animals have defects in learning. Hydrocephalus severity seems to depend on the particular mouse strain used to create the knockouts, suggesting that modifier genes play a role in the disease phenotype. The mechanism by which L1 causes hydrocephalus or aqueductal stenosis is not understood.

Because of the very wide variety of mutations causing the CRASH syndrome and the large size of the gene, molecular genetic analysis of the whole gene as prenatal work-up in previously unaffected families is a substantial undertaking [35, 36]. Detection of carriers can be determined through analysis of markers at Xq28 if other male patients are alive and if the family is large enough [115]. Mutational analysis can be performed by a method known as single-strand conformational polymorphism analysis (SSCP) of polymerase chain

reaction (PCR)-amplified genomic DNA or reverse transcriptase PCR from RNA samples from amniotic fluid cells or chorionic villus samples. It is important to identify clinical features in family members in order to assess risk. Females in the family should be examined for adducted thumbs and learning difficulties. Perhaps with increased sophistication of MRI, abnormalities of the corticospinal tracts can be detected in the brains of affected individuals to help with prenatal diagnosis. Prenatal ultrasound has detected morphological abnormalities characteristic of the syndrome early in pregnancy [95, 121]. Because of the extremely wide spectrum of mutations in a very large gene and uncertain genotype-phenotype correlation, the identification of a mutation does not necessarily predict the severity of the disease in the affected individual.

Autosomal Recessive Hydrocephalus

Hydrocephalus inherited as an autosomal recessive disorder is rare and has a greater chance of being manifest in children born to consanguineous parents. Candidate genes for hydrocephalus inherited in this manner have not been isolated.

Dandy-Walker Malformation

Dandy-Walker malformation (DWM) is characterized by hydrocephalus, partial or complete absence of the cerebellar vermis, and a large posterior fossa cyst continuous with the fourth ventricle. It occurs with an estimated incidence of 1:25000 births. There may be a slight female preponderance [74, 92]. Dandy-Walker malformation is responsible for less than 5% of hydrocephalus cases. The etiology of this malformation is poorly understood. It has been associated with mendelian genetic disorders, chromosomal abnormalities, and teratogenic exposure (see Table 2).

Table 2. Conditions associated with Dandy-Walker syndrome (see [13, 86])

Mendelian disorders	Chromosomal abnormalities	Teratogens
Walker-Warburg syndrome (AR)	Trisomy 8, 9, 13, 18, 21	Maternal insulin-dependent diabetes
Meckel-Gruber syndrome (AR)	Triploidy 69	Alcohol
Joubert syndrome (AR)	Deletions 2q, 3q, 6p	Cytomegalovirus infection
Aicardi syndrome (XL)	Duplications 5p, 8p, 8q, 17q, 22	Rubella infection
Many others	Many others	Warfarin Valproic acid Vitamin A

DWM is part of a heterogeneous group of disorders occurring as an isolated CNS abnormality or as part of a malformation syndrome involving other parts of the CNS or other organ systems. The list of mendelian disorders and chromosomal abnormalities associated with DWM is very extensive and has been previously detailed in the report by Chitayat et al. [13]. DWM occurs in the context of autosomal recessive conditions such as Walker-Warburg syndrome, Meckel-Gruber syndrome, and Joubert syndrome, as well as others. The genes for these three disorders remain unknown. Trisomy 18, trisomy 13, and triploidy are the most common associated chromosomal abnormalities. Recurrence risk has been estimated at 1-5% when not associated with Walker-Warburg syndrome or Meckel syndrome [86].

The pathogenesis of DWM has been debated for years, but it is probably generally accepted now that there is a primary defect in cerebellar development as opposed to atresia of the outlets of the fourth ventricle. The cerebellar vermis begins to form in the 9th week of human development beginning superiorly and is completed inferiorly by the 15th week [10]. The cerebellum emerges rather late in development. It begins as a proliferation of cells in the alar aspect of the first rhombomere of the hindbrain (also called the metencephalon) [66]. The most numerous cells in the cerebellar cortex, the granule neurons, arise along the edge of the fourth ventricle in a region known as the rhombic lip [82]. A critical region, known as the "isthmus," between the developing mesencephalon and metencephalon, acts as an organizer for the proper regional development of the brain stem and cerebellum. Cerebellar hemispheres develop from the metencephalon and the vermis develops from the mesencephalon adjacent to the isthmus. Ectopic transplantation of the isthmus more caudally in the rhombencephalon in mice leads to ectopic cerebellar formation [66]. Molecular analysis of the midbrain-hindbrain organizer region has lead to the discovery of a number of genes encoding for transcription factors or secreted factors involved in the proper development of the cerebellum (Otx1, Otx2, Gbx2, Engrailed 1, Engrailed 2, Pax2, Pax5, fibroblast growth factor 8). The discussion of the midbrain-hindbrain organizer and molecular control of cerebellar development is beyond the scope of this chapter, but the reader is referred to a number of excellent reviews [66, 82, 98, 134]. DWM cannot be diagnosed before 18 weeks as it has been estimated that the vermis is still open in 4% of fetuses at 17.5 weeks [74].

Walker-Warburg syndrome (cerebro-oculomuscular syndrome) is characterized by severe hydrocephalus, type II lissencephaly, cerebellar or posterior fossa malformation, eye and retinal abnormalities

(retinal dysplasia, retinal detachment), and congenital muscular dystrophy [30]. The posterior fossa abnormality consists of DWM or occipital encephalocele. A diagnosis of Walker-Warburg syndrome can be made with clinical features in the context of lissencephaly on MRI, elevated muscle enzymes, and abnormal muscle biopsy. Prognosis is very poor [97]. Joubert syndrome is characterized by hypotonia, ataxia, mental retardation, characteristic facies, and ocular abnormalities. Hypoplasia of the cerebellar vermis occurs and in some patients there is DWM [97]. Meckel-Gruber syndrome consists of a variety of features, most importantly cystic kidney dysplasia, liver fibrosis, polydactyly, and CNS abnormalities including DWM and encephalocele [15, 138]. This disease has been mapped to chromosome 17q21-24 [91].

A posterior fossa malformation consistent with DWM also can occur in the context of Aicardi syndrome, which is characterized clinically by infantile spasms, agenesis of the corpus callosum, and pathognomonic retinal abnormalities (chorioretinal lacunae) [1, 31, 63, 88]. There can also be enlarged ventricles, choroid plexus cysts, and cerebral heterotopias [14, 123]. Spinal vertebral anomalies and cleft palate can also occur. The intellectual prognosis is generally very poor [80]. Visual prognosis is also poor and dependent on the location of the chorioretinal lacunae. Aicardi syndrome is considered to be an X-linked dominant disease, lethal in hemizygous males. All reported cases occur in females (except one male with a 47XXY karyotype). The disease has been mapped to chromosome Xp22, but the gene is unknown [31, 88].

It is clear that genetic analysis of affected persons with DWM has shed little light on the pathogenesis of the malformation. In the past decade, however, a staggering amount of knowledge has been accumulated about the genes involved in development of the brainstem and cerebellum (as discussed above). The use of mouse models in which these genes have been knocked out or misexpressed has led to some exciting discoveries that may now illuminate the pathogenesis of this complex malformation. Other animal models with cerebellar malformations are being screened to identify the gene responsible for cerebellar defects [82]. A recent transgenic mouse model suggests that misexpression of a homeodomain transcription factor called Engrailed-1 (En-1) leads to a posterior fossa malformation reminiscent of DWM [109]. The animals have hydrocephalus involving all ventricles associated with a cyst in the posterior cerebellar vermis contiguous with the fourth ventricle. Interestingly, the timing of development of hydrocephalus in the mouse resembles the course in humans, presenting in the postnatal period. Hemo-

siderin deposits in the walls of the posterior fossa cyst suggest that, as in humans, hemorrhage may contribute to the hydrocephalus observed postnatally.

This transgenic mouse model involves expression of En-1 driven under the control of an enhancer element of a gene from the Wingless developmental signaling pathway, Wnt-1. Both Wnt-1 and En-1 have been shown to be essential genes for cerebellar development, as knockouts for these genes in mice lead to absence of cerebellar development. The expression of Wnt and Engrailed genes in the developing human fetal brain is similar to that in the mouse. Normally, Wnt-1 is expressed in a slightly more rostral position at the midbrain-hindbrain junction than En-1. Increased gene dosage of En-1 therefore in a more rostral position during development may cause abnormal cell fate determination, abnormal cell migration, or inappropriate cell death, thereby altering cerebellar development, leading to a Dandy-Walker-like malformation. Obviously there is a great leap between finding out that misexpression of a particular gene leads to a Dandy-Walker-like malformation and understanding how that perturbation in function explains the abnormal brain morphology. It is clear, however, that such models promise to bring forth understanding far beyond the stalemate that exists.

Holoprosencephaly

Holoprosencephaly (HPE) is characterized by incomplete cleavage of the forebrain into two hemispheres, including telencephalon, diencephalon, and olfactory and optic bulbs and tracts [84, 104, 128]. In its most severe form, there is a single ventricle and single forebrain, without an interhemispheric fissure. Brain malformations are associated with facial malformations including nasal proboscis, single nostril, and cleft lip. Hydrocephalus is often associated. HPE is a spectrum of brain abnormalities but is classified as alobar (most severe, no midline separation), semilobar (partial interhemispheric fissure), or lobar (interhemispheric fissure except for ventral frontal lobes) [47]. There is a wide spectrum of clinical manifestations of HPE, varying from cyclopia with single hemisphere in alobar HPE to subtle facial anomalies such as absence of a superior labial frenulum in lobar HPE [4, 77]. All HPE patients are not expected to have a sense of smell [4]. Mortality and developmental delay correlate with the severity of CNS anomalies. Patients with cyclopia die shortly after birth, and most other patients with alobar HPE do not live beyond 6 months [4]. The incidence of HPE is about 1:16000 births, although the incidence in conceptuses is 1:250, suggesting high

lethality in utero. Most cases of HPE are sporadic and there is variable severity even within families, suggesting incomplete penetrance of disease genes.

HPE is caused by disruption of development of the ventral forebrain and midline facial structures [84]. It has been known for nearly 100 years that experimental removal of the prechordal mesoderm, specialized mesodermal tissue that lies in the midline of the developing embryo ventral to the developing forebrain, can cause HPE. These experiments suggested that the prechordal mesoderm supplies a factor for induction of proper ventral forebrain development. The etiology of this disorder is heterogeneous, with environmental and genetic factors playing a role in its pathogenesis. Numerous teratogens have been implicated, including maternal diabetes, vitamin A, alcohol, low cholesterol and solvents. About 25% of HPE cases are due to a single gene mutation. Chromosomal abnormalities such as trisomy 13 and 18 are associated with HPE [105]. HPE is more commonly seen as a sporadic disease than a familial one. There are five genetic loci known so far to be associated with HPE, but there may be as many as a dozen [105]. The HPE1 locus is unknown. The genes at the other HPE loci include sonic hedgehog (Shh) (HPE3 locus, chromosome 7q36), Zic2 (HPE5, chromosome 13q32), Six3 (HPE2, chromosome 2p21), and TGIF (HPE4, chromosome 18p11). These genes associated with HPE represent the minority of familial and sporadic cases. There is a much longer list of genes associated with HPE in model organisms such as mice or zebrafish, but mutations in human homologues have not yet been found [105]. Shh is the best characterized of these genes and has emerged as a critically important gene for pattern formation of tissues in the developing embryo. HPE also occurs in the context of other disorders such as Smith-Lemli-Opitz syndrome, Pallister-Hall syndrome, and Rubenstein-Taybi syndrome. In these three disorders a genetic mutation is thought to perturb a component of the Shh signaling pathway.

The Shh gene was initially defined in *Drosophila* (Hedgehog, Hh). It is a secreted protein that undergoes post-translational cleavage and lipid modification by cholesterol and palmitate. These latter lipid modifications are important for determining its extracellular diffusion and tissue targeting. Shh acts on adjacent cells and exerts its effects through alteration of gene expression. A discussion of the signaling effects of Shh is beyond the scope of this chapter (see [48, 126]). Shh is required for proper dorsal-ventral patterning of the entire CNS. It is secreted by midline axial mesoderm, either prechordal mesoderm in the head for development of the telencephalon or by the notochord or specialized ventral cells in the neural tube for the brainstem and spinal cord. Elimination of Shh in homozygous knockout mice produces hol-

prosencephaly [48, 126]. A large number of different mutations in the Shh gene have been discovered in humans [105]. Loss of a single copy of the gene in humans is sufficient to cause HPE in humans [103, 105]. In an HPE family, individuals with the same mutation may be affected very differently.

Neural Tube Defects

Neural tube defects (NTDs) are amongst the most common human congenital malformations. The incidence is about 1:1000 live births, with geographical and racial variations, being highest in Ireland, the United Kingdom, and Mexico [29]. The birth incidence in NTDs is falling in many developing countries. NTDs are thought to be due to failure of elevation of the neural folds with subsequent failure of fold fusion, leading to anencephaly, myelomeningocele, and craniorachischisis. These three forms of NTDs are respectively caused by failure of anterior neuropore closure, failure of posterior neuropore closure, or complete failure of neural fold fusion, resulting in an open nervous system [53]. Encephalocele is thought to be a postneurulation defect arising from a protrusion of brain and meninges through the skull due to an abnormal opening in the skull or a failure of separation of cutaneous and neural ectoderm [53]. Spina bifida occulta is also a secondary failure of mesenchymal tissues to completely cover a closed neural tube [29].

The etiology of NTDs has long been thought to be heterogeneous, due to gene mutations, chromosomal abnormalities, and environmental factors such as teratogens and dietary deficiencies. Genetic etiology is suggested by a familial incidence of about 3% and risk to subsequent offspring of parents with an affected child. Genetic susceptibility to environmental factors may be very important. An understanding of the etiology is also confused somewhat by terminology and the heterogeneous phenotypes. Consider the following that can make discussion of NTDs confusing: open versus closed neural tube defects, anencephaly versus myelomeningocele versus craniorachischisis, isolated NTD versus syndromic NTD, defects of primary neurulation versus secondary neurulation, neurulation defect versus postneurulation defect. This review will focus on myelomeningocele, anencephaly, and craniorachischisis, with particular emphasis on myelomeningocele as it is the typical entity seen by clinical specialists. There are likely common and unique mechanisms genetically involved in this phenotypic spectrum of NTDs. With recent tremendous progress made in understanding

the molecular genetic mechanisms of the dorsal-ventral and anterior-posterior (rostral-caudal) patterning of the nervous system during development, our knowledge of the pathogenesis of NTDs will rapidly increase. The human genome sequence with cataloguing of individual DNA sequence variations will hopefully lead to identification of the constellation of multiple genes that are involved together with environmental factors to produce these complex defects.

Etiologies of NTDs have also been elusive because of the fact that neurulation is an extremely complex process controlled by coordinated expression of many different genes throughout the developing nervous system. Errors in many different genes are likely to cause similar disease phenotypes. However, NTDs also consist of several phenotypes, with different sets of genes involved in different processes leading to different phenotypes. It is likely that a significant number of genes involved in the process of neurulation are involved in the same biochemical or molecular pathway, and therefore dysfunction of one of a large number of different genes in a single pathway may be sufficient to produce an NTD. Also, for many important biological processes there exist redundant pathways enabling the organism to compensate for error; therefore, the effects of a single gene defect may not be readily apparent and may depend on interaction with other modifier genes or on environmental factors. This means that the gene defect will not be manifest unless these other contributing genetic or environmental conditions are also present.

A major breakthrough in recent years in understanding the pathogenesis of NTDs has been the discovery that periconceptual folic acid supplementation can decrease the risk of having a child with a NTD. Another important breakthrough has been the creation of multiple mouse models with NTDs, and new molecular insights gained into mice that spontaneously get NTDs. In a transgenic mouse, an exogenous gene is introduced into a fertilized egg, causing widespread or tissue-specific expression of the gene in the developing mouse. In a knockout mouse, a gene of interest is targeted for elimination in cultured mouse embryonic stem cells. These manipulated embryonic stem cells are subsequently implanted into a recipient pseudopregnant mouse for embryonic development. These founder mice are then bred so progeny are either heterozygous for the targeted allele or homozygous for the targeted allele in every cell of the organism. These models have resulted in NTDs occurring as a result of manipulation of some rather unexpected genes.

Current mouse models now number more than 50 different natural or genetically engineered mice with NTDs (see Table 3) [53, 67]. It is rather surpris-

Table 3. Partial list of mouse models of neural tube defects (see [29, 53, 67])

Name	Genetics	Features of NTD	Response to nutritional supplementation
Splotch mouse (spontaneous mouse mutant)	Pax3 homeodomain transcription factor 32 base pair deletion results in protein truncation Normally expressed in dorsal half of developing neural tube	Waardenburg syndrome in humans is caused by Pax3 mutations in one allele Cranial and caudal NTDs	Folic acid or thymidine administered to pregnant mice reduces the frequency of NTDs in splotch homozygote offspring
Loop tail (spontaneous)	Gene unknown, mechanism unknown	Cranioraschischisis	Unknown
Cart1 knockout	Cart1, homeodomain transcription factor	Cranial NTD	Folic acid
p53 knockout	P53, transcription factor, cell cycle and apoptosis regulator	Cranial NTD	Unknown
Crooked tail (spontaneous)	Unknown gene	Cranial NTD	Folic acid
Open brain (spontaneous)	Unknown gene	Cranial NTD	Unknown
Curly tail (spontaneous)	Unknown gene deficiency in retinoic acid signaling from hindgut	Mainly caudal NTDs	Inositol (water soluble vitamin)
Axd, axial defects mouse (spontaneous)	Unknown gene	Caudal NTDs	Methionine

NTD, neural tube defect

ing how several of these animal models clinically parallel the human disease; for example, several mouse models for NTDs ("splotch," "crooked," "Cart1") have a significant reduction in the risk of the NTD following folic acid administration [67]. The genes involved in mouse NTDs also display a surprising diversity of function (transcription factors, signaling molecules, enzymes, and cell surface receptors), suggesting that a great variety of mechanisms can produce an NTD [67]. The hypothesized mechanisms by which a gene defect causes an NTD include: (1) abnormal ventral bending of the embryo, leading to disturbed neural fold fusion dorsally; (2) lack of supporting mesenchyme, causing failure of fold elevation; (3) defective basal lamina of surface ectoderm, leading to lack of support in forcing adjacent neural fold to elevate; (4) abnormally broad notochord and floor plate; (5) excessive neu-

roepithelial cell death; and (6) delayed/failed elevation of neural folds [53].

NTDs can occur in isolation or in the context of complex congenital malformations. A minority of myelomeningoceles has an identified chromosomal abnormality by karyotyping by traditional G-banding techniques. A myelomeningocele occurring in isolation, with a Chiari II malformation and hydrocephalus only, is associated with a 2.6% chance of a variety of different chromosomal abnormalities by karyotyping [70]. A 38% chance of a chromosomal abnormality exists in the context of myelomeningocele associated with other prenatal ultrasound-identified abnormalities [70]. Occasionally a chromosomal abnormality is also detected in a parent, suggesting a significant increased risk for subsequent pregnancies. Anencephaly is more common in females, but myelomeningocele occurs equally in males and females.

Only rarely are human myelomeningoceles seen associated with a single gene defect. Waardenburg syndrome type I is an autosomal dominant disorder clinically characterized by a wide nasal bridge, skin pigmentation abnormalities, and deafness [25, 83]. Patients with this syndrome occasionally get NTDs [56, 83]. Waardenburg syndrome is caused by mutation in the Pax3 gene [58, 120]. Pax3 mutations may occasionally also be associated with familial NTDs. Pax3 is a one of a family of homeodomain transcription factors that plays a crucial role in development of the nervous system. In the early developing neural tube Pax3 expression defines the dorsal half of the spinal cord. Genetic studies in mouse models reveal that Pax3 is critically important for proper spinal cord development. The splotch mouse is naturally mutant for Pax3, and these animals have NTDs predominantly affecting the lumbosacral region but also anencephaly (in 50%) [34, 83]. Mice that are homozygous for the Pax3 mutation (loss of both Pax3 alleles) die during embryogenesis. Restoration of Pax3 expression to the dorsal neural tube in splotch mice using transgenic techniques rescues homozygotes from NTDs, underlying its importance in the proper formation of the neural tube [76]. Interestingly, administration of folic acid to mice pregnant with splotch homozygotes substantially reduces the incidence of NTDs [37]. As the splotch mouse model illustrates, animal models can be surprisingly similar to the human condition. Other animal models of NTDs are also responsive to nutritional supplementation [67].

NTDs can be prevented by folic acid [2, 19, 23, 24, 96]. The mechanism is not clear, as maternal serum and red cell folate levels are normal or only mildly deficient [19]. Fetal genetic defects in enzymes involved in folate metabolism and maternal placental folate transport defects are now being intensively studied. One enzyme receiving a significant amount of attention is methylenetetrahydrofolate reductase (MTFHR) [3, 19]. There is a thermolabile variant of this enzyme that has been associated with some NTD patients and their family members, but definitive association with NTDs has not been established.

Encephalocele

Encephaloceles are thought to be caused by a post-neurulation defect, either from a mesenchymal abnormality involving the skull or a problem with the normal separation of the neural ectoderm from the cutaneous ectoderm [46, 59, 139]. Encephaloceles of all types have an incidence of 0.1–0.5 per 1000 live births. Posterior encephaloceles are more common in

Western countries and anterior encephaloceles are more commonly seen in Asia, particularly Thailand [93]. The etiology of encephaloceles is probably multifactorial, with interaction between genetic and environmental factors playing a role in their pathogenesis [93]. Almost nothing is known about which gene or genes may be involved in this malformation. Encephaloceles occur in the context of systemic or brain malformation syndromes of unknown etiologies such as Meckel-Gruber syndrome, Walker-Warburg syndrome, Dandy-Walker syndrome, and others [63]. Chromosomal aberrations are also associated with encephaloceles [135].

Achondroplasia

Achondroplasia is the most common cause of short-limbed dwarfism and is an autosomal dominant disorder (see Table 4). The incidence is about 1 in 15 000 births [63]. Most cases are sporadic and are caused by new mutations. Penetrance is complete. Achondroplasia is associated with increased morbidity and mortality in all ages. The disease is characterized by short stature with a long narrow trunk and short extremities, especially proximal segments (rhizomelia) [60]. Macrocephaly with frontal bossing is common, and there is hypoplasia of the midface. Specific head circumference charts for achondroplastic children have been developed and can be found in Smith's textbook [63]. Macrocephaly is caused by megaencephaly or is due to ventriculomegaly from venous stenosis of the jugular foramina [94, 112, 119]. Ventriculomegaly without hydrocephalus is common. Neurologically, there is diffuse hypotonia and delayed development of motor milestones but generally normal intelligence. There is risk of sudden death within the 1st year of life due to stenosis at the craniocervical junction, but prophylactic treatment of patients without clinical symptoms and signs of craniocervical compression is controversial. Standard measurements of the size of the foramen magnum have been published [55] and together with MR imaging and neurophysiological studies may identify those asymptomatic individuals at risk of neurological deterioration from cervicomedullary stenosis [69]. Spinal stenosis with neurological deterioration in leg function is also relatively common in adulthood. The pathological substrate for the disease is believed to be an impaired rate of endochondral ossification, causing reduced bone elongation. Longitudinal growth of the skeleton occurs because of endochondral ossification at the ends of long bones. The growth plate of patients with achondroplasia demonstrates severe disorganization.

Table 4. Features of achondroplasia

	Clinical genetics	Key clinical features	Gene	Gene mutations in disease
Achondroplasia	1:15 000 births Many sporadic cases due to new mutations Chromosome 4p16	Short stature Short proximal limbs Macrocephaly Ventriculomegaly without hydrocephalus Midface hypoplasia Craniocervical junction stenosis Spinal stenosis	FGFR3 fibroblast growth factor receptor type 3 Receptor Tyrosine kinase	Mutation at nucleotide 1138 of the cDNA causes characteristic glycine to arginine amino acid substitution (G380R) in the transmembrane part of the receptor Mutation causes inappropriate activation of the FGFR3 Genetic diagnosis is straightforward because of stereotypical mutation, G380→R

The genetic locus of this disease was initially localized to chromosome 4p16 by linkage analysis study of affected families. In 1994, a mutation in the fibroblast growth factor receptor 3 (FGFR3) was found to be the genetic cause of the disease [108, 117]. In almost every case of achondroplasia a mutation results in a glycine-to-arginine amino acid change in the transmembrane portion of the receptor protein (G380→R). Prenatal genetic diagnosis is possible and more straightforward because of the stereotypical genetic abnormality in the context of ultrasound findings [81]. Reverse transcriptase PCR of small cDNA fragments derived from RNA followed by sequencing will determine the mutation. Homozygotes for the mutation are extremely severely affected and die shortly after birth, and heterozygotes survive with characteristic skeletal abnormalities [27]. Thanatophoric dysplasia is another form of dwarfism with neonatal lethality that also has a mutation in the extracellular or intracellular portion of FGFR3. Hypochondroplasia is a less severe form of chondrodysplasia without craniofacial abnormalities that also has a mutation in FGFR3.

The FGFR3 belongs to a family of protein receptor tyrosine kinases (FGFR1-4 in humans) that have high affinity binding to fibroblast growth factors (FGF1-10) [27]. Binding of an FGF ligand by an FGFR in conjunction with a cell-surface heparin sulfate proteoglycan results in clustering of the receptors and autoactivation of the receptor by phosphorylation. The phosphorylation occurs on the intracellular portion of the receptor and serves to activate the kinase activity of the receptor, leading to

further phosphorylation and activation of downstream signaling molecules. Phosphorylation of the receptor also creates docking sites for other signaling molecules, allowing recruitment of a variety of intermediates to the site of an activated receptor. Activation of the receptor causes pleiotropic effects on the cell. FGFs and FGFRs play a role in cell proliferation, cell differentiation, cell survival, and cell motility. The effect of FGFR activation depends on the cell type and the developmental stage of that cell. FGFR3 has high expression in the nervous system and in prebone cartilage. The characteristic mutation in FGFR3 that occurs in achondroplasia results in constitutive activation of receptor signaling, even in the absence of appropriate FGF ligand [87, 130]. The mutation is thought to cause inappropriate activation of the receptor by stabilization of clustering of receptors.

Mouse models for achondroplasia suggest that FGFR3 normally acts as a negative regulator of chondrocyte proliferation. Mice completely devoid of FGFR3 expression (knockout mice) demonstrate enhanced endochondral bone growth, with an enlarged growth plate and increased chondrocyte proliferation [18, 28]. Bones of these mice are longer and thicker than normal. The achondroplasia mutation (G380→R) actually results in “gain of function” for the FGFR3 gene, leading to more potent inhibition of chondrocyte proliferation. Mice genetically engineered to have the human achondroplasia mutation have dwarfism and craniofacial abnormalities analogous to the human condition [129].

Neurofibromatosis

The neurofibromatoses consist of a group of autosomal dominant inherited disorders characterized by abnormalities of the neural crest, particularly tumor formation (see Table 5) [78, 99]. The two classical forms, neurofibromatosis I (NF1; formerly von Recklinghausen neurofibromatosis) and neurofibromatosis II (bilateral acoustic neuromas) will be the focus of discussion in this segment. Other so-called NF variants, with some clinical characteristics similar to NF1 but also with other manifestations, have been described but are not clearly distinct genetic entities (so-called neurofibromatosis types 3–6; including segmental neurofibromatosis, familial café au lait spots, familial spinal neurofibromatosis) [9, 110].

The genes whose mutations are responsible for NF1 and NF2 were discovered 10 years ago. These discoveries have led to remarkable advances in the understanding of these diseases, especially with respect to an understanding of mechanisms of tumor formation. However, despite these genetic advances, the diagnosis of NF1 and NF2 remains a clinical one. Relatively little is still known about the potential normal role of these genes in the normal development of the central and peripheral nervous systems.

Neurofibromatosis 1

NF1 is one of the most common autosomal dominant inherited diseases, with an estimated incidence of 1 in 4000 individuals [9, 42, 110]. It occurs in all races and in all countries. The disease has 100% penetrance but there is a remarkable variable degree of expressivity. Affected individuals within a single family, where all the affected persons carry the same genetic mutation, can have extremely variable clinical manifestations, with some individuals being mildly affected and others severely affected. About 50% of NF1 patients do not have a family history of the disease, and these cases are therefore caused by new mutations that occur in the developing gametes of the father (usually) or the mother. Reasons for the high new mutation rates in the NF1 gene are unknown.

The disease characteristically involves neural crest tissues largely, but not exclusively. Most manifestations of the disease increase in frequency with age, so that it may be relatively difficult to make a certain clinical diagnosis in infancy or early childhood, but the disease is usually apparent in affected individuals by age 8 and in 100% by age 20 [50]. There are well-established clinical criteria developed by the United States' National Institute of Health (NIH) for making the diagnosis of NF1 [85, 90]. These criteria are most

Table 5. Neurofibromatosis and tuberous sclerosis

Disease	Clinical genetics	Gene, protein	Gene function	Gene mutations in disease
Neurofibromatosis type 1	1:4000 births autosomal dominant variable severity in families 50% of cases new mutations	<i>NF1</i> , Neurofibromin Chromosome 17q.11	Ras-GAP downregulates the function of the proto-oncogene Ras	Huge variety of different mutations (no hotspots), poor genotype-phenotype correlation
Neurofibromatosis type 2	1:40 000 births autosomal dominant 50% new mutations	<i>NF2</i> , Schwannomin (merlin) Chromosome 22q12	ERM protein, acts as a molecular bridge between plasma membrane and cell cytoskeleton	Protein truncation mutations more common and are more easily screened, truncation mutations associated with more severe disease
Tuberous sclerosis	1:10 000 births autosomal dominant new mutations in 2/3 of patients (mostly <i>TSC2</i> gene related)	<i>TSC1</i> , Hamartin Chromosome 9q34 50% of tuberous sclerosis	Bind to ERM proteins and is therefore involved in plasma membrane and cell cytoskeletal function	Protein truncation mutations mainly
	<i>TSC2</i> patients may have more severe intellectual disability Most sporadic cases have <i>TSC2</i> mutations	<i>TSC2</i> , Tuberin Chromosome 16p13 50% of tuberous sclerosis	Rap-GAP, Rab-GAP downregulates the function of these other Ras-like small molecules, analogous to <i>NF1</i> function	Wide variety of mutations

reliable in adults [26]. Almost all NF1 patients have two or more cardinal clinical features at age 8, but under age 1, 30% have only one of the features. The usual order of appearance of clinical features is café au lait macules (present at birth or developing by 2 years), axillary or inguinal (skin fold) freckling (starts at age 2-3, in 80% by age 6), Lisch nodules, and dermal neurofibromas (usually by preadolescence) [50]. Patients with NF1 can have learning difficulties but are usually without mental retardation [50, 110].

Tumors of the central and peripheral nervous systems are characteristic. Optic nerve gliomas are usually diagnosed within the first 5 years of life and affect up to 20% of patients [110]. These lesions can be asymptomatic or present with diminished vision; characteristically, clinical progression is uncommon even if visual symptoms are present. Gliomas occur in other locations, particularly involving the brainstem, and most are low-grade. Malignant astrocytomas can occur [6]. Macrocephaly is also common (independent of hydrocephalus), and aqueductal stenosis causing hydrocephalus has been reported, possibly from proliferation of subependymal glial cells with aqueductal obstruction [57, 110, 116]. Dermal neurofibromas (very common) and plexiform neurofibromas (in about 25% of patients) also occur, and the latter but not the former can become malignant (in about 10%). NF1 patients can also get neoplasms outside the nervous system, such as myeloid leukemia, pheochromocytoma, and rhabdomyosarcoma. The lifelong risk of a malignant neoplasm has been estimated at 5% [50].

NF1 patients are also at increased risk of cerebrovascular disease including moyamoya disease and cerebral arterial dysplasia with aneurysms [72, 110, 114, 118]. Hypertension also occurs due to pheochromocytomas and renal artery abnormalities [50, 110].

Modification of NIH criteria has been suggested to improve the ability to make the diagnosis in children; such modifications might include short stature, macrocephaly, or unidentified bright objects (UBOs). UBOs are present in 50%-75% of children with NF1 and can be seen as lesions without enhancement on T2-weighted MRI scans of the brain [26]. The presence of UBOs has been associated with learning difficulties. These lesions are most commonly seen in the basal ganglia, thalamus, cerebellum, and brainstem, and seem to be more frequently observed in children, suggesting that they may tend to disappear [110]. An infant with multiple café au lait spots most likely has NF1, but the NIH criteria for the diagnosis will not be established until the child is older [50].

The clinical disease of NF1 is now known to be caused by mutations in one copy of the *NF1* gene (meaning patients are heterozygotes) that resides on chromosome 17q [9]. The *NF1* gene was originally cloned in 1990 (Cawthon 1990, Wallace 1990). Every

somatic cell acquires the mutation, but it is not clear why the disease is manifest predominantly in neural crest tissues. The gene is normally expressed in all tissues but has highest expression in the adult central and peripheral nervous system. Some of the clinical NF variants (such as segmental neurofibromatosis) may be caused by somatic mosaicism of the *NF1* mutation, meaning that only a portion of the individual's cells were heterozygous for the *NF1* mutation [110].

The *NF1* gene is a very large gene spanning 300 kb of genomic DNA with 60 exons and a large protein with 2818 amino acids. The large size of this gene has made it technically laborious and difficult to routinely determine mutations in individuals, especially in the case of those without a family history. About 5% of affected individuals have complete deletion of one allele, and these patients are thought to have more severe intellectual impairment, facial dysmorphism, and greater numbers of plexiform and dermal neurofibromas [110]. Aside from this group, there is poor correlation between genotype and disease phenotype.

Screening for gene mutations is difficult due to the large size of the gene, high rate of spontaneous mutations, and lack of clustering (or hotspots) of mutations in segments of the gene. The variability in alterations in the gene necessitates multiple different screening strategies that are costly. No single test is currently available to determine the mutation. Also, identification of a mutation may tell an individual if he/she is affected but will not be able to predict severity. In families, screening for alterations in the *NF1* gene involves analysis of linkage of DNA markers associated with the disease trait. Screening for sporadic *NF1* gene alterations can be done using fluorescence in situ hybridization (FISH) with intragene probes. Lack of a signal using the probe implies deletion of that segment of the gene. PCR techniques, which amplify fragments of DNA, can also be used to screen for gene loss or truncation by using two complementary probes (primers) chosen to flank all or part of the gene. Detection of point mutations use PCR and a technique called SSCP (single-strand conformational polymorphism analysis) that detects alterations in migration of fragments of the gene based on single base pair alterations (these regions of DNA with aberrant migration in gel electrophoresis are then confirmed by direct DNA sequence analysis). These techniques will probably improve and become more efficient in the future.

The protein product of the *NF1* gene, neurofibromin, is a guanosine triphosphatase (GTPase)-activating protein, known as a GAP [49]. Neurofibromin is thought to restrain the activity of a molecule called *ras*, a potent proto-oncogene associated with the cell membrane that is activated by growth factor and other cell signaling events. Neurofibromin enhances the natural GTPase function of *ras*, converting it from an activated form as-

sociated with GTP (*ras*-GTP) to an inactive form associated with GDP (*ras*-GDP). *NF1* therefore helps to regulate the activity of *ras* that acts as a molecular switch shuttling between active GTP-bound forms and inactive GDP-bound forms. *ras*-GTP activates intracellular signaling pathways leading to cell proliferation. Mutant (oncogenic) forms of *ras* are predominantly associated with GTP and have been found in many cancers, contributing to aberrant intracellular signaling and proliferation. Loss of neurofibromin is thought to lead to increased levels of *ras*-GTP (activated form), causing inappropriate activation of cell proliferation and tumor formation. One copy of *NF1* is sufficient to specify production of neurofibromin, but a second hit to the intact allele, leading to complete absence of neurofibromin expression, is thought to be an important step leading to tumor formation. A distinct hit to another important gene in cells heterozygous for the *NF1* mutation can also contribute to tumor formation (see below).

These mechanisms have been identified through studies of knockout mice for the *NF1* gene [7, 12, 62, 127]. Mice homozygous for *NF1* deletions die early in embryogenesis, precluding an analysis of tumor formation but suggesting that the *NF1* gene plays a critical role in normal mouse development. Mice heterozygous for mutations in *NF1* do not exactly mimic the human disease as they do not get neurofibromas, but acquire instead other *NF1*-associated tumors, pheochromocytomas, and leukemias [62]. However, studies in mice performed with somatic inactivation of the second allele through creation of chimeric mice (so 20% of the cells in the mouse have a homozygous *NF1* deletion) have led to formation of neurofibromas and malignant peripheral nerve sheath tumors [12]. These studies demonstrate that a complete loss of the expression of neurofibromin is associated with the development of the most common *NF1*-associated tumor. Human peripheral nerve tumors from *NF1* patients have also been identified to completely lack neurofibromin expression, suggesting inactivation of the second *NF1* allele [17, 113], but other events are also thought to contribute to neurofibroma formation [111]. Heterozygous inactivation of *NF1* with heterozygous inactivation of the *p53* tumor suppressor gene (which is a tumor suppressor gene involved in cell proliferation and cell death regulation) causes malignant peripheral nerve tumors in mice, suggesting alternative and cooperative mechanisms between two genes leading to neoplastic transformation [12].

Neurofibromatosis 2

Neurofibromatosis 2 is also inherited in an autosomal dominant fashion but is considerably less com-

mon than *NF1*, with an incidence of about 1 in 40 000 live births [78, 110]. Penetrance is nearly 100%. About half the cases show no family history and are due to new mutations. There is a maternal effect on disease severity, with earlier onset of disease in offspring of affected females. The clinical hallmark of this disease is deafness caused by bilateral vestibular schwannomas, but affected individuals are also prone to develop schwannomas of other cranial nerves, spinal dorsal roots, and peripheral nerves, as well as meningiomas and glial tumors, particularly ependymomas [50, 78, 110]. Other characteristic features are hairy cutaneous plaques (a skin tumor), café au lait spots (less frequent and fewer in number than in *NF1* patients), and posterior lens opacities (juvenile cataracts). *NF2* presents later than *NF1*, usually in late adolescence or in early adulthood. Only 10% of cases present before age 10 [50].

Patients with *NF2* inherit a mutant copy in the *NF2* gene. This gene is located on chromosome 22 and was identified in 1993. The gene spans 110 kb of genomic DNA and has 17 exons, specifying a protein product of 595 amino acids [107, 122]. The protein product is called merlin or schwannomin. The name merlin came from recognition that the *NF2* gene product relates structurally to the moezin-, ezrin-, radixin-like protein family (called ERM proteins). These proteins interact with cell membrane glycoproteins at their amino termini and with the actin cytoskeleton at their carboxy termini, suggesting that these proteins mediate actin cytoskeletal organization in response to extracellular signals. ERM proteins are particularly localized to dynamic actin structures such as membrane ruffles [51]. There are some distinct differences in merlin structure compared to ERM proteins, suggesting unique functions. Very little is presently definitely known about merlin's function, but it is suspected to play an important role in cell motility, cell adhesion, cell proliferation, and membrane trafficking. Integration of extracellular adhesion to cell proliferation may be the most critical function. Mice heterozygous for an *NF2* mutation develop a surprising variety of cancers including osteosarcoma, lymphoma, fibrosarcoma, and lung adenocarcinoma as well as schwannomas [45, 79]. Most of these tumors have loss of the second *NF2* allele and are particularly metastatic [79]. In transgenic mice expressing *NF2* mutations in Schwann cells, Schwann cell tumors arise, suggesting that the mutant protein may act to interfere with retained wildtype allele function [44].

Although many of the same arguments apply with genetic testing for *NF2* as *NF1*, mutational analysis of patients with *NF2* suggests that most *NF2* mutations result in protein truncations with altered function [140]. This fact means that genetic screening is more feasible. Study of *NF2* patients over the past 8 years in

light of the gene discovery suggests that there may be two different clinical subgroups with the disease, with particular genotype-phenotype correlation [110]. In some families the disease is relatively more severe, with symptoms appearing before age 25 with multiple tumors with progressive growth, and in others the disease is milder, presenting at older ages with a smaller number of more slowly growing tumors [110]. The more severely affected families have mutations in the *NF2* gene that result in protein truncations, and in more mildly affected families, missense mutations are more common, resulting possibly in a milder dysfunction of the protein. Screening is possible for protein truncation mutants, using PCR techniques to amplify fragments of the gene.

Tuberous Sclerosis

Tuberous sclerosis (TSC) is an autosomal dominant syndrome affecting multiple body systems including the brain, eye, skin, kidneys, and heart (see Table 5) [21, 22]. Less frequently, other organ systems such as the lungs, skeleton, and endocrine systems are involved. The incidence is 1:10 000 births. There is a significant incidence of new mutations so there may not be a family history. Some apparently unaffected parents of affected children could have somatic or gonadal mosaicism. The parents with somatic mosaicism may not demonstrate typical features of the disease as only a proportion of their cells have the mutation, and parents with gonadal mosaicism will not have any features, as the mutation is only present in germ cells. Future children would be at risk if mosaicism were present in a parent.

The characteristic lesions of TSC are hamartomas comprised of tissues that are derived from all three germ layers. In the CNS these lesions include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas. These latter lesions can cause hydrocephalus by obstruction of the foramen of Monro. As with NF, exciting discoveries have been made in the understanding of TSC since the discovery of the two genes *TSC1* and *TSC2* [21, 22]. In particular, parallels between NF1 and TSC seem to be striking as the respective genes *NF1* and *TSC2* encode for proteins that regulate small *ras*-related molecules involved in intracellular signaling and both diseases are associated with benign nervous system tumors.

Clinical diagnosis of TSC can be made on the basis of clinical and radiologic criteria that have been divided into major and minor features [21, 100-102]. The disease has extremely variable clinical features although the penetrance of the disease within families

is very high. A definitive diagnosis can be made with one major feature. Major features include facial angiofibromas (formerly adenoma sebaceum), ungual fibromas (seen in older children and adults), retinal hamartomas, more than three hypopigmented macules (ash leaf spots, often present early in life), shagreen patch, renal angiomyoma (usually multiple and bilateral), cardiac rhabdomyoma (usually congenital but often regressing), pulmonary lymphangiomyomatosis, cortical tubers, subependymal nodules, and giant cell astrocytomas. Minor features include dental pits, bone cysts, renal cysts, gingival fibromas, and hamartomatous rectal polyps. Common clinical problems with TSC include epilepsy, mental retardation, and behavioral problems. Guidelines for investigations of individuals suspected of having TSC can be found in a recent report [102].

The *TSC2* gene, located on chromosome 16p13, was identified in 1993 [61]. The gene contains 41 exons and spans 43 kb of genomic DNA. The gene product is a 1807-amino-acid protein called tuberin. The *TSC1* gene was discovered in 1997 and is found at chromosome 9q34 [125]. The *TSC1* gene product is called hamartin and has 1164 amino acids. Familial TSC has been linked to *TSC1* in 50% and *TSC2* in 50% of cases [64]. Up to two-thirds of TSC patients do not have a family history and therefore bear new mutations. Eighty percent of these sporadic cases have *TSC2* mutations. *TSC2* gene mutations comprise a wide variety of different DNA alterations, and combined with the large size of the gene make routine screening currently impractical. *TSC1* mutations are more uniform, resulting in protein truncation, making screening potentially easier for this gene. Mutations in each of the TSC genes result in variable and overlapping patterns of disease, although patients with *TSC2* mutations may have more severe intellectual disability than patients with *TSC1* mutations [64]. Diagnosis remains predominantly based on clinical and imaging features.

Both genes have been classified as tumor suppressor genes as loss of heterozygosity or mutations have been identified in the remaining wildtype allele in tumors from TSC patients. Sporadic tumors in non-TSC patients have been identified with *TSC2* gene alterations. An animal model, the "Eker rat," which has a natural *TSC2* mutation in one allele, develops tumors characteristic of TSC, including subependymal giant cell tumors, providing further supporting evidence of the role for this gene in tumor suppression [73]. Tumors in these mice lose the normal *TSC2* allele and lack tuberin expression. Eker homozygotes die in mid-gestation due to brain malformations, with papillary overgrowth of neuroepithelium, reminiscent of hamartomas. The Eker rat models the human disease well as there is also variable severity of disease between

different strains of rats, possibly as a result of influences of modifier genes which have differing impacts in the different strains on the loss of tuberin function.

Tuberin (TSC2) has GTPase-activating protein (GAP) function, similar to neurofibromin, and acts on distinct small molecule GTPases that share 50% amino acid identity with *ras*, called Rapi and Rab5 [21, 131, 136]. These molecules play roles in cell proliferation and cell endocytosis. Loss of tuberin function through mutation leads to unregulated Rapi/Rab5 activity. It is presently unclear how this activity contributes to tumor formation. Rapi has been shown to have a role in the promotion of DNA synthesis (and therefore progression through the cell division cycle) [21]. Rab5 plays a role in endocytosis, a process that has been shown to be critical in regulation of growth factor receptor signaling [21]. Loss of tuberin therefore could lead to inappropriate cell cycle progression and inappropriate trafficking or processing of growth factor receptors, leading to increased activity of these molecules and also to increased stimulation of cell cycle progression. Hamartin (TSC1) is a protein of unique structure and unclear function associated with the cell membrane and the cell cytoskeleton. It associates with members of the ERM family (see section on NF2, p. 12) [43, 75]. Interestingly, both TSC proteins may function in a single growth regulatory pathway, as shown by experiments which have found that these two proteins bind together, possibly enabling one protein to regulate the function of the other [89].

Conclusion

A genetic understanding of hydrocephalus and diseases associated with hydrocephalus has made remarkable progress in the past decade. With the human genome now sequenced, we stand to accelerate our knowledge of human CNS diseases even more rapidly. A basic understanding of the genetics of hydrocephalus is essential for the neurosurgeon to care for and to counsel his or her patients and their families. With improved prenatal diagnosis, neurosurgeons are being called upon with greater frequency to provide prenatal counseling for expectant parents and it will be their obligation to keep up with an understanding of the molecular genetics of CNS malformations.

References

1. Aicardi J, Chevrie JJ, Rousselie F: Spasma-in-flexion syndrome, callosal agenesis, chorioretinal abnormalities. Arch Fr Pediatr 26: 1103-1120, 1969
2. Allen WP: Folic acid in the prevention of birth defects. Curr Opin Pediatr 8: 630-634, 1996
3. Barber RC, Lammer EJ, Shaw GM, et al: The role of folate transport and metabolism in neural tube defect risk. Mol Genet Metab 66: 1-9, 1999
4. Barr M Jr, Cohen MM Jr: Holoprosencephaly survival and performance. Am J Med Genet 89: 116-120, 1999
5. Bateman A, Jouet M, MacFarlane J: Outline structure of the human L1 cell adhesion molecule and the sites where mutations cause neurological disorders. Embo J 15: 6050-6059, 1996
6. Blatt J, Jaffe R, Deutsch M, et al: Neurofibromatosis and childhood tumors. Cancer 57: 1225-1229, 1986
7. Brannan CI, Perkins AS, Vogel KS, et al: Targeted disruption of the neurofibromatosis type-1 gene leads to developmental abnormalities in heart and various neural crest-derived tissues. Genes Dev 8: 1019-1029, 1994
8. Burton BK: Recurrence risks for congenital hydrocephalus. Clin Genetics 16: 47-53, 1979
9. Carey JC, Viskochil DH: Neurofibromatosis type 1: A model condition for the study of the molecular basis of variable expressivity in human disorders. Am J Med Genet 89: 7-13, 1999
10. Chang MC, Russell SA, Callen PW, et al: Sonographic detection of inferior vermian agenesis in Dandy-Walker malformations: prognostic implications. Radiology 193: 765-770, 1994
11. Chiang C, Litingtung Y, Lee E, et al: Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function. Nature 383: 407-413, 1996
12. Cichowski K, Shih TS, Schmitt E, et al: Mouse models of tumor development in neurofibromatosis type 1. Science 286: 2172-2176, 1999
13. Chitayat D, Moore L, Del Bigio MR, et al: Familial Dandy-Walker malformation associated with macrocephaly, facial anomalies, developmental delay, and brain stem dysgenesis: prenatal diagnosis and postnatal outcome in brothers. A new syndrome? Am J Med Genet 52: 406-415, 1994
14. Cihangiroglu M, Franca C, Ramsey RG: Aicardi's syndrome: a new finding. Pediatr Radiol 30: 499-500, 2000
15. Cincinnati P, Neri ME, Valentini A: Dandy-Walker anomaly in Meckel-Gruber syndrome. Clin Dysmorphol 9: 35-38, 2000
16. Cohen NR, Taylor JS, Scott LB, et al: Errors in corticospinal axon guidance in mice lacking the neural cell adhesion molecule L1. Curr Biol 8: 26-33, 1998
17. Colman SD, Williams CA, Wallace MR: Benign neurofibromas in type 1 neurofibromatosis (NF1) show somatic deletions of the NF1 gene. Nat Genet 11: 90-92, 1995
18. Colvin JS, Bohne BA, Harding GW, et al: Skeletal overgrowth and deafness in mice lacking fibroblast growth factor receptor 3. Nat Genet 12: 390-397, 1996
19. Copp AJ: Prevention of neural tube defects: vitamins, enzymes and genes. Curr Opin Neurol 11: 97-102, 1998
20. Cowan WM, Kandel ER: Prospects for neurology and psychiatry. JAMA 285: 594-600, 2001
21. Crino PB, Henske EP: New developments in the neurobiology of the tuberous sclerosis complex. Neurology 53: 1384-1390, 1999
22. Curatolo P: Neurological manifestations of tuberous sclerosis complex. Childs Nerv Syst 12: 515-521, 1996
23. Czeizel AE, Dudas I: Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation. N Engl J Med 327: 1832-1835, 1992

62. Jacks T, Shih TS, Schmitt EM, et al: Tumour predisposition in mice heterozygous for a targeted mutation in Nf1. *Nat Genet* 7: 353-361, 1994
63. Jones KL: Smith's Recognizable Patterns of Human Malformation, p. 861. Saunders, Philadelphia, 1997
64. Jones AC, Shyamsundar MM, Thomas MW, et al: Comprehensive mutation analysis of TSC1 and TSC2-and phenotypic correlations in 150 families with tuberous sclerosis. *Am J Hum Genet* 64: 1305-1315, 1999
65. Jouet M, Feldman E, Yates J, et al: Refining the genetic location of the gene for X linked hydrocephalus within Xq28. *J Med Genet* 30: 214-217, 1993
66. Joyner AL, Liu A, Millet S: Otx2, Gbx2 and Fgf8 interact to position and maintain a mid-hindbrain organizer. *Curr Opin Cell Biol* 12: 736-741, 2000
67. Juriloff DM, Harris MJ: Mouse models for neural tube closure defects. *Hum Mol Genet* 9: 993-1000, 2000
68. Kamiguchi H, Hlavin ML, Lemmon V: Role of L1 in neural development: what the knockouts tell us. *Mol Cell Neurosci* 12: 48-55, 1998
69. Keiper GL Jr, Koch B, Crone KR: Achondroplasia and cervicomедullary compression: prospective evaluation and surgical treatment. *Pediatr Neurosurg* 31: 78-83, 1999
70. Kennedy D, Chitayat D, Winsor EJ, et al: Prenatally diagnosed neural tube defects: ultrasound, chromosome, and autopsy or postnatal findings in 212 cases. *Am J Med Genet*, 77: 317-321, 1998
71. Kenrick S, Watkins A, Angelis ED: Neural cell recognition molecule L1: relating biological complexity to human disease mutations. *Hum Mol Genet* 9: 879-886, 2000
72. Kestle JR, Hoffman HJ, Mock AR: Moyamoya phenomenon after radiation for optic glioma. *J Neurosurg* 79: 32-35, 1993
73. Kobayashi T, Hirayama Y, Kobayashi E, et al: A germline insertion in the tuberous sclerosis (Tsc2) gene gives rise to the Eker rat model of dominantly inherited cancer. *Nat Genet* 9: 70-74, 1995
74. Kolble N, Wisser J, Kurmanavicius J, et al: Dandy-Walker malformation: prenatal diagnosis and outcome. *Prenat Diagn* 20: 318-327, 2000
75. Lamb RF, Roy C, Diefenbach TJ, et al: The TSC1 tumour suppressor hamartin regulates cell adhesion through ERM proteins and the GTPase Rho. *Nat Cell Biol* 2: 281-287, 2000
76. Li J, Liu KC, Jin F, et al: Transgenic rescue of congenital heart disease and spina bifida in Splotch mice. *Development* 126: 2495-2503, 1999
77. Martin RA , Jones KL: Absence of the superior labial frenulum in holoprosencephaly: a new diagnostic sign. *J Pediatr* 133: 151-153, 1998
78. Martuza RL, Eldridge R: Neurofibromatosis 2 (bilateral acoustic neurofibromatosis). *N Engl J Med* 318: 684-688, 1988
79. McClatchey AI, Saotome I, Mercer K, et al: Mice heterozygous for a mutation at the Nf2 tumor suppressor locus develop a range of highly metastatic tumors. *Genes Dev* 12: 1121-1133, 1998
80. Menezes AV, MacGregor DL, Buncic JR: Aicardi syndrome: natural history and possible predictors of severity. *Pediatr Neurol* 11: 313-318, 1994
81. Mesoraca A, Pilu G, Perolo A, et al: Ultrasound and molecular mid-trimester prenatal diagnosis of de novo achondroplasia. *Prenat Diagn* 16: 764-768, 1996
82. Millen KJ, Millonig JH, Wingate RJ, et al: Neurogenetics of the cerebellar system. *J Child Neurol* 14: 574-581; discussion 581-572, 1999
83. Moase CE, Trasler DG: Splotch locus mouse mutants: models for neural tube defects and Waardenburg syndrome type I in humans. *J Med Genet* 29: 145-151, 1992
84. Muenke M, Beachy PA: Genetics of ventral forebrain development and holoprosencephaly. *Curr Opin Genet Dev* 10: 262-269, 2000
85. Mulvihill JJ, Parry DM, Sherman JL, et al: NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. *Ann Intern Med* 113: 39-52, 1990
86. Murray JC, Johnson JA, Bird TD: Dandy-Walker malformation: etiologic heterogeneity and empiric recurrence risks. *Clin Genet* 28: 272-283, 1985
87. Naski MC, Wang Q, Xu J, et al: Graded activation of fibroblast growth factor receptor 3 by mutations causing achondroplasia and thanatophoric dysplasia. *Nat Genet* 13: 233-237, 1996
88. Neidich JA, Nussbaum RL, Packer RJ, et al: Heterogeneity of clinical severity and molecular lesions in Aicardi syndrome. *J Pediatr* 116: 911-917, 1990
89. Nellist M, van Slegtenhorst MA, Goedbloed M, et al: Characterization of the cytosolic tuberin-hamartin complex. Tuberin is a cytosolic chaperone for hamartin. *J Biol Chem* 274: 35647-35652, 1999
90. Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. *Arch Neurol* 45: 575-578, 1988
91. Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda MD), 2001
92. Osenbach RK, Menezes AH: Diagnosis and management of the Dandy-Walker malformation: 30 years of experience. *Pediatr Neurosurg* 18: 179-189, 1992
93. Peter JC, Fieggen G: Congenital malformations of the brain-a neurosurgical perspective at the close of the twentieth century. *Childs Nerv Syst* 15: 635-645, 1999
94. Pierre-Kahn A, Hirsch JF, Renier D, et al: Hydrocephalus and achondroplasia. A study of 25 observations. *Childs Brain* 7: 205-219, 1980
95. Pomili G, Venti Donti G, Alunni Carrozza L, et al: MASA syndrome: ultrasonographic evidence in a male fetus. *Prenat Diagn* 20: 1012-1014, 2000
96. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. *Lancet* 338: 131-137, 1991
97. Quisling RG, Barkovich AJ, Maria BL: Magnetic resonance imaging features and classification of central nervous system malformations in Joubert syndrome. *J Child Neurol* 14: 628-635; discussion 669-672, 1999
98. Rhinn M, Brand M: The midbrain-hindbrain boundary organizer. *Curr Opin Neurobiol* 11: 34-42, 2001
99. Riccardi VM: Von Recklinghausen neurofibromatosis. *N Engl J Med* 305: 1617-1627, 1981
100. Roach ES, Smith M, Huttenlocher P, et al: Diagnostic criteria: tuberous sclerosis complex. Report of the Diagnostic Criteria Committee of the National Tuberous Sclerosis Association. *J Child Neurol* 7: 221-224, 1992
101. Roach ES, Gomez MR, Northrup H: Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. *J Child Neurol* 13: 624-628, 1998
102. Roach ES, DiMario FJ, Kandt RS, et al: Tuberous Sclerosis

24. Czeizel AE: Primary prevention of neural-tube defects and some other major congenital abnormalities: recommendations for the appropriate use of folic acid during pregnancy. *Paediatr Drugs* 2: 437-449, 2000
25. da-Silva EO: Waardenburg I syndrome: a clinical and genetic study of two large Brazilian kindreds, and literature review. *Am J Med Genet* 40: 65-74, 1991
26. DeBella K, Szudek J, Friedman JM: Use of the National Institutes of Health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics* 105: 608-614, 2000
27. De Moerlooze L, Dickson C: Skeletal disorders associated with fibroblast growth factor receptor mutations. *Curr Opin Genet Dev* 7: 378-385, 1997
28. Deng C, Wynshaw-Boris A, Zhou F, et al: Fibroblast growth factor receptor 3 is a negative regulator of bone growth. *Cell* 84: 911-921, 1996
29. DeSesso JM, Scialli AR, Holson JF: Apparent inability of neural tube closure in laboratory animals and humans. *Am J Med Genet* 87: 143-162, 1999
30. Dobyns WB, Pagon RA, Armstrong D, et al: Diagnostic criteria for Walker-Warburg syndrome. *Am J Med Genet* 32: 195-210, 1989
31. Donnenfeld AE, Packer RJ, Zackai EH, et al: Clinical, cytogenetic, and pedigree findings in 18 cases of Aicardi syndrome. *Am J Med Genet* 32: 461-467, 1989
32. Edwards JH: The syndrome of sex-linked hydrocephalus. *Arch Dis Child* 36: 486-493, 1961
33. Edwards JH, Norman RM, Roberts JM: Sex-linked hydrocephalus. Report of a family with 15 affected members. *Arch Dis Child* 36: 481-485, 1961
34. Epstein DJ, Vekemans M, Gros P: Splotch (Sp2H), a mutation affecting development of the mouse neural tube, shows a deletion within the paired homeodomain of Pax-3. *Cell* 67: 767-774, 1991
35. Finckh U, Gal A: Prenatal molecular diagnosis of L1-spectrum disorders. *Prenat Diagn* 20: 744-745, 2000
36. Finckh U, Schroder J, Ressler B, et al: Spectrum and detection rate of L1CAM mutations in isolated and familial cases with clinically suspected L1-disease. *Am J Med Genet* 92: 40-46, 2000
37. Fleming A, Copp AJ: Embryonic folate metabolism and mouse neural tube defects. *Science*, 280: 2107-2109, 1998
38. Fransen E, Lemmon V, Van Camp G, et al: CRASH syndrome: clinical spectrum of corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis and hydrocephalus due to mutations in one single gene, L1. *Eur J Hum Genet* 3: 273-284, 1995
39. Fransen E, Vits L, Van Camp G, et al: The clinical spectrum of mutations in L1, a neuronal cell adhesion molecule. *Am J Med Genet* 64: 73-77, 1996
40. Fransen E, D'Hooge R, Van Camp G, et al: L1 knockout mice show dilated ventricles, vermis hypoplasia and impaired exploration patterns. *Hum Mol Genet* 7: 999-1009, 1998
41. Fransen E, Van Camp G, D'Hooge R, et al: Genotype-phenotype correlation in L1 associated diseases. *J Med Genet* 35: 399-404, 1998
42. Friedman JM: Epidemiology of neurofibromatosis type 1. *Am J Med Genet* 89: 1-6, 1999
43. Fukuhara S, Gutkind JS: A new twist for the tumour suppressor hamartin [news; comment]. *Nat Cell Biol* 2: E76-78, 2000
44. Giovannini M, Robanus-Maandag E, Niwa-Kawakita M, et al: Schwann cell hyperplasia and tumors in transgenic mice expressing a naturally occurring mutant NF2 protein. *Genes Dev* 13: 978-986, 1999
45. Giovannini M, Robanus-Maandag E, van der Valk M, et al: Conditional biallelic Nf2 mutation in the mouse promotes manifestations of human neurofibromatosis type 2. *Genes Dev* 14: 1617-1630, 2000
46. Gluckman TJ, George TM, McLone DG: Postneurulation rapid brain growth represents a critical time for encephalocele formation: a chick model. *Pediatr Neurosurg* 25: 130-136, 1996
47. Golden JA: Towards a greater understanding of the pathogenesis of holoprosencephaly. *Brain Dev* 21: 513-521, 1999
48. Goodrich LV, Scott MP: Hedgehog and patched in neural development and disease. *Neuron* 21: 1243-1257, 1998
49. Gutmann DH, Collins FS: Neurofibromatosis type 1. Beyond positional cloning. *Arch Neurol* 50: 1185-1193, 1993
50. Gutmann DH, Aylsworth A, Carey JC, et al: The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2 [see comments]. *JAMA* 278: 51-57, 1997
51. Gutmann DH, Geist RT, Xu H, et al: Defects in neurofibromatosis 2 protein function can arise at multiple levels. *Hum Mol Genet* 7: 335-345, 1998
52. Halliday J, Chow CW, Wallace D, et al: X linked hydrocephalus: a survey of a 20 year period in Victoria, Australia. *J Med Genet* 23: 23-31, 1986
53. Harris MJ, Juriloff DM: Mini-review: toward understanding mechanisms of genetic neural tube defects in mice. *Teratology* 60: 292-305, 1999
54. Haiverkamp F, Wolfle J, Aretz M, et al: Congenital hydrocephalus internus and aqueduct stenosis: aetiology and implications for genetic counselling. *Eur J Pediatr* 158: 474-478, 1999
55. Hecht JT, Nelson FW, Butler IJ, et al: Computerized tomography of the foramen magnum: achondroplastic values compared to normal standards. *Am J Med Genet* 20: 355-360, 1985
56. Hol FA, Hamel BC, Geurds MP, et al: A frameshift mutation in the gene for PAX3 in a girl with spina bifida and mild signs of Waardenburg syndrome. *J Med Genet* 32: 52-56, 1995
57. Horwitz A, Riccardi VM, Francke U: Brief clinical report: aqueductal stenosis leading to hydrocephalus-an unusual manifestation of neurofibromatosis. *Am J Med Genet* 14: 577-581, 1983
58. Hoth CF, Milunsky A, Lipsky N, et al: Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *Am J Hum Genet* 52: 455-462, 1993
59. Hoving EW, Vermeij-Keers C, Mommaas-Kienhuis AM, et al: Separation of neural and surface ectoderm after closure of the rostral neuropore. *Anat Embryol* 182: 455-463, 1990
60. Hunter AG, Bankie A, Rogers JG, et al: Medical complications of achondroplasia: a multicentre patient review. *J Med Genet* 35: 705-712, 1998
61. Identification and characterization of the tuberous sclerosis gene on chromosome 16. The European Chromosome 16 Tuberous Sclerosis Consortium. *Cell* 75: 1305-1315, 1993

- Consensus Conference: recommendations for diagnostic evaluation. National Tuberous Sclerosis Association. *J Child Neurol* 14: 401-407, 1999
103. Roessler E, Belloni E, Gaudenz K, et al: Mutations in the human Sonic Hedgehog gene cause holoprosencephaly. *Nat Genet* 14: 357-360, 1996
 104. Roessler E, Muenke M: Holoprosencephaly: a paradigm for the complex genetics of brain development. *J Inherit Metab Dis* 21: 481-497, 1998
 105. Roessler E, Muenke M: The molecular genetics of holoprosencephaly: a model of brain development for the next century. *Childs Nerv Syst* 15: 646-651, 1999
 106. Rosenthal A, Jouet M, Kenrick S: Aberrant splicing of neural cell adhesion molecule L1 mRNA in a family with X-linked hydrocephalus. *Nat Genet* 2: 107-112, 1992
 107. Rouleau GA, Merel P, Lutchman M, et al: Alteration in a new gene encoding a putative membrane-organizing protein causes neurofibromatosis type 2. *Nature* 363: 515-521, 1993
 108. Rousseau F, Bonaventure J, Legeai-Mallet L, et al: Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. *Nature* 371: 252-254, 1994
 109. Rowitch DH, Danielian PS, McMahon AP, et al: Cystic malformations of the posterior cerebellar vermis in transgenic mice that ectopically express Engrailed-1, a homeodomain transcription factor. *Teratology* 60: 22-28, 1999
 110. Ruggieri M: The different forms of neurofibromatosis. *Childs Nerv Syst* 15: 295-308, 1999
 111. Rutkowski JL, Wu K, Gutmann DH, et al: Genetic and cellular defects contributing to benign tumor formation in neurofibromatosis type 1. *Hum Mol Genet* 9: 1059-1066, 2000
 112. Sainte-Rose C, LaCombe J, Pierre-Kahn A, et al: Intracranial venous sinus hypertension: cause or consequence of hydrocephalus in infants? *J Neurosurg* 60: 727-736, 1984
 113. Sawada S, Florell S, Purandare SM, et al: Identification of NF1 mutations in both alleles of a dermal neurofibroma. *Nat Genet* 14: 110-112, 1996
 114. Schievink WI, Piepgas DG: Cervical vertebral artery aneurysms and arteriovenous fistulae in neurofibromatosis type 1: case reports. *Neurosurgery* 29: 760-765, 1991
 115. Schrandt-Stumpel C, Fryns JP: Congenital hydrocephalus: nosology and guidelines for clinical approach and genetic counselling. *Eur J Pediatr* 157: 355-362, 1998
 116. Senveli E, Altinors N, Kars Z, et al: Association of von Recklinghausen's neurofibromatosis and aqueduct stenosis. *Neurosurgery* 24: 99-101, 1989
 117. Shiang R, Thompson LM, Zhu YZ, et al: Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. *Cell* 78: 335-342, 1994
 118. Sobata E, Ohkuma H, Suzuki S: Cerebrovascular disorders associated with von Recklinghausen's neurofibromatosis: a case report. *Neurosurgery* 22: 544-549, 1988
 119. Steinbok P, Hall J, Flodmark O: Hydrocephalus in achondroplasia: the possible role of intracranial venous hypertension. *J Neurosurg* 71: 42-48, 1989
 120. Tassabehji M, Read AP, Newton VE, et al: Mutations in the PAX3 gene causing Waardenburg syndrome type 1 and type 2. *Nat Genet* 3: 26-30, 1993
 121. Timor-Tritsch IE, Monteagudo A, Haratz-Rubinstein N, et al: Transvaginal sonographic detection of adducted thumbs, hydrocephalus, and agenesis of the corpus callosum at 22 postmenstrual weeks: the masa spectrum or L1 spectrum. A case report and review of the literature. *Prenat Diagn* 16: 543-548, 1996
 122. Trofatter JA, MacCollin MM, Rutter JL, et al: A novel moesin-, ezrin-, radixin-like gene is a candidate for the neurofibromatosis 2 tumor suppressor. *Cell* 75: 826, 1993
 123. Uchiyama CM, Carey CM, Cherny WB, et al: Choroid plexus papilloma and cysts in the Aicardi syndrome: case reports. *Pediatr Neurosurg* 27: 100-104, 1997
 124. Van Camp G, Vits L, Coucke P, et al: A duplication in the L1CAM gene associated with X-linked hydrocephalus. *Nat Genet* 4: 421-425, 1993
 125. van Slegtenhorst M, de Hoogt R, Hermans C, et al: Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. *Science* 277: 805-808, 1997
 126. Villavicencio EH, Walterhouse DO, Iannaccone PM: The sonic hedgehog-patched-gli pathway in human development and disease. *Am J Hum Genet* 67: 1047-1054, 2000
 127. Vogel KS, Klesse LJ, Velasco-Miguel S, et al: Mouse tumor model for neurofibromatosis type 1. *Science* 286: 2176-2179, 1999
 128. Walsh CA: Genetic malformations of the human cerebral cortex. *Neuron* 23: 19-29, 1999
 129. Wang Y, Spatz MK, Kannan K, et al: A mouse model for achondroplasia produced by targeting fibroblast growth factor receptor 3. *Proc Natl Acad Sci U S A* 96: 4455-4460, 1999
 130. Webster MK, Donoghue DJ: Constitutive activation of fibroblast growth factor receptor 3 by the transmembrane domain point mutation found in achondroplasia. *EMBO J* 15: 520-527, 1996
 131. Wienecke R, Konig A, DeClue JE: Identification of tuberin, the tuberous sclerosis-2 product. Tuberin possesses specific Rap1GAP activity. *J Biol Chem* 270: 16409-16414, 1995
 132. Willems PJ, Brouwer OF, Dijkstra I, et al: X-linked hydrocephalus. *Am J Med Genet* 27: 921-928, 1987
 133. Willems PJ, Dijkstra I, Van der Auwera BJ, et al: Assignment of X-linked hydrocephalus to Xq28 by linkage analysis. *Genomics* 8: 367-370, 1990
 134. Wingate RJ: The rhombic lip and early cerebellar development. *Curr Opin Neurobiol* 11: 82-88, 2001
 135. Wininger SJ, Donnenfeld AE: Syndromes identified in fetuses with prenatally diagnosed cephaloceles. *Prenat Diagn* 14: 839-843, 1994
 136. Xiao GH, Shoarnejad F, Jin F, et al: The tuberous sclerosis 2 gene product, tuberin, functions as a Rab5 GTPase activating protein (GAP) in modulating endocytosis. *J Biol Chem* 272: 6097-6100, 1997
 137. Yamasaki M, Thompson P, Lemmon V: CRASH syndrome: mutations in L1CAM correlate with severity of the disease. *Neuropediatrics* 28: 175-178, 1997
 138. Yapar EG, Ekici E, Dogan M, et al: Meckel-Gruber syndrome concomitant with Dandy-Walker malformation: prenatal sonographic diagnosis in two cases. *Clin Dysmorphol* 5: 357-362, 1996
 139. Zanata G: Encephalocele: experimental model. Morphogenesis, pathogenesis and clinical correlations discussion. *J Neurosurg Sci* 41: 235-248, 1997
 140. Zucman-Rossi J, Legoix P, Der Sarkissian H, et al: NF2 gene in neurofibromatosis type 2 patients. *Hum Mol Genet* 7: 2095-2101, 1998

Development of the Cerebrospinal Fluid Pathways During Embryonic and Fetal Life in Humans

MARTIN CATALA

*Pour qu'une chose soit intéressante,
il suffit de la regarder longtemps.*
Gustave Flaubert

Trying to understand the mechanisms involved in human development is both a complex and fascinating problem. It is also the absolute prerequisite for an analysis of human malformations. Self-evidently, the genesis of malformation syndromes cannot be understood without a knowledge of the normal steps of development. This contradicts the classical works of human embryology, which were devoted to the analysis of malformation syndromes in the attempt to decipher the normal steps of human development – a method that may be called “reverse embryology”. Nowadays, this old method is of no value and it has been necessary to develop new paradigms to discover the normal pathways of development.

Descriptive studies are of limited value since they cannot give reliable answers. A tremendous amount of data have been gained in embryology by performing experimental analyses in different animal models. However, there is no single perfect animal model, and one has to adapt a suitable experimental model for each specific question. This has prompted the development of comparative embryology to try to find steps that are conserved during evolution. This conservation of biological processes between different species is not very surprising since the different modern phyla are thought to derive from a common ancestor. As it is not possible to study the common ancestor experimentally, comparative embryology tries to find similarities between modern phyla. Two basic kinds of similarities can be observed: (i) homologies, which are similarities inherited from a character present in the common ancestor, and (ii) analogies, which are similarities that develop independently and are not present in the common ancestor. Obviously, homologies are much more potent means to finding a common mechanism of development than analogies. For example, the wings of flies and of birds are analogous because they arise from different structures (the imaginal disk in the case of the fly and the limb bud in the case of birds). By contrast, the wings of birds and

the forelimbs of mammals are homologous since they both arise from the forelimb bud of vertebrates.

This shows that comparative embryology is a complex science and the reader must be very cautious before accepting any concept of homologies. For example, Couly [39, 40], in a famous article published twice, considers that the symmetry of the human body is homologous to the five-fold radial symmetry of the starfish. The five appendages of the starfish are thought to be homologous to five human buds (the head and the four limbs). This so-called homology allows him to consider the mouth as a modified hand! All these arguments are obviously nonsense and cannot be accepted in terms of comparative embryology. In fact, embryonic mammals develop six buds, not five as stated by Couly [39, 40]. In all mammals, there are four limb buds, a rostral bud (the prospective head) and a caudal bud (or tail bud) which is fated to disappear only in tailless animals. The mammalian embryonic symmetry is thus not five-fold radial but bilateral. The second problem with this speculation is that starfish like all the echinoderms develop first into a larva that presents a bilateral symmetry. The acquisition of the five-fold radial symmetry is a secondary event taking place during metamorphosis (see [275] for a review). So, these arguments rule out the homology between the mouth and the hand put forward by Gérard Couly [39, 40].

This example is just to remind the reader to be cautious in interpreting comparative embryology studies. However, comparative embryology, when correctly studied, is very powerful for finding analogies and homologies between species. Meninges are observed in protostomes [78] like *Amphioxus*, which is considered as very close to the common ancestor of all the vertebrates. However, in this species, the rostral end of the central nervous system (CNS) is open and communicates freely with the environment, namely the sea water. There is no specific cerebrospinal fluid (CSF) and no choroid plexus [78] since the sea water plays the role of the CSF. In contrast, all the verte-

brates display a closed brain and develop specific devices to produce a liquid that bathes the CNS. All these data indicate that the structures involved in CSF physiology have been highly conserved during evolution of the vertebrates. This fact justifies the use of different models of vertebrates to try to elucidate the mode of formation of these structures in humans.

Formation of the Ventricular System

Neurulation and the Formation of the Central Neurocele

The development of the embryo involves a series of complex steps characterized by cell interactions, highly regulated morphogenetic movements and a complexification leading to the creation of the body shape. It is obviously beyond the scope of this review to present a thorough and extensive overview of these processes. Gastrulation is probably the earliest important check

point of embryonic development. It takes place at the 3rd week of gestation in humans and is considered by the famous British embryologist Lewis Wolpert to be the “most important time in your life”. Gastrulation allows the formation of the three germinal layers from the sole epiblast (i.e. the most superficial layer of the so-called bi-layered embryo). At the end of gastrulation, three germinal layers are built: the dorsal ectoderm, the intermediate mesoderm and the ventral endoderm.

The second important step during development is the formation of the primordium of the CNS. This phenomenon is described as “neural induction”, which corresponds to the acquisition by primitive ectodermal cells of a neural identity. The exact mechanisms by which neural induction is acquired are still disputed. Anyway, whatever the involved mechanisms, the salient result of neural induction is the individualisation of a neural primordium within the ectodermal layer; this primordium appears as a sheet of prismatic cells forming the so-called neural plate (Fig. 1A). The third morphogenetic event is called neurulation and occurs during the 4th week of gestation in humans. We will follow the classical description of neurulation put forward by Gary Schoenwolf and his group [209, 217].

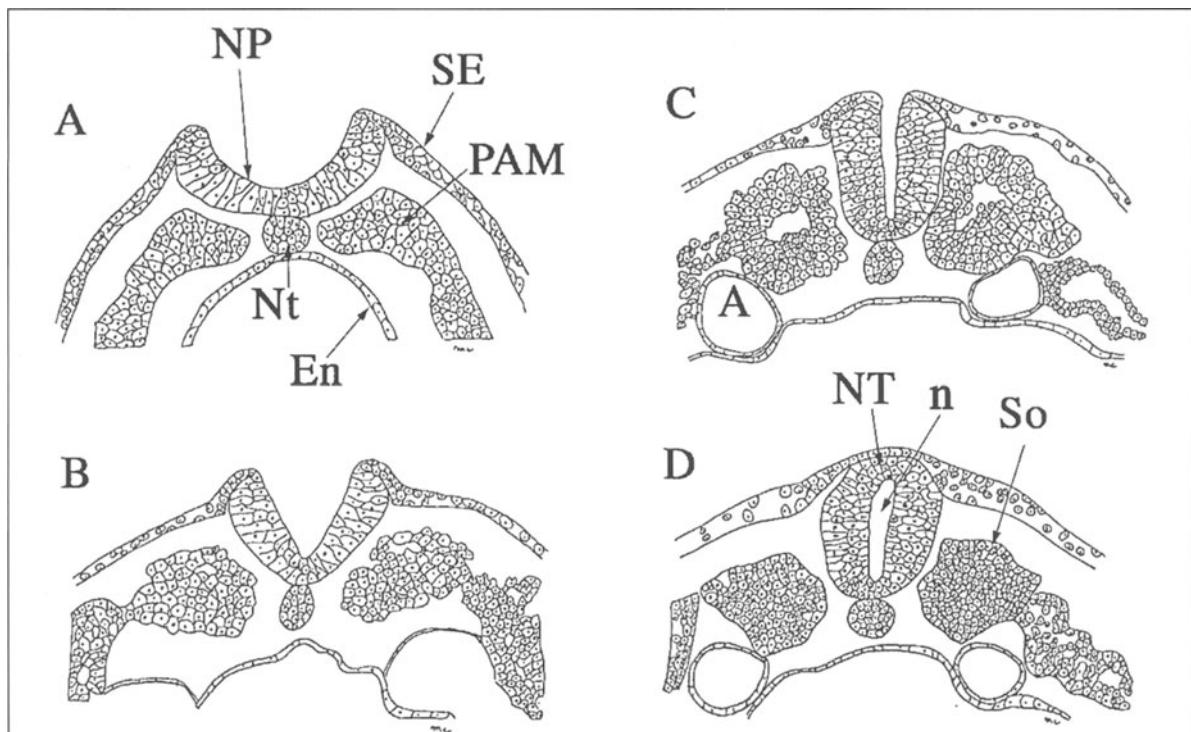


Fig. 1A-D. Primary neurulation in the chick embryo as evidenced on transverse sections. **A** After neural induction, the primitive ectoderm is subdivided into the medial neural plate (NP) and the lateral surface ectoderm (SE). The mesoderm is subdivided into the medial notochord (Nt) and the paraxial mesoderm (PAM). The most ventral tissue of the embryo is the endoderm (En). **B** The formation of the medial hinge point leads to the upfolding of the lateral borders of the neural plate. **C** The lateral borders of the neural plate converge to the midline. A, aorta. **D** After neurulation is achieved, the neural tube (NT) is formed, delineating a central cavity (the neurocele, n). The paraxial mesoderm develops and gives rise to somites (So)

The first evidence of neurulation is the movement of shaping of the neural plate; during this phase, the neural plate undergoes dorsoventral thickening, mediolateral shrinking and craniocaudal extension. The phenomena responsible for this morphogenetic movement are cell rearrangements along the mediolateral axis and cell mitosis along both longitudinal and transverse axes [212]. These forces are generated within the neural plate and do not require any interactions with the neighbouring tissues [6, 210, 211, 216]. The second morphogenetic movement that takes place during neurulation is called bending. Bending can be subdivided into furrowing and folding. Furrowing is generated by a modification of the cellular shape of the cells located just above the notochord and thus forming the midline of the neural plate (Fig. 1B). This shape modification is due to contraction of apical actin filaments and is thought to be generated by an interaction played by the underlying notochord [232]. Folding is due to the surface ectoderm [6] and causes the apposition of the folds of the neural groove in the dorsal part of the embryo (Fig. 1C). This leads to the ultimate fusion of the folds, which will be separated from the lateral surface ectoderm, now forming the most dorsal structure of the embryo (Fig. 1D).

One of the salient results of neurulation is that the neural plate gives rise to a neural tube that delineates a central cavity, the neurocèle. In amniotes, neurulation is not synchronous along the anteroposterior axis but begins at the level of the first somite in humans and then proceeds both rostrally and caudally. So, the neurocèle freely communicates with the amniotic fluid by both rostral and caudal neuropores.

Occlusion of the Spinal Neurocèle

After the closure of the anterior neuropore [on embryonic day 24 (E24) in humans], the central neurocèle still communicates with the amniotic fluid via the posterior neuropore. The posterior neuropore closes on E26 in humans. However, between E24 and E26 (corresponding respectively to 13- and 29-somite stages [155, 156], the central neurocèle has ceased to be in communication with the amniotic fluid because of so-called occlusion of the spinal neurocèle (Fig. 2). This occlusion is characterized by apposition of the walls of the neural tube [49] between the levels of the first to the ninth somites. This histological feature has been illustrated in human [49], mouse [105] and chick embryos [52, 53, 180, 213, 214, 216] and has been extensively studied in this last species. I will describe the occlusion of the spinal neurocèle in the chick embryo since it is the species in which this morphogenetic event is the best understood.

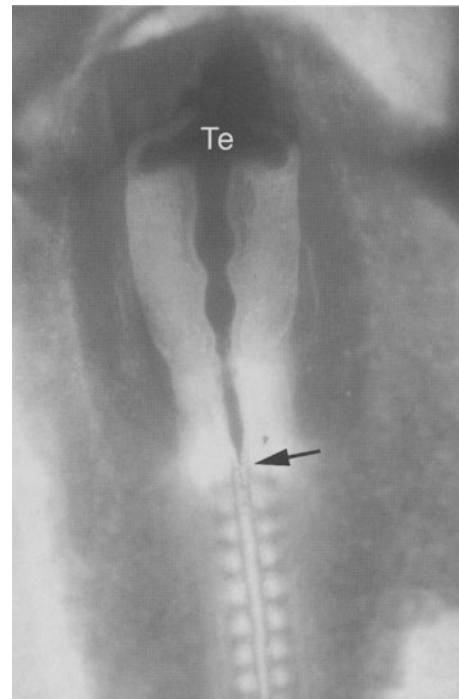


Fig. 2. The occlusion of the central neurocèle observed in a chick embryo. Indian ink was injected into the telencephalic vesicle (Te). The dye can diffuse through the diencephalon, mesencephalon and a part of the rhombencephalon. The diffusion of the dye is prevented by the occlusion of the spinal neurocèle (arrow)

The occlusion begins as early as the 10- to 13-somite stage [53, 213, 214], a stage that corresponds with the phase of rapid brain enlargement [180]. The closure is only transient and reopening begins at the 22-somite stage [216] and is complete at the 26-somite stage [216]. The regulation of this mechanism shows that it is intrinsic to the neural tube and does not need any interaction with neighbouring tissues [54]. The closure of the neurocèle is not prevented by destruction of basement membranes, depletion of extracellular matrix or cytoskeleton disruption [54]. The closure of the spinal neurocèle is a process that is calcium-dependent and can be reversed by the use of divalent cation-chelating agents (EDTA or EGTA) [51, 54] or by calcium-blockers. Furthermore, reopening of the neurocèle is elicited by blocking the protein calmodulin (a calcium-dependent protein involved in the contraction of cytoplasmic actomyosin) and by increasing the cellular level of cAMP [51]. This shows the crucial role played by calcium in the maintenance of neurocèle closure.

The salient result of both the closure of the anterior neuropore and the occlusion of the spinal neurocèle is that the central canal of the neural tube at

its rostral moiety represents a true compartment separated from the amniotic fluid. This compartment is called the primitive ventricular system. The pressure within the primitive ventricular system increases compared to that of the amniotic fluid [95] and this increase is concomitant with the onset of enlargement of the embryonic brain. This observation suggests that there is a correlation between this increase of pressure and the enlargement of the brain. Expansion of the ventricular cavities is linear, in contrast to the growth of the brain, which is exponential [180]. If the intraventricular pressure is lowered by intubating the chick embryonic brain, the ventricular cavities do not enlarge [38, 52] and the tissue of the neural tube is prevented from growing [50].

The increase of the ventricular pressure suggests that there exists a system devoted to active secretion of the ventricular fluid. Furthermore, if one removes a large amount of ventricular fluid, the ventricular pressure returns to normal between 2 and 2.5 h [95]. The likely cells involved in this secretion are the neural tube cells. Indeed, Weiss demonstrated in vitro that neuroepithelial cells display a secretory phenotype at their ventricular pole [269].

Origin and Development of the Meninges

The meninges, which enwrap the entire central nervous system, are composed of dura mater (or pachymeninges) and pia-arachnoid (or leptomeninges) (Fig. 3). The dura mater is formed of fibroblasts, whose cytoplasmic processes are arranged parallel to the surface of the brain, and dense collagen bundles [65, 159]. The internal part of the dura is constituted by a few layers of flat and joined cells that form the subdural mesothelium (or neurothelium). This neurothelium is limited at its internal face by a basement membrane which delineates dura from arachnoid [196]. The cells of the subdural mesothelium are in fact the so-called dural border cells described by Nabeshima et al. [159]. Their cytoplasm is rich in alkaline phosphatase and magnesium-dependent adenosine triphosphatase [7].

The arachnoid can be subdivided into two sublayers [2, 135, 159, 197, 169]. The more external arachnoid layer corresponds to the arachnoid border cells [65].

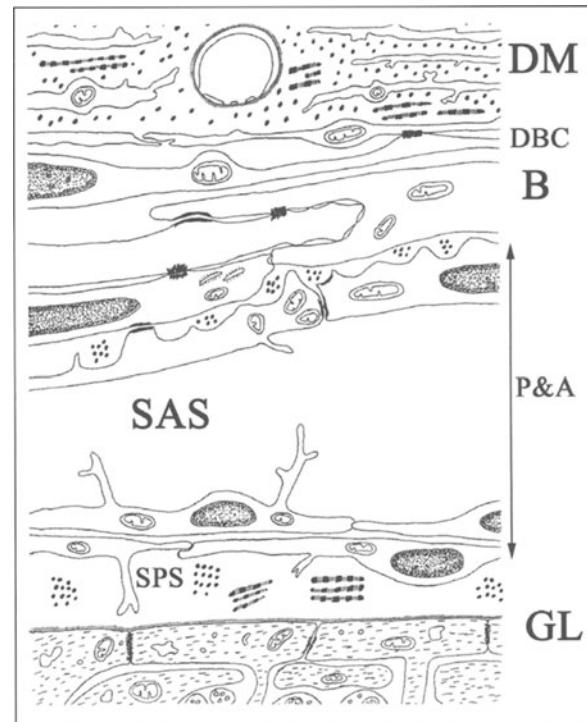


Fig. 3. Schematic view of the meninges. The most superficial layer is the dura mater (DM), which is made of a fibrous connective tissue. Dural border cells (DBC) are located at the interface between dura and arachnoid. The most superficial layer of the arachnoid forms the arachnoid barrier layer (B). The pia-arachnoid complex (P&A) delimits the subarachnoid space (SAS) and the subpial space (SPS). The superficial region of the cortex is limited by the glia limitans (GL)

Organization of the Meninges

This layer is in close apposition with the basement membrane of the dural border cells and is made up of one to a few layers of flat cells containing numerous vimentin filaments, alkaline phosphatase activity but not magnesium-dependent adenosine triphosphatase activity [7]. These arachnoid cells (or leptomeningeal cells) are joined together by both gap junctions and desmosomes [2, 159, 169]. They constitute a continuous sheet of cells that could account for the barrier property of the arachnoid [159]. The more internal part of the arachnoid is formed by trabeculae that connect arachnoid with pia mater [135, 169]. Like the more superficial arachnoid cells, these internal cells are joined together by both gap junctions and desmosomes [2, 159]. The intercellular space delineated by these trabeculae forms the so-called arachnoid space, which is filled with CSF, a few collagen fibres and a microfibrillar material.

The pia mater is constituted by a single cell layer in rodents [159, 161, 169] and by one to three cell layers in humans [2]. Like arachnoid cells, pial cells are

joined together by both gap junctions and desmosomes [2]. No histological criteria allow a distinction between pial and arachnoid cells [159]. This suggests that these two types of cells in fact represent the same phenotype, namely leptomeningeal cells. Several authors [134, 169, 194] have described the pia mater as a discontinuous sheet. This feature seems to be artifactual and the human pia mater is in fact continuous [2].

There is a space between the pia mater and the basement membrane that covers the brain surface. This space represents the so-called subpial space and contains a few collagen fibres [2, 159, 169, 194].

Meningeal Delimitation of Isolated Circulation Compartments

The histological description of the meninges does not help us to understand the mode of circulation of physiological fluids between cells. To detect compartments, it is necessary to inject a non-diffusible tracer such as HRP (horseradish peroxidase) and to follow the circulation of this molecule. This has been extensively studied in the rat by the group of Brigitte Krisch [110, 111]. Using this technique, it is possible to recognize five different spaces. Five minutes after an intracerebral injection of HRP, the cerebral intercellular space communicates with the subpial space, the perivascular space and finally the intercellular space of the neurothelium. After injection within the pia mater, the tracer delineates the so-called pial space, which does not communicate with another compartment. If HRP is injected in the arachnoid space, it remains within the space delimited by the arachnoid trabeculae, confirming that this arachnoid space is a true compartment. Finally, injection into the dura labels both the dura and the intercellular space between dural border cells. However, this conception needs to be modulated, for if the histological analysis is not performed immediately after the injection, it is possible to show that different compartments can communicate. For example, Zervas et al. [281] have demonstrated in the cat that the subarachnoid space communicates with the perivascular space.

Embryonic Origins of the Meninges

When one has to deal with the embryonic origin of a structure, it is necessary to perform experiments that make it possible to follow the fate of a tissue during the development of an organism. The question of the right marker is thus pivotal for such experiments.

The development of microsurgical techniques used on embryos allows performance of such fate-mapping experiments. The first were developed during the nineteenth century on amphibian embryos [20, 258]. Born [20] described a technique in which he transplanted a tissue from a donor to a host and observed perfect healing and subsequent normal development [83]. This was the birth of amphibian chimaeras. If one uses different species of amphibians with specific histological features (such as cytoplasmic pigmentation), these species-specific markers could serve as marker of the origin of the cells and allow the fate and differentiation of the transplanted cells to be followed.

Consequently, the question of the origin of the meninges was first assessed experimentally in amphibian embryos (*Ambystoma punctatum*) [88, 89]. The finding of this experiment in this species was that the neural crest gives rise to the pia-arachnoid complex whereas the mesoderm produces the dura. Nicole Le Douarin [115] described a differential characteristic between quail and chick cells. The nuclear heterochromatin in quail cells is condensed and associated with the nucleolus whereas it is more evenly distributed in chick cells. This marker helps to distinguish cells from the donor from those from the host after the construction of interspecific avian chimaeras. This technique is very useful for constructing fate maps in birds, which belong to the higher vertebrates.

In birds, all the meningeal cells of the spinal cord derive exclusively from the somite [10-12] and not from the neural tube [81] (Fig. 4). So, unlike the case in amphibians, bird spinal cord meninges are of pure mesodermal origin. The cephalic mesoderm lies rostrally to the somites and belongs to the paraxial domain of the mesoderm (Fig. 4). This mesoderm gives rise to the meninges of the brain stem and the cerebellum [42]. The problem of the embryonic origin of the telencephalic meninges is far from simple. Neural crest cells play a major role in the development of the cephalic mesoderm. This was postulated as early as the end of the nineteenth century by Julia Platt [188, 189] working on *Necturus* development. In this amphibian species, the yolk platelets in ectodermal cells such as neural crest cells are conspicuously smaller than those of the other lineages (i.e. mesodermal and endodermal cells). This cell characteristic makes it possible to follow the migration of these cells. Using this marker, cephalic neural crest cells were found to migrate and populate the mesodermal structures of the head. Julia Platt coined the term "mesectoderm" for this compartment of neural crest cells with mesodermal derivatives. This neural crest origin was revisited using more recent experimental techniques.

Neural crest cells can be labelled by incubation with tritiated thymidine in the chick embryo. This paradigm was used by Johnston [96], who demonstrated the neural crest origin of the chick telencephalic meninges. The precise rostrocaudal origin of neural crest cells giving rise to the telencephalic meninges has been assessed using the quail-chick chimaera technique at the three-somite stage [42]. The telencephalic meninges derive from mesencephalic neural crest cells. Furthermore, these cells give rise to the media of the meningeal vessels, whereas the endothelial cells of these vessels derive from the cephalic mesoderm [41]. However, this situation may be much more complex in mammalian embryos. Prosencephalic neural folds give rise to neural crest cells in mouse [178], unlike in birds, in which no rostral crest cells are evidenced. These prosencephalic neural crest cells populate the frontonasal mass and could participate in the formation of the most anterior part of the meninges.

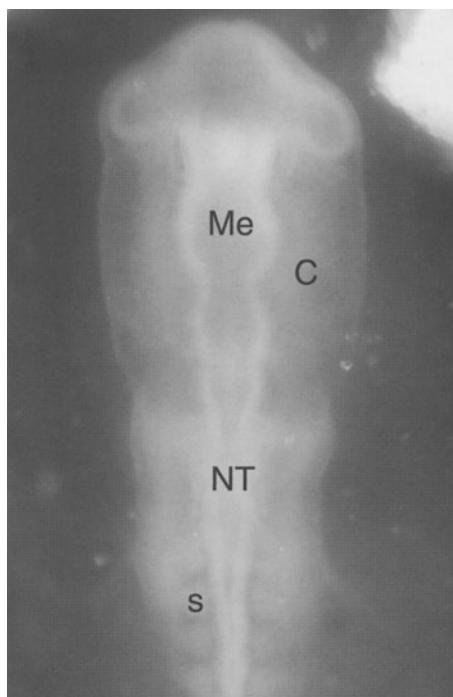


Fig. 4. Dorsal view of a chick embryo at the 14-somite stage. The neural tube (NT) gives rise to the epithelium of the choroid plexus. The somites (s) produce the spinal meninges and their vessels. Neural crest cells arising from the mesencephalic vesicle (Me) develop into the telencephalic meninges and the mesenchymal cores of the choroid plexus at the prosencephalic level. The cephalic mesoderm (C) gives rise to the meninges of the midbrain and hindbrain and to the endothelium of the choroid vessels and the telencephalic meninges

Histogenesis of the Meninges

It is possible to recognize the three adult layers of the meninges as early as the 3rd fetal month [109]. However, cytological changes within the layers are much more protracted. For example, the subdivision of arachnoid cells into two populations begins only in the 7th fetal month [109]. One of the major problems related to CSF is the formation of the subarachnoid space. Weed [265-267] made a significant contribution to this problem using the pig embryo. He analysed the timing of spreading of the CSF out of the ventricular cavities by introducing a coloured solution into the ventricles. He found that the time of CSF issue out of the fourth ventricle was concurrent with the time of differentiation of the choroid plexuses [265]. Before the first circulation of the CSF, the neural anlage is wrapped by the meninx primitiva (a mesenchymal tissue with an extracellular matrix characterized by a high protein content). Weed [266, 267] found that the formation of the subarachnoid space is concomitant with CSF circulation. This timing was found to be similar in human embryos and in pig [266]. The major conclusion from Weed's studies was that the subarachnoid space is formed by delamination of the extracellular matrix of the mesenchymatous perineural tissue due to CSF movements.

This classic view remained unchallenged from 1916 to 1980. At that time, Osaka et al. [176] revisited the problem of the formation of the subarachnoid space in microscopic sections of 60 normal human embryos from E6 to E57. This study allowed the authors to describe carefully the timing of this formation. The first evidence of the differentiation of the subarachnoid space was found in the ventral region of the mesencephalon and the rhombencephalon at E32. Then, the space spread according to a double anteroposterior gradient (cranially to the prosencephalon and caudally to the spinal cord) and in a ventrodorsal direction. The direction of spread of this formation contradicts the role postulated by Weed in the genesis of the subarachnoid space. It seems that the formation of this space is due to other factors than CSF circulation. Such evidence is also found using rat embryos. In this species, the subarachnoid space is present as soon as E14, whereas CSF circulation begins at E17 [103].

Induction by Meningeal Cells of the Formation of the Superficial Glia Limitans

The so-called superficial glia limitans is a nervous region that constitutes the interface with the meninges. This glia limitans is made up of astrocyt-

ic endfeet attached to each other by gap junctions [181]. This astrocytic sheet is covered by a basement membrane containing fibronectin, type IV collagen and laminin [227].

It is possible in newborn rodents (rats or hamsters) to selectively destroy the meningeal cells by injecting 6-hydroxydopamine (6-OHDA) in the arachnoid space [4, 84, 223-225, 228, 255]. Using this experimental paradigm, it is thus possible to address the question of the interactions between meninges and the overlying neural tissue. Destroying the meningeal cells leads to the disappearance of the basement membrane of the glia limitans [186, 223, 224, 226-228]. This disappearance is associated with a decrease in the concentration of both fibrillary collagens (types I, III and VI) and molecules of the basement membrane (type IV collagen, fibronectin, laminin) [227]. It has been demonstrated in vitro that meningeal cells can produce all these molecules [227]. It is thus tempting to speculate that the disappearance of fibrillary collagens and the molecules of the basement membrane are directly due to the destruction of the meningeal cells.

It is possible to culture in vitro an embryonic mouse spinal cord [from E 13-14] and to study its growth. If this spinal cord is isolated from its overlying meninges, its basement membrane covering the glia limitans disappears [113]. In contrast, if the spinal cord is maintained within the meninges, this basement membrane persists [114]. We can thus conclude that the meninges are mandatory to maintain the integrity of the glia limitans of the nervous system and its overlying basement membrane. One of the candidate molecules that could account for this interaction is the system of parathyroid hormone-related protein (PTHrp) and its receptor. Indeed, meningeal cells synthesize and secrete PTHrp whereas astrocytes express the PTHrp receptor [241]. However, the exact role of this system needs to be further determined for the control of glia limitans formation.

Promotion by Meningeal Cells of the Development of Cells Arising from the Neural Tube in Culture

Co-culture of meningeal cells and neuroblasts shows that meningeal cells stimulate the proliferation rate [15, 29, 70], the differentiation of neuroblasts [70] and the growth of their neurites [146]. This promoting activity is stage-dependent and, for example, meningeal cells act on chick neural cells at E5 or E6 but not on cells at E7 [15, 29]. Meningeal cells secrete a chondroitin sulphate proteoglycan, the so-called

biglycan [102], which has been associated with the neurotrophic activity of these cells. In contrast, both laminin-proteoglycan complexes and fibronectin are involved in neurite-promoting activity [146].

Morphogenetic Role of Meningeal Cells in Neural Structures

Since all these trophic activities of the meningeal cells have been demonstrated in vitro, their relevance in normal development *in vivo* is under debate. However, it has been possible to study this trophic role *in vivo* in three different nervous structures: the cerebellum [4, 186, 223, 224, 226, 228, 255], the hippocampus [84] and the cerebral cortex [242a]. Indeed, in rodents, the development of these structures is protracted after birth. It is thus possible to selectively destroy meningeal cells in newborns and to study the consequences on neural development. Destruction of the cerebellar meninges leads to cerebellar hypoplasia, induction of neuronal heterotopia in the subarachnoid space, fusion of adjacent folia, displacement of glial processes into the subarachnoid space and reduction of the total number of granular cells [4, 186, 223, 224, 226, 228, 255]. Meningeal cells play a promoting role on the migration of neuroblasts coming from the external granular layer of the cerebellum [85, 86] and promotes the development of the radial phenotype of glial cells [86]. Destruction of the meninges overlying the hippocampus leads to a secondary malformation of the dentate gyrus [84]. In the cortex, the most superficial neurons (i.e. Cajal-Retzius cells) are sensitive to destruction of the meninges [242a].

From these experiments, we can conclude that meningeal cells do play a role in CNS morphogenesis. However, the exact role played by these cells in mammals remain to be established. The development of CNS structures is mainly pre-natal, a period of poor embryonic access in the mammalian embryo. It would be both interesting and challenging to use whole embryo cultures to test such a role in the early period of CNS development.

Choroid Plexuses

Choroid Plexuses Formed of Both Neural and Connective Tissues

Choroid plexuses extend from the ependyma into the ventricular lumen. They are present in the later-

al, the third and the fourth ventricles. They form villous structures made of the apposition of two different tissues (Fig. 5). The epithelial surface of the plexus lies in continuity with the ependyma whereas the axis is made of leptomeningeal cells and numerous vessels. The choroidal epithelium is constituted by cubic cells that are polarized with a brush border at their apical pole (i.e. the ventricular domain) in all the species except for a lizard, *Gecko japonicus* [158]. This epithelium lies on a continuous basement membrane. The basal domain of the cell is rich in mitochondria which are located within interspaces delineated by folds of the cell membrane. The epithelial cells are tightly joined by junctional complexes. The connective axis of the villus is very rich in blood vessels. At this level, the capillaries are fenestrated.

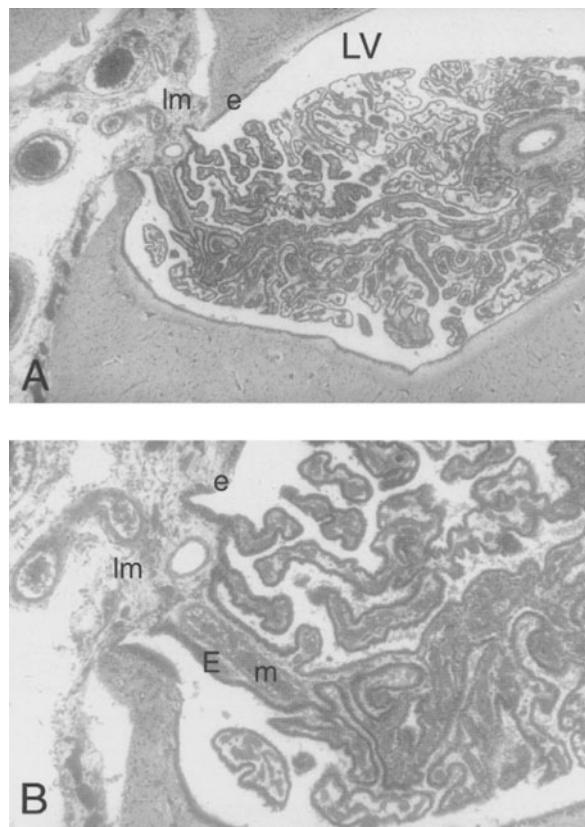


Fig. 5A, B. Frontal sections of a fetal human brain (40th week of gestation) at the level of the temporal horn of the lateral ventricle (LV). **A** Note that the choroid plexus bulges into the lumen of the ventricle, which is limited by ependyma (e). **B** The epithelium (E) of the choroid plexus lies in continuity with the ependyma (e); the mesenchymal core (m) of the choroid plexus is continuous with the leptomeninges (lm).

Location of Numerous Enzymes Within the Choroid Plexuses

Numerous enzymes and enzymatic systems have been described within epithelial or endothelial cells of the choroid plexuses (see [31, 143] for reviews). It is obviously outside the scope of this chapter to deal with all the enzymes expressed by choroidal cells. I will restrict my purpose to the enzymes involved in CSF formation.

Sodium-Potassium-ATPase (Na^+/K^+ -ATPase)

Na^+/K^+ -ATPase is one of the key enzymes responsible for CSF formation through active secretion of Na^+ from the cytoplasm of epithelial cells to the ventricle. This enzyme is constituted by three subunits: α , β and γ . The catalytic domain (responsible for the hydrolysis of ATP) is localized on the α subunit. Furthermore, cardiac glycosides (ouabain, digitalis) bind the α subunit. The β subunit plays a regulatory role on the α subunit. The role of the γ subunit remains to be established. Na^+/K^+ -ATPase is present in the apical domain of the cell membrane of the epithelial cells in the choroid plexus in adult dogs [141, 142], adult mice [63, 222], neonatal rats [247] and adult rabbits [151]. The subunits of this enzyme are encoded by a multigene family. The epithelial cells of the choroid plexus express the $\alpha 1$, $\beta 1$ and $\beta 2$ isoforms [77, 263, 282]. The isoforms of the γ subunit expressed by the choroid plexus are still undetermined. The total activity of Na^+/K^+ -ATPase is constant during both fetal and adult life [151]. However, a change in the cell localization of the enzyme is observed during development. From E16 to E18 in rat embryos, the enzyme is expressed both at the apical pole of the cell and at the basolateral pole [247]. This basolateral presence of the enzyme is concomitant with the absence of tight junctions between epithelial cells. It can thus be postulated that these junctions may play a crucial role in the control of addressing Na^+/K^+ -ATPase to the apical domain of the cell. At the apical pole of the cell, Na^+/K^+ -ATPase is linked with different cytoskeletal proteins such as fodrin, ankyrin [5, 139], actin, myosin and α -actinin [5]. However, the presence of both fodrin and ankyrin is not sufficient for this enzyme to be inserted into the cell membrane, since these cytoskeletal proteins are present at the basolateral domain of the cell, a region devoid of Na^+/K^+ -ATPase [139].

Carbonic anhydrase catalyses the hydration of CO_2 to produce H_2CO_3 , which is dissociated into H^+ and HCO_3^- . HCO_3^- is then transported into the CSF,

allowing the passage of an H₂O molecule. This enzyme activity plays a crucial role in CSF production since acetazolamide, a specific inhibitor of carbonic anhydrase, dramatically reduces the rate of CSF secretion. Seven different isozymes account for this enzymatic activity. These isozymes are encoded by a multigene family and differ in their physiological properties and their cellular localization (see [231] for a review). The epithelial cells of the choroid plexus express both carbonic anhydrase types II [204] and III [168]. Furthermore, endothelial cells of the capillaries of the plexus express carbonic anhydrase IV [71]. Both carbonic anhydrase types II and III are cytosolic; carbonic anhydrase type II is a high activity isoform whereas type III displays very low activity [231]. The expression of carbonic anhydrase type II takes place very early during development in humans since it is observed at least as soon as the 9th week of gestation [30].

The two enzymes involved in CSF formation are thus present very early during development and may account for this formation in both embryonic and fetal life.

Embryology of the Choroid Plexus

Participation of Different Embryonic Layers in the Formation of the Choroid Plexus

Both development and differentiation of the choroid plexuses have been studied in various species by the performance of several histological procedures [33, 61, 62, 92, 157, 175, 179, 221]. Table 1 presents comparative data showing the different times of onset of choroidal differentiation noted for different laboratory animals and for humans. However, these data are only descriptive events and do not explain the mode of formation of the plexus itself.

Table 1. First histological evidence of choroidal differentiation in several species

Species	Lateral ventricle	Third ventricle	Fourth ventricle	Duration of gestation
Chick	E5-6	E6-8		21 days
Rat	E13	E16	E13	21 days
Mouse	E13	E14.5	E13	21 days
Sheep	E24		E21	150 days
Man	W7 (E44)	W8 (E57)	W6-7 (E41-44)	38 weeks

E, embryonic day; *W*, week of gestation

The first question to answer is the embryonic origin of cells which yield the choroid plexus. The technique quail-chick chimaera has been extensively used to test this question. The epithelial cells of the plexus derive from the neural tube itself [273]. In contrast, mesenchymal and endothelial cells do not derive from the neural tube. The endothelial cells of all the choroid plexuses derive from the paraxial mesoderm, namely the cephalic one [41]. Mesenchymal cells of the axis of the choroid plexus of the fourth ventricle are also derived from the cephalic mesoderm, whereas those of the lateral and third ventricles derive from the mesencephalic neural crest that gives rise to mesectodermal cells.

A second question related to embryogenesis is to try to decipher the relationships between these tissues of origin. The problem is to determine whether one tissue is acting as an inducer. For this purpose, Wilting and Christ [273] performed heterotopic transplantation of neural tube cells in a new mesenchymal environment and of cephalic mesoderm cells in a new neural environment. They showed that only neural tube cells are able to induce the development of the plexus mesenchyme. In contrast, the mesenchyme is able neither to self-differentiate into a plexic mesenchyme nor to induce the formation of an extraplexus by the neural tube. Furthermore, the same authors found that chick neurectodermal cells are already committed to forming choroid plexus as early as 50 h of incubation (corresponding to an embryo with 22 pairs of somites). Indeed, at this stage, prospective telencephalic choroidal epithelium grafted into the coelomic cavity of chicken embryos differentiates into normal choroid plexus [273]. This capacity to form a plexus is regionalized in the embryo at this stage since it was impossible to force the development of a plexus from a neural region which is not normally fated to give rise to such a structure.

A third question related to the development of the plexus is the problem of specification. This

problem should be studied using *in vitro* culture devices. Thomas and Dziadek [244] used this experimental approach to study the intrinsic capacity of neural tube cells to differentiate into choroid plexus epithelial cells. The cell differentiation into choroidal cells was assessed by demonstrating the expression of the gene coding for transthyretin. In mouse embryos at E8.5 (before the start of neurulation) the capacity to self-differentiate into choroidal cells is widely distributed along the anteroposterior axis of the brain. One day later, this capacity is much more restricted along the axis and is maximal at the future level of the plexuses.

In conclusion, the commitment of neural tube cells to differentiate into epithelial choroid cells is a very early event during development. This capacity is not uniform along the anteroposterior axis but is restricted to discrete areas that are fated to form the choroid plexus. This is a general feature of antero-posterior regionalization observed in the embryonic neural tube.

Morphological Modifications of the Choroid Plexuses During Development

In humans, the first cell differentiation that indicates the future development of the choroid plexus

is observed at E41 [173], although the changes are inconspicuous at this stage. Cell differentiation becomes more and more obvious as development proceeds, and villi appear progressively at the surface of the plexuses [157, 174, 175, 179]. It is interesting to note that the development of the choroid plexuses is not synchronous for all the ventricles. The sequence of differentiation is as follows: the fourth ventricle, the lateral ventricles [27] and finally the third ventricle.

The development of the human choroid plexus is assessed according to the classic staging of Shuangshoti and Netsky [56, 221]. Four stages can be recognized (Table 2). Stage 1 begins during the early 7th week of gestation and ends after the 8th week of gestation. The primordium of the choroid plexus is made of a tall pseudo-stratified epithelium whose cells display a large central nucleus. These cells do not contain any glycogen granules in their cytoplasm. The stroma of the plexus is composed of a loose mesenchyme containing ill-defined vascular walls and islets of blood cells.

Stage 2 lasts from the 9th week of development to the 16th week. The size of the plexus increases with progressive lobulation. One of the salient feature is the modification of the epithelium, which becomes low columnar and whose cells fill with abundant glycogen granules concentrated at the basal pole of the cell while the nucleus adopts an apical position

Table 2. Stages of differentiation of the human telencephalic plexus according to Shuangshoti and Netsky [221] and Dontchev and Hadjoloff [56]

	Stage 1	Stage 2	Stage 3	Stage 4
Time of development	7th week	9th week	17th week	29th week
Duration of development	2 weeks	8 weeks	12 weeks	11 weeks
Epithelium	Pseudo-stratified, tall, central nuclei	Low columnar, apical nuclei	Cuboid, apical and central nuclei	Cuboid or squamous, central and basal nuclei
Glycogen	Absent	Abundant	Moderate	Minimal and absent
Villi	Absent	Sparse	Primary villi	Villi with multiple fronds
Tubules	May be present	Several	Numerous	Numerous
Stroma	Loose mesenchyme	Small numbers of connective fibres	Moderate numbers of fibres	Large numbers of fibres and meningocytes
Blood vessels	Ill-defined vascular walls	Defined vascular walls	Well formed vascular walls	Same
Size in relation to ventricle	Tiny	Extremely large	Moderately large	Small
Alkaline phosphatase and esterase activities	Mild	Intense	Moderate	Moderate

(Fig. 6A). The stroma is still loose with accumulation of mucin and progressive organization of the vessels.

During the third stage (between the 17th week of development and the 28th week), the brain grows more than the choroid plexus, and the latter thus occupies less space in the ventricle. The primary villi of the plexus develop further. The shape of the epithelium changes and it adopts a cuboid appearance while the total glycogen content decreases. The mesenchyme is progressively replaced by a connective tissue containing numerous fibres.

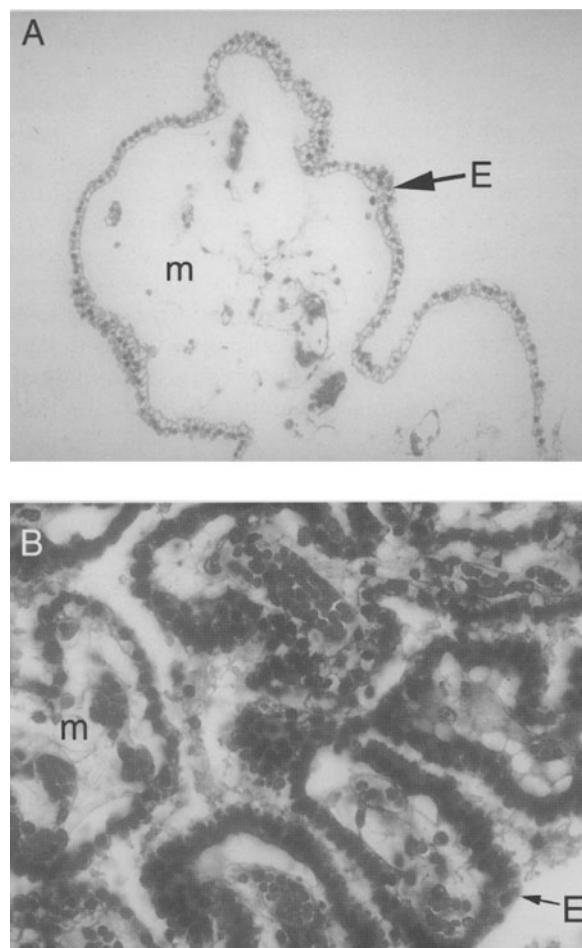


Fig. 6A. Histological section of a human choroid plexus in a fetus at the 9th week of gestation (corresponding to stage 2). The epithelium (*E*) is low columnar and its cells are filled with abundant glycogen granules that concentrate at the basal pole of the cell, whereas the nucleus adopts an apical position. The stroma (*m*) is loose. **B** Histological section of a human choroid plexus in a fetus at the 35th week of gestation (corresponding to stage 4). The epithelium (*E*) is small with basal nuclei. The stroma (*m*) is more and more fibrous

Lasting from the 29th week of gestation to birth, stage 4 is characterized by small epithelial cells with basal nuclei (Fig. 6B). The glycogen content of the epithelial cell vanishes progressively to the extent that it disappears at birth. The fibres become more and more prominent in the stroma.

It is particularly surprising to note that the epithelium of choroid plexus in the human fetus plexus contains a large amount of glycogen like the plexus in lower vertebrates (adult fish and amphibian). Furthermore, this high content of glycogen is observed in hibernating mammals, in which the choroid plexus cells are again filled with glycogen for the hibernation period [112]. These data suggest that the content of glycogen parallels the metabolic status of the subject and that fetal life is very similar to hibernating periods.

Secretion and Circulation of CSF

Secretion of CSF

If the aqueduct of Sylvius is blocked experimentally, an internal hydrocephalus is produced [45, 69]. Using the same experimental method, Dandy [44] further found that removal of the choroid plexus of the lateral ventricle prevents the formation of hydrocephalus after blocking of the foramen of Monro. This result prompted him to conclude that all CSF is produced by the choroid plexus. This conclusion was widely accepted until the work of Milhorat and his group [147, 150]. Milhorat et al. [150] performed choroid plexectomy in the lateral ventricle of rhesus monkeys, and observed that the production of CSF was reduced by only one-third. The exact proportion of CSF produced by the choroid plexus is still a matter for debate, but is currently estimated to be between 60% and 90% [167]. The rate of formation of CSF during embryonic and fetal life has never been directly assessed in humans. Using different species, several authors have shown a post-natal increase in the rate of formation of CSF (see [270] for a review) (Table 3). In kittens as in calves, the post-natal increase in the rate of formation of CSF is greater than the increase in the weight of the choroid plexus. This result suggests that the enzymatic systems responsible for CSF secretion mature after birth. Ashby and Butler [8] showed an increase in carbonic anhydrase activity during fetal life in calves. A study of the enzymatic systems involved in CSF formation during human fetal life remains to be performed.

Table 3. Rate of formation of CSF (as reviewed in [270])

Species	Adult (cm ³ /min)	Neonate (N) or fetal (F) (cm ³ /min)
Man	0.35	
Monkey	0.03	
Dog	0.045	
Cat	0.015	0.009 (N)
Rat	0.002	0.00034 (N)
Rabbit	0.009	
Goat	0.16	
Sheep	0.12	0.011 (F)
Calf	0.3	0.16 (N)
Chicken	0.0014	
Freshwater turtle	0.0014	
Dogfish	0.004	
Nurse shark	0.003	
Lemon shark	0.004	

Roof of the Fourth Ventricle

The problem of the timing of permeability of the roof of the fourth ventricle is still a matter of controversy. First, the existence of true foramina allowing free communication between the fourth ventricle and the subarachnoid space is still disputed. In amphibians, there are indeed intercellular pores that allow this communication [97, 98, 100]. These pores begin to form during the larval stage [100]. However, no direct communication between the fourth ventricle and the subarachnoid space has been evidenced in pigeon and chick [99], dog, cat, rabbit, goat [36] and mouse [170]. The mammalian observations raise some doubts about the formation of an aperture between the fourth ventricle and the subarachnoid space described by different authors during embryogenesis (see [27] for an example). These histological features could be due to mechanical destruction of the thin epithelial membrane that forms the roof of the fourth ventricle.

However, even in absence of true foramina, the fourth ventricle may communicate with the subarachnoid space through the thin epithelial sheet that forms the ventricular roof. Such permeability of the roof membrane could be experimentally analysed by injecting dyes in the ventricle and studying their diffusion. Jones and Sellars [101] demonstrated that the roof of the fourth ventricle in the rat embryo begins permeable from E17 onwards. The timing is still unknown in the human embryo.

Regulatory Mechanisms of Choroid Plexus Functions

The functions of the choroid plexuses are highly regulated by both nervous and endocrine mechanisms. A complete review of such mechanisms is obviously beyond the scope of this chapter. Readers who are interested in these particular aspects are referred to a recent and very extensive review by Nilsson et al. [167].

Neurogenic Regulation

Three main types of innervation deserve description.

Sympathetic Innervation

The choroid plexus is densely innervated by sympathetic nerves provided almost exclusively by the superior cervical ganglion [123]. Several experimental lines of evidence suggest a role for sympathetic nerves in the regulation of CSF formation. Electrical stimulation of the superior cervical ganglion produces a decrease in the rate of CSF formation in cat and rabbit without interfering with choroid plexus blood flow [90, 122], while sympathetic denervation results in an increase in CSF production, active transport of choline and Na⁺/K⁺-ATPase activity [122, 126, 127]. The effects of sympathetic stimulation can be mimicked by intravenous or intraventricular injection of noradrenaline [90, 123] via activation of β-receptors [124, 160] which stimulate adenylate cyclase and cAMP synthesis.

The choroid plexus cells express the enzymes involved in catecholamine inactivation:

- Catechol-O-methyltransferase (COMT) catalyses the transfer of a methyl group on a variety of catechol compounds. It is one of the key enzymes involved in the inactivation of catecholamines. COMT is heavily expressed by pia and arachnoid cells, choroidal epithelial cells and ciliary epithelium [104].
- Type A and B monoamine oxidases (MAO) are present in the secretory epithelium of the choroid plexus [125]. These enzymes are involved in the inactivation of catecholamines, as is the case for COMT. COMT and MAO are likely to play a regulatory role for the sympathetic innervation of the plexus.

Cholinergic Innervation

This type of regulation is poorly understood because of technical problems in demonstrating the presence of acetylcholine. Choroid plexuses have

been tested for their ability to accumulate choline and synthesise and release acetylcholine [82]. However, these structures failed to exhibit markers that support the hypothesis of a functional cholinergic innervation. This result shed some doubt upon the contribution of cholinergic systems in the neurogenic regulation of choroid plexus activities.

Peptidergic Innervation

Fibres containing vasoactive intestinal peptide (VIP) have been identified around plexus arteries, in the connective tissue and close to the choroid epithelium [122]. It is interesting to note that the concentration of VIP in the choroid plexus varies in different species: the concentration of VIP nerves is high in pig and rabbit whereas it is low in rat and guinea-pig [164]. The exact site of origin of VIP nerve is not known. VIP-positive fibres are also positive for neuropeptide Y [164]. Receptors for VIP have been found in pig epithelial cells of the choroid plexus [165]. These receptors are of both VIP₁ and VIP₂ types [254]. In vivo, VIP produces a 20% increase in cerebral blood flow [163, 166] and a 30% decrease in CSF synthesis [166]. VIP leads to stimulation of cAMP formation [129]. Furthermore, VIP increases noradrenaline release. All these results indicate that VIP may regulate choroid plexus functions.

Endocrine Regulation

Hydroxytryptamine

Different serotoninergic receptors are expressed by the choroid plexuses: type 1C [276], 2A [137], 2C [34, 136, 185]. However, serotoninergic fibres have not been found in the choroid plexus [184]. A rich plexus made up of serotoninergic fibres originating from the dorsal raphe nucleus ends at the ependymal surface of the ventricles [184]. Nilsson et al. [167] thus propose that serotonin is released in the CSF and acts upon membranous receptors located on epithelial choroid cells. One of its biological effects might be to promote the expression of the gene coding for transferrin [250]. Banks and Kastin [14] postulate an alternative role for serotonin on the choroid plexus. They propose that activation of the 5HT_{1c} receptor is responsible for inhibition of transport of opiate peptides from the CSF, allowing an increase in their concentration.

Melatonin

Melatonin is metabolized from serotonin and secreted by the pineal gland in a diurnal rhythm and acts through an endocrine path. However, there is experimental evidence that melatonin is also directly released in the third ventricle, since melatonin levels in the lateral ventricles are seven-fold lower than those found in the third ventricle [230]. The source of origin of this neural compartment is largely unknown. Melatonin binding sites have been identified in the choroid plexus [235, 272]. These sites are probably G-protein-coupled receptors [235, 272]. In hamsters [48], melatonin has been found to cause cell swelling of the choroid plexus and an increase in mitochondria and in the length of apical microvilli. These changes suggest a stimulatory effect on CSF production.

Atrial Natriuretic and Related Peptides

Atrial natriuretic peptide (ANP) was first isolated from the heart and consists of a polypeptide 28 amino acids long. ANP was subsequently found in brain neurons, where it functions as a neuromediator. Other related peptides have been evidenced in different sites: brain (BNP) and C-type natriuretic peptide (CNP). The three peptides are coded by three different genes. ANP can be found in the epithelial cells of the human choroid plexus by immunohistochemical technique [193]. However, this technique does not help to localize the cells that are actively involved in ANP secretion. Binding sites for ANP are present in the epithelium of the choroid plexus [140, 256]. Three different receptors for these peptides have been isolated: ANPR-A, ANPR-B, and ANPR-C. ANPR-A and B are transmembrane molecules with a guanylate cyclase cytoplasmic domain. They are responsible for the biological effect of ANP. In contrast, ANPR-C is devoid of any guanylate cyclase activity and does not mediate any biological cell activity. This receptor could act as a clearance receptor involved in the inactivation of an excess of ANP. The number of these binding sites is developmentally regulated since it increases after birth and reaches its maximal level post-natally [246]. It is interesting to note that the increase in number of the binding sites parallels the gradual post-natal increase of CSF production seen in rats. ANP might be involved in volume, ion and pressure balance in the brain, hence its action on the choroid plexus represents only one component of its general regulatory activity.

Vasopressin

Arginine vasopressin (AVP) was first isolated from the neurohypophysis. AVP acts on two different classes of receptors: V₁ and V₂. Furthermore, V₁ receptors can be now subdivided into V_{1a} and V_{1b} receptors. Intravenous treatment of rabbits with vasopressin leads to a decrease of the blood flow to the choroid plexus and a decrease in CSF production [64]. These effects are reversed by the addition of V₁-receptor antagonists, suggesting that vasopressin acts exclusively through V₁-mediated signalling [64]. Epithelial cells of the choroid plexus express mRNA coding for V_{1a} receptors [177]. The vasopressin gene is expressed by the cells of the choroid plexus [35, 145]. Consequently, in the choroid plexus, vasopressin acts from two different sources: the blood flow, since the choroid vessels are permeable to vasopressin, and a local source from the plexus itself.

Insulin

Receptors for insulin are present in the choroid plexus, but their functional significance is largely unknown (see [219] for a review).

Glucocorticoid Hormones

These hormones are widely used in neurological and neurosurgical practice because they relieve brain oedema and intracranial hypertension. Treatment of rabbits with betamethasone induces a decrease of CSF formation and a decrease of Na⁺/K⁺-ATPase activity [128, 131]. Since choroid plexus cells express the gene coding for the glucocorticoid receptor [233], a direct action of these hormones could be postulated. Furthermore, glucocorticoids may play a role during development since their receptor is present on the choroid plexus as soon as E13 in rat [108]. Indeed, treatment of chick embryos aged from E13 to E15 with glucocorticoids leads to a reduction of the growth of the choroid plexuses [237]. However, the role of glucocorticoids on plexus cells during fetal development is far from being understood. For example, glucocorticoids display an opposite effect in the chick embryo on γ -glutamyl-transpeptidase activity of the choroid plexus, depending on the embryonic period studied [236].

Sex Steroids

Magnetic resonance imaging studies have shown an increase in the cranial CSF volume in women dur-

ing the premenstrual period. This increase could be caused by sex steroids, but the exact mechanism underlying such a change is still unknown. However, the treatment of rabbits with 17- β -oestradiol induces a discrete increase of Na⁺/K⁺-ATPase activity and choline uptake by the choroid plexus [128]. This effect is strengthened by the co-treatment of rabbits with progesterone [128, 131]. This suggests that oestrogens and progesterone act synergistically to activate the secretion of CSF by the plexuses. Furthermore, the choroid plexuses could be involved in hormonal transport to the CSF. Indeed, choroid plexus cells express a specific carrier involved in the transport of oestrone-3-sulphate that allows this hormone to be transported from blood to CSF [107].

Thyroid Hormones

The nuclear receptor for thyroid hormones (T₃) is expressed by epithelial cells of the choroid plexus [191]. Furthermore T₃ can stimulate the Na⁺/K⁺-ATPase activity of the choroid plexus in the rat and considerably decrease the choline uptake of the plexus [129]. The exact physiological role of thyroid hormones in the control of plexus activity remains to be established.

In conclusion, numerous systems may be involved in the regulation of CSF production by the choroid plexus, suggesting that the regulation is a very complex problem. Little is known about the ontogenesis of these systems and their relevance for CSF regulation during fetal life. A great deal of work will be needed to achieve an understanding of how the regulation comes into play during ontogenesis.

Choroid Plexus as a Source of Signals Targeted to the Brain

Insulin-like Growth Factor II

The insulin gene family represents a group of structurally related polypeptides comprising insulin, relaxin and insulin-like growth factors I and II (IGF-I and IGF-II). IGF-I and IGF-II are required for growth and development [87] since targeted mutations giving rise to null alleles impair embryonic growth in mice [13, 47, 132, 190]. Furthermore, their trophic effects on neural tissues have been demonstrated using cell culture [117]. IGFs are single-chain proteins; IGF-1 is 70 amino acids long and

IGF-II 67 amino acids long. The gene encoding IGF-I is located on chromosome 12 in humans [26, 248]. The gene encoding IGF-II is located on the short arm of chromosome 11 near the genes coding for proto-oncogene c-Ki-ras2 and for insulin [26, 248]. The embryonic expression pattern of IGF-II has been extensively studied in rats: it is highly expressed in epithelial choroid plexus cells as early as E13 [9, 242], that is, as early as choroid plexus differentiation is observed. Its expression is maintained in the plexus throughout adulthood, whereas it is switched off in the other tissues [17, 242]. IGF-II is found in CSF, but direct evidence confirming that IGF-II is secreted by the choroid plexus is lacking. However, the choroid plexuses represent the most likely source of IGF-II in CSF. Since receptors for IGF-II are expressed by cells of the CNS, this growth factor may act upon these cells. Thus, choroid plexus cells could mediate trophic effects on the CNS by secreting IGF-II.

The mode of regulation of the IGF-II gene coding is puzzling. Autosomal genes are present in somatic cells in two different copies (alleles) which are inherited from each parental genome. For the great majority of autosomal genes, both the paternal and maternal alleles are co-expressed in the same cell. Thus, transcribed messenger RNA (mRNA) and translated proteins are of mixed allelic origin. For a small number of autosomal genes, only one allele is transcribed; this phenomenon is known as genomic imprinting. Genomic imprinting explains why embryos produced by the fusion of two male or two female pronuclei never develop. The IGF-II gene is imprinted such that only the paternal allele is expressed in most areas of the body [72, 172]. However, both alleles of the IGF-II gene are concomitantly expressed in a few sets of tissues: the choroid plexuses and leptomeninges and the post-natal liver [171]. One of the best molecular candidates to explain the differential expression of the alleles according to their parental origin is the methylation state of their regulatory sequences. Methylation of CpG islands is normally associated with non-expression of the gene. Furthermore, normal DNA methyltransferase activity is required to control the differential expression of imprinted genes [118, 119]. The problem for IGF-II is more complex since expression of its gene is controlled by four different promoters in man (P1, P2, P3 and P4), and alternate splicing and poly(A) addition sites exist [243, 252]. Furthermore, P2, P3 and P4 control the expression of the paternal allele, whereas P1 acts on both alleles [60]. The latter result could indicate that imprinting of such genes is promoter-dependent. The study of regulation of such events at the molecular level is in progress.

Prolactin

High-affinity prolactin binding sites have been found in the epithelium of the choroid plexus [262]. These sites represent prolactin receptors that are expressed by the epithelial cells of the choroid plexus [28, 187, 203]. It is well known that the prolactin concentration in CSF increases with elevation of the plasma prolactin level [133]. One can infer that the binding sites in the epithelium are related to a saturable transport mechanism allowing the passage of prolactin from blood to CSF. This type of mechanism allows the blood-CSF barrier to be circumvented. This transport property is not functional at birth but has been found on day 14 post-natally in rats [229].

Transthyretin

Transthyretin is a plasma protein involved in the transport of both thyroid hormones (mainly thyroxine, T₄, and to a lesser degree triiodothyronine, T₃) and the retinol-binding globulin/retinol complex. It represents the dominant carrier of T₄ in the CSF [80, 182, 234] and is by far the most abundant plasma protein synthesized by the choroid plexus [55]. Transthyretin produced by choroidal cells is mainly secreted into CSF. Virtually all transthyretin in the CSF originates from the choroid plexus. However, its exact role in CSF is not fully understood. The role of transthyretin seems to be important during phylogenesis. Indeed, the expression of its gene begins in reptiles, coinciding with the first arousal of a cerebral cortex derived from the telencephalic vesicle [218]. Furthermore, during phylogenesis the affinity of transthyretin for T₄ decreases whereas its affinity for T₃ increases [218]. The exact role in the transport of thyroid hormones in the brain has now been established by using a transthyretin-null mouse line [182]. In this mouse, the level of thyroid hormones in the CSF is dramatically reduced whereas the brain level of these hormones is normal. This suggests that other carrier proteins than transthyretin are involved in the control of thyroid hormone access to the brain parenchyma.

Ontogenesis of the Blood-Brain and Blood-CSF Barriers

The Controversy About Blood-Brain Barrier Development

Vascularization of the neural anlage is present at an early stage of development: blood vessels have been

found in chick brain as early as E4 [66] and in rat brain as early as E13 [278]. Molecules circulating in the intravascular space cannot penetrate freely into the brain parenchyma because of the presence of a “cytological barrier”. This barrier has been called the blood-brain barrier. It plays a crucial protective role in limiting the access of blood-borne molecules to the CNS. Numerous studies have been devoted to illuminating the physiological basis of this property. However, since the constituents of mechanisms of the blood-brain barrier are not fully understood, its development is still the subject of controversy [201, 202, 205].

Classic works from Reese and Karnovsky [198] and Brightman and Reese [25] have demonstrated the existence of tight junctions between adjacent endothelial cells. Furthermore, by injecting HRP into the bloodstream, Reese and Karnovsky [198] precisely localized the barrier to endothelial cells. The presence of tight junctions is developmentally regulated, since the first vessels which penetrate the brain parenchyma are fenestrated and progressively become a continuous layer of cells intimately connected by tight junctions. For example, fenestrae dramatically decrease between E13 and E16 in the brain of rat embryos [239, 278]. Furthermore, the disappearance of capillary fenestrae is not an intrinsic capacity of blood vessels but is induced by the surrounding nervous tissue [240]. Developing nervous tissue can also induce the formation of endothelial tight junctions in vessels that do not normally vascularize the CNS [240]. These results definitively establish that the blood-brain barrier is not an intrinsic property of brain capillaries but is induced by nervous tissue. In order to identify the precise cell population responsible for this induction, Janzer and Raff [93] placed astrocyte aggregates into the anterior chamber of the rat eye or onto the chorio-allantoic membrane of the chick embryo. They showed that these aggregates remain unstained after injection of Evan's blue, unlike fibroblast aggregates, which become intensely stained. It was proposed that the blood-brain barrier is induced by astrocytes, and this conclusion was widely accepted. However, the concept of an astrocyte-induced blood-brain barrier was recently challenged by Holash et al. [91]. They grafted astrocytes, fibroblasts and spinal cord into the anterior chamber of the eye or onto the chorio-allantoic membrane. The astrocytes implanted in the eye were poorly vascularized, whereas the fibroblasts were highly vascularized. This suggests that Janzer and Raff's results could be due to a difference in angiogenesis and not to the induction of a barrier. Furthermore, spinal cord grafted into the coelomic cavity promotes both vascular growth and expression of the barrier molecules. In contrast, spinal cord grafted onto the chorio-allantoic

membrane was unable to elicit vascular growth or the expression of molecules specific to the blood-brain barrier. The negative results of chorio-allantoic grafting could be explained by the resultant inflammatory response. In conclusion, the role of astrocytes in the induction of the blood-brain barrier has not yet been fully demonstrated and further studies are required to clarify the situation.

The endothelial cells that vascularize nervous tissue have different histological properties to other endothelial cells. Alkaline phosphatase, cholinesterase, γ -glutamyl transpeptidase and transferrin receptor have been identified in nervous endothelial cells [94, 199, 240]. These histochemical markers are not present when vascularization of the nervous system is first established, but are developmentally regulated, appearing at the same time as the blood-brain barrier [200]. However, the link between these two phenomena could be coincidental.

In order to test directly the time of development of the blood-brain barrier, intravenous injection of HRP has been performed throughout embryogenesis. The results are contradictory, depending both upon the species and the methods used. Wakai and Hirokawa [260] injected HRP in the chick embryo and found that before E12 the enzyme crosses freely from the bloodstream to the brain. From E13 to E15, its passage is progressively restricted, and the blood-brain barrier is fully established from E15 onwards. Wisniewski's group [138, 257] used the same method in mice. They injected 100 μ l of HRP solution into the femoral vein and found that the blood-brain barrier is fully established between post-natal days 12 and 24. In contrast, Risau et al. [199] injected 20-40 μ l of a HRP solution into the mouse embryo. They observed the blood-brain barrier to be progressively established between E13 and E16. These discrepancies between results obtained in the same species could be explained by the difference in the injected volume. However, Møllgård and Saunders [153] consider that HRP injections cannot be used to demonstrate the immaturity of the embryonic blood-brain barrier since the injection itself results in a tremendous increase in the plasma protein concentration. They conclude that the blood-brain barrier is fully established as soon as the embryonic brain vessels develop. I feel that this controversy cannot be resolved by similar experiments. Instead, it is crucial to understand the mechanisms underlying the blood-brain barrier before its presence can be analysed during development. Here, I present two alternative approaches that could resolve these controversies.

The first way to study blood-brain barrier ontogenesis would be to produce antibodies directed selectively against a cellular component of endothelial brain cells. Risau et al. [200] have described HT₇, a

monoclonal antibody produced by immunizing a mouse with chick retina. This antibody selectively recognizes a 74-kDa plasma membrane antigen located on embryonic blood cells, endothelial brain cells and epithelial cells of the proximal tubule of the kidney. Its expression begins at E10 in the chick embryo. If mouse neural tissue is grafted onto the chick chorio-allantoic membrane, the host capillaries which invade the mouse tissue express HT7 antigen. The authors concluded that the protein recognized by this antibody is related to blood-brain barrier functions. Sternberger and Sternberger [238] immunized a mouse with rat brain homogenates. They produced anti-EBA (endothelial-barrier antigen), a monoclonal antibody which selectively stains brain endothelia, the brush border of proximal kidney tubule and bile canaliculi. This monoclonal antibody recognizes a protein triplet of 30, 25 and 23.5 kDa. The functions and the sequences of these proteins are still unknown. By immunizing mouse with chick retina, Schlosshauer and Herzog [208] produced 1W5, a monoclonal antibody directed against a glycoprotein, called neurothelin, expressed by brain endothelial cells and located at their luminal surface. The expression of neurothelin begins on endothelial brain cell at E10 in the chick embryo [207, 208]. Using the same experimental approach as Risau et al. [200], they demonstrated that the expression of neurothelin can be induced by nervous tissue on systemic endothelial cells. Taken as a whole, these results show that brain endothelial cells differ from other endothelial cells at the molecular level. Furthermore, these differences are developmentally regulated, indicating maturation of the blood-brain barrier. These monoclonal antibodies could be used as specific markers for brain vessels. Furthermore, the proteins they recognize could play a pivotal role in the physiology of the blood vessels. Thus, these antibodies may be used to analyse functional proteins in order to decipher the molecular events that are linked to the blood-brain barrier. However, their exact cytological role and their relevance in the establishment of the blood-brain barrier need to be further clarified.

The second approach is to inactivate a single protein whose function is likely to be linked with the blood-brain barrier. Some cancer cells are able to express transporters that can extrude drugs out of the cytoplasm, thus explaining at the molecular level the so-called multidrug resistance phenomenon. At least three families of proteins are involved in such a phenomenon: (i) the three products of the *MDR1* gene that codes for P glycoproteins, which are transmembrane transporters; (ii) the breast cancer resistance protein; and (iii) the multidrug resistance protein (MRP1). Schinkel et al. [206] generated mice homozygous for a disruption of the *mdriα* gene, which en-

codes a drug-transporting glycoprotein. Homozygous mice (*mdriα -/-*) are normal, with normal fertility. Analysis of physiology, anatomy and histology fails to detect any clear abnormalities. However, these mice are dramatically sensitive to drugs such as ivermectin (a centrally neurotoxic pesticide) and vinblastine. These drugs accumulate within brain parenchyma owing to the lack of a blood-brain barrier. To the best of my knowledge, this experiment is the first one definitively to link a molecule to blood-brain barrier function. The gene *mdriα* is expressed by endothelial cells of the embryonic brain as early as E10.5 in the mouse [192]. The expression of this gene increases progressively to reach the adult level at post-natal day 21 (P21) [249]. However, the pattern is different for rats since the homologous gene is only expressed from P7 onwards [144]. It is thus important to test the expression of this gene in different species before drawing conclusions for the problem of blood-brain barrier maturation.

Ontogeny of the Blood-CSF Barrier

The vessels which are present at choroid plexus levels are fenestrated with endothelial cells devoid of tight junctions, unlike vessels found elsewhere in the CNS [148]. However, a barrier exists between blood and CSF at the choroid plexus level. Following intravenous injection of HRP [18], the protein is found in the extracellular space and in cytoplasmic membrane-bound vesicles in choroid epithelial cells. However, no HRP is found in the CSF. Hence, the barrier is present in choroid plexus epithelial cells. As these cells are connected at their apical poles by tight junctions (see [251] for a review), it has been postulated that these intercellular junctions account for the barrier property. However, the problem of the blood-CSF barrier is much more complex. At least two different elementary mechanisms can account for the existence of a barrier between blood and CSF. The first is the above-mentioned physical barrier consisting of intercellular tight junctions that prevent the transfer of molecules between epithelial cells. The second mechanism is a cellular functional barrier. Molecules such as cytochrome c are incorporated into membrane-bound vesicles within the choroid cell cytoplasm and are removed by lysosomal degradation [46, 149]. This second mechanism is an active one lying inside the cell cytoplasm.

As with the blood-brain barrier, the ontogeny of the blood-CSF barrier has been studied using HRP injection. Wakai and Hirokawa [261] demonstrated that, before E9 in the chick embryo, HRP can freely cross the choroid epithelium. Between E9 and E10,

HRP passage from blood to CSF is progressively restricted inasmuch as the barrier is fully established at E10. However, the methodological objections to HRP injections put forward by Møllgård and Saunders [153] still hold for blood-CSF studies.

As previously described, CSF is mainly produced by the choroid plexuses. If one considers that blood and CSF are two compartments separated by a single membrane (the blood-CSF barrier), then comparison of the chemical composition of blood and CSF may help to distinguish the mechanisms of CSF formation. If the two compartments are in equilibrium, one may conclude that CSF is produced by plasma filtration. In contrast, if the two compartments are markedly in disequilibrium, CSF production cannot be due to plasma filtration. The chemical composition of CSF was determined during fetal life in the pig by Flexner [67]. Up to E40, the content of Na^+ , Cl^- and urea in the CSF is in equilibrium with the plasma. However, after E43, these substances are no longer in equilibrium, indicating a change in the mode of CSF formation during this embryonic period. This could be related to a general mechanism of maturation taking place in the choroid plexus. One of the probable explanations for this change is the acquisition of a barrier property. This type of kinetics were confirmed by Birge et al. [19] for the chick embryo. They studied protein concentrations in blood and CSF from E5 to E20. The CSF protein level increases up to E10 and remains stable from E10 to E12. Thereafter, it progressively drops and the normal definitive range is reached at E20. Such an increase in protein levels in CSF was also demonstrated during human [1], sheep [32, 57], and rat fetal life [58, 162, 183]. Some authors conclude from these results that the blood-CSF barrier is not functional during fetal life, accounting for the high CSF protein concentration [1]. This conclusion would be acceptable if the model of an inert barrier separating two compartments is valid. However, the barrier is not an inert membrane but is made up of cells which synthesize and secrete proteins into the CSF. Active protein or mRNA synthesis has been demonstrated in epithelial choroidal cells after [^3H]leucine incubation [59], [^{14}C]leucine incubation [245] and in situ hybridization [152]. Thus, both epithelial choroid and brain cells synthesize plasma proteins during fetal life, accounting for the high concentration of proteins in fetal CSF. In conclusion, there is no concrete experimental evidence to suggest that the blood-CSF barrier is immature during fetal life.

Epithelial cells of the choroid plexus express genes that code for transporters involved in the phenomenon of multidrug resistance such as MDR1 and MRP1 [195, 271]. The blood-CSF barrier is impaired in the triple knock-out mice *Mdr1a* $-/-$, *Mdr1b* $-/-$ and *Mrp1*

$-/-$, whereas it is still functional in the double knock-out mice *Mdr1a* $-/-$, *Mdr1b* $-/-$ [271]. These results show that MDR and MRP proteins play a complementary role in the generation of the blood-CSF barrier.

Reabsorption of the CSF

CSF reabsorption involves different structures in the CNS. Two major pathways allow the drainage of the CSF: arachnoid granulations and villi promote CSF drainage into the dural venous sinuses, while there is an alternative drainage via the cervical lymphatics. The contribution of these two systems is equal in sheep [21, 22, 24] and rat [23]. The absorption of CSF via arachnoid granulations was firmly established by the experiments of Key and Retzius [106] and Weed [264, 268] (see [280] for a historical perspective). However, additional sites of reabsorption have been reported. Mott [154] postulated that the brain capillaries lying in the subarachnoid space could be involved in reabsorption; this was clearly demonstrated by Brightman and Reese [25] and Wagner et al. [259]. It has been shown that CSF may reach lymphatics via leptomeningeal sheaths of cranial and spinal nerves and via adventitia of vessels traversing the subarachnoid space [264]. A further site of CSF reabsorption is the choroid plexuses [68]. Finally, Zenker et al. [280] demonstrated that CSF can directly penetrate dural blood and lymphatic vessels through the arachnoid membrane.

Arachnoid Villi and Granulations: Complex Devices Devoted to CSF Resorption

Arachnoid villi and granulations are protrusions of arachnoid cells which penetrate into the lumen of the superior sagittal sinus and lateral lacunae through small defects in the dura mater. Arachnoid villi are microscopic structures whereas granulations are more prominent and can be observed with the naked eye. The endothelium lining of the dural sinus is continuous with the surface endothelium of the granulation. The endothelium is made up of a continuous sheath of cells closely connected by tight junctions [3, 37, 220, 277]. Are these covering cells true or modified endothelial cells? To the best of my knowledge, this question remains open [277]. In the opinion of the great majority of workers, there is no direct continuity between the CSF and the venous blood of the sinus. The core of arachnoid granulations and villi is formed by arachnoid cells and by subarachnoid space filled with CSF. The morphology of these structures

depends on the existence of a pressure gradient between the subarachnoid space and the lumen of the sinus [75].

Development of Arachnoid Granulations and Villi at the End of Gestation

For obvious reasons, functional studies of CSF reabsorption in the human fetus cannot be performed. Consequently, the maturation of this system during embryonic and fetal life is poorly understood. On the other hand, anatomical, radiological and histological studies have been performed to try to analyse the development and the functions of these structures. First, it is well known that the presence of arachnoid granulations involves the formation of depressions on the inner part of the calvarium [16]. Thus, arachnoid granulations may be indirectly observed on a lateral radiograph of the skull vault since they appeared as impressions on the adjacent inner table of the skull [79]. Using this criterion, Grossman and Potts [79] found no radiological evidence to suggest the presence of arachnoid granulations before 7 years of age; the impressions developed progressively between 7 and 20 years of age [79]. However, the exact morphological correspondence of the radiological depressions is doubtful and, in particular, the arachnoid granulations may be fully developed even in absence of the bony depressions. Consequently, direct observations of arachnoid granulations are needed for a better description of their ontogeny.

A few histological studies have been performed to study the development of these structures in human fetuses. The timing of the first appearance of arachnoid granulations is disputed. Some authors state that arachnoid granulations are never encountered in children [274], while others describe granulations after the 18th post-natal month [116, 279]. What factors can account for these discrepancies? Experimental animal studies have shown that arachnoid villi and granulations are extremely difficult to detect unless the CSF pressure is maintained at a high level during fixation [75, 76]. Hence, the mode of fixation could explain the different results. In recent studies performed on human fetuses from 26 weeks of gestation to birth [73, 74], the development of arachnoid villi and granulations was re-assessed. Oval depressions were present at the surface of the superior sagittal sinus and its tributary veins as early as the 26th week of gestation. This depression is a zone of direct contact between arachnoid and endothelial cells. Typical arachnoid villi were found at the 35th post-menstrual week and arachnoid granulations after the 39th post-menstrual week. These observations indicate that the morpho-

logical devices allowing CSF resorption are present at the end of gestation in humans. However, their functional significance still remains unknown.

References

- Adinolfi M, Beck SE, Haddad SA, et al: Permeability of the blood-cerebrospinal fluid barrier to plasma proteins during foetal and perinatal life. *Nature* 259:140-141, 1976
- Alcolado R, Weller RO, Parrish EP, et al: The cranial arachnoid and pia mater in man: anatomical and ultrastructural observations. *Neuropathol Appl Neurobiol* 14:1-17, 1988
- Alksne JF, Lovings ET: Functional ultrastructure of the arachnoid villus. *Arch Neurol* 27:371-377, 1972
- Allen C, Sievers J, Berry M, et al: Experimental studies on cerebellar foliation. II. A morphometric analysis of cerebellar fissuration defects and growth retardation after neonatal treatment with 6-OHDA in the rat. *J Comp Neurol* 203:771-783, 1981
- Alper SL, Stuart-Tilley A, Simmons CF, et al: The fodrin-ankyrin cytoskeleton of choroid plexus preferentially colocalizes with apical Na⁺K⁺-ATPase rather than with basolateral anion exchanger AE2. *J Clin Invest* 93:1430-1438, 1994
- Alvarez IS, Schoenwolf GC: Expansion of surface epithelium provides the major extrinsic force for bending the neural plate. *J Exp Zool* 261:340-348, 1992
- Angelov DN: Distribution of activity of alkaline phosphatase and Mg-dependent adenosine triphosphatase in the cranial dura mater-arachnoid interface zone of the rat. *Cell Tissue Res* 260: 595-600, 1990
- Ashby W, Butler E: Carbonic anhydrase in the central nervous system of the developing fetus. *J Biol Chem* 175:425-432, 1948
- Ayer-Le Lièvre C, Ståhlbom P-A, Sara VR: Expression of IGF-I and -II mRNA in the brain and craniofacial region of the rat fetus. *Development* 111:105-115, 1991
- Bagnall KM: The migration and distribution of somite cells after labelling with the carbocyanine dye, Dil: the relationship of this distribution to segmentation in the vertebrate body. *Anat Embryol* 185:317-324, 1992
- Bagnall KM, Higgins SJ, Sanders EJ: The contribution made by a single somite to the vertebral column: experimental evidence in support of resegmentation using the quail-chick chimaera model. *Development* 103:69-85, 1988
- Bagnall KM, Higgins SJ, Sanders EJ: The contribution made by cells from a single somite to tissues within a body segment and assessment of their integration with similar cells from adjacent segments. *Development* 107:931-943, 1989
- Baker J, Liu J-P, Robertson EJ, et al: Role of insulin-like growth factors in embryonic and postnatal growth. *Cell* 75:73-82, 1993
- Banks WA, Kastin AJ: Saturable transport of peptides across the blood-brain barrier. *Life Sci* 41:1319-1338, 1987
- Barakat I, Wittendorp-Rechenmann E, Rechenmann RV, et al: Influence of meningeal cells on the proliferation of neuroblasts in culture. *Dev Neurosci* 4:363-372, 1981
- Basmajian JV: The depressions for the arachnoid granulations as a criterion of age. *Anat Rec* 112:843-846, 1952

17. Beck F, Samani NJ, Byrne S, et al: Histochemical localization of IGF-I and IGF-II mRNA in the rat between birth and adulthood. *Development* 104:29-39, 1988
18. Becker NH, Novikoff AB, Zimmerman HM: Fine structure of the uptake of intravenously injected peroxidase by the rat choroid plexus. *J Histochem Cytochem* 15:160-165, 1967
19. Birge WJ, Rose AD, Haywood JR, et al: Development of the blood-cerebrospinal fluid barrier to proteins and differentiation of cerebrospinal in the chick embryo. *Dev Biol* 41:245-254, 1974
20. Born G: Über Verwachsungsversuche mit Amphibienlarven. *Archiv Entwickelungsmechanik der Organismen* 4:349-465 (quoted by Harrison 1908), 1897
21. Boulton M, Flessner M, Armstrong D, et al: Lymphatic drainage of the CNS: effects of lymphatic diversion / ligation on CSF protein transport to plasma. *Am J Physiol* 272:1613-1619, 1997
22. Boulton M, Flessner M, Armstrong D, et al: Determination of volumetric cerebrospinal fluid absorption into extracranial lymphatics in sheep. *Am J Physiol* 274:88-96, 1998
23. Boulton M, Flessner M, Armstrong D, et al: Contribution of extracranial lymphatics and arachnoid villi to the clearance of a CSF tracer in the rat. *Am J Physiol* 276:818-823, 1999
24. Boulton M, Young A, Hay J, et al: Drainage of CSF through lymphatic pathways and arachnoid villi in sheep: measurement of ¹²⁵I-albumin clearance. *Neuropathol Appl Neurobiol* 22: 325-333, 1996
25. Brightman MW, Reese TS: Junctions between intimately apposed cell membranes in the vertebrate brain. *J Cell Biol* 40:648-677, 1969
26. Brissenden JE, Ullrich A, Francke U: Human chromosomal mapping of genes for insulin-like growth factors I and II and epidermal growth factor. *Nature* 310:781-784, 1984
27. Brocklehurst G: The development of the human cerebrospinal fluid pathway with particular reference to the roof of the fourth ventricle. *J Anat* 105:467-475, 1969
28. Brooks PJ, Funabashi T, Kleopoulos SP, et al: Prolactin receptor messenger RNA is synthesized by the epithelial cells of the choroid plexus. *Mol Brain Res* 16:163-167, 1992
29. Cam Y, Sensenbrenner M, Mandel P: A comparative study of the effects of brain extracts and mesodermal membrane extracts on nerve cell differentiation. *Experientia* 31:1430-1431, 1975
30. Catala M: Carbonic anhydrase activity during development of the choroid plexus in the human fetus. *Childs Nerv Syst* 13:364-368, 1997
31. Catala M: Embryonic and fetal development of structures associated with the cerebro-spinal fluid in man and other species. Part I: the ventricular system, meninges and choroid plexuses. *Arch Anat Cytol Pathol* 46:153-169, 1998
32. Cavanagh ME, Cornelis MEP, Dziegielewska KM, et al: Comparison of proteins in CSF of lateral and IVth ventricles during early development of fetal sheep. *Dev Brain Res* 11:159-167, 1983
33. Chamberlain JG: Analysis of developing ependymal and choroidal surfaces in rat brains using scanning electron microscopy. *Dev Biol* 31:22-30, 1973
34. Chang M, Zhang L, Tam JP, et al: Dissecting G protein-coupled receptor signalling pathways with membrane-permeable blocking peptides. *Endogenous 5-HT(2C) receptors in the choroids plexus epithelial cells. J Biol Chem* 275:7021-7029, 2000
35. Chodobski A, Wojcik BE, Loh YP, et al: Vasopressin gene expression in rat choroid plexus. *Adv Exp Med Biol* 449:59-65, 1998
36. Cohen LA: Absence of a foramen of Magendie in the dog, cat, rabbit and goat. *Arch Neurol* 16: 524-528, 1967
37. Cooper ERA: Arachnoid granulations in man. *Acta Anat (Basel)* 34:187-200, 1958
38. Coulombre AJ, Coulombre JL: The role of mechanical factors in brain morphogenesis. *Anat Rec* 130:289-290, 1958
39. Couly G: Concepts nouveaux de la biologie du développement céphalique humain, observations et hypothèses. *Ann Genet* 25:201-206, 1982
40. Couly G: Concepts nouveaux de la biologie du développement céphalique humain, observations et hypothèses. *Semin Hop Paris* 59:1699-1704, 1983
41. Couly GF, Coltey PM, Eichmann A, et al: The angiogenic potentials of the cephalic mesoderm and the origin of brain and head blood vessels. *Mech Dev* 53:97-112, 1995
42. Couly GF, Coltey PM, Le Douarin NM: The developmental fate of the cephalic mesoderm in quail-chick chimeras. *Development* 114:1-15, 1992
43. Couly GF, Le Douarin NM: Mapping of the early neural primordium in quail-chick chimeras. II. The prosencephalic neural plate and neural folds: implications for the genesis of cephalic human congenital abnormalities. *Dev Biol* 120:198-214, 1987
44. Dandy WE: Experimental hydrocephalus. *Ann Surg* 70:129-142, 1919
45. Dandy WE, Blackfan KD: Internal hydrocephalus. An experimental, clinical and pathological study. *Am J Dis Child* 8:406-482, 1914
46. Davis DA, Milhorat TH: The blood-brain barrier of the rat choroid plexus. *Anat Rec* 181:779-790, 1975
47. De Chiara TM, Efstratiadis A, Robertson EJ: A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. *Nature* 345:78-80, 1990
48. Decker JF, Quay WB: Stimulatory effects of melatonin on ependymal epithelium of choroid plexuses in golden hamsters. *J Neural Transm* 55:53-67, 1982
49. Desmond ME: Description of the occlusion of the spinal cord lumen in early human embryos. *Anat Rec* 204:89-93, 1982
50. Desmond ME: Reduces number of brain cells in so-called neural overgrowth. *Anat Rec* 212: 195-198, 1985
51. Desmond ME, Duzy MJ, Federici BD: Second messenger regulation of occlusion of the spinal neurocoel in the chick embryo. *Dev Dyn* 197:291-306, 1993
52. Desmond ME, Jacobson AG: Embryonic brain enlargement requires cerebrospinal fluid pressure. *Dev Biol* 57:188-198, 1977
53. Desmond ME, Schoenwolf GC: Timing and positioning of occlusion of the spinal neurocoel in the chick embryo. *J Comp Neurol* 235:479-487, 1985
54. Desmond ME, Schoenwolf GC: Evaluation of the roles of intrinsic and extrinsic factors in occlusion of the spinal neurocoel during rapid brain enlargement in the chick embryo. *J Embryol Exp Morphol* 97:25-46, 1986
55. Dickson PW, Aldred AR, Marley PD, et al: Rat choroid plexus specializes in the synthesis and the secretion of transthyretin (prealbumin). Regulation of transthyretin

- synthesis in choroid plexus is independent from that in liver. *J Biol Chem* 261:3475-3478, 1986
56. Dontchev N, Hadjioloff A-I: Histogénèse et histochimie du plexus choroïde du télencéphale chez l'embryon humain. *Bull Assoc Anat* 146:480-485, 1971
57. Dziegielewska KM, Evans CAN, Fossan G, et al: Proteins in CSF and plasma of fetal sheep during development. *J Physiol* 300:441-455, 1980
58. Dziegielewska KM, Evans CAN, Lai PCW, et al: Proteins in cerebrospinal fluid and plasma of fetal rats during development. *Dev Biol* 83:193-200, 1981
59. Dziegielewska KM, Evans CAN, New H, et al: Synthesis of plasma proteins by rat fetal brain and choroid plexus. *Int J Dev Neurosci* 2:215-222, 1984
60. Ekström TJ, Cui H, Li X, et al: Promoter-specific IGF2 imprinting status and its plasticity during human liver development. *Development* 121:309-316, 1995
61. el-Gammal S: The development of the diencephalic choroid plexus in the chick, a scanning electron-microscopic study. *Cell Tissue Res* 219:297-311, 1981
62. el-Gammal S: Regional surface changes during the development of the telencephalic choroid plexus in the chick, a scanning-electron microscopic study. *Cell Tissue Res* 231:251-263, 1983
63. Ernst SA, Palacios JR, Siegel GJ: Immunocytochemical localization of Na⁺, K⁺-ATPase catalytic polypeptide in mouse choroid plexus. *J Histochem Cytochem* 34:189-195, 1986
64. Faraci FM, Mayhan WG, Heistad DD: Effect of vasopressin on production of cerebrospinal fluid: possible role of vasopressin (V1)-receptors. *Am J Physiol* 258 (1Pt2):94-98, 1990
65. Fawcett DW: Bloom and Fawcett, a Textbook of Histology, 12th edn. Chapman and Hall. New York, 1994
66. Feeney JF, Watterson RL: The development of the vascular pattern within the walls of the central nervous system of the chick embryo. *J Morphol* 78:231-303, 1946
67. Flexner LB: Changes in the chemistry and nature of the cerebrospinal fluid during fetal life in the pig. *Am J Physiol* 124:131-135, 1938
68. Foley F: Resorption of the cerebrospinal fluid by the choroid plexuses under the influence of intravenous injection of hypertonic salt solutions. *Arch Neurol Psychiatry* 5:744-745, 1921
69. Frazier CH, Peet MM: Factors of influence in the origin and circulation of the cerebrospinal fluid. *Am J Physiol* 35:268-282, 1914
70. Gensburger C, Labourdette G, Sensenbrenner M: Influence of meningeal cells on the proliferation and maturation of rat neuroblasts in culture. *Exp Brain Res* 63:321-330, 1986
71. Ghadour MS, Langley OK, Zhu XL, et al: Carbonic anhydrase IV on brain capillary endothelial cells: a marker associated with the blood-brain barrier. *Proc Natl Acad Sci USA* 89: 6823-6827, 1992
72. Giannoukakis N, Deal C, Paquette J, et al: Parental genomic imprinting of the human IGF2 gene. *Nature Genet* 4: 98-101, 1993
73. Gomez DG, Di Benedetto AT, Pavese AM, et al: Development of arachnoid villi and granulations in man. *Acta Anat* 111:247-258, 1981
74. Gomez DG, Ehrmann JE, Gordon-Potts D, et al: The arachnoid granulations of the newborn human: an ultrastructural study. *Int J Dev Neurosci* 1:138-147, 1983
75. Gomez DG, Potts G: The surface characteristics of arachnoid granulations. A scanning electron microscopical study. *Arch Neurol* 31:88-93, 1974
76. Gomez DG, Potts G, Deonarine V, et al: Effects of pressure gradient changes on the morphology of arachnoid villi and granulations of the monkey. *Lab Invest* 28:648-657, 1973
77. Gonzalez-Martinez LM, Avila J, Martí E, et al: Expression of the b-subunit isoforms of the Na, K-ATPase in rat embryo tissues, inner ear and choroid plexus. *Biol Cell* 81:215-222, 1994
78. Grasset P-P: Traité de Zoologie. Tome XI. Les procordés. Masson, Paris 1948
79. Grossman CB, Potts DG: Arachnoid granulations: radiology and anatomy. *Radiology* 113:95-100, 1974
80. Hagen GA, Elliott WJ: Transport of thyroid hormones in serum and cerebrospinal fluid. *J Clin Endocrinol Metab* 37:415-422, 1973
81. Halata Z, Grim M, Christ B: Origin of spinal cord meninges, sheaths of peripheral nerves, and cutaneous receptors including Merkel cells. An experimental and ultrastructural study with avian chimeras. *Anat Embryol* 182:529-537, 1990
82. Hamel E, Assumel Lurdin C, Fage D, et al: Small pial vessels, but not choroid plexus, exhibit specific biochemical correlates of functional cholinergic innervation. *Brain Res* 516:301-309, 1990
83. Harrison RG: Embryonic transplantation and the development of the nervous system. *Anat Rec* 2:385-410, 1908
84. Hartmann D, Sievers J, Pehleemann FW, et al: Destruction of meningeal cells over the medial cerebral hemisphere of newborn hamsters prevents the formation of the infrapyramidal blade of the dentate gyrus. *J Comp Neurol* 320:33-61, 1992
85. Hartmann D, Schulze M, Sievers J: Meningeal cells stimulate and direct the migration of cerebellar external granule cells in vitro. *J Neurocytol* 27:395-409, 1998 a
86. Hartmann D, Ziegenhagen MW, Sievers J: Meningeal cells stimulate neuronal migration and the formation of radial glial fascicles from the cerebellar external granular layer. *Neurosci Lett* 244: 129-132, 1998 b
87. Harvey MB, Kaye PL: IGF-2 stimulates growth and metabolism of early mouse embryos. *Mech Dev* 38:169-174, 1992
88. Harvey SC, Burr HS: An experimental study of the origin of the meninges. *Proc Soc Exp Biol Med* 22:52-53, 1924
89. Harvey SC, Burr HS: The development of the meninges. *Arch Neurol Psychiatry* 15:545-567, 1926
90. Haywood JR, Vogh BP: Some measurements of autonomic nervous system influence on production of cerebrospinal fluid in the cat. *J Pharmacol Exp Ther* 208:341-346, 1979
91. Holash JA, Noden DM, Stewart PA: Re-evaluating the role of astrocytes in blood-brain barrier induction. *Dev Dyn* 197:14-25, 1993
92. Jacobsen M, Møllgård K, Reynolds ML, et al: The choroid plexus in fetal sheep during development with special reference to intracellular plasma protein. *Dev Brain Res* 8:77-88, 1983
93. Janzer RC, Raff MC: Astrocytes induce blood-brain barrier properties in endothelial cells. *Nature* 325: 253-257, 1987
94. Jefferies WA, Brandon MR, Hunt SV, et al: Transferrin receptor on endothelium of brain capillaries. *Nature* 312:62-163, 1984

95. Jelínek R, Pexieder T: Pressure of the CSF and the morphogenesis of the CNS. *Folia Morphol (Praha)* 18:102-110, 1970
96. Johnston MC: A radioautographic study of the migration and fate of cranial neural crest cells in the chick embryo. *Anat Rec* 156:143-156, 1966
97. Jones HC: Continuity between the ventricular and subarachnoid cerebrospinal fluid in an amphibian, *Rana pipiens*. *Cell Tissue Res* 195:153-167, 1978
98. Jones HC: The ultrastructure of the roof of the rhombencephalic posterior tela and adjacent tissues in an amphibian, *Rana pipiens*. *J Anat* 134:91-102, 1982
99. Jones HC, Dolman GS: The structure of the roof of the fourth ventricle in pigeon and chick brains by light and electron microscopy. *J Anat* 128: 13-39, 1979
100. Jones HC, Jopling CA: The development of interependymal pores in the rhombencephalic posterior tela in late embryonic, larval and metamorphosing stages of *Rana pipiens*. *Brain Res* 283:121-130, 1983
101. Jones HC, Sellars RA: The movement of fluid out of the cerebral ventricles in fetal and neonatal rats. *Z Kinderchir* 37:130-133, 1982
102. Junghans U, Koops A, Westmeyer A, et al: Purification of a meningeal cell-derived chondroitin sulphate proteoglycan with neurotrophic activity for brain neurons and its identification as biglycan. *Eur J Neurosci* 7:2341-2350, 1995
103. Kamiryo T, Orita T, Nishizaki T, et al: Development of the rat meninx: experimental study using bromodeoxyuridine. *Anat Rec* 227:207-210, 1990
104. Kaplan GP, Hartman BK, Creveling CR: Localization of catechol-O-methyltransferase in the leptomeninges, choroid plexus and ciliary epithelium: implications for the separation of central and peripheral catechols. *Brain Res* 204:353-360, 1981
105. Kaufman MH: Occlusion of the neural lumen in early mouse embryos analysed by light and electron microscopy. *J Embryol Exp Morphol* 78:211-228, 1983
106. Key EAH, Retzius MG: Studien in der Anatomie des Nervensystems und des Bindegewebes. Samson and Wallin. Stockholm. (Quoted by Zenker et al. 1994), 1875
107. Kitazawa T, Hosoya K, Takahashi T, et al: In-vivo and in-vitro evidence of a carrier-mediated afflux transport system for oestrone-3-sulphate across the blood-cerebrospinal fluid barrier. *J Pharm Pharmacol* 52:281-288, 2000
108. Kitraki E, Alexis MN, Papalopoulou M, et al: Glucocorticoid receptor gene expression in the embryonic rat brain. *Neuroendocrinology* 63:305-317, 1996
109. Klika E: L'ultrastructure des méninges en ontogénèse chez l'homme. *Z Mikrosk Anat Forsch* 79:209-222, 1968
110. Krisch B, Leonhardt H, Oksche A: The meningeal compartments of the median eminence and the cortex. A comparative analysis in the rat. *Cell Tissue Res* 228:597-640, 1983
111. Krisch B, Leonhardt H, Oksche A: Compartments and perivascular arrangement of the meninges covering the cerebral cortex of the rat. *Cell Tissue Res* 238:459-474, 1984
112. Kuhlenbeck H. The central nervous system of vertebrates. Volume 3 part 1: Structural elements: biology of nervous tissue. Karger, Basel, 1970
113. Kusaka H, Hirano A, Bornstein MB, et al: The organization of astrocytes in organotypic mouse spinal cord culture: an electron microscope study. *Neuropathol Appl Neurobiol* 10:411-422, 1984
114. Kusaka H, Hirano A, Bornstein MB, et al: Basal lamina formation by astrocytes in organotypic cultures of mouse spinal cord tissue. *J Neuropath Exp Neurol* 44:295-303, 1985
115. Le Douarin NM: Particularités du noyau interphasique chez la Caille japonaise (*Coturnix coturnix japonica*). Utilisation de ces particularités comme "marquage biologique" dans les recherches sur les interactions tissulaires et les migrations cellulaires au cours de l'ontogénèse. *Bull Biol Fr Belg* 103: 435-452, 1969
116. Le Gros Clark WE: On the Pacchionian bodies. *J Anat* 55:40-48, 1920
117. Lenoir D, Honegger P: Insulin-like growth factor I (IGF I) stimulates DNA synthesis in fetal rat brain cell cultures. *Dev Brain Res* 7:205-213, 1983
118. Li E, Beard C, Jaenisch R: Role for DNA methylation in genomic imprinting. *Nature* 366:362-365, 1993
119. Li E, Bestor TH, Jaenisch R: Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. *Cell* 69:915-926, 1992
120. Lindvall M: Fluorescence histochemical study on regional differences in the sympathetic nerve supply from various laboratory animals. *Cell Tissue Res* 198:261-267, 1979
121. Lindvall M, Alumets J, Edvinsson L, et al: Peptidergic (VIP) nerves in the mammalian choroid plexus. *Neurosci Lett* 9:77-82, 1978
122. Lindvall M, Edvinsson L, Owman C: Sympathetic nervous control of cerebrospinal fluid production from the choroid plexus. *Science* 201:176-178, 1978
123. Lindvall M, Edvinsson L, Owman C: Effects of sympathomimetic drugs and corresponding receptor antagonists on the rate of cerebrospinal fluid production. *Exp Neurol* 64:132-145, 1979
124. Lindvall M, Gustafson A, Hedner P, et al: Stimulation of cyclic adenosine 3',5'-monophosphate formation in rabbit choroid plexus by b-receptor agonists and vasoactive intestinal polypeptide. *Neurosci Lett* 54:153-157, 1985
125. Lindvall M, Owman C: Evidence for the presence of two types of monoamine oxidase in rabbit choroid plexus and their role in breakdown of amines influencing cerebrospinal fluid formation. *J Neurochem* 34:518-522, 1980
126. Lindvall M, Owman C, Winbladh B: Sympathetic influence on transport functions in the choroid plexus of rabbit and rat. *Brain Res* 223:160-164, 1981
127. Lindvall M, Owman C, Winbladh B: Sympathetic influence on sodium-potassium activated adenosine triphosphatase activity of rabbit and rat choroid plexus. *Brain Res Bull* 9:761-763, 1982
128. Lindvall-Axelsson M, Hedner P, Owman C: Corticosteroid action on choroids plexus: reduction in Na⁺ - K⁺-ATPase activity, choline transport capacity, and rate of CSF formation. *Exp Brain Res* 77: 605-610, 1989
129. Lindvall-Axelsson M, Hedner P, Owman C, et al: Influence of thyroid hormones on transport function and Na⁺-K⁺-ATPase activity in the rat choroid plexus. *Acta Physiol Scand* 125:627-632, 1985
130. Lindvall-Axelsson M, Owman C: Changes in transport functions of isolated rabbit choroid plexus under the influence of oestrogen and progesterone. *Acta Physiol Scand* 136:107-111, 1989

131. Lindvall-Axelsson M, Owman C: Actions of sex steroids and corticosteroids on rabbit choroid plexus as shown by changes in transport capacity and rate of cerebrospinal fluid formation. *Neurol Res* 12:181-186, 1990
132. Liu J-P, Baker J, Perkins AS, et al: Mice carrying null mutations of the genes encoding insulin-like growth factor I (Igf-1) and type 1 IGF receptor (Igfr). *Cell* 75:59-72, 1993
133. Login IS, Mac Leod RM: Prolactin in human serum and cerebrospinal fluid. *Brain Res* 132: 477-483, 1977
134. Lopes CAS, Mair WGP: Ultrastructure of the outer cortex and the pia mater in man. *Acta Neuropathol (Berl)* 28:79-86, 1974 a
135. Lopes CAS, Mair WGP: Ultrastructure of the arachnoid structure in man. *Acta Neuropathol (Berl)* 28:167-173, 1974 b
136. Lopez-Gimenez JF, Mengod D, Palacios JM, et al: Regional distribution and cellular localization of 5-HT_{2C} receptor mRNA in monkey brain: comparison with [³H] mesulergine binding site and choline acetyltransferase mRNA. *Synapse* 42:12-26, 2001 a
137. Lopez-Gimenez JF, Vilardo MT, Palacios JM, et al: Mapping of 5-HT_{2A} receptors and their mRNA in monkey brain: [³H] MD₂ 100, 907 autoradiography and in situ hybridization studies. *J Comp Neurol* 429:571-598, 2001 b
138. Lossinsky AS, Vorbrot AW, Wisniewski HM: Characterization of endothelial cell transport in the developing mouse blood-brain barrier. *Dev Neurosci* 8:61-75, 1986
139. Maars JA, Napolitano EW, Murphy-Erdosh C, et al: Distinguishing roles of the membrane-cytoskeleton and cadherin mediated cell-cell adhesion in generating different Na⁺, K⁺-ATPase distributions in polarized epithelia. *J Cell Biol* 123:149-164, 1993
140. Mantyth CR, Kruger L, Brecha NC, et al: Localization of specific sites for atrial natriuretic factor in the central nervous system of rat, guinea pig, cat and human. *Brain Res* 412:329-342, 1987
141. Masuzawa T, Ohta T, Kawamura M, et al: Immunohistochemical localization of Na⁺, K⁺-ATPase in the choroid plexus. *Brain Res* 302:357-362, 1984
142. Masuzawa T, Ohta T, Kawakami K, et al: Immunocytochemical localization of Na⁺, K⁺-ATPase in the canine choroid plexus. *Brain* 108:625-646, 1985
143. Masuzawa T, Sato F: The enzyme histochemistry of the choroid plexus. *Brain* 106:55-99, 1983
144. Matsuoka Y, Okazaki M, Kitamura Y, et al: Developmental expression of P-glycoprotein (multidrug resistance gene product) in the rat brain. *J Neurobiol* 39:383-392, 1999
145. Matthews SG, Parrott RF, Sirinathsinghji DJ: Distribution and cellular localization of vasopressin mRNA in the ovine brain, pituitary and pineal glands. *Neuropeptides* 25:11-17, 1993
146. Matthiessen HP, Schmalenbach C, Müller HW: Identification of meningeal cell released neurite promoting activities for embryonic hippocampal neurons. *J Neurochem* 56:759-768, 1991
147. Milhorat TH: Choroid plexus and cerebrospinal fluid production. *Science* 166:1514-1516, 1969
148. Milhorat TH: Structure and function of the choroid plexus and other sites of cerebrospinal fluid formation. *Int Rev Cytol* 47:225-288, 1976
149. Milhorat TH, Davis DA, Lloyd BJ: Two morphologically distinct blood-brain barriers preventing entry of cytochrome c into cerebrospinal fluid. *Science* 180:76-78, 1973
150. Milhorat TH, Hammock MK, Fenstermacher JD, et al: Cerebrospinal fluid production by the choroid plexus and brain. *Science* 173:330-332, 1971
151. Mitchell W, Kim CS, O'Tuama LA, et al: Choroid plexus, brain and kidney Na⁺,K⁺-ATPase: comparative activities in fetal, newborn and young adult rabbits. *Neurosci Lett* 31:37-40, 1982
152. Møllgård K, Dziegielewska KM, Saunders NR, et al: Synthesis and localization of plasma proteins in the developing human brain. Integrity of the fetal blood-brain barrier to endogenous proteins of hepatic origin. *Dev Biol* 128:207-221, 1988
153. Møllgård K, Saunders NR: The development of the human blood-brain and blood-CSF barriers. *Neuropathol Applied Neurobiol* 12:337-358, 1986
154. Mott FW: The Oliver-Sharpey lectures on the cerebrospinal fluid. Lecture I: the physiology of the cerebrospinal fluid. *Lancet* ii 1-8, 1910
155. Müller F, O'Rahilly R: The development of the human brain and the closure of the rostral neuropore at stage 11. *Anat Embryol* 175:205-222, 1986
156. Müller F, O'Rahilly R: The development of the human brain, the closure of the caudal neuropore, and the beginning of secondary neurulation at stage 12. *Anat Embryol* 176:413-430, 1987
157. Müller F, O'Rahilly R: The human brain at stages 18-20, including the choroid plexuses and the amygdaloid and septal nuclei. *Anat Embryol* 182:285-306, 1990
158. Murakami M: An electron microscopic study of the choroid plexus in the lizard, *Gecko japonicus*. *J Electron-microsc* 10:77-86, 1961
159. Nabeshima S, Reese TS, Landis DMD, et al: Junctions in the meninges and marginal glia. *J Comp Neurol* 164:127-170, 1975
160. Nathanson JA: b-adrenergic-sensitive adenylate cyclase in secretory cells of choroid plexus. *Science* 204:843-844, 1979
161. Nelson E, Blinzing K, Hager H: Electron microscopic observations on subarachnoid and perivascular spaces of the Syrian hamster brain. *Neurology* 11:285-295, 1961
162. New H, Dziegielewska KM, Saunders NR: Transferrin in fetal rat brain and cerebrospinal fluid. *Int J Dev Neurosci* 1:396-373, 1983
163. Nilsson C, Billa SF: Vasoactive intestinal polypeptide (VIP): effects in the eye and on regional blood flow. *Acta Physiol Scand* 121:385-392, 1984
164. Nilsson C, Ekman R, Lindvall-Axelsson M, et al: Distribution of peptidergic nerves in the choroid plexus, focusing on coexistence of neuropeptide Y, vasoactive intestinal polypeptide and peptide histidine isoleucine. *Regul Pept* 27:11-26, 1990
165. Nilsson C, Fahrenkrug J, Lindvall-Axelsson M, et al: Epithelial cells purified from choroid plexus have receptors for vasoactive intestinal polypeptide. *Brain Res* 542:241-247, 1991 a
166. Nilsson C, Lindvall-Axelsson M, Owman C: Simultaneous and continuous measurement of choroid plexus blood flow and cerebrospinal fluid production. Effects of vasoactive intestinal polypeptide. *J Cereb Blood Flow Metab* 11:861-867, 1991 b
167. Nilsson C, Lindvall-Axelsson M, Owman C: Neuroendocrine regulatory mechanisms in the choroid plexus-cerebrospinal fluid system. *Brain Res Rev* 17:109-138, 1992

168. Nógrádi A, Kelly C, Carter ND: Localization of acetazolamide-resistant carbonic anhydrase III in human and rat choroid plexus by immunocytochemistry and in situ hybridisation. *Neurosci Lett* 151:162-165, 1993
169. Oda Y, Nakanishi I: Ultrastructure of the mouse leptomeninges. *J Comp Neurol* 225:448-457, 1984
170. Oda Y, Nakanishi I: Ultrastructure of the caudal portion of the fourth ventricular roof in the mouse. *J Comp Neurol* 256:299-307, 1987
171. Ohlsson R, Hedborg F, Holmgren L, et al: Overlapping patterns of IGF2 and H19 expression during human development: biallelic IGF2 expression correlates with a lack of H19 expression. *Development* 120:361-368, 1994
172. Ohlsson R, Nyström A, Pfeifer-Ohlsson S, et al: IGF2 is parentally imprinted during human embryogenesis and in the Beckwith-Wiedemann syndrome. *Nature Genet* 4:94-97, 1993
173. O'Rahilly R, Müller F, Hutchins GM, et al: Computer ranking of the sequence of appearance of 73 features of the brain and related structures in staged human embryos during the sixth week of development. *Am J Anat* 180:69-86, 1987
174. O'Rahilly R, Müller F, Hutchins GM, et al: Computer ranking of the sequence of appearance of 40 features of the brain and related structures in staged human embryos during the seventh week of development. *Am J Anat* 182:295-317, 1988
175. O'Rahilly R, Müller F: Ventricular system and choroid plexuses of the human brain during the embryonic period proper. *Am J Anat* 189:285-302, 1990
176. Osaka K, Handa H, Matsumoto S, et al: Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. *Childs Brain* 6:26-38, 1980
177. Ostrowski NL, Lolait SJ, Young WS: Cellular localization of vasopressin V1a receptor messenger ribonucleic acid in adult male rat brain, pineal, and brain vasculature. *Endocrinology* 135:1511-1528, 1994
178. Osumi-Yamashita N, Ninomiya Y, Doi H, et al: The contribution of both forebrain and midbrain crest cells to the mesenchyme in the frontonasal mass of mouse embryos. *Dev Biol* 164:409-419, 1994
179. Otani H, Tanaka O: Development of the choroid plexus anlage and supraependymal structures in the fourth ventricular roof plate of human embryos: scanning electron microscopic observations. *Am J Anat* 181:53-66, 1988
180. Pacheco MA, Marks RW, Schoenwolf GC, et al: Quantification of the initial phases of rapid brain enlargement in the chick embryo. *Am J Anat* 175:403-411, 1986
181. Palay SL, Chan-Palay V: Cerebellar cortex. Cytology and organization. Springer, New York, 1974.
182. Palha JA, Fernandes R, de Escobar GM, et al: Transthyretin regulates thyroid hormone levels in the choroid plexus, but not in the brain parenchyma: study in a transthyretin-null mouse model. *Endocrinology* 141:3267-3272, 2000
183. Panrucker DE, Dziegielewska KM, Lorscheider FL, et al: Acute-phase a2-macroglobulin in CSF during development of the fetal rat. *Int J Dev Neurosci* 1:31-34, 1983
184. Paspalas CD, Papadopoulos GC, Michaloudi H: Serotonergic supraependymal plexus in the ventricular system of the hedgehog: organization principles and functional implications. *J Hirnforsch* 35:333-342, 1994
185. Pasqualetti M, Ori M, Castagna M, et al: Distribution and cellular localization of the serotonin type 2C receptor messenger mRNA in human brain. *Neuroscience* 92:601-611, 1999
186. Pehlemann FW, Sievers J, Berry M: Meningeal cells are involved in foliation, lamination, and neurogenesis of the cerebellum: evidence from 6-hydroxydopamine-induced destruction of meningeal cells. *Dev Biol* 110:136-146, 1985
187. Pi X, Voogt JL, Grattam DR: Detection of prolactin receptor mRNA in the corpus striatum and substantia nigra of the rat. *J Neurosci Res* 67:551-558, 2002
188. Platt JB: Ectodermic origin of the cartilages of the head. *Anat Anz* 8:506-509, 1893
189. Platt JB: The development of the cartilaginous skull and of the branchial and hypoglossal musculature in *Necturus*. *Morphol Jahrb* 25:375-465, 1898
190. Powell-Braxton L, Hollingshead P, Warburton C, et al: IGF-I is required for normal embryonic growth in mice. *Genes Dev* 7:2609-2617, 1993
191. Puymirat J, Miehle M, Marchand R, et al: Immunocytochemical localization of thyroid hormone receptors in the adult rat brain. *Thyroid* 1:173-184, 1991
192. Qin Y, Sato TN: Mouse multidrug resistance 1a/3 gene is the earliest known endothelial cell differentiation marker during blood-brain barrier development. *Dev Dyn* 202:172-180, 1995
193. Raiddo DM, Narotam PK, van Dellen J, et al: Cellular orientation of atrial natriuretic peptide in the human brain. *J Chem Neuroanat* 14:207-213, 1998
194. Ramsey HJ: Fine structure of the surface of the cerebral cortex of human brain. *J Cell Biol* 26: 323-333, 1965
195. Rao VV, Dahlheimer JL, Bardgett ME, et al: Choroid plexus epithelial expression of MDR1 P-glycoprotein and multidrug resistance-associated protein contribute to the blood-cerebrospinal-fluid drug-permeability barrier. *Proc Natl Acad Sci USA* 96:3900-3905, 1999
196. Rascol M, Izard J: The subdural neurothelium of the cranial meninges in rat. *Anat Rec* 186: 429-436, 1976
197. Rascol M, Izard J: Arachnoidea and subarachnoid spaces of the vault of the skull in man. *Acta Neuropathol (Berl)* 41:41-44, 1978
198. Reese TS, Karnovsky MJ: Fine structural localization of a blood-brain barrier to exogenous peroxidase. *J Cell Biol* 34:207-217, 1967
199. Risau W, Hallmann R, Albrecht U: Differentiation-dependent expression of proteins in brain endothelium during development of the blood-brain barrier. *Dev Biol* 117:537-545, 1986 a
200. Risau W, Hallmann R, Albrecht U, et al: Brain induces the expression of an early cell surface marker for blood-brain barrier-specific endothelium. *EMBO J* 5:3179-3183, 1986 b
201. Risau W, Wolburg H: Development of the blood-brain barrier. *Trends Neurosci* 13:174-178, 1990
202. Risau W, Wolburg H: Reply. *Trends Neurosci* 14:15, 1991
203. Roky R, Paut-Pagano L, Goffin V, et al: Distribution of prolactin receptors in the rat forebrain. Immunohistochemical study. *Neuroendocrinology* 63:422-429, 1996
204. Roussel G, Delaunoy J-P, Nussbaum J-L, et al: Demonstration of a specific localization of carbonic anhydrase C in the glial cells of rat CNS by an immunohistochemical method. *Brain Res* 160:47-55, 1979

205. Saunders NR, Dziegielewska KM, Møllgård K: The importance of the blood-brain barrier in fetuses and embryos. *Trends Neurosci* 14:14, 1991
206. Schinkel AH, Smit JJM, Van Tellingen O, et al: Disruption of the mouse mdr 1a P-glycoprotein gene leads to a deficiency in the blood-brain barrier and to increased sensitivity to drugs. *Cell* 77: 491-502, 1994
207. Schlosshauer B: Neurothelin: molecular characteristics and developmental regulation in the chick CNS. *Development* 113:129-140, 1991
208. Schlosshauer B, Herzog K-H: Neurothelin: an inducible cell surface glycoprotein of blood-brain barrier-specific endothelial cells and distinct neurons. *J Cell Biol* 110:1261-1274, 1990
209. Schoenwolf GC: Shaping and bending of the avian neuroepithelium: morphometric analyses. *Dev Biol* 109: 127-139, 1985
210. Schoenwolf GC: Microsurgical analyses of avian neurulation: separation of medial and lateral tissues. *J Comp Neurol* 276: 498-507, 1988
211. Schoenwolf GC: Cell movements during neurulation in avian embryos. *Development* S2: 157-168, 1991
212. Schoenwolf GC, Alvarez IS: Roles of neuroepithelial cell rearrangement and division in shaping of the avian neural plate. *Development* 106:427-439, 1989
213. Schoenwolf GC, Desmond ME: Neural tube occlusion precedes rapid brain enlargement. *J Exp Zool* 230:405-407, 1984 a
214. Schoenwolf GC, Desmond ME: Descriptive studies of occlusion and reopening of the spinal canal of the early chick embryo. *Anat Rec* 209:251-263, 1984 b
215. Schoenwolf GC, Desmond ME: Timing and positioning of reopening of the occluded spinal neurocèle in the chick embryo. *J Comp Neurol* 246:459-466, 1986
216. Schoenwolf GC, Everaert S, Bortier H, et al: Neural plate- and neural tube-forming potential in isolated epiblast areas in avian embryos. *Anat Embryol* 179:541-549, 1989
217. Schoenwolf GC, Sheard P: Shaping and bending of the avian neural plate as analyzed with a fluorescent-histochemical marker. *Development* 105:17-25, 1989
218. Schreiber G, Richardson SJ, Prapunpoj P: Structure and expression of the transthyretin gene in the choroid plexus: a model for the study of the mechanisms of evolution. *Microsc Res Tech* 52: 21-30, 2001
219. Schulingkamp RJ, Pagano TC, Hung D, et al: Insulin receptors and insulin action in the brain: review and clinical implication. *Neurosci Biobehav Res* 24:855-872, 2000
220. Shabo AL, Maxwell DS: The morphology of the arachnoid villi: a light and electron microscopic study in the monkey. *J Neurosurg* 29:451-463, 1968
221. Shuangshoti S, Netsky MG: Histogenesis of choroid plexus in man. *Am J Anat* 118:283-316, 1966
222. Siegel GJ, Holm C, Schreiber JH, et al: Purification of mouse brain Na⁺-K⁺-ATPase catalytic unit, characterization of antiserum, and immunocytochemical localization in cerebellum, choroid plexus, and kidney. *J His tochem Cytochem* 32:1309-1318, 1984
223. Sievers J, Mangold U, Berry M: 6-OHDA-induced ectopia of external granule cells in the subarachnoid space covering the cerebellum. Genesis and topography. *Cell Tissue Res* 230:309-336, 1983
224. Sievers J, Mangold U, Berry M, et al: Experimental studies on cerebellar foliation. I. A qualitative morphological analysis of cerebellar fissuration defects after neonatal treatment with 6-OHDA in the rat. *J Comp Neurol* 203:751-769, 1981
225. Sievers J, Pehlemann F-W, Baumgarten H-G, et al: Selective destruction of meningeal cells by 6-hydroxydopamine: a tool to study meningeal-neuroepithelial interaction in brain development. *Dev Biol* 110:127-135, 1985
226. Sievers J, Pehlemann FW, Gude S, et al: A time course study of the alterations in the development of the hamster cerebellar cortex after destruction of the overlying meningeal cells with 6-hydroxydopamine on the day of birth. *J Neurocytol* 23:117-134, 1994 a
227. Sievers J, Pehlemann FW, Gude S, et al: Meningeal cells organize the superficial glia limitans of the cerebellum and produce components of both the interstitial matrix and the basement membrane. *J Neurocytol* 23:135-149, 1994 b
228. Sievers J, Von Knebel Doeberitz C, et al: Meningeal cells influence cerebellar development over a critical period. *Anat Embryol* 175:91-100, 1986
229. Silverman WF, Walsh RJ, Posner BI: The ontogeny of specific prolactin binding sites in the rat choroid plexus. *Dev Brain Res* 24:11-19, 1986
230. Skinner DC, Malpaux B: High melatonin concentration in third ventricular cerebrospinal fluid are not due to Galen vein blood recirculating through the choroid plexus. *Endocrinology* 140: 4399-4405, 1999
231. Sly WS, Hu PY: Human carbonic anhydrases and carbonic anhydrase deficiencies. *Annu Rev Biochem* 64:375-401, 1995
232. Smith JL, Schoenwolf GC: Notochordal induction of cell wedging in the chick neural plate and its role in neural tube formation. *J Exp Zool* 250:49-62, 1989
233. Sousa RJ, Tannery NH, Lafer EM: In situ hybridisation mapping of glucocorticoid receptor messenger ribonucleic acid in rat brain. *Mol Endocrinol* 3:481-494, 1989
234. Southwell BR, Duan W, Allorn D, et al: Thyroxine transport to the brain: role of protein by the choroid plexus. *Endocrinology* 133:2116-2126, 1993
235. Stankov B, Cozzi B, Lucini V, et al: Localization and characterization of melatonin binding sites in the brain of rabbit (*Oryctolagus cuniculus*) by autoradiography and in vitro ligand-receptor binding. *Neurosci Lett* 133:68-72, 1991
236. Stasny F, Lisy V: Cortisol regulation of gamma-glutamyl-transpeptidase in liver, choroids plexus, blood plasma and cerebrospinal fluid of developing chick embryo. *Dev Neurosci* 4:408-415, 1981
237. Stasny F, Rychter Z: Effect of hydrocortisone on the growth of choroid plexus and composition of cerebrospinal fluid in the developing chick embryo. *Acta Neurol Scand* 53:260-274, 1976
238. Sternberger NH, Sternberger LA: Blood-brain barrier protein recognized by monoclonal antibody. *Proc Natl Acad Sci USA* 84:8169-8173, 1987
239. Stewart PA, Hayakawa K: Early ultrastructural changes in blood-brain barrier vessels of the rat embryo. *Dev Brain Res* 78:25-34, 1994
240. Stewart PA, Wiley MJ: Developing nervous tissue induces formation of blood-brain barrier characteristics in invading endothelial cells: a study using quail-chick transplantation chimeras. *Dev Biol* 84:183-192, 1981

241. Struckhoff G, Turzynski A: Demonstration of parathyroid hormone-related protein in meninges and its receptor in astrocytes: evidence for a paracrine meningo-astrocytic loop. *Brain Res* 676:1-9, 1995
242. Stylianopoulou F, Efstratiadis A, Herbert J, et al: Pattern of the insulin-like growth factor II gene expression during rat embryogenesis. *Development* 103:497-506, 1988
- 242a. Super H, Martinez A, Soriano E: Degeneration of Cajal-Retzius cells in the developing cerebral cortex of the mouse after ablation of meningeal cells by 6-hydroxydopamine. *Brain Res Dev Brain Res* 98:15-20, 1997
243. Sussenbach JS, Steenbergh PH, Jansen E, et al: Structural and regulatory aspects of the human genes encoding IGF-I and -II. *Adv Exp Med Biol* 293:1-14, 1991
244. Thomas T, Dziadek M: Capacity to form choroid plexus-like cells in vitro is restricted to specific regions of the mouse neural ectoderm. *Development* 117:253-262, 1993
245. Thomas T, Schreiber G, Jaworowski A: Developmental patterns of gene expression of secreted proteins in brain and choroid plexus. *Dev Biol* 134:38-47, 1989
246. Tong Y, Pelletier G: Ontogeny of atrial natriuretic factor (ANF) binding in various areas of rat brain. *Neuropeptides* 16:63-68, 1990
247. Toyama E, Doi Y, Kudo H, et al: Diversity in distribution of Na⁺-K⁺-ATPase of the choroid epithelium of prenatal rats; an immunocytochemical study. *Arch Histol Cytol* 60:235-244, 1997
248. Tricoli JV, Rall LB, Scott J, et al: Localization of insulin-like growth factor genes to human chromosome 11 and 12. *Nature* 310:784-786, 1984
249. Tsai CE, Daood MJ, Lane RH, et al: P-glycoprotein expression in mouse brain increases with maturation. *Biol Neonate* 81:58-64, 2002
250. Tsutsumi M, Skinner MK, Sanders-Bush E: Transferrin gene expression and synthesis by cultured choroid plexus epithelial cells. *J Biol Chem* 264:9626-9631, 1989
251. Van Deurs B: Structural aspects of brain barriers, with special reference to the permeability of the cerebral endothelium and choroidal epithelium. *Int Rev Cytol* 65: 117-191, 1980
252. Van Dijk MA, Van Schaik FMA, Bootsma HJ, et al: Initial characterization of the four promoters of the human insulin-like growth factor II gene. *Mol Cell Endocrinol* 81:81-94, 1991
253. Vanecek J: Melatonin binding sites. *J Neurochem* 51:1436-1440, 1988
254. Vertongen P, Schiffmann SN, Gourlet P, et al: Autoradiographic visualization of the receptor subclasses for vasoactive intestinal polypeptide (VIP) in rat brain. *Peptides* 18:1547-1554, 1997
255. Von Knebel Doeberitz C, Sievers J, Sadler M., et al: Destruction of meningeal cells over the newborn hamster cerebellum with 6-hydroxydopamine prevents foliation and lamination in the rostral cerebellum. *Neuroscience* 17:409-426, 1986
256. Von Schroeder HP, Nishimura E, Mc Intosh CH, et al: Autoradiographic localization of binding sites for atrial natriuretic factor. *Can J Physiol Pharmacol* 63:1373-1377, 1985
257. Vorbrodt AW, Lossinsky AS, Wisniewski HM: Localization of alkaline phosphatase activity in endothelia of developing and mature mouse blood-brain barrier. *Dev Neurosci* 8:1-13, 1986
258. Vulpian MA: Note sur les phénomènes de développement qui se manifestent dans la queue des très-jeunes embryons de grenouille, après qu'on l'a séparée du corps par une section transversale. *C R Acad Sci* 48:807-811, 1859
259. Wagner HJ, Pilgrim CH, Brandl J: Penetration and removal of cerebral horseradish peroxidase injected into the cerebrospinal fluid: role of cerebral perivascular spaces, endothelium, and microglia. *Acta Neuropathol* 27:299-315, 1974
260. Wakai S, Hirokawa N: Development of the blood-brain barrier to horseradish peroxidase in the chick embryo. *Cell Tissue Res* 195:195-203, 1978
261. Wakai S, Hirokawa N: Development of blood-cerebrospinal fluid barrier to horseradish peroxidase in the avian choroidal epithelium. *Cell Tissue Res* 214:271-278, 1981
262. Walsh RJ, Posner BI, Kopri BM, et al: Prolactin binding sites in the rat brain. *Science* 201: 1041-1043, 1978
263. Watts AG, Sanchez-Watts G, Emanuel JR, et al: Cell-specific expression of mRNAs encoding Na⁺, K⁺-ATPase α and β-subunit isoforms within the rat central nervous system. *Proc Natl Acad Sci USA* 88:7425-7429, 1991
264. Weed LH: Studies on cerebro-spinal fluid. III. The pathways of escape from the subarachnoid spaces with particular reference to the arachnoid villi. *J Med Res* 31:51-91, 1914
265. Weed LH: The establishment of the circulation of cerebro-spinal fluid. *Anat Rec* 10:256-258, 1916 a
266. Weed LH: The formation of the cranial subarachnoid spaces. *Anat Rec* 10:475-481, 1916 b
267. Weed LH: The development of the cerebro-spinal spaces in pig and man. *Contrib Embryol Carnegie Inst* 5:1-116, 1917
268. Weed LH: The absorption of cerebrospinal fluid into the venous system. *Am J Anat* 31:191-221, 1923
269. Weiss P: Secretory activity of the inner layer of the embryonic mid-brain of the chick as revealed by tissue culture. *Anat Rec* 58:299-302, 1934
270. Welch K: The principles of physiology of the cerebrospinal fluid in relation to hydrocephalus including normal pressure hydrocephalus. *Adv Neurol* 13:247-332, 1975
271. Wijnholds J, de Lange ECM, Scheffer GL, et al: Multidrug resistance protein 1 protects the choroid plexus epithelium and contributes to the blood-cerebrospinal fluid barrier. *J Clin Invest* 105:279-285, 2000
272. Williams LM, Hannah LT, Bassett JM: Melatonin receptors in neonatal pig brain and pituitary gland. *J Pineal Res* 26:43-49, 1999
273. Wilting J, Christ B: An experimental and ultrastructural study on the development of the avian choroid plexus. *Cell Tissue Res* 255:487-494, 1989
274. Winkelman NW, Fay T: The Pacchionian system, histologic and pathologic changes with particular reference to the idiopathic and symptomatic convulsive states. *Arch Neurol Psychiatry* 23:44-64, 1930
275. Wray GA. Echinoderms. In: Gilbert SF, Raunio AM (eds) *Embryology, constructing the organism*. Sinauer, Sunderland pp. 309-329, 1997
276. Wright DE, Serogy RB, Lundgren KH, et al: Comparative localization of serotonin 1A, 1C, and 2 receptor subtype mRNAs in rat brain. *J Comp Neurol* 351:357-373, 1995
277. Yamashima T: Functional ultrastructure of cerebrospinal fluid drainage channels in human arachnoid villi. *Neurosurgery* 22:633-641, 1988
278. Yoshida Y, Yamada M, Wakabayashi K, et al: Endothelial fenestrae in the rat fetal cerebrum. *Dev Brain Res* 44:211-219, 1988

279. Zaki W: Développement des granulations arachnoïdiennes. Bull Assoc Anat 61:131-138, 1977
280. Zenker W, Bankoul S, Braun JS: Morphological indications for considerable diffuse reabsorption of cerebrospinal fluid in spinal meninges particularly in the areas of meningeal funnels. Anat Embryol 189:243-258, 1994
281. Zervas NT, Lisczak TM, Meyberg MR, et al: Cerebrospinal fluid may nourish cerebral vessels through pathways in the adventitia that may be analogous to systemic vasa vasorum. J Neurosurg 56:475-481, 1982
282. Zlokovic BV, Mackic JB, Wang L, et al: Differential expression of Na,K-ATPase alpha and beta subunits isoforms at the blood-brain barrier and the choroid plexus. J Biol Chem 268:8019-8025, 1993

Cerebrospinal Fluid Dynamics

MAREK CZOSNYKA¹, ZOFIA H. CZOSNYKA², PETER C. WHITFIELD² AND JOHN D. PICKARD¹

Introduction

Historically, the saga of cerebrospinal fluid (CSF) dynamics almost always starts with the Monro-Kellie doctrine. This states that the sum of volumes of brain, blood and CSF (although in the time of Kellie, i.e. the early nineteenth century, the volume of CSF was not considered) must be constant due to the fixed volume of the skull and spinal canal. This may be expressed mathematically as:

$$\text{Volume of brain} + \text{volume of blood} + \text{volume of CSF} = \text{const} \quad (1)$$

This equation describes the static equilibrium of intracerebral space. The static ("trapped") volume model is probably inadequate to describe the highly dynamic process of cerebral blood flow and CSF circulation. Therefore, evaluating changes in volumes of both sides of Eq. 1 may be more appropriate to an expression of dynamic conditions:

$$\Delta\text{Brain volume} + \Delta\text{blood volume} + \Delta\text{CSF volume} = 0 \quad (2)$$

This can be itemized further, taking into account that the time derivative of the volume is equivalent to the flow:

$$\begin{aligned} & \Delta\text{Brain volume} + \text{cerebral blood inflow} - \\ & - \text{arterial blood storage} - \text{venous blood storage} - \\ & - \text{cerebral blood outflow} + \text{CSF production} - \\ & - \text{CSF storage} - \text{CSF outflow} - \text{CSF drainage} = \\ & = 0 \end{aligned} \quad (3)$$

(where CSF drainage represents drainage via an implanted drain or shunt system).

Under controlled conditions some simplifying assumptions can be made: if the volume of the brain is constant, i.e. there is no evolving oedema,

rapid dehydration, etc., the first component can be cancelled. If cerebral blood inflow is identical to the outflow (i.e. there is no change in the total cerebral blood volume), four further components can be cancelled. What remains is the law of continuity of CSF flow:

$$\begin{aligned} \text{CSF production} = \\ = \text{CSF storage} + \text{CSF outflow} + \text{CSF drainage} \end{aligned} \quad (4)$$

To consider this formal equation, all its components should be thoughtfully analysed.

Three Components Influencing CSF Dynamics: Production, Circulation, Drainage

CSF Production

CSF is derived by active secretion from cerebral arterial blood [25, 26, 65]. The site of this process is only conceptually limited to the choroid plexus of the ventricular system. The surgical removal of plexuses (plexectomy), postulated in the 1910s [24] as a remedy for hydrocephalus, has failed to produce satisfactory results. Extrachoroidal secretion or super-secretion in the remaining plexuses has been postulated to account for the failure of this type of surgery [68].

The rate of CSF production is reported to be constant under normal and stable conditions. Due to the lack of a direct method of measuring CSF production over short periods of time, the dynamics of CSF secretion has not been accurately reported. Authors can only hypothesise that the components of the CSF pressure waveform – i.e. slow vasogenic (B)

¹ Neurosurgery, Addenbrookes Hospital, Cambridge, UK; ² South West Neurosurgical Unit, Derriford Hospital, Plymouth, UK

waves, respiratory and pulsatile waves – may influence the rate of CSF formation.

Secretion of CSF requires adenosine triphosphates (ATP) to pump sodium and potassium ions across epithelial walls. Globally, the average secretion rate is $0.35 \text{ ml} \cdot \text{min}^{-1}$ ($0.27\text{--}0.45 \text{ ml} \cdot \text{min}^{-1}$ as a 95% confidence range for a mean value [27]) and remains proportional to the brain metabolism rate. However, it is notable that cerebral blood flow is normally coupled to the brain metabolism. Therefore, it may be possible that all studies demonstrating correlation between cerebral perfusion pressure, arterial CO_2 , hypothermia, cerebrovascular vasodilation of a general nature, and CSF secretion rate (for review see [26]), may simply reflect the relationship between choroidal blood flow and CSF production.

Current methods of CSF formation measurement are imprecise. The Messner technique [26, 64], whereby the time taken for intracranial pressure (ICP) to return to the baseline value after withdrawal of a known volume of CSF, is notoriously inaccurate because this time is theoretically infinite. Ekstedt [27, 28] used continuous CSF drainage at an outlet pressure lower than sagittal sinus pressure, assuming that with zero absorption the rate of production should equilibrate the rate of drainage. This technique is undoubtedly more accurate but may be traumatic to patients (due to the effects of CSF overdrainage). Constant perfusion of a liquid containing tracer, introduced by Pappenheimer et al. [71], is probably the most accurate but requires long periods of measurement. Therefore, it averages over all possible dynamic components of CSF production. The method relies on the assumption that after a long term of perfusion, the difference in concentration of the tracer at input and output describes the CSF production rate. The method has to assume that there is no CSF leakage into the brain tissue; such assumptions are usually far from realistic.

Recently, studies have been published referring to the age-related changes in CSF secretion [64, 77]. Our own finding that the resistance to CSF outflow increases above the 55th year of age (see also [2]), while baseline ICP remains unaffected, leads to the conclusion that the CSF production rate must decrease provided that sagittal sinus pressure stays constant [27] (Fig. 1). This agrees with the study of May et al. [64] reporting a 50% decrease in CSF formation rate in elderly subjects (mean age 77 years) in comparison to young healthy people (mean age 28 years). In contrast, neither Ekstedt [27] nor Gideon et al. [34] reported any evidence of an age-related decrease in CSF production.

This decrease may be hypothetically explained by calcification or other degenerative changes of the

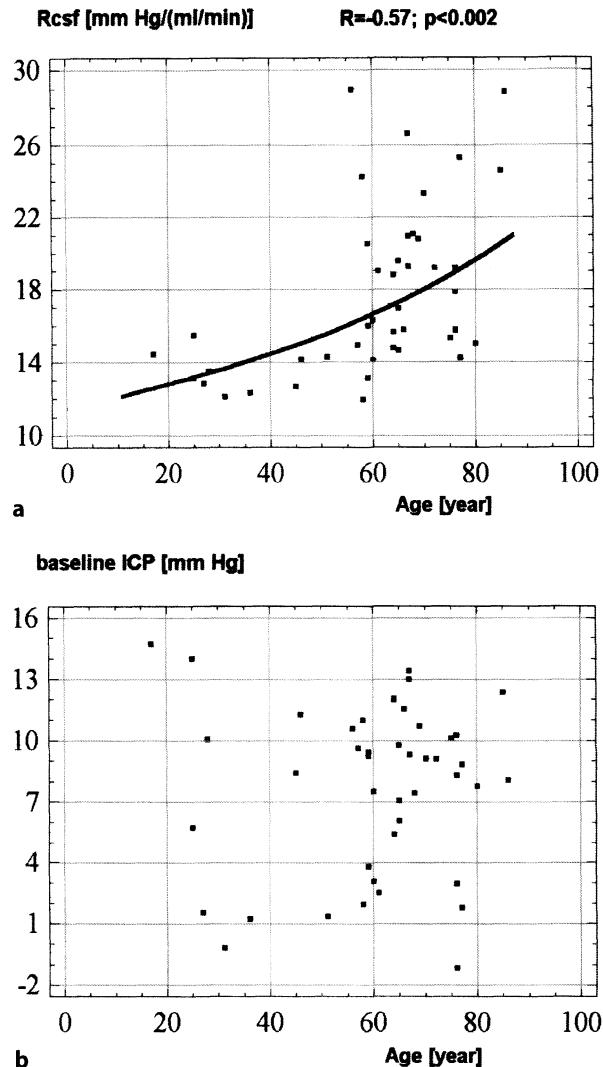


Fig. 1. **a** Relationship between resistance to CSF outflow (y axis) and age (x axis) in patients presenting with symptoms of hydrocephalus. **b** In patients presenting with symptoms of hydrocephalus ICP does not depend on age. This suggests that CSF formation rate decreases with age

choroid plexus. On the other hand, lack of a significant decrease in CSF production following plexectomy [68] demonstrates that extrachoroidal sources of CSF formation may easily compensate for a decrease in choroidal CSF secretion. An interesting hypothesis based on experimental studies has been put forward by James et al. [45], stating that, when resistance to CSF outflow (R_{csf}) increases acutely, a decrease in CSF production rate may be regarded as a compensatory mechanism. If it may be transferred from experimental hydrocephalus to an aging paradigm, an age-related decrease in CSF production may prevent a rise in baseline ICP when R_{csf} increases. If this is true, a hypothesis [77] that Alzheimer-related dementia may be caused by too slow CSF exchange, resulting in

accumulation of toxins which damage nerve cells [3], may be justified. Therefore, a proposal to treat early-stage dementia by shunting to reduce the resistance to CSF outflow, and thus encourage increase in CSF production, may be the right strategy. However, one should keep in mind that the estimator of CSF production approximates CSF absorption rather than production rate. Part of the CSF produced leaks into brain parenchyma, resulting in a serious underestimation of the CSF production value. The rate of this leakage may increase with age. This may be indirectly proven by an age-related increase in the area and intensity of so-called periventricular lucency seen on CT scans in patients with normal-pressure hydrocephalus (NPH). Hence, the presented age-related decrease in CSF production may signify an increase in CSF parenchymal drainage rather than a decrease in the CSF formation rate.

CSF Circulation

CSF, produced mainly in the lateral and third ventricles, flows along the aqueduct of Sylvius to reach the fourth ventricle. Passage through the narrow aqueduct is fast, and its pulsatile nature can be detected by precision dynamic MRI techniques. Although first observed a long time ago, these pulsations have not yet been proven to have any diagnostic significance in any of the diseases producing abnormal patterns of CSF circulation [12]. This is probably related to the very limited correlation between the shape of the CSF pulse pressure waveform and specific disorders of CSF circulation. None of the methods described previously have become established in clinical practice [6, 14, 30, 73]. An interesting study would be to investigate the pattern of CSF aqueductal flow during slow vasomotor waves (B waves), which are well established in the diagnosis of hydrocephalus [35, 36, 39, 55, 72].

CSF flows out of the fourth ventricle through the midline foramen of Magendie and the lateral foramina of Luschka into the subarachnoid space, which comprises a network of interconnected CSF cisterns located principally around the basal aspect of the brain. It flows around the tentorium, upward to the superior sagittal sinus, where most is absorbed. Some CSF flows downwards towards the lumbar subarachnoid space. This downward flow is important for fluid exchange and volume compensation, since the total volume of lumbar space may expand at the expense of venous plexuses in the spinal channel. There is a strong evidence that, if this downward CSF flow is disturbed – as for example in patients with Arnold-Chiari malformations – fluid-filled syrinxes may develop within the central canal of the spine. This may

have marked clinical consequences [95]. Several hypotheses have been proposed to explain this phenomenon. CSF may be forced to flow along the central canal when the outflow from the fourth ventricle is obstructed. This approach has been criticized because in most adults the central canal is not patent [42]. Another theory suggests that the formation of strong gravitational pressure waves, in the presence of craniospinal pressure dissociation, causes syringomyelia. Hypothetically, the cranial space works as a shock absorber for the long vertical lumbar space (like a cistern on top of a water tower). If this space is cut off, CSF pressure waves may arise [95]. When gravitational waves form along the spinal cord (during walking and other bodily exercises), the probability of syrinx formation increases, as the spinal cord may be physically delaminated along the normally closed central canal.

Undisturbed circulation of CSF is one of the fundamental mechanisms assuring favourable conditions for the structures of the central nervous system. First, the brain and spinal cord float in the fluid, losing their relative weight according to Archimedes' law. As a result, these structures are less prone to injury in the case of environmental mechanical shocks. Secondly, all gradients of the ICP are cancelled out by the free circulation of CSF fluid. Therefore, there is neither a pressure gradient nor a risk of volume shifts or herniations. This role of CSF is important for understanding why, following a head injury, there is critical threshold for increased ICP in the range of 20-25 mmHg. In head injury, due to brain swelling, normal pathways of CSF circulation are usually closed. Therefore, the probability of developing intracerebral pressure gradients is much higher. Midline shifts and upward or downward herniations are among the factors that seriously contribute to fatal outcome following brain trauma. Meanwhile, in communicating hydrocephalus, during pressure-volume studies, patients tolerate a rise in ICP up to 40-50 mmHg without any subsequent sensations or adverse effects. In communicating hydrocephalus, the possibility of pressure gradients arising is minimized by free CSF circulation.

Obstruction of CSF flow between the third and fourth ventricle produces accumulation of CSF in the lateral and third ventricles. This is described as non-communicating hydrocephalus and can be due to congenital stenosis or a mass occluding the aqueduct. Endoscopic fenestration of the floor of third ventricle (ventriculostomy) by a trained specialist has recently become the preferred treatment for this condition. In patients with communicating hydrocephalus in whom there is impaired CSF flow in the subarachnoid space (e.g. post-meningitic, post-haemorrhagic), third ventriculostomy is unlikely to be successful and shunting is the treatment of choice.

CSF Drainage

Drainage of CSF fluid into the venous compartment takes place predominantly (in human) through arachnoid granulations that penetrate the walls of the sagittal sinus [26]. It is important to recognise that reverse transport through the arachnoid granulations is impossible, i.e. drainage ceases if subarachnoid ICP is less than sagittal sinus pressure (P_{ss}). The nature of the venous drainage is linear, i.e. proportional to the pressure gradient between the CSF side of the granulation and the sagittal sinus. The inverse of proportionality coefficient is called the resistance to CSF outflow (R_{csf}) and has been assessed in normal subjects as ranging from 6 to 10 mmHg \cdot ml $^{-1} \cdot$ min [1, 27].

Various non-linear theories describing decreases in R_{csf} when the drainage rate increases, preventing an increase in ICP, have been discussed in the past, but are mainly based on animal models [66] or supported by measurements of R_{csf} made by inaccurate methods.

In quadrupeds, alternative pathways of CSF drainage exist along the neural roots of the spinal cord [26]. The resistance of these pathways may be pressure-dependent as the fluid spaces around the roots widen when ICP rises. In humans, this route for CSF drainage has been eliminated in the course of evolution and this is attributed to the vertical body position. One may imagine the CSF space as a long bottle in which fluid is continuously produced and from which it constantly leaks out. The bottle must remain filled, i.e. production should equilibrate leakage. When the bottle is horizontal (quadrupeds), leakage points can be distributed along the whole bottle. If the bottle is vertical and leakage points are close to the bottom, it may empty according to gravitational forces. For this reason the leakage points close to the bottom (neural roots) have been sealed in the course of evolution and only those close to the top (sagittal sinus) remain functional (Fig. 2).

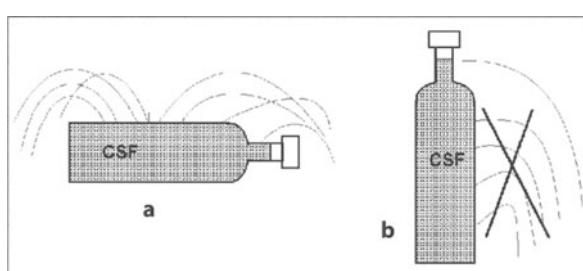


Fig. 2a,b. Comparison of possible routes of CSF absorption. **a** Quadrupeds: CSF absorption is distributed along the neural axis. **b** Human: CSF absorption takes place only at the very top of the system, i.e. the sagittal sinus

Model of CSF Dynamics

The mathematical model of CSF pressure-volume compensation, introduced by Marmarou in 1978 [59, 62] and modified in later studies [5, 33, 84], provides a theoretical basis for the differential diagnosis in hydrocephalus. Mathematical modelling of CSF dynamics has several applications including diagnostic testing and evaluating the efficacy of therapeutic procedures.

As already stated in the Introduction, under normal conditions, without long-term fluctuations of the cerebral blood volume, the production of CSF and external infusion into CSF spaces is balanced by its storage and reabsorption:

$$\text{Production of CSF} + \text{External infusion of CSF} = \text{Storage of CSF} + \text{Reabsorption of CSF} \quad (5)$$

Production of CSF is almost constant. However, reabsorption is proportional to the gradient between CSF pressure (P) and pressure in sagittal sinuses (P_{ss}):

$$\text{Reabsorption} = \frac{P - P_{ss}}{R}. \quad (6)$$

The coefficient R is termed the resistance to CSF reabsorption or outflow (units: mmHg \cdot ml $^{-1} \cdot$ min).

Storage of CSF is proportional to the cerebrospinal compliance C (units: mmHg/ml):

$$\text{Storage} = C \cdot \frac{dp}{dt}. \quad (7)$$

The compliance of the cerebrospinal space is inversely proportional to the gradient of CSF pressure P and the reference pressure P_o [5, 75]:

$$C = \frac{1}{E \cdot (P - P_o)}. \quad (8)$$

Some authors suggest that the relationship described by Eq. 8 is valid only above a certain pressure level called the “optimal pressure” [84]; however, this is still a point of some dispute. E is the cerebral elastance coefficient (units: ml $^{-1}$). Elevated elastance (>0.18 ml $^{-1}$) signifies a poor pressure-volume compensatory reserve [16]. The reference pressure P_o is a parameter of uncertain significance. Some authors suggest that it is the pressure in the venous compartment and may be equal to P_{ss} . Others assume that this variable can be neglected [62].

The relationship described by Eq. 8 reflects the most important law of the cerebrospinal dynamic compensation: The compliance of the brain decreases when the CSF pressure increases. Combination of Eq. 5 with Eqs. 6 and 8 gives a final Eq. 9:

$$\frac{1}{E \cdot (P - P_0)} \cdot \frac{dp}{dt} \cdot \frac{P - P_b}{R} = I(t), \quad (9)$$

where $I(t)$ is the rate of external volume addition and P_b is a baseline pressure. The model described by this equation may be presented in the form of its electric equivalent as an aid to understanding (Fig. 3).

Equation 9 can be solved for various types of external volume additions $I(t)$. The most common in clinical practice are:

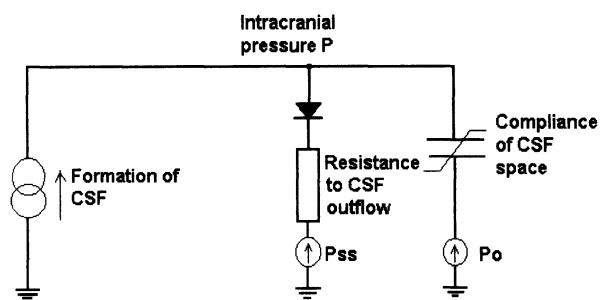


Fig. 3. Electrical model of CSF circulation

1. *A constant infusion of CSF: ($I(t) = 0$ for $t < 0$ and $I(t) = I_{inf}$ for $t > 0$)* (Fig. 4a):

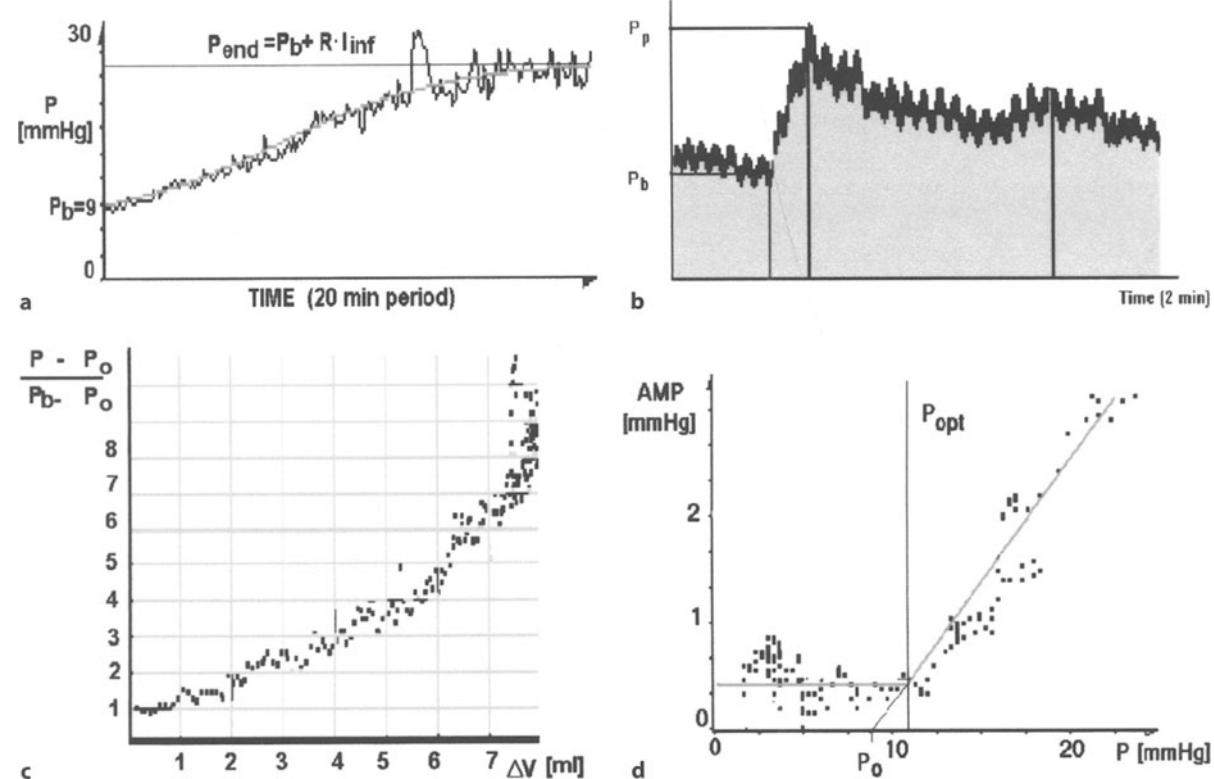


Fig. 4a-d. Different numerical techniques used for the analysis of the pressure-volume tests. **a** An example of CSF pressure recorded during infusion test and a modelling curve described by Eq. 10. The least-mean-square fit of the analytical curve to the real pressure enables accurate measurement of the compensatory parameters. **b** An example of the pressure response to the bolus injection of saline. Pressure increases from P_b to P_p after a very rapid addition of volume ΔV (Eq. 11). **c** Real volume-pressure relationship detected during infusion test. Volume load ΔV is calculated as the balance of the volume infused, produced and reabsorbed during infusion. Pressure rise (y axis) is expressed as the ratio of actual pressure and baseline pressure (Eq. 13). **d** The relationship between pulse amplitude (AMP) and mean pressure (P) recorded during the infusion test (Eq. 14). This is a one of the rare cases where the lower breakpoint, marked as P_{opt} , was detected. In such a case all equations (Eqs. 4-8) are valid only for $P > P_{opt}$, which is taken into account in the computer calculations (such a breakpoint can be detected in 1%-3% of infusion tests). Figure reproduced from [20], with permission

$$P(t) = \frac{\left[I_{\text{inf}} + \frac{P_b - P_o}{R} \right] \cdot [P_b - P_o]}{\frac{P_b - P_o}{R} + I_{\text{inf}}} + P_o \quad (10)$$

$$\frac{P_b - P_o}{R} + I_{\text{inf}} \cdot \left[e^{-E \left[\frac{P_b - P_o}{R} + I_{\text{inf}} \right] t} \right]$$

The analytical curve described by Eq. 10 can be matched to the real recording of the pressure during the test, which results in an accurate estimation of the unknown parameters R , E and P_o .

2. A bolus injection of CSF (volume ΔV) (Fig. 4b):

$$P(t) = \frac{(P_b - P_o) \cdot e^{E \left[\frac{P_b - P_o}{R} \cdot t \right]}}{1 + e^{E \Delta V} \cdot \left[e^{E \frac{P_b - P_o}{R} \cdot t} - 1 \right]} + P_o. \quad (11)$$

The bolus injection can be used for calculation of the so-called pressure-volume index (PVI), defined as the volume added externally to produce a ten-fold increase in the pressure [59]:

$$PVI \stackrel{\text{def}}{=} \frac{\Delta V}{\log_{10} \left(\frac{P_p - P_o}{P_b - P_o} \right)}; PVI \approx \frac{1}{0.434 \cdot E}. \quad (12 \text{ a,b})$$

PVI is theoretically the inverse of the brain elastance coefficient E . The pressure-volume compensatory reserve is insufficient when PVI is less than 13 ml. A value of PVI above 26 ml signifies an “over-compliant” brain. These norms are given for the PVI calculated using slow infusion. If the bolus test is used, norms for PVI are higher [62, 81].

Equation 11 for time $t=0$ describes the shape of the relationship between the effective volume increase ΔV and the CSF pressure, called the pressure-volume curve (Fig. 4c):

$$P = (P_b - P_o) \cdot e^{E \Delta V} + P_o. \quad (13)$$

Finally, Eq. 11 can be helpful in the theoretical evaluation of the relationship between the pulse wave amplitude of ICP and the mean CSF pressure. If we presume that the rise in the blood volume after a heart contraction is equivalent to a rapid bolus addition of CSF fluid at the baseline pressure P_b , the pulse amplitude (AMP) can be expressed as:

$$AMP = P_p - P_b = (P_b - P_o) \cdot (e^{E \Delta V} - 1). \quad (14)$$

In almost all cases, when CSF pressure is increased by external volume addition, the pulse amplitude rises. The gradient of the regression line between AMP and P is proportional to the elastance coefficient. The intercept, theoretically, marks the reference pressure P_o (Fig. 4d).

In all pressure-volume testing techniques, the parameters of Eq. 8 are estimated using various algorithms and various volume-adding techniques. However, the model presented in Eq. 8 has limited scope: it cannot interpret dynamic interactions between the rising CSF pressure, expanding ventricles and cerebral blood volume. More sophisticated [18, 44, 93], or even multi-compartmental models have been since proposed [76, 85], but none of them has yet become established in clinical practice.

Testing of CSF Dynamics

Hydrocephalus is more complex than a simple disorder of CSF circulation. Because shunting for hydrocephalus is a purely mechanical treatment, ideally the biomechanics of the patient's own CSF circulation should be examined before a shunt is implanted. A whole range of tests have been developed which are very widely used in patients with hydrocephalus. These tests may be used diagnostically and in assessing possible complications such as shunt blockage and under- and overdrainage.

Measurement of the Resistance to CSF Outflow

Measurement of resistance to CSF outflow (R_{csf}) is useful both in the evaluation of patients with possible hydrocephalus and in assessing patients with shunts in whom malfunction is possible. Several methods to measure the R_{csf} have been published:

- Bolus injection of fluid into the CSF space [51, 59, 81] is the quickest and least invasive. However, this method of R_{csf} measurement is probably the least accurate because strong vasogenic contamination is commonly present [88].
- Katzman's constant rate infusion study [15, 48] is undoubtedly more accurate, but its application is limited to truly communicating hydrocephalus.
- Lumbo-ventricular perfusion [11] is probably the most accurate but the most invasive method.
- Servo-controlled constant-pressure infusion [28] and multiple rate infusion studies [46] are equally accurate but time-consuming.

Computerized Infusion Test

During the infusion, the computer calculates and presents mean pressure and pulse amplitude (with time along the x-axis, see Fig. 5). The resistance to CSF outflow can be calculated using simple arithmetic as the difference between the value of the plateau pressure during infusion and the resting pressure divided by the infusion rate. However, in many cases strong vasogenic waves or excessive elevation of the pressure above the safe limit of 40 mmHg do not allow precise measurement of the final pressure plateau. Computerised analysis, on the other hand, produces results even in difficult cases when the infusion is terminated prematurely (i.e. without reaching end plateau). The algorithm uses a sophisticated time series analysis for volume-pressure curve retrieval, the least-mean-square model fitting and an examination of the relationship between the pulse amplitude and the mean CSF pressure. The model of cerebrospinal volume compensation investigated during this test has been described in the previous section. Apart from resting CSF pressure and the resistance to CSF outflow, the elastance coefficient or pressure-volume index, cerebrospinal compliance, CSF formation rate and the pulse wave amplitude of CSF pressure are calculated. Although not all patients presenting with abnormal CSF circulation may improve after shunting, the computerised infusion test is important in the diagnosis of hydrocephalus in these patients. Considered in conjunction with the hydrodynamic properties of the hydrocephalus shunt, it provides a valuable method for testing shunt function *in vivo*.

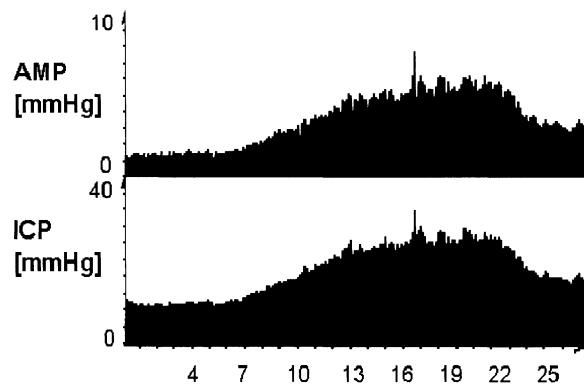
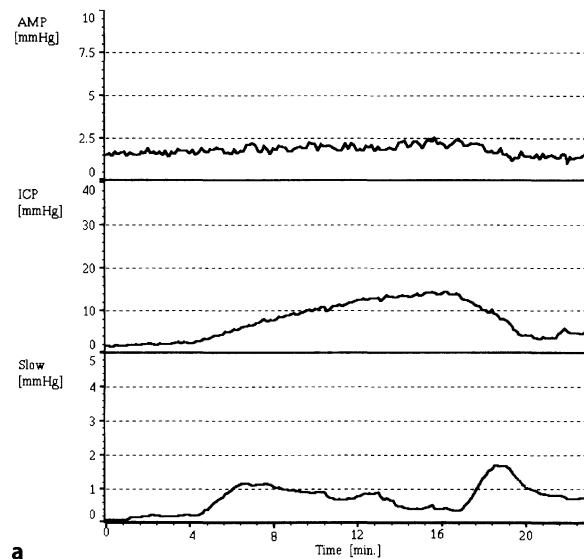


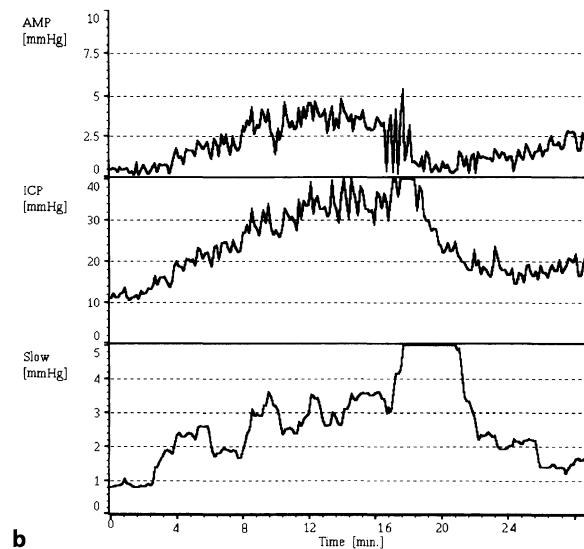
Fig. 5. Mean pulse amplitude of CSF pressure (AMP) and mean pressure (ICP) recorded during infusion test (x axis: time in minutes from the beginning of recording). The infusion of 1.5 ml/min starts in the 5th min and finishes around the 22nd min. Figure reproduced from [20], with permission

Differentiation between Brain Atrophy and Normal-Pressure Hydrocephalus

In contrast to hydrocephalic patients, those suffering predominantly from brain atrophy have normal CSF circulation. Typically, their opening pressure, resistance to CSF outflow and pulse amplitude are low ($ICP < 12$ mmHg, $R_{csf} < 12$ $\text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$, amplitude < 2 mmHg). The pressure volume index is high ($PVI > 20$ ml), reflecting low elastance of the atrophic brain. Vasogenic waves are not seen in the pressure recording (Fig. 6a). The mean ICP increases smoothly during the infusion and decreases in a similar fashion following infusion, like the inflation and deflation of a balloon.



a



b

Fig. 6. Typical infusion tests performed in patients presented with **a** brain atrophy, **b** NPH. AMP, pulse amplitude of ICP; ICP, mean CSF pressure; Slow, detected power of B waves (presented as an equivalent amplitude in millimetres of mercury)

Normal-pressure hydrocephalus is characterised by a normal opening pressure ($ICP < 15 \text{ mmHg}$) and high PVI ($> 20 \text{ ml}$). Again, as in brain atrophy, the CSF system is very compliant. The increased resistance to CSF outflow ($> 13 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$) and B waves seen during infusion, particularly when ICP increases, distinguish normal-pressure hydrocephalus from atrophy (Fig. 6b).

Non-communicating Hydrocephalus

Lumbar infusion is not recommended in non-communicating hydrocephalus because of the risk of brain herniation following the lumbar puncture. However, this type of hydrocephalus may not always be detected by the initial CT scan. In those few cases when lumbar infusion is performed, the resistance to CSF outflow is normal, because the lumbar infusion is not able to detect the proximal narrowing in CSF circulatory pathways. The resting pressure, pulse amplitude and, paradoxically, PVI are all relatively high ($ICP > 12 \text{ mmHg}$, pulse amplitude $> 4 \text{ mmHg}$, PVI $> 18 \text{ ml}$).

Obstructive hydrocephalus can be safely assessed using ventricular infusion (via a reservoir). This demonstrates high intracranial resting pressure and high resistance to CSF outflow ($ICP > 15 \text{ mmHg}$, $R_{csf} > 13 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$). The PVI is low ($< 13 \text{ ml}$) and the pulse amplitude is high ($> 4 \text{ mmHg}$), indicating poor compensatory reserve. Acute communicating hydrocephalus (such as following subarachnoid haemorrhage), in which there is insufficient reabsorption or circulation of CSF over the brain convexity, presents the same pattern of parameters whether the lumbar or ventricular approach is used.

Testing of CSF Dynamics in Shunted Patients

When a shunt is functioning properly, the resting pressure remains at or below the shunt's opening pressure.

Tests repeated after shunting should always be considered in comparison with the tests performed before surgery. Abnormal cerebrospinal compensatory parameters such as high resting pressure, increased resistance to CSF outflow or decreased PVI should return to normal after successful shunting [56, 87]. In valves with a low hydrodynamic resistance and a well-defined opening pressure, a sharp plateau of the pressure trend is seen about 1–5 mmHg above the level of the shunt's opening pressure [91] (Fig. 7). The magnitude of this plateau should not exceed:

$$\begin{aligned} \text{Shunt operating pressure} + R_{shunt} \cdot \\ \cdot \text{Infusion rate} + 5 \text{ mmHg} \end{aligned}$$

where R_{shunt} is the hydrodynamic resistance of the opened shunt and 5 mmHg is a "safety margin". Both the

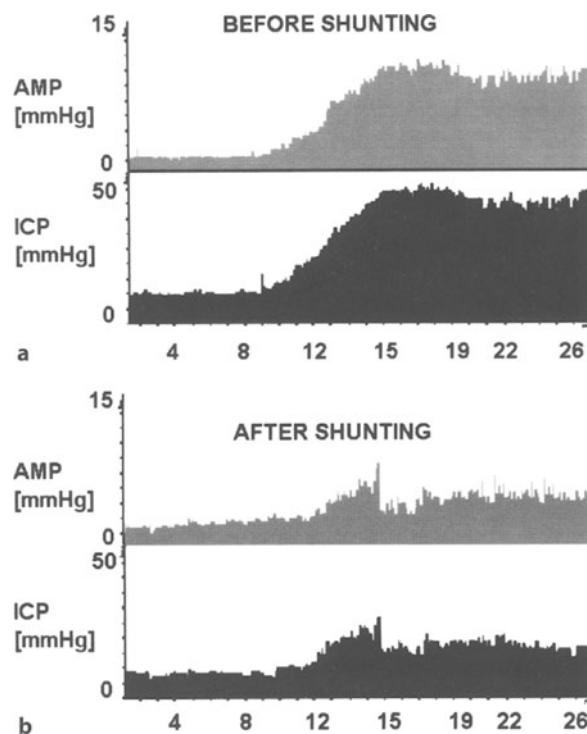


Fig. 7. Infusion test made in patient (after subarachnoid haemorrhage) **a** before and **b** after shunting (Pudenz, medium pressure valve). The opening pressure did not change (8 mmHg before, 7 mmHg after), but resistance to CSF outflow decreased from $20 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$ to $6 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$. Pressure-volume index did not change. Figure reproduced from [20], with permission

shunt operating pressure and R_{shunt} should be painstakingly and repeatedly measured in the laboratory. Once established, however, these values provide an invaluable guideline for shunt testing *in vivo* [18] (Fig. 8).

There are three main methods of assessing CSF space in shunted patients. The simplest and least invasive way is an infusion study through a previously implanted subcutaneous CSF reservoir. Lumbar puncture in communicating hydrocephalus or measurement of the pressure inside the chamber of the shunt are also possible.

Pressure measurement and infusion into the shunt chamber are only possible with shunts that have a CSF sampling reservoir proximal to the valve. Therefore, the method is not useful for the testing of all burr-hole valves.

With the pressure measurement inside the shunt chamber, the presence of a CSF pressure pulse wave and a pressure increase in response to coughing should confirm transmission of pressure between the needle and the CSF space, showing patency of ventricular catheter.

When a shunted patient presents with low-pressure headache, small or slit ventricles, subdural collections or chronic haematomas, the possibility of

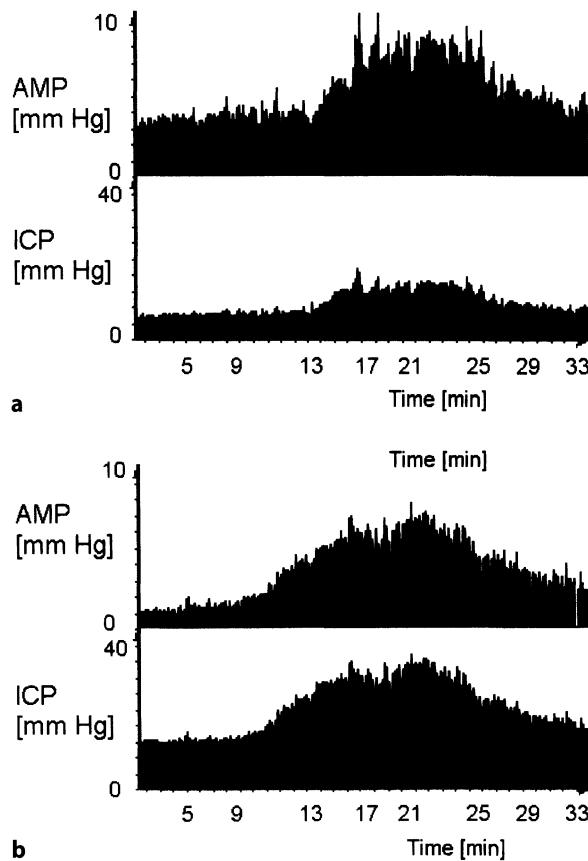


Fig. 8a, b. Infusion test performed to test shunt function in vivo. **a** Patient with Delta valve level 2, no evidence of shunt blockage according to Eq. 15. **b** Patient with Medos valve set for 150 mm H₂O. Opening pressure was within the norm, but the end pressure reached during the test was much higher than that resulting from the laboratory measurement. The shunt was revised and the patient subsequently improved

CSF overdrainage should be considered. Overdrainage related to body posture may be assessed using a tilting armchair. If the baseline pressure measured in the horizontal body position is low (usually negative), overdrainage may have occurred. A change of posture to sitting, with the transducer kept at the same level as the patient's ear, usually produces a further decrease in pressure. If the pressure drops to a value lower than -15 mmHg, overdrainage is likely. If, after 10–15 min of sitting, the pressure and pulse amplitude in horizontal position are lower than at baseline, overdrainage is confirmed (Fig. 9).

The majority of contemporary valves usually have a low hydrodynamic resistance [4], a feature which may result in overdrainage related to the periodic oscillations of the cerebrovascular volume. The expanding cerebrovascular bed acts like the membrane of a water pump with a distal low-resistance valve. Overdrainage seen after a period of moderately elevated oscillating ICP during REM sleep is usually manifested by a period of low

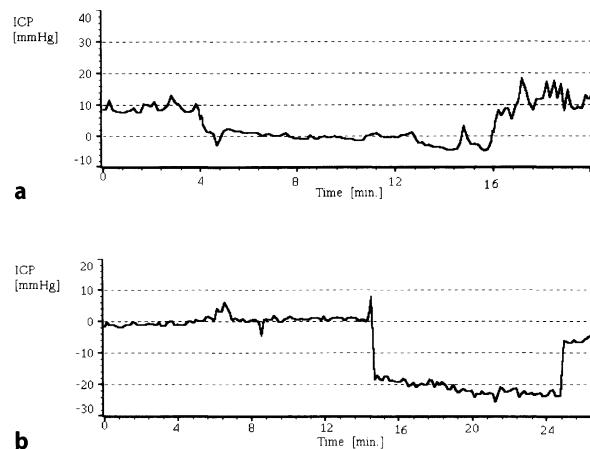


Fig. 9a, b. Tilt tests in patients with overdrainage-like symptoms and different types of shunts. **a** Patient with the Delta valve: with tilting from 4 to 16 min, ICP decreased to 0 and returned to the baseline value after the test. Posture-related overdrainage was excluded. **b** Patient with a shunt with a siphon-preventing device: with tilting from 14 to 26 min, ICP decreased to below 20 mmHg with significantly negative values after the test. Posture-related overdrainage was possible

(negative) pressure and low amplitude of the ICP pulse wave (Fig. 10). Early morning headache should not be assumed to be "high-pressure" – it may be a consequence of low pressure caused by nocturnal overdrainage.

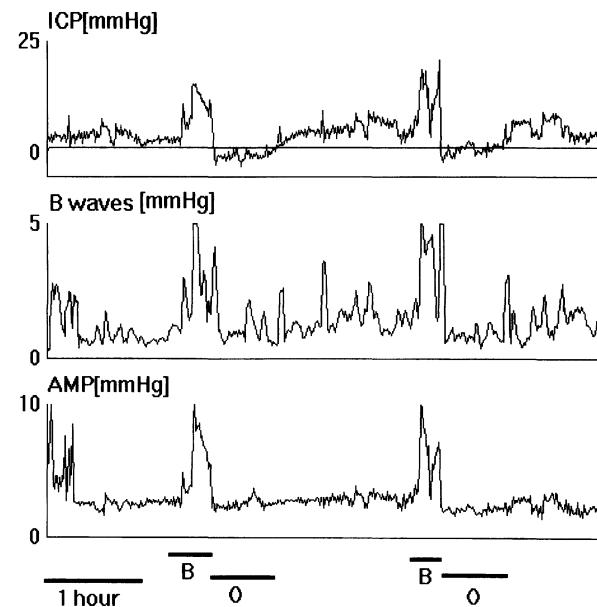


Fig. 10. Overdrainage related to the nocturnal vasomotor waves. Patient with a valve equipped with a siphon-control device (Delta, performance level 2). Two episodes of strong B wave activity lasting for around 30 min were recorded (elevated ICP, pulse amplitude AMP, and computer-detected power of B waves). After each episode the baseline pressure fell to negative values (0) for at least 1 h. Figure reproduced from [20], with permission

How Accurate is a Measurement of Resistance to CSF Outflow?

Although the accuracy and repeatability of the various pressure-volume tests used to assess R_{csf} outflow have been studied in the past, the conclusions are contradictory. In a study of human NPH and benign intracranial hypertension, infusion studies were found to be highly reproducible, with a clear indication that there was no need to repeat them [80] (Fig. 11). On the other hand, in a similar human study, infusion tests were found to be affected by a random error, making misclassification possible [82]. In experimental animals, CSF drainage

was reported to be highly ICP- and situation-dependent [65].

Other Compensatory Parameters Derived from the Infusion Test

There is a very little evidence that other compensatory parameters have any proven clinical value. Resting (baseline) ICP, when elevated, may give information about an uncompensated cerebrospinal volume-expanding process. This is specific to acute rather than NPH. However, the definition of NPH is based on clinical evidence rather than physiological measurements: “normal pressure” is understood as lack of clinical symptoms of intracranial hypertension. Therefore, in some patients clinically assessed as having NPH, baseline ICP can be elevated well above 15 mmHg.

The elastance coefficient (E) is not fully understood. Tans and Poortvliet [90] showed that it correlates with the resistance to CSF outflow. There were no further studies following this concept. Tisell et al. [92] demonstrated that E correlated positively with the result of third ventriculostomy: those with stiffer brain (higher E) have a better chance of improving after surgery.

The pressure-volume curve can be retrieved from the results of infusion study. Frieden and Eksted [32] demonstrated this along with the analysis of the curve when the pressure is lowered during perfusion studies. Kasprowicz et al. [47] demonstrated the phenomenon, perhaps not very precisely designated as “hysteresis”. The curve retrieved from the descending phase of the test is shifted upwards in comparison to the ascending one. These results are very preliminary, yet they indicate that the biomechanics of cerebrospinal system is complex and many novel methods may be introduced into the clinical practice in the future.

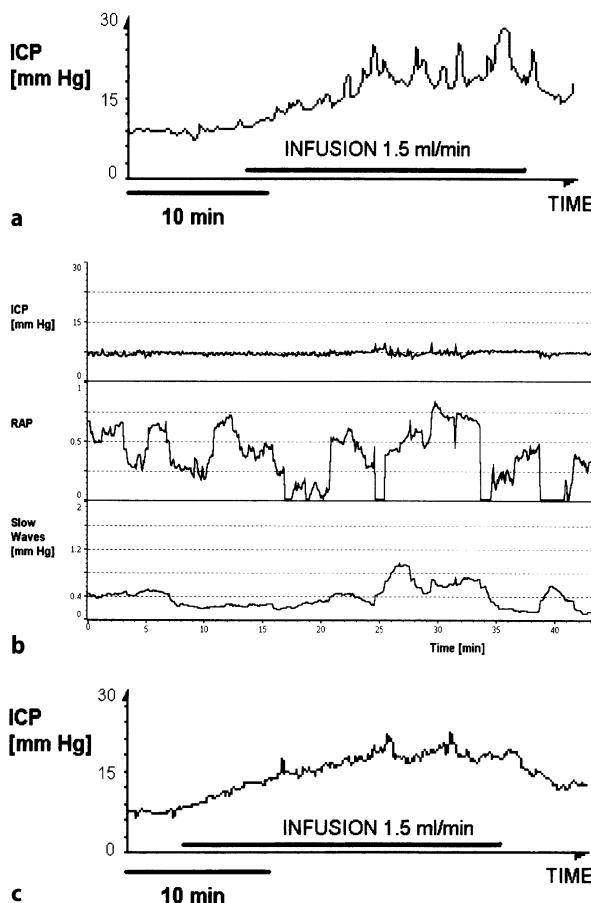


Fig. 11a-c. Assessing the repeatability of infusion study. A patient with only moderate ventricular dilatation and slow improvement after subarachnoid hemorrhage (SAH) was studied **a** 3 months after SAH, **b** 3.5 months after SAH (overnight monitoring; RAP is the correlation coefficient between pulse amplitude and mean ICP – a value around 0 indicates good compensatory reserve) and **c** 4 months after SAH. All tests were identical and failed to indicate any disturbance in CSF dynamics. The patient slowly improved (moderate disability at 6 months) without shunting

CSF Dynamics Testing Versus Overnight ICP Monitoring: The Same or Complementary Information?

Overnight monitoring of ICP has been well established as a useful form of assessment of CSF dynamics in patients presenting with symptoms of hydrocephalus or shunt malfunction. Classically [35, 72], when so-called “B waves” were present for more than 80% of time of monitoring, shunting was recommended. However, using computer detection, “B waves” (slow waves of a period from

20 s to 2 min) are almost universally present, probably even in healthy volunteers. A variable has been proposed which is an equivalent amplitude (i.e. the sine wave amplitude bearing the same energy) within the range of periods from 20 s to 2 min. This amplitude has to remain greater than 1 mmHg for a duration longer than 15 min (Fig. 12) to qualify as a sign of a pathological level of B waves (although the original Borgesen and Gjerris method [10] recorded the presence of B waves when they reached the relatively great amplitude of 5–10 mm Hg). Overall, in our own study, the average energy of slow waves did not correlate well with R_{csf} in those patients in whom both overnight monitoring and infusion test were performed (Fig. 13). This result is quite disturbing; the negative results may be explained by the fact that the survey was conducted in a limited group of “difficult” patients, in whom the results of infusion study indicated a borderline verdict or a picture dramatically divergent from the clinical or radiological findings.

More recent work [63] indicates a correlation between all vasogenic components of ICP detected before the infusion (i.e. pulse amplitude, respiratory wave and B waves) and resistance to CSF outflow. In our opinion, the value of B waves in the diagnosis of hydrocephalus should be confirmed (or rejected) in a prospective randomized trial.

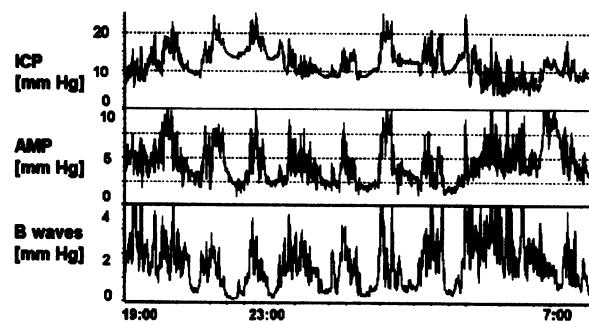


Fig. 12. An example of overnight monitoring of ICP in a 35-year-old woman suffering from symptoms of NPH. Baseline ICP was around 10 mmHg with frequent peaks reaching above 20 mmHg, correlating strongly with elevations of pulse amplitude (AMP). The detected amplitude of B waves increased consistently with peaks of ICP, suggesting that they are of vasogenic origin. The overall amplitude of pulse waves was above 1 mmHg for more than 70% of the time. The patient underwent shunting and improved subsequently

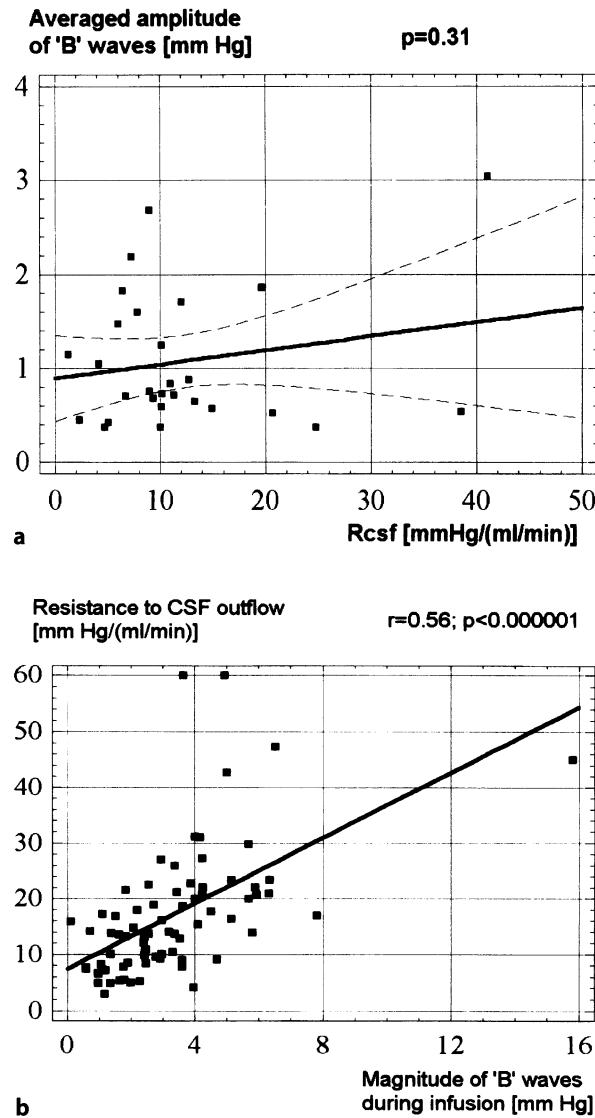


Fig. 13. **a** Overall, the magnitude of slow waves (measured overnight) and the resistance to CSF outflow do not seem to be in correlation. This study was based on 28 patients. **b** Positive correlation shown between slow waves and resistance to CSF outflow measured during infusion study [63], $n=73$ patients

Vascular Components of CSF Compensation

Prediction of improvement after shunt placement in NPH is dependent upon the pre-shunt CSF circulatory profile, shunt function after implantation and the potential co-existence of hydrocephalus with other disease states, particularly of a cerebrovascular nature [8, 52]. Decreased cerebral blood flow, particularly in frontal areas, followed by a marked increase after

shunting was demonstrated to be associated with clinical improvement [37, 94]. These results have also been confirmed in experimental studies [23, 43]. An increase in cerebral blood flow in response to a CSF tap test has also been described as a positive predictor of improvement after shunting [58]. In contrast, in other atrophic diseases, cerebral blood flow tended to decrease after CSF tap [40, 58]. More recently, improvement following shunting was suggested to occur only in those patients in whom cerebral blood flow was normal before shunting [89]. However, these results are controversial; Klinge et al. [50] demonstrated with PET studies that patients with decreased cerebral blood flow before shunting have a better chance of improving than those with normal cerebral blood flow.

Vasodilatory responses to acetazolamide were found to be preserved in patients with NPH who did not improve after shunting. These responses were partially disturbed in white matter regions pre-operatively in those patients who improved after shunting [89]. Klinge et al. [50] reported that the response to acetazolamide increased immediately after successful shunting but decreased in those patients who did not improve. CO₂ reactivity (measured with ¹³³Xe) was found to be decreased in patients with NPH [67]. This was partially confirmed by Owler et al. [69] investigating a decrease in cerebral blood flow during elevation of ICP caused by infusion study. On the other hand, their results may indicate an interaction between CSF intraparenchymal leak during infusion and a decrease in cerebral blood flow, particularly since the aforementioned reduction in cerebral blood flow was more vigorous in the areas adjacent to dilated ventricles. More recently, transcranial Doppler ultrasonography showed CO₂ reactivity in the territory of the anterior and middle cerebral artery to increase following successful shunting [54]. Thus, an interaction between cerebrovascular profile and CSF dynamics has been ambiguously documented in pathological states. A comprehensive review has been recently published by Owler and Pickard [70].

During infusion studies an increase in ICP affects cerebral blood flow and cerebral blood volume. Changes in cerebral blood volume usually cause additional changes in ICP, not accounted for by the infusion, which affect calculated compensatory parameters. This illustrates the need to extend the model of CSF circulation as presented in the previous section.

As we stated before, a balance between cerebrospinal volume and pressure results from the dynamic equilibrium between the volumetric changes in brain tissue, fluctuations in the volume of CSF, and variations in cerebral blood volume. Due to the confines of the rigid skull vault, any malfunction may generate a pressure response that affects the entire cerebral circulation.

One approach to the theoretical evaluation of intracranial parameters is the concept of pressure-flow

modelling, which is helpful in understanding the dynamic relationships between cerebral blood flow, ICP and arterial blood pressure. The quantitative relationship between cerebral blood flow, ICP and arterial blood pressure cannot be expressed using one simplified formula. A hydrodynamic model and its electrical equivalent describing this relationship is shown in Fig. 14. In this model cerebral blood flow is controlled by two external variables, ABP (equivalent to a central arterial blood pressure), and P_{ss} , simulating venous pressure in the sagittal sinus. Modelling software can calculate the internal variables: cerebral venous pressure, ICP, pressure in brain small arteries, and cerebral blood flow through the resistance vessels and larger arteries. All of these variables are simulated as time-dependent waveforms, and may be described by their mean, systolic and diastolic components, or the pulse amplitude values. The model contains two major flow pathways representing blood and CSF. The cerebral blood flow pathway begins with arterial inflow to the brain through the basal intracranial vessels (R_a). Arterial blood is stored in vessels with an arterial compliance (C_a). Forward flow through the resistance vessels (CVR) is influenced by cerebral autoregulation. Capillary and venous blood is stored as compliance (C_v). Finally, venous blood flows out to the sagittal sinus through the bridging veins which offer resistance (R_b).

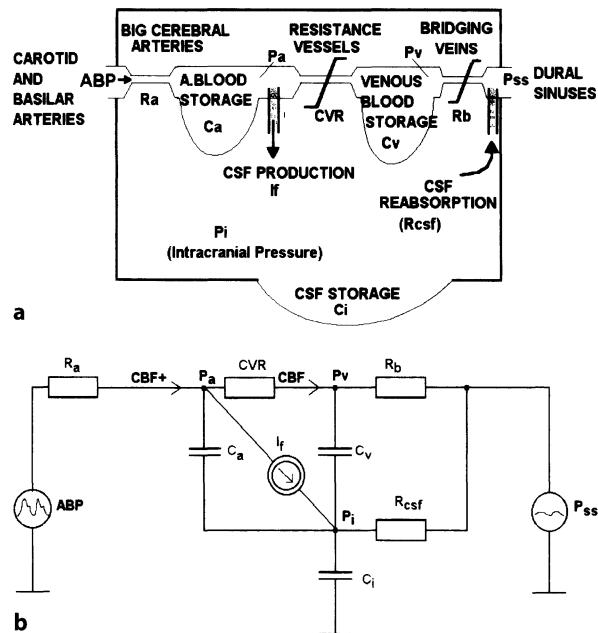


Fig. 14. **a** Hydrodynamic representation of the dynamic pressure-flow model of cerebrospinal space, describing interactions between CSF dynamics and cerebral blood flow. The elements of the model are explained in the text. **b** Equivalent electrical circuit representing the model. Electrical resistance is equivalent to hydrodynamic resistance and capacitors to hydrodynamic compliance, represented in **a**. Figure reproduced from [18], with permission

The CSF circulation pathway consists of fluid formation (I_f), storage in distensible fluid structures (C_i) and reabsorption into venous blood (R_{csf}). A set of non-linear differential equations may be solved numerically, reflecting the haemodynamic response to variations in the cerebral perfusion pressure. Use of such a model allows the study and interpretation of numerous problems in CSF and cerebrovascular dynamics.

Overdrainage: Uncoupling Between Cerebral Venous Pressure and ICP

Long ventriculo-peritoneal tubing produces a hydrostatic pressure gradient which, despite some ingenious technological advances, can still constitute an important source of secondary clinical complications [13, 31, 74]. From the model of cerebral blood flow-CSF circulation, it emerges that ICP is always coupled to and a little higher than the venous pressure in the sagittal sinuses. This coupling is due to cerebral blood flow through collapsible cortical and bridging veins. When ICP increases above venous pressure (P_v) these vessels collapse, increasing their hydrodynamic resistance and automatically increasing P_v . Therefore, any change in venous pressure would affect P_{ss} (sagittal sinus pressure), P_v and ICP. The P_v -ICP gradient is always positive but lower than 5 mmHg as long as ICP stays above P_{ss} .

After ventriculo-peritoneal shunting, ICP may decrease in the upright body position to a value much lower than P_{ss} . Therefore, the P_v -ICP gradient may rise infinitely as P_v is no longer coupled to ICP. It may be noticeable in an upright body position, but also during coughing and other bodily movements associated with an acutely raised central venous pressure. Such an unphysiological situation may contribute to increasing the risk of subdural bleeding.

Why Is ICP Higher than Predicted by the Davson Equation?

According to Davson's equation, the mean ICP, explained solely by CSF circulation, is proportional to the resistance to CSF outflow, CSF production rate and sagittal sinus pressure. Marmarou et al. [61] proposed a modification to this formula, stating that average ICP can be described by two components: CSF circulation and vasogenic. Thus, the Davson formula can be rewritten as:

$$\begin{aligned} \text{ICP} &= \text{ICP}_{\text{csf circulation}} + \text{ICP}_{\text{vasogenic}} = \\ &= R_{\text{csf}} \cdot I_{\text{formation}} + P_{ss} + \text{ICP}_{\text{vasogenic}}. \end{aligned} \quad (16)$$

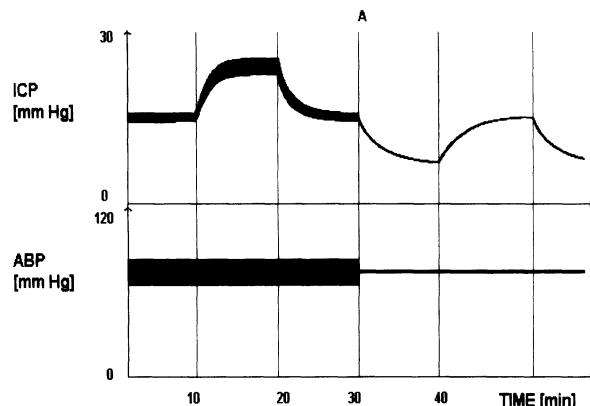


Fig. 15. Results of simulation of ICP during infusion study made under two conditions of the pulsatile component of ABP. When pulsations were normal (20 mmHg), baseline ICP was higher than predicted by Davson's equation and resistance to CSF outflow calculated from the simulated infusion was greater than real parameter ($8.7 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$ versus $6 \text{ mmHg} \cdot \text{ml}^{-1} \cdot \text{min}$). When the pulse of ABP was reduced to 0 (point A), mean ICP dropped to a value predicted Davson's formula, and the measured resistance to CSF outflow calculated from the subsequent infusion was exactly equal to the value of the real resistance to CSF outflow. Figure reproduced from [19], with permission

It is difficult to understand why, under steady conditions, a vascular bed which is anatomically separated from the CSF compartment may modify mean ICP. Although CSF formation is dependent on choroid plexus perfusion pressure, this dependence has never been reported as very significant. Theoretically, only pulsatile changes in cerebral blood volume can influence mean ICP. The model of integrated cerebral blood and CSF circulation [20] may suggest an explanation that in all simulations the vascular component is proportional to the pulsatile ABP. The mean ICP decreases abruptly when blood pressure pulsations in the model cease without changing mean ABP (Fig. 15). Moreover, the vascular component is modified by autoregulation, cerebrovascular resistance, mean arterial pressure, and ICP. It is also proportional to the ratio of cerebrovascular to CSF compartmental compliances. Therefore, the hypothesis may be proposed that the continuously fluctuating volume of the arterial bed produces a constant vasogenic ICP component which cannot be explained by Davson's formula.

Modulation of CSF Dynamics by Vascular Factors

The tone of cerebral vessels has been reported to influence CSF compensatory reserve as described by

brain compliance, pressure volume index, brain stiffness, or CSF pulse amplitude [6]. Generally, with cerebral vasodilation, the overall compliance of cerebrospinal space is believed to decrease. A similar effect has been confirmed with increasing brain oedema, inflation of an extradural balloon, and other expanding mass lesions [78, 79]. However, no significant change of the elastance coefficient during arterial hypotension was reported in a recently published study [19]. In contrast, during hypercapnia the elastance coefficient increases, signifying an increase in the brain stiffness. These data suggest that, during hypercapnia, when the parenchymal arterioles dilate, the elastance coefficient decreases in a similar way to that seen during experimental brain oedema or in patients suffering from benign intracranial hypertension. The most intriguing finding in this study is a change in the resistance to CSF outflow observed during different cerebral vasodilatory manoeuvres. The R_{csf} decreased with hypotension but increased with hypercapnia. On the other hand, with hypercapnia, arterial pressure increased consistently. Therefore, it is possible that R_{csf} was not influenced by hypercapnia alone, but varied proportionally with arterial blood pressure. This phenomenon has not been described so far, and it is difficult to find a satisfactory explanation.

Narrowing of CSF flow pathways due to brain expansion as a result of an increase in cerebral blood volume may only be hypothetical. Similarly, we can speculate that accessory pathways of CSF circulation may become more effective during hypotension. Nevertheless, changes of R_{csf} with deep hypotension (reduction in ABP by 50%) are re-

stricted (30% change in R_{csf}). In practice, during infusion tests in human, changes in ABP are limited to 10% of the mean value, and any possible error in the calculation of R_{csf} did not exceed the random error as assessed during the repeatability study.

Relationship Between R_{csf} and Cerebral Autoregulation

Some studies have indicated that cerebral blood flow may be compromised in areas around the ventricles in patients presenting with a degree of ventricular dilatation and clinical symptoms of NPH. Those in whom the resistance to CSF outflow is increased are believed to improve when their CSF drainage is facilitated by implantation of a shunt system. Recently a relationship between the resistance to CSF outflow and cerebral autoregulation in patients diagnosed with NPH has been reported [21]. An index of autoregulation was calculated in 40 patients during infusion study using transcranial Doppler ultrasonography. It correlated significantly with the resistance to CSF outflow (negatively, $R=-0.34$; $p<0.03$; $n=40$), indicating better autoregulation in those patients with higher R_{csf} (Fig. 16). Patients presenting with ventricular dilatation may have either low (atrophy) or increased (NPH) resistance to CSF outflow. Increased resistance correlates with preserved autoregulation. Those with a low resistance, suggestive of brain atrophy, have severely disturbed autoregulation in the middle cerebral artery territory.

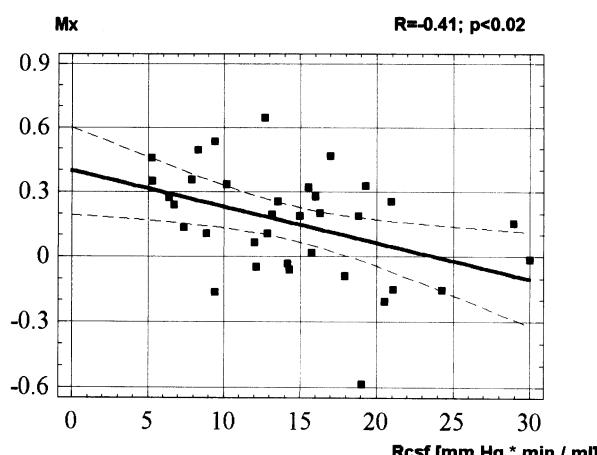


Fig. 16. Regression relationship between the index of autoregulation (M_x , y axis) and the resistance to CSF outflow (R_{csf} , x axis). The relationship is significant ($p<0.02$) and indicates that patients with greater R_{csf} have a better autoregulatory reserve. Figure reproduced from [21], with permission

References

1. Albeck MJ, Borgesen SE, Gjerris F, et al: Intracranial pressure and cerebrospinal fluid outflow conductance in healthy subjects. *J Neurosurg* 74:597-600, 1991
2. Albeck MJ, Skak C, Nielsen PR, et al: Age dependency of resistance to cerebrospinal fluid outflow. *J Neurosurg* 89:275-278, 1998
3. Andreasen N, Minthon L, Clarberg A, et al: Sensitivity, specificity, and stability of CSF-tau in AD in community-based patient sample. *Neurology* 53:1488-1494, 1999
4. Aschoff A, Kremer P, Benesch C, et al: Overdrainage and shunt technology. *Child's Nerv Syst* 11: 193-202, 1995
5. Avezaat CJJ, Eijndhoven JHM: Cerebrospinal fluid pulse pressure and craniospinal dynamics. A theoretical, clinical and experimental study (thesis). Jongbloed A, The Hague. 1984
6. Avezaat CJJ, van Eijndhoven JHM, Wyper DJ: Cerebrospinal pulse-pressure and intracranial volume-pressure relationships. *J Neurol Neurosurg Psychiatry* 42: 687-700, 1979
7. Boon AJ, Tans JT, Delwel EJ, et al: Dutch normal-pressure hydrocephalus study: prediction of outcome after shunting by resistance to outflow of cerebrospinal fluid. *J Neurosurg* 87: 687-693, 1997
8. Boon AJ, Tans JT, Delwel EJ, et al: Dutch Normal-Pressure Hydrocephalus Study: the role of cerebrovascular disease. *J Neurosurg* 90: 221-226, 1999
9. Borgesen SE, Albeck MJ, Gjerris F, et al: Computerized infusion test compared to steady pressure constant infusion test in measurement of resistance to CSF outflow. *Acta Neurochir* 119: 12-16 1992
10. Borgesen SE, Gjerris F: The predictive value of conductance to outflow of CSF in normal pressure hydrocephalus. *Brain* 105: 65-86, 1982
11. Borgesen SE, Gjerris F, Sorensen SC: The resistance to cerebrospinal fluid absorption in humans. A method of evaluation by lumbo-ventricular perfusion ,with particular reference to normal pressure hydrocephalus. *Acta Neurol Scand* 57: 88-96, 1978
12. Bradley WG Jr; Whittemore AR; Kortman KE; et al: Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. *Radiology* 178: 459-466, 1991
13. Chapman PH, Cosman ER, Arnold MA: The relationship between ventricular fluid pressure and body position in normal subjects and subjects with shunts: a telemetric study. *Neurosurgery* 26: 181-189 1990
14. Chopp M, Portnoy HD: System analysis of intracranial pressure. Comparison of volume-pressure test and CSF-pulse amplitude analysis. *J Neurosurg* 53:516-527, 1980
15. Costabile G, Probst C: Intrathecal infusion test and decrease in shunt revisions and infections. *Neurochirurgia* Stuttg 31: 134-135, 1988
16. Czosnyka M, Batorski L, Roszkowski M, et al: Cerebrospinal compensation in hydrocephalic children. *Child's Nerv Syst* 9: 17-22, 1993
17. Czosnyka M, Batorski L, Laniewski P, et al: A computer system for the identification of the cerebrospinal compensatory model. *Acta Neurochir (Wien)* 105: 112-116, 1990
18. Czosnyka M, Piechnik S, Richards HK, et al: Contribution of mathematical modelling to the bedside tests of cerebrovascular autoregulation. *J Neurol Neurosurg Psychiatry* 63: 721-731, 1997
19. Czosnyka M, Richards HK, Czosnyka Z, et al: Vascular components of cerebrospinal fluid compensation. *J Neurosurg* 90: 752-759, 1999
20. Czosnyka M, Whitehouse H, Smielewski P, et al: Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients: a guide to interpretation based on observational study. *J Neurol Neurosurg Psychiatry* 60: 549-558, 1996
21. Czosnyka ZH, Czosnyka M, Whitfield PC, et al: Cerebral autoregulation among patients with symptoms of hydrocephalus. *Neurosurgery* 50:526-32, 2002
22. Czosnyka Z, Czosnyka M, Richards HK, et al: Posture-related overdrainage: comparison of the performance of 10 hydrocephalus shunts in vitro. *Neurosurgery* 42: 327-333, 1998
23. Da Silva MC, Michowicz S, Drake JM, et al: Reduced local cerebral blood flow in periventricular white matter in experimental neonatal hydrocephalus - restoration with CSF shunting. *J Cerebr Blood Flow Metab* 15: 1057-1065, 1995
24. Dandy WE: Extrication of the choroid plexus of the lateral ventricles in a communicating hydrocephalus of the lateral ventricle in communicating hydrocephalus. *Ann Surg* 68: 569-579, 1918
25. Davson H: Formation and drainage of the CSF in hydrocephalus. In: Shapiro K, Marmarou A, Portnoy H (eds) *Hydrocephalus*. Raven Press, New York, pp 112-160, 1984
26. Davson H, Welch K, Segal MB: The physiology and pathophysiology of cerebrospinal fluid. Churchill Livingstone, New York, 1987
27. Ekstedt J: CSF hydrodynamic studies in man. Normal hydrodynamic variables related to CSF pressure and flow. *J Neurol Neurosurg Psychiatry* 41: 345-353, 1978
28. Ekstedt J: CSF hydrodynamic studies in man. Method of constant pressure CSF infusion. *J Neurol Neurosurg Psychiatry* 40: 105-119, 1977
29. Epstein F; Lapras C; Wisoff JH: 'Slit-ventricle syndrome': etiology and treatment. *Pediatr Neurosci* 14: 5-10, 1988
30. Foltz EL, Blanks JP, Yonemura K: CSF pulsatility in hydrocephalus: respiratory effect on pulse wave slope as an indicator of intracranial compliance. *Neurol Res* 12: 67-74, 1990
31. Foltz EL, Blanks JP: Symptomatic low intracranial pressure in shunted hydrocephalus. *J Neurosurg* 68: 401-8, 1988
32. Frieden H, Ekstedt J: Estimation of CSF outflow resistance: Model validation and resistance calculation by the method of CSF volume accounting. In: Gjerris F, Borgesen SE, Sorensen PS (eds) *Outflow of cerebrospinal fluid*. Munksgaard, Copenhagen, p 198-210, 1989
33. Frieden H, Ekstedt J: Instrumentation for cerebrospinal fluid hydrodynamic studies in man. *Med Biol Eng Comput* 20: 167-180, 1982
34. Gideon P, Thomsen C, Stahlberg F, et al: Cerebrospinal fluid production and dynamics in normal aging: a MRI phase-mapping study. *Acta Neurol Scand* 89: 362-366, 1994
35. Gjerris F, Borgesen SE: Patophysiology of CSF circulation. In: Crockard A, Hayward A, Hoff JT (eds) *Neurosurgery. The scientific basis of clinical practice*. Blackwell Scientific Publications, pp 146-174, 1992
36. Gjerris F, Borgesen SE, Sorensen PS, et al: Resistance to cerebrospinal fluid outflow and intracranial pressure in patients with hydrocephalus after subarachnoid haemorrhage. *Acta Neurochir (Wien)* 88(3-4): 79-86, 1987

37. Graff J, Radford NR, Rezai K, et al: Regional cerebral blood flow in normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry* 50: 1589-1596, 1987
38. Hakim S, Adams RD: The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure. Observations on cerebrospinal fluid hydrodynamics. *J Neurol Sci* 2:307-327, 1965
39. Hara K, Nakatani S: Detection of the B waves in the oscillation of intracranial pressure by fast Fourier transform. *Med Inf Lond* 15 : 125-331, 1990
40. Hartman A, Alberti E: Cerebral blood flow and cerebral blood volume in communicating hydrocephalus. *Arch Psychiatr Nervkr* 225:291-306, 1978
41. Hatashita S, Hoff JT: Biomechanics of brain edema in acute cerebral ischemia in cats. *Stroke* 19: 91-97, 1988
42. Heiss JD, Patronas N, DeVroom HL, et al: Elucidating the pathophysiology of syringomyelia. *J Neurosurg* 91: 553-562, 1999
43. Higashi K, Asahisa H, Ueda N, et al: Cerebral blood flow and metabolism in experimental hydrocephalus. *Neurol Res* 8: 169-176, 1986
44. Hoffmann O: CSF dynamics: Integration of Pulsatory Components and Autoregulation into Mathematical Model. In: Ishii S, Nagai H, Brock M (eds) Intracranial pressure V. Springer, Berlin Heidelberg, pp 169-173, 1983
45. James AE Jr, Novak G, Bahr AL, et al: The production of cerebrospinal fluid in experimental communicating hydrocephalus. *Exp Brain Res* 27: 553-557, 1977
46. Jurkiewicz J, Czernicki Z, Berdyga J, et al: Three-phase infusion test. *G Neurol Neurochir Pol* 28:363-369, 1994
47. Kasprowicz M, Czosnyka Z, Momjian S, et al: Hysteresis of cerebrospinal pressure-volume curve among patients with hydrocephalus. *Neurosurgery* 2002 (in submission).
48. Katzman R, Hussey F: A simple constant infusion manometric test for measurement of CSF absorption. *Neurology* (Minneapolis), 20:534-544, 1970
49. Klinge P, Fischer J, Brinker T, et al: PET and CBF studies of chronic hydrocephalus: a contribution to surgical indication and prognosis. *J Neuroimaging* 8: 205-209, 1998
50. Klinge PM, Berding G, Brinker T, et al: A positron emission tomography study of cerebrovascular reserve before and after shunt surgery in patients with idiopathic chronic hydrocephalus. *J Neurosurg* 91: 605-609, 1999
51. Kosteljanetz M, Nehen AM, Kaalund J: Cerebrospinal fluid outflow resistance measurements in the selection of patients for shunt surgery in the normal pressure hydrocephalus syndrome. A controlled trial. *Acta Neurochir (Wien)* 104(1-2): 48-53, 1990
52. Kristensen B, Malm J, Fagerlund M, et al: Regional cerebral blood flow, white matter abnormalities , and cerebrospinal fluid hydrodynamics in patients with idiopathic adult hydrocephalus syndrome. *J Neurol Neurosurg Psychiatry* 60: 282-288, 1996
53. Larsson A, Moonen M, Bergh AC, et al: Predictive value of quantitative cisternography in normal pressure hydrocephalus. *Acta Neurol Scand* 81: 327-332, 1990
54. Lee EJ, Hung YC, Chang CH, et al: Cerebral blood flow velocity and vasomotor reactivity before and after shunting surgery in patients with normal pressure hydrocephalus. *Acta Neurochir (Wien)* 140: 599-604, 1998
55. Lemaire JJ, Chazal J, Gutknecht JL, et al: Effects of acute compliance fluctuation on slow ICP waves: frequential aspects. In: Nagai H, Kamiya K, Ishii S (eds) Intracranial pressure IX. Springer, Berlin Heidelberg New York, pp 498-501, 1994
56. Maksymowicz W,Czosnyka M,Koszewski W, et al.: The role of cerebrospinal system compensatory parameters in estimation of functioning of implanted shunt system in patients with communicating hydrocephalus. *Acta Neurochir* 101: 112-116, 1989
57. Malm J, Kristensen B, Karlsson T, et al: The predictive value of cerebrospinal fluid dynamic tests in patients with th idiopathic adult hydrocephalus syndrome. *J Arch Neurol* 52:783-789, 1995
58. Mamo HL, Meric PC, Ponsin JC, et al: Cerebral blood flow in normal pressure hydrocephalus. *Stroke* 18: 1074-1080, 1987
59. Marmarou A: A theoretical model and experimental evaluation of the cerebrospinal fluid system. Thesis, Drexel University, Philadelphia, PA, 1973
60. Marmarou A, Foda MA, Bandoh K, et al: Posttraumatic ventriculomegaly: hydrocephalus or atrophy? A new approach for diagnosis using CSF dynamics. *J Neurosurg* 85:1026-1035, 1996
61. Marmarou A, Maset AL, Ward JD, et al: Contribution of CSF and vascular factors to elevation of ICP in severely head injured patients. *J Neurosurg* 66: 883-890, 1987
62. Marmarou A, Shulman K, Rosende RM: A non-linear analysis of CSF system and intracranial pressure dynamics. *J Neurosurg* 48: 332-344, 1978
63. Momjian S, Czosnyka M, Czosnyka Z, et al: Correlation between the resistance to cerebrospinal fluid outflow and vasogenic waves of intracranial pressure in hydrocephalus. *Brit J Neurosurg* 2004 (in press)
64. May C, Kaye JA, Atack JR, et al: Cerebrospinal fluid production is reduced in healthy aging. *Neurology* 40(3 Pt 1): 500-503, 1990
65. McComb: Recent research into the nature of cerebrospinal fluid formation and absorption. *J Neurosurg* 59: 369-383, 1983
66. McComb JG, Davson H, Hyman S, et al: Cerebrospinal fluid drainage as influenced by ventricular pressure in the rabbit. *J Neurosurg* 56: 790-797, 1982
67. Meyer JS, Tachibana H, Hardenberg JP, et al: Normal pressure hydrocephalus. Influence on cerebral hemodynamics and cerebrospinal fluid pressure-chemical autoregulation. *Surg Neurol* 21: 195-203, 1984
68. Milhorat TH: Failure of choroid plexectomy as treatment for hydrocephalus. *Surg Gynecol Obstet* 139:505-508, 1974
69. Owler BK, Harris NG, Pena A, et al: Global and regional CBF changes in patients with normal pressure hydrocephalus with changes in ICP. *J Cereb Blood Flow Metab* 21 (Suppl 1): S419, 2001
70. Owler BK, Pickard JD: Normal pressure hydrocephalus and cerebral blood flow: a review. *Acta Neurol Scand* 104: 325-342, 2001
71. Pappenheimer JR, Heisey SR, Jordan EF, et al: Perfusion of the cerebral ventricular system in unanaesthetized goats. *Am J Physiol* 203: 763-774, 1962
72. Pickard JD, Teasdale G, Matheson M, et al: Intraventricular pressure waves - the best predictive test for shunting in normal pressure hydrocephalus. In: Shulman K, Marmarou A, Miller JD et al (eds) Intracranial pressure IV. Springer, Berlin Heidelberg New York, pp 498-500, 1980
73. Portnoy HD, Chopp M, Branch C, et al: Cerebrospinal fluid pulse waveform as an indicator of cerebral autoregulation. *J Neurosurg* 56: 666-678, 1982

74. Pudenz RH, Foltz EL: Hydrocephalus: overdrainage by ventricular shunts. A review and recommendations. *Surg Neurol* 35: 200-212, 1991
75. Raabe A, Czosnyka M, Piper I, et al: Monitoring of intracranial compliance: correction for a change in body position. *Acta Neurochir (Wien)* 141: 31-36, 1999
76. Rekate HL, Brodkey JA, Chizeck HJ, et al: Ventricular volume regulation: a mathematical model and computer simulation. *Pediatr Neurosci* 14: 77-84, 1988
77. Rubenstein E: Relationship of senescence of cerebrospinal fluid circulatory system to dementias of the aged. *Lancet* 351: 283-285, 1998
78. Schettini A, Walsh EK: Brain tissue elastic behavior and experimental brain compression. *Am J Physiol* 255: R799-R805, 1988
79. Schettini A, Walsh EK: CSF dynamics and cerebral hemodynamics in ATP-induced hypotension. In: Avezaat CJ, Eijndhoven JHM, Maas AIR, Tans JTJ (eds) *Intracranial pressure VIII*. Springer, Berlin Heidelberg New York, pp 738-743, 1993
80. Schmidt JF, Fedders O, Borgesen SE, et al: Reproducibility of measurements of resistance to CSF outflow. In: Gjerris F, Borgesen SE, Sorensen PS (eds) *Outflow of cerebrospinal fluid*. Copenhagen, Munksgaard, pp 224-232, 1989
81. Shapiro K, Fried A, Takei F, et al: Effect of the skull and dura on neural axis pressure-volume relationships and CSF hydrodynamics. *J Neurosurg* 63:76-81, 1985
82. Sklar FH, Beyer CW, Ramanathan M, et al: Servo-controlled lumbar infusions: a clinical tool for determination of CSF dynamics as a function of pressure. *Neurosurgery* 3: 170-178, 1978
83. Sklar FH, Giller C, Shapiro K: Manometric determination of CSF absorption: variance considerations. In: Gjerris F, Borgesen SE, Sorensen PS (eds) *Outflow of cerebrospinal fluid*. Copenhagen, Munksgaard, pp 249-255, 1989
84. Sliwka S: A clinical system for the evaluation of selected dynamic properties of the intracranial system. PhD Thesis, Polish Academy of Sciences, Warsaw, 1980
85. Sorek S, Bear J: Models of Cerebral System Mechanics. Scientific Report No. 2, Technion - Israel Institute of Technology, Haifa 1986
86. Sorenson PS, Gjerris F, Schmidt J: Resistance to CSF outflow in benign intracranial hypertension (pseudotumor cerebri). In: Gjerris F, Borgesen SE, Sorensen PS (eds) *Outflow of cerebrospinal fluid*. Copenhagen, Munksgaard, pp 343-355, 1989
87. Sprung C, Collman H, Fuchs EC, et al: Pre- and postoperative evaluation of hydrocephalus using the infusion test. *Adv Neurosurg* 4: 463-70, 1977
88. Stochetti N, Rossi S, Cacerelli P, et al: The pattern of ICP after bolus injection as an indicator of intracranial disturbances. In: Nagai H, Kamiya K, Ishii S (eds) *Intracranial pressure IX*. Springer, Tokyo, pp 172-174, 1994
89. Tanaka A, Kimura M, Nakayama Y, et al: Cerebral blood flow and autoregulation in normal pressure hydrocephalus. *Neurosurgery* 40: 1161-1165, 1997
90. Tans JT, Poortvliet DC: Relationship between compliance and resistance to outflow of CSF in adult hydrocephalus. *J Neurosurg* 71: 59-62, 1989
91. Taylor R, Czosnyka Z, Czosnyka M, et al: A laboratory model of testing shunt performance after implantation. *Br J Neurosurg* 16: 30-35, 2002
92. Tisell M, Edsbagge M, Stephensen H, et al: Elastance correlates with outcome after endoscopic third ventriculostomy in adults with hydrocephalus caused by primary aqueductal stenosis. *Neurosurgery* 50: 70-76, 2002
93. Ursino M, Di Giacomo P: A mathematical model of the relationship between cerebral blood volume and intracranial pressure changes: the generation of plateau waves. *Ann Biomed Eng* 19: 15-25, 1991
94. Vorstrup S, Christensen J, Gjerris F, et al: Cerebral blood flow in patients with normal pressure hydrocephalus before and after shunting. *J Neurosurg* 66: 379-87, 1987
95. Williams B: Progress in syringomyelia. *Neurol Res* 8: 130-45, 1986

Pathophysiology of Hydrocephalus

MÁRCIA C. DA SILVA

Hydrocephalus is a pathological entity that has been known since Hippocrates and Galen [33]. It is one of the most common disorders treated by neurosurgeons. The overall incidence and prevalence of the disease can be difficult to estimate, as it can occur as an isolated entity or in association with other neurological disorders. Congenital hydrocephalus is present in 3 of 1000 live births [97]. Aside from the congenital etiology, hydrocephalus can result from a series of neurological conditions such as head trauma, intracranial hemorrhage, tumor, or infection of the central nervous system at any time during life.

Whatever its cause, the symptomatology of hydrocephalus is remarkably similar among patients. The radiological appearance is also deceptively alike for most age groups. However, age is an important factor in determining the clinical picture. Hydrocephalus due to a congenital infection of the central nervous system in a neonate is a different disorder from the normal-pressure hydrocephalus of the adult, despite the fact that both are morphologically represented by ventriculomegaly. Like the etiology, the specific damage caused by hydrocephalus is also strongly influenced by the age at onset of the disease.

The pathophysiology of hydrocephalus is much more complex than its clinical or radiological presentation, going beyond the ventricular dilatation and mantle thinning obvious at first inspection. Together with gross macroscopic changes, hydrocephalus leads to alterations of the normal physiology, biochemistry, and ultrastructure of the brain. Three factors are basic for the determination of the severity of the injuries caused by hydrocephalus and the ultimate outcome. They are: age at onset, etiology, and the duration of the disease.

The stage of maturation of the brain afflicted by hydrocephalus must be taken into account when discussing pathophysiology. Development is a fundamental aspect of the physiology of the brain in young immature animals and humans: metabolic pathways are maturing, neuronal activity is greatly increased, biosynthetic activity is intense, and myelination proceeds at a

fast pace [4, 18, 29, 38, 43, 49, 52, 63, 66, 69, 84, 91, 104, 107, 108, 109, 113, 134, 143, 145, 146, 148]. In young children, as compared to adults, hydrocephalus may jeopardize the normal maturational processes of the developing brain, in addition to all other deleterious effects, leading to devastating results. As will be discussed later, some of the normal maturational processes may be permanently arrested following an external injury, and normal development does not always follow elimination of the insult. In contrast, the adult mature brain will not have its building processes damaged by hydrocephalus. Thus, given a similar insult, the injury to the adult brain tends to be less severe than that to the immature brain.

Etiology is also an important factor in the determination of the pathophysiology of the disease. Depending on the cause, there may be other significant injury mechanisms at play besides those associated with the hydrocephalus per se. For example, hydrocephalus due to congenital toxoplasmosis infection may present areas of necrosis and cavitation that are directly related to the pathogen, not to the ventriculomegaly, and that in themselves will produce extensive destruction of the cerebral tissue. Tuberculous meningitis may cause severe damage to the brain parenchyma and at the same time lead to hydrocephalus (Fig. 1).

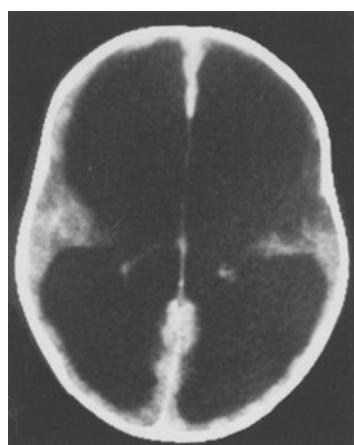


Fig. 1. CT scan of a 9-month-old child who presented with hydrocephalus secondary to tuberculous meningitis. There is extreme ventricular dilatation and periventricular edema. Also, an area of necrosis of the brain parenchyma due to tuberculous encephalitis can be seen in the left parietal region

Duration of the disease is another important determinant of the pathophysiology, having a crucial role in determining the reversibility of the injuries. Long-standing damage tends to lead to poor recovery of function after treatment.

This chapter will focus on the pathophysiological changes that take place in the brain as a result of hydrocephalus. It encompasses a review of clinical and experimental findings in both adults and infantile hydrocephalus. Whenever pertinent, the distinct features of the immature brain will be highlighted.

Gross Morphological Changes

Macroscopic changes are the most obvious feature of hydrocephalus. All cases of the disease, human or experimental, show a significant increase of the ventricular volume due to the accumulation of cerebrospinal fluid (CSF) (Figs. 1-5) [53, 62, 70, 71, 72, 93, 94, 95, 99, 111, 137, 150, 151]. In experimental models, the increase of ventricular volume due to hydrocephalus reached 60 [18] or even more than 100 times [53] that of control animals. This enlargement in turn leads to gross dis-

tortion of the nearby structures, with thinning of the cortical mantle and compression of the adjacent white matter. The gray matter may be reduced to as little as 1-2 mm of thickness. This compression/distortion of the structures is thought to be one of the mechanisms of injury in hydrocephalus.

Damage may be due to the direct effects of compression of structures and/or to indirect injury caused by compression/distortion of structures such as the cerebral blood vessels.

Although its function is still not fully defined [7], the ependyma covering the ventricles is one of the first structures to be damaged in the course of the disease. Ependymal cells lose their cilia and microvilli. The cell layer may be stretched, interrupted, or even totally absent and replaced by a gliotic ventricular wall. The more severe the hydrocephalus, the more serious the damage to the ependyma [16, 20, 22, 23, 25, 26, 27, 111, 120, 121, 122, 139, 150].

The septum pellucidum is also damaged by the increase in ventricular volume. Initially it becomes fenestrated, but in more severe cases the septum pellucidum will eventually disappear, giving rise to one single large ventricular cavity in the more extreme cases of hydrocephalus (Fig. 2).

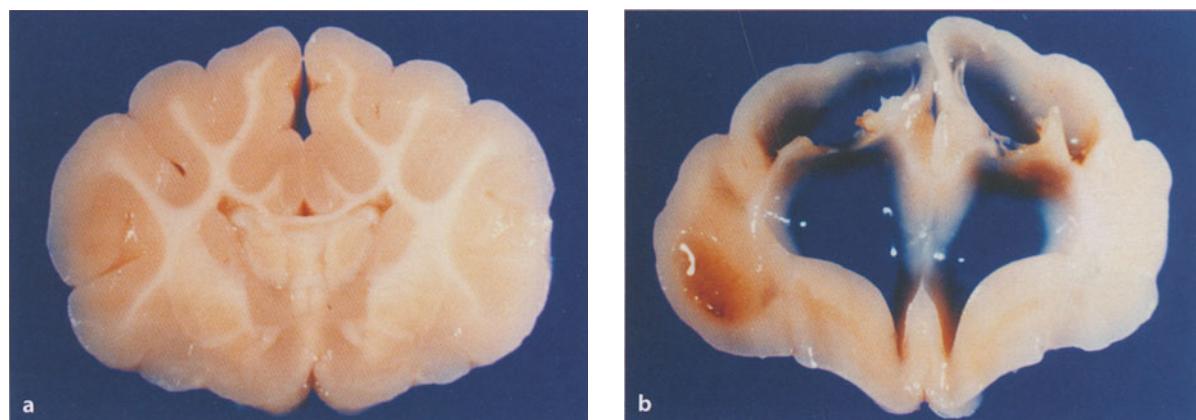


Fig. 2. Coronal sections of the brain of **a** control and **b** hydrocephalic kittens at 4 weeks of age (and 3 weeks after induction of hydrocephalus for **b**). Besides the ventriculomegaly, there are large cavitations of the periventricular white matter. There is also severe distortion of the periventricular structures

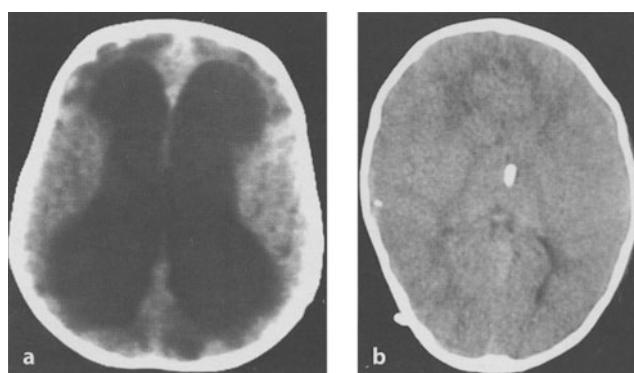


Fig. 3. **a** CT scan of a 1-month-old child presenting with hydrocephalus due to intraventricular hemorrhage. Note the significant periventricular edema. **b** CT scan of the same child 1 year after CSF shunting (performed shortly after **a**). There is re-expansion of the cerebral mantle and marked reduction of the ventriculomegaly. Despite normal brain morphology, this child presents a mild to moderate degree of developmental delay and minor motor sequelae

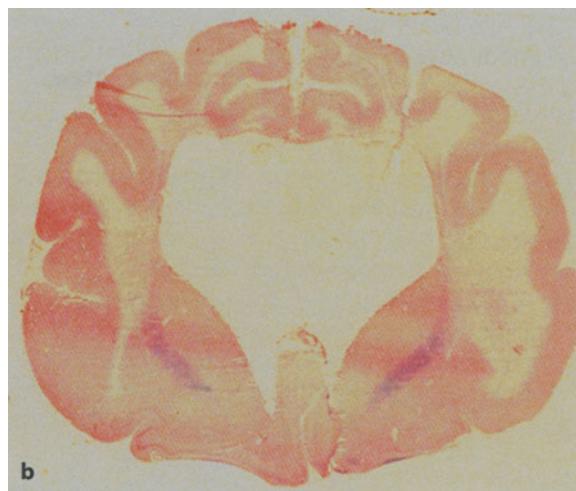
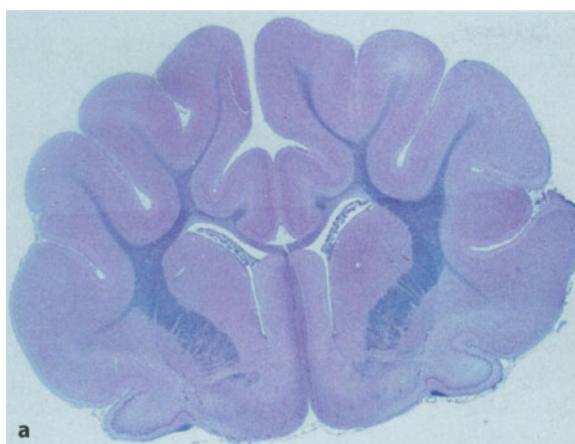


Fig. 4a, b. Coronal cuts of experimental feline neonatal hydrocephalus stained by Luxol fast blue. **a** Control kitten, 4 weeks of age. Myelination of the internal capsule is complete and also reaches the white matter of the gyri. **b** Hydrocephalic kitten, 4 weeks of age, 3 weeks after hydrocephalus induction by cisternal kaolin injection. There is marked ventriculomegaly and periventricular edema. The myelination pattern is altered with delayed myelination of the internal capsule. White matter from gyri presents only a tiny portion of the normal expected myelination



Fig. 5. ^{14}C -Iodoantipyrine autoradiography of **a** control and **b** hydrocephalic kittens at 4 weeks of age (3 weeks after hydrocephalus induction). Note severe decrease of blood flow of periventricular structures, especially white matter

Cerebral Blood Vessels and Cerebral Blood Flow

The distortion of the brain anatomy due to hydrocephalus may involve the cerebral blood vessels, from large arteries to capillaries. Damage may compromise both peripheral and deep vessels. Despite their distance from the dilated ventricles, those vessels coming from the cortical surface will become distorted in an effort to supply the corresponding cerebral tissue [106]. Deeper vessels, however, are the ones that suffer most from the ventricular compression. They may be greatly distorted and displaced from their usual path, being so close to the most severe morphological

changes. They may also be significantly compressed by the expanding ventricular cavities. Capillary density has been shown to be significantly decreased, mostly in the periventricular region in experimental hydrocephalus [23, 25, 71, 106, 115, 150]. Also, changes in the plexus of the sympathetic nerves on the cerebral vessels following the advent of hydrocephalus have been demonstrated [9]. In this event, there is incomplete adrenergic denervation of the cerebral vessels, though axon integration is not distorted. Axonal transport is thought to be impaired here due to functional damage to sympathetic fibers.

Cerebral blood flow (CBF) has been studied in human subjects and in animal models of hydrocephalus. Human studies using transcranial Doppler ultra-

sonography demonstrated that there is a reduction of cerebral perfusion in the presence of decompensated hydrocephalus [26, 48, 66, 114]. Also, studies in hydrocephalic infants using positron emission tomography (PET) showed hypoperfusion in various regions of the cerebral cortex [127]. In the experimental setting, CBF has been studied by the hydrogen clearance method and autoradiography. These studies have shown that CBF is indeed decreased with hydrocephalus, in both acute and chronic stages of the disease [19, 26, 60, 72, 106]. Interestingly, blood flow is globally reduced in the acute phases, while in the later stages of hydrocephalus the decrease is seen mostly in the periventricular white matter, the area most severely affected by the disorder [19] (Fig. 5).

CBF is altered as discussed above, diminished to ischemic levels in some circumstances. Interestingly, the hypoperfusion that has been demonstrated in hydrocephalus does not as a rule lead to manifest ischemia.

Infarction has only rarely been seen in conjunction with hydrocephalus, mostly in experimental series (Fig. 2). The slowly progressive, longstanding hypoperfusion induces damage to neurons and glia that is, in general, subtle and does not lead to acute cell death. As a group, however, the changes may become disabling for normal cell functioning.

Endothelial cells of cerebral blood vessels in hydrocephalus have been studied. Human biopsies and experimental material have demonstrated large quantities of pinocytic vesicles as well as enlarged extracellular spaces [10, 45, 47]. Permeability is also shown to be altered. Separation of endothelial tight junctions was observed in human biopsies [10]. The importance of these changes becomes obvious if one thinks of the normal physiological role of these structures. The endothelial layer of cerebral blood vessels is an essential constituent of the brain-blood barrier (BBB) that makes the brain unique in relation to metabolite exchanges. Evidence of disruption of the BBB, such as changes of CSF composition or extravasated blood elements in the neuropil, have been reported in the presence of hydrocephalus [24, 79].

Brain Energy Metabolism

The brain is an avid consumer of energy. In adults, the brain alone accounts for 20% of the resting total body oxygen consumption. In children the brain may take as much as 50% of the total body oxygen consumption [131]. Also, except in very critical and specific situations, it uses glucose as its sole source

of energy. Thus, decreases in CBF can certainly induce severe changes in the normal brain metabolism, as oxygen and glucose availability drop. Various studies that looked into the energy metabolism in hydrocephalus showed that energy metabolism is indeed impaired in the course of the disease. There is a decrease of high-energy phosphate molecules, such as phosphocreatine (PCR), and an increase of inorganic phosphate (Pi) in the presence of hydrocephalus [18, 54, 60, 98, 140]. In some of these studies, besides PCR, adenosine triphosphate (ATP) levels were also decreased [60, 98, 140] (PCR is metabolized in the brain to maintain levels of ATP and also to shuttle energy to sites of utilization [15, 98]). In those studies that used ³¹P nuclear magnetic resonance spectroscopy (³¹P MRS), the PCR/Pi ratio, which can be used as an index of energy metabolism, was significantly decreased in the presence of hydrocephalus [18, 98, 140]. This ratio was found to be of prognostic value in at least one model of experimental hydrocephalus [98]. Lactate concentration is elevated in cerebral tissue and in the CSF [24, 54, 56, 60]. It is a product of the anaerobic utilization of glucose by the brain cells. Tissue lactic dehydrogenase also increases in concentration during hydrocephalus [24, 56]. Purine-xanthine metabolites are reported to be elevated in the CSF [12, 24, 126]. All these changes are indicative of a disruption of the normal balance of the energy metabolism of the brain. Similar findings have been demonstrated in cerebral hypoxia and ischemia, though in these instances the changes seen are more dramatic [3, 8, 13, 37, 40, 50, 64, 65, 76, 77, 82, 83, 129, 130, 152]. Increases of lactate levels and diminished PCR levels have been demonstrated experimentally in conditions of increased intracranial pressure by increased CSF volume [136]. Areas of decreased local glucose utilization have been detected in the white matter in experimental hydrocephalus [14, 116, 117]. There is also evidence of lowered cytochrome oxidase activity (which can be used as a marker of oxidative metabolism) corresponding to the areas of decreased glucose utilization in these animals [14]. The sum of decreased glucose utilization and low cytochrome oxidase activity points to the presence of anaerobic activity in these areas. Hydrocephalus, then, seems to lead to a state of sustained hypoperfusion, leaving the cerebral tissue especially vulnerable to hypoxic and ischemic lesions. As oxidative energy metabolism is so impaired during hydrocephalus, cerebral tissue resorts to other means of energy production. Overall, the impairment of energy metabolism described may play a critical role in the origin of some of the damage caused by the disease, especially in hydrocephalus manifested at an early age. During the normal maturation period a significant percent-

age of the brain energy requirements are assigned to “developing” activities, such as myelination, protein production, metabolic pathway maturation, and other developmental processes. Lack of adequate blood flow and energy availability may hinder this normal maturation procedure and permanently disturb normal development mechanisms.

Cerebrospinal Fluid

Pathological accumulation of CSF is the landmark of hydrocephalus. The excess of CSF inside the ventricles initiates the various changes being discussed here. As it is simple to obtain large quantities of CSF in the event of hydrocephalus, CSF studies are easy to do in the clinical and laboratory settings. A number of metabolites have been shown to accumulate in the CSF in the course of hydrocephalus. It is not known whether these levels represent increased metabolite production or simply a diminished or delayed excretion pathway. Levels of myelin basic protein have been reported to be elevated [24, 85, 86, 135]. These changes are believed to denote alterations of myelination and/or demyelination. Levels of purine metabolites, xanthine and hypoxanthine are elevated, indicative of some degree of hypoxia [12, 126]. Neurotransmitter metabolite levels are also altered in hydrocephalus [24, 68, 89]. However, much debate still exists in the literature as to in what direction these changes happen and their exact significance.

The function of the normal ependyma and choroid plexus can be altered in hydrocephalus [24]. Aside from changes of the intercellular junctions, other alterations have been reported. Ependymal cells have shown a decrease of superoxide dismutase (SOD) levels in the congenitally hydrocephalic NIC-Hyd rat [105]. This diminished ability to produce SOD, a scavenger of active oxygen species, may lead to changes in function that could progress and aggravate the damage to the brain tissues. The Cl^- efflux from the choroid plexus epithelium is significantly decreased in experimental hydrocephalus [75]. These changes may affect CSF formation by these cells. The number of α -natriuretic peptide (ANP) binding sites in the choroid plexus of hydrocephalic rats has been shown to be increased [144]. It has been suggested that ANP plays a significant role in the regulation of water and electrolyte fluxes across the BBB and blood-CSF barrier. ANP binding sites are found in choroid plexus, endothelial cells of intraparenchymal cerebral capillaries, and pia-arachnoid. They may, then, play a role in the regulation of CSF production in the choroid plexus. The basal lamina of mutant rats that develop prenatal

hydrocephalus is altered [110], which appears to result in neuroepithelium disorganization in the brain of these animals, again disturbing normal function.

Extracellular Space and Brain Water Content

Extracellular space is increased in the presence of hydrocephalus [22, 27, 57, 79, 122]. This increase seems to be restricted to the periventricular region. The extent of the increase varies from one study to another. Enlarged extracellular space is seen 60–200 mm from the ventricular surface [20, 21, 25, 88]. Similarly, water content is elevated in the periventricular white matter to a comparable extent. From that point on, the excess fluid would be removed by blood vessels [45]. Conversely, studies performed in the cerebral cortex have demonstrated that the water content of the area is normal or mildly decreased [25, 28, 79]. A possible explanation for this discrepancy between white and gray matter water content is the Hakim hypothesis [21]: the increased cerebral volume caused by hydrocephalus leads to extrusion of water and blood from the cranial cavity. Water content of the gray matter, and part of the white matter, is thus shed, while the periventricular region retains water in its increased extracellular space. Also, it has been demonstrated in experimental hydrocephalus in rats that extracellular fluid movement through the cerebral cortex is impaired [92, 128].

Even though histological studies show an increase of extracellular space and water content only in a very limited region of the periventricular white matter, brain imaging of patients and experimental animals suffering from decompensated hydrocephalus show a sizable increase of the water content around the lateral ventricles, mainly around the frontal horns (Figs. 1–4) [14, 32, 34, 42, 79, 115]. Nevertheless, the origin of the retained water in the periventricular region is not yet completely clarified. Some authors believe that the periventricular edema represents an alternative pathway to the retained CSF out of the lateral ventricles [11, 21, 32, 88, 123]. Others postulate that the periventricular edema results from a barrier to normal CSF drainage to the lateral ventricles due to the increased pressure inside [27].

White Matter

Macroscopically, the white matter, particularly the periventricular region, is the brain region most affect-

ed by hydrocephalus. There is thinning of the corpus callosum and compression of the periventricular white matter (Fig. 2). Interestingly, the degree of white matter involvement seems related to age: damage in adult models of hydrocephalus is usually milder than that present in infantile ones.

In experimental models of hydrocephalus and in human patients, white matter structures are frequently injured. Regardless of species or etiology, the type of damage is similar in all cases studied. The phospholipid metabolism of the cerebral tissue is altered in experimental hydrocephalus, and the myelin content of the brain is decreased [74]. There is extracellular edema. Axonal damage is a common injury. It may be represented by axonal swelling and ballooned axons [27, 28, 121, 122, 151], axonal degeneration [22, 127], axonal loss (mostly in long-standing hydrocephalus) [27, 115, 122, 123, 124, 151], or axonal demyelination [151]. More than one injury may coexist in the same individual. Degenerative changes of descending tracts have been reported, leading to secondary loss of periventricular myelin. Reactive gliosis follows axonal injury [27, 151].

Myelination may also be severely affected by hydrocephalus. Studies performed in experimental and human hydrocephalus that developed during the brain maturation period show that the normal process of myelination may be significantly delayed (Fig. 4) [14, 27, 28]. Also, normal age-maturation of the phospholipid metabolism is impaired in a model of neonatal feline hydrocephalus. These delays pose another important threat to the developing brain affected by hydrocephalus: myelination happens at preset times, one stage being essential to the next. Each of the steps is crucial to the normal development of the brain. When one step is delayed, it does not necessarily occur at a later date. According to the critical interval hypothesis originally derived from Stockard's work [148], at periods when a given process is predominant it can be permanently arrested by outside conditions. Normal development does not follow restoration of normal environment conditions. The step is most often lost, leading to irreversible damage to normal maturation.

Injuries to the white matter may be due to at least two factors: (1) the mechanical traction of axons and long tracts caused by the enlarging ventricles may physically distract and break them. Ballooning of the axons, similar to those seen in trauma, have been shown in hydrocephalus [27, 151]. (2) low blood flow and ischemia may play an important role in the genesis of the injuries of the white matter. Infarcts can be the final result of such phenomena, further aggravating the damage (Fig. 2) [14, 27, 70, 122, 125] (though some may argue that the causal relationship may be inverted, i.e., decreased CBF leading to infarcts leading to hydrocephalus [6]). More subtle mechanisms of

injury may occur with "nonischemic" low blood flow, especially for the maturing brain. The cumulative effect of a longstanding decrease in CBF, even though at levels not low enough to produce general energy failure and infarction acutely, may produce damage only expected at more pronounced levels of decreased blood flow. The reduced CBF reported in hydrocephalus [19, 60] means lower energy availability and less "building material," which may hinder the normal brain-developing process. Oligodendrocytes are known to have a high level of creatine phosphokinase (CPK) activity and high PCR levels that are thought to be linked to their role in myelin formation [91]. A decrease (or lack of increase) of energy availability could lead to decreased myelin deposition. An ensuing delay in myelination retards the brain's normal development and may be an added factor in determining the neurological deficits seen with hydrocephalus. Decrease of energy availability can also inhibit protein synthesis [81, 96], which could delay the normal maturation process even further.

Cerebral Cortex and Basal Ganglia

The cerebral cortex also undergoes gross macroscopic changes with the onset of hydrocephalus. There is gross distension and thinning of the cortex, which is more pronounced in the occipital lobe if hydrocephalus started early in infancy. Severe early-onset hydrocephalus may distend and compress the cerebral tissue to such an extent that the brain becomes a thin ribbon of tissue surrounding enormous ventricular cavities (Fig. 1).

At one time, there were doubts concerning the occurrence of injury to the cortical neurons due to hydrocephalus. A number of earlier studies in experimental and human disease have failed to demonstrate evidence of neuronal damage [35, 58, 120, 121, 122]. One should be careful, though, before accepting the hypothesis of this lack of injury to neurons. Unlike those seen in the white matter, histological changes of the cerebral cortex in hydrocephalus tend to be subtle and may be easily missed. Furthermore, they are seldom seen in the acute stages of the disease. Rather, neuronal damage is usually demonstrated in the later stages of hydrocephalus. It should be noted that these subtle conditions refer to the damage seen by microscopic morphological methods. As discussed elsewhere in this chapter, striking biochemical changes can and do occur in neurons at earlier stages of hydrocephalus.

A myriad histological changes have been demonstrated in neurons affected by hydrocephalus. Pykno-

sis and cytoplasmic vacuolization have been reported in neurons from the cortex and hippocampus [5, 150]. Dark neurons, chromatolysis, swelling, and vacuolization are also seen [25, 58, 115, 150]. Cell density in the cerebral cortex is reduced at later stages of hydrocephalus [71]. In experimental hydrocephalus a decrease in the quantity and size of pyramidal neurons has been noted [150, 151]. Shrunken neurons, denuded of their glial protection, are seen in deep cortical lamina [10, 79]. Retrograde neuronal degeneration has been seen in retinal ganglion neurons and cortex in an experimental model of neonatal feline hydrocephalus and in human frontal cortex [44, 79, 149]. Areas of infarction, though rare, may appear in the cerebral cortex or basal ganglia. Reactive astrogliosis occurs in the deep cortical layers. Neurofibrillary tangles have been described in neurons of cortex and hippocampus in hydrocephalus. Their appearance has been associated with long courses of the disease [2, 26, 39]. Dendrites may also be affected by hydrocephalus. A decrease in dendritic ramifications, loss of spines, and increase in varicosities were seen in experimental neonatal hydrocephalus [55, 79, 94, 101, 102, 133]. Dendrites and axonal processes of hippocampal pyramidal cells exhibited hydropic cellular degeneration [80]. Fewer mature dendrites were seen in pyramidal cells in the presence of hydrocephalus [5]. Decreased cortical synaptic density and altered synaptogenesis, demonstrated, for instance, by reduction of the protein SVP38 (a protein related to synapsis in neurons), can be a part of the damage caused by hydrocephalus [11, 103, 132, 133, 150]. It should be noted, however, that at least one investigator showed normal synaptogenesis (of monoamine synapses) in the presence of early-onset experimental hydrocephalus [137]. These alterations of the synaptic apparatus are believed to lead to disturbances of the learning ability and cognitive functions.

Electron microscopy shows alterations in neurons injured by hydrocephalus [5, 10, 11, 57]. Intracellular edema has been reported. Also, changes of the endoplasmic reticulum, perinuclear cisterns, and Golgi apparatus have been demonstrated. In advanced stages, there are signs of degenerative changes. Mitochondria of neurons afflicted by hydrocephalus may exhibit edema ranging from mild to very severe. The extracellular space is clearly enlarged. On occasion, degenerating mitochondria and electron-dense bodies are seen in neurons in hydrocephalus.

Biochemical disturbances of the cerebral cortex are noted in hydrocephalus. Overexpression of transforming growth factor β_1 (TGF- β_1) in the brain has been related to the induction of hydrocephalus in mice [41, 138]. There is significant change of the tissue (and CSF) concentration of neurotransmitters. Norepinephrine neuronal pathways show a reduction of

norepinephrine levels [36]. The pattern of decrease is suggestive of damage to the periventricular pathways themselves and not to the norepinephrine neurons. In another study, levels of norepinephrine in the brain were unchanged in experimental hydrocephalus, but activity of norepinephrine neurons was decreased after stimulation [100]. Yet another study shows divergent results, with norepinephrine levels increased in some areas of the brain and decreased in others [25]. In an experimental adult rat model of hydrocephalus norepinephrine levels were increased in the brain [60]. Dopamine levels are decreased in the cortex of rabbits in which hydrocephalus was induced by silicon-oil injection [25]. However, kaolin-induced hydrocephalus in rats did not increase brain levels of dopamine [100]. Activity of dopaminergic neurons was decreased in the same model after stimulation. Increased dopamine levels have been described in another model of hydrocephalus [60]. Neurotransmitter metabolites can also be analyzed. They provide an estimate of the release status of the neurotransmitter. Concentration of homovanillic acid (HVA), the major metabolite of dopamine, is increased in some areas of the brain and decreased in others, associated with unchanged tissue levels of dopamine [99]. The same author reports elevated concentrations of norepinephrine metabolites in all regions of the brain, associated with decreased to normal tissue levels of norepinephrine. Elevated levels of HVA have been demonstrated in the brain and in the CSF in hydrocephalus [25, 60, 68, 89]. Results of studies on neurotransmitters in hydrocephalus are, thus, still controversial. The discrepancies encountered may be due to differences in techniques, animal models, and areas of brain examined, or to the timing of measurements in the course of the disease. Whatever the changes, they are thought to reflect disturbances of the neuronal function and altered metabolite clearance. It is presumed that hydrocephalus leads to functional damage to the neuronal pathways, with no destruction of the neuronal bodies being necessary for the impairment. Studies in experimental hydrocephalus in rats showed a decrease in the number of cholinergic and GABAergic neurons in the basal ganglia, even though no reduction in the cellular density of total neostriatal neurons was demonstrated [141]. Severe stretching of the periventricular pathways may represent one of the mechanisms of injury of these pathways fibers. Interestingly, in some patients with decompensated hydrocephalus some symptoms may be due to damage to neurotransmitter neuronal pathways, as they resemble neurotransmitter-deficient diseases and are relieved by neurotransmitter agonist medications [1, 17].

Specific damage may happen to the neurons of maturing brains afflicted by hydrocephalus. Their structural development may be significantly affect-

ed. Microgyria is a possible damage. Normal migration and proliferation of neuronal precursors is disturbed [111]. The laminar structure of the cortex may be altered [71, 150, 151]. Areas of dysgenesis may appear as a result of lesions to deep layers of the cortex [27]. Neuronal maturation is delayed [111]. Also, synaptogenesis is altered, as dendrites and their spine are defective due to hydrocephalus [79, 94, 101, 102, 133].

Not only the neurons, but also the glial cells are affected by hydrocephalus. Astrocyte processes may present edema [10, 28, 79]. There is vacuolization of the glial cells [46, 79]. The oligodendrocytes, responsible for myelination and maintenance of myelin, are altered [10, 28, 79]. It should be noted that the microglial response elicited by hydrocephalus is not limited to the periventricular white matter, but is also present in the gray matter [90].

on the pathological changes demonstrated in hydrocephalus. These works deal exclusively with treatment by CSF diversion with a shunt, and so do the results discussed below. Nevertheless, these conclusions probably apply to any other effective method of hydrocephalus treatment. The efficacy of CSF shunts in restoring normality varies widely, depending on which particular injury is being analyzed. While for some changes (e.g., morphological changes) there is complete recovery to normal after treatment, for other injuries (e.g., to myelination) improvement is at best limited. The sensitivity of a specific structure or pathway to the injury inflicted, its extent and duration, together with the timing of treatment in the natural course of the disease are important aspects in the determination of the reversibility of the injuries. Many more tough questions are as yet unanswered. There is still much work to be done to understand better the extent of the effect of treatment of hydrocephalus.

CSF shunting is a very effective means of reversing the morphological changes caused by hydrocephalus. There is immediate decrease of the ventricular size and the periventricular edema disappears. The cortical mantle is reconstituted, usually to its normal thickness [14, 18, 19, 22, 23, 25, 51, 78, 79, 95, 123, 132, 151]. The ependymal lining may be restored, although gliosis may prevent full recovery of the ependyma [16, 22, 27]. The corpus callosum goes back to its normal area and shape [119].

Cerebral vessels respond well to treatment. Angioarchitecture configuration usually returns to normal if treatment is instituted in time [22, 23, 25, 106]. CBF returns to physiological levels once hydrocephalus is properly handled [19, 48, 66, 106, 127]. Similarly, energy metabolism changes are reversed (or prevented) by treatment. High-energy phosphate metabolism returns to normal levels [18, 54, 73] and glucose utilization achieves a normal pattern [14, 147]. It should be noted that the timing of treatment seems to be important for the reversal/prevention of changes to the energy metabolism [73].

Many of the neuronal alterations discussed previously seem to be reversible or preventable by adequate treatment. Except in areas of infarction, neurons return to their typical appearance after treatment of hydrocephalus [51]. Conversely, permanent gliosis prevents normalization of retinal ganglion cells in shunted hydrocephalic cats [149]. Synaptogenesis may become normal if treatment is instituted early, though not if it is performed at later stages [132, 133]. Dendrite density seems to return to normal after CSF shunting in the superficial regions, but the spines remain altered, becoming bulbous or multiloculated [79]. Spine number is persistently decreased in shunted hydrocephalic

Effect of Treatment on the Changes Caused by Hydrocephalus

The main goals of hydrocephalus treatment are to prevent further damage due to the progression of the disease and, if possible, to reverse the injury already inflicted on the brain. In clinical and experimental settings, CSF diversion shunts have been shown to alleviate intracranial pressure, reduce ventricular size, and grossly reconstitute the distorted anatomy. The associated clinical symptoms are also usually reversed. This overall improvement is thought to be achieved by improvement of the remaining cerebral functions. Lost elements cannot be recovered by CSF shunts. Thus, timing is of crucial importance when treating hydrocephalus. In order to achieve maximal results, shunts should be implanted before permanent damage of the cerebral tissue ensues. Consequently, the reversibility of brain injuries that have already occurred is a critical aspect of hydrocephalus treatment and is directly related to the final results and outcome.

The success of CSF diversion shunts leads to the impression that hydrocephalus is a totally reversible process. Those who work closely with patients afflicted by the disease know that this is not always entirely true. Patients who have a good "imaging recovery" after treatment but who do not improve clinically are well known in clinical practice (Fig. 3). Clinical and experimental studies have shown alteration of important variables such as IQ and permanent neurological deficits in children, kittens, and rat pups who have been "successfully shunted" [30, 31, 61, 59, 87, 118, 149, 150]. A series of studies have been performed analyzing the effects of treatment

rats [102]. Dendrite density in HTX hydrocephalic rats is reversed by early shunting, with the return (or preservation) of normal learning ability [132]. Late shunting, on the other hand, failed to show any improvement of dendrite density in the same animal model [102].

Impairment of cholinergic, dopaminergic, and noradrenergic systems may also be prevented by early shunting, but not by late shunting [142].

There is evidence that some of the CSF changes can be improved by shunting. Levels of myelin basic protein decreased significantly after adequate treatment [85, 86].

Myelination is the injury least responsive to treatment. Axon degeneration and myelin disruption may persist [27, 124]. Recovery of myelination is usually partial [14, 27, 28]. Phospholipid metabolism does not return to normal. This unresponsiveness to therapy can be particularly evident (and important) in those patients (or animals) afflicted by hydrocephalus at the maturing stages of the brain. (Re)myelination is incomplete; the normal pattern of myelin maturation is delayed and resembles that in untreated hydrocephalus. The reason for this lack of good results is not clear. Perhaps the mechanisms responsible for myelination are more severely affected by hydrocephalus. Myelination tracts are anatomically closer to the lateral ventricles, and the distortion endured by them during the course of the disease, associated with white matter sensitivity to ischemic injuries, may lead to more extensive damage before treatment is performed. As a consequence, less function can be recovered by therapy. Also, myelination is a process that starts early in life and proceeds for an extended period of time. Damage due to hydrocephalus may thus be more extensive, again leaving less recoverable function. Furthermore, as discussed before, myelination is a step process, each step essential to the next. If sabotaged by external conditions, these steps may become permanently arrested, preventing normalization of the process even after effective removal of the initial insult.

Conclusion

Hydrocephalus leads to significant changes of the brain, not only of its morphology, but also of its circulation, biochemistry, metabolism, and maturation. Adequate treatment does not always reverse the injuries caused by the disease. The timing of therapy is crucial in determining the reversibility of the lesions, and, hence, the outcome.

References

- Anderson B: Relief of akinetic mutism from obstructive hydrocephalus using bromocriptine and ephedrine. *J Neurosurg* 76:152-155, 1992
- Ball MJ, Vis CL: Relationship of granulovacuolar degeneration in hippocampal neurones to aging and to dementia in normal pressure hydrocephalus. *Can J Neurol Sci* 3:815-824, 1978
- Behar KL, Rothman DL, Hossmann KA: NMR spectroscopy investigation of the recovery of energy and acid-base homeostasis in the cat brain after prolonged ischemia. *J Cereb Blood Flow Metab* 9:655-665, 1989
- Boesch C, Gruetter R, Martin E, et al: Variations in the in vivo P31 MR spectra of the developing human brain during postnatal life. *Radiology* 172:197-199, 1989
- Boillat CA, Jones HC, Kaiser GL, et al: Ultrastructural changes in the deep cortical pyramidal cells of infant rats with inherited hydrocephalus and the effect of shunt treatment. *Exp Neurol* 147:377-88, 1997
- Bradley WG, Whittemore AR, Watanabe AS, et al: Association of deep white matter infarction with chronic communicating hydrocephalus: implications regarding the possible origin of normal-pressure hydrocephalus. *AJNR* 12:31-39, 1991
- Bruni JE, Del Bigio MR, Clattenburg RE: Ependyma: normal and pathological. A review of the literature. *Brain Res Rev* 9:1-19, 1985
- Cady EB, Dawson MJ, Hope PL, et al: Non-invasive investigation of cerebral metabolism in newborn infants by phosphorus nuclear magnetic resonance spectroscopy. *Lancet* 1:1059-1062, 1983
- Caner H, Peker S, Ozcan OE: Effects of hydrocephalus on the sympathetic nerves of cerebral arteries, investigated with WGA-HRP anterograde tracing in the rat. *Acta Neurochir (Wien)* 111:143-146, 1991
- Castejon OJ: Transmission electron microscope study of human hydrocephalic cerebral cortex. *J Submicrosc Pathol* 26:29-39, 1994
- Castejon OJ, Diaz M, Valero C: Ultrastructural alterations of Golgi apparatus in the nerve cells of cerebral cortex in human hydrocephalus. A qualitative study using cortical biopsies. *Scanning Microsc* 8:89-96, 1994
- Castro-Gago M, Rodriguez-Segade S, Camina F, et al: Indicators of hypoxia in cerebrospinal fluid of hydrocephalic children with suspected shunt malfunction. *Child's Nerv Syst* 9:275-277, 1993
- Chopp M, Helpern JA, Ewing JR, et al: Anoxia followed by hyperoxia: in vivo 31P NMR of the cat brain. *Magn Reson Imaging* 2:329-333, 1984
- Chumas PD, Drake JM, Del Bigio MR, et al: Anaerobic glycolysis preceding white-matter destruction in experimental neonatal hydrocephalus. *J Neurosurg* 80:491-501, 1994
- Clarke DD, Lajtha A L, Makr H: Intermediary metabolism. In: Siegel GJ, Agranoff BW, Albers RW, Molinoff PB (eds) *Basic neurochemistry*. Molecular, cellular and medical aspects. Raven Press, New York pp 541-564, 1989
- Collins P, Goulding DA: Subependymal cells provide a faster response to ependymal injury than astrocytes in the hydrocephalic brain. *Neuropathol Appl Neurobiol* 18:387-394, 1992
- Curran T, Lang AE: Parkinsonian syndromes associated with hydrocephalus: case reports, a review of the literature

- and pathophysiological hypothesis. *Mov Disord* 9:508-520, 1994
18. Da Silva MC, Drake JM, Lemaire C, et al: High energy phosphate metabolism in a neonatal model of hydrocephalus before and after shunting. *J Neurosurg* 81:544-553, 1994
 19. Da Silva MC, Michowicz S, Drake JM, et al: Reduced local cerebral blood flow in periventricular white matter in experimental neonatal hydrocephalus-restoration with CSF shunting. *J Cereb Blood Flow Metab* 15:1057-1065, 1995
 20. Del Bigio MR, Bruni JE, Fewer HD: Human neonatal hydrocephalus. An electron microscopic study of the periventricular tissue. *J Neurosurg* 63:56-63, 1985
 21. Del Bigio MR, Bruni JE: Cerebral water content in silicone oil-induced hydrocephalic rabbits. *Pediat Neurosci* 13:72-77, 1987
 22. Del Bigio MR, Bruni JE: Periventricular pathology in hydrocephalic rabbits before and after shunting. *Acta Neuropathol* 77:186-195, 1988
 23. Del Bigio MR, Bruni JE: Changes in periventricular aviculture of rabbit brain following induction of hydrocephalus and after shunting. *J Neurosurg* 69:115-120, 1988
 24. Del Bigio MR: Hydrocephalus-induced changes in the composition of cerebrospinal fluid. *Neurosurgery* 25:416-423, 1989
 25. Del Bigio MR, Bruni JE: Silicone oil-induced hydrocephalus in the rabbit. *Child's Nerv Syst* 7:79-84, 1991
 26. Del Bigio MR: Neuropathological changes caused by hydrocephalus. *Acta Neuropathol* 85:573-585, 1993
 27. Del Bigio MR, da Silva MC, Drake JM, et al: Acute and chronic cerebral white matter damage in neonatal hydrocephalus. *Can J Neurol Sci* 21:299-305, 1994
 28. Del Bigio MR, Kanfer JN, Zhang YW: Myelination delay in the cerebral white matter of immature rats with kaolin-induced hydrocephalus is reversible. *J Neuropathol Exp Neurol* 56:1053-66, 1997
 29. Delivoria-Papadopoulos M, DiGiacomo JE: ^{31}P nuclear magnetic resonance spectroscopy in the human neonatal brain. *Semin Perinatol* 14:248-257, 1990
 30. Dennis M, Fitz CR, Netley CT, et al: The intelligence of hydrocephalic children. *Arch Neurol* 38:607-615, 1981
 31. Dennis M, Jacennik B, Barnes MA: The content of narrative discourse in children and adolescent after early onset hydrocephalus and in normally developing age peers. *Brain Lang* 46:129-165, 1994
 32. Deo-Narine V, Gomez DG, Vullo T, et al: Direct in vivo observation of transventricular absorption in the hydrocephalic dog using magnetic resonance imaging. *Invest Radiol* 29:287-293, 1994
 33. Di Rocco C: The treatment of infantile hydrocephalus. CRC Press Inc, Boca Raton, 1987
 34. Drake JM, Potts DG, Lemaire C: Magnetic resonance imaging of silastic-induced canine hydrocephalus. *Surg Neurol* 31:28-40, 1989
 35. Edwards MSB, Harison MR, Halks-Miller M, et al: Kaolin-induced congenital hydrocephalus in utero fetal lamb and rhesus monkeys. *J Neurosurg* 60:111-122, 1984
 36. Ehara K, Matsumoto S, Yoshida N, et al: Ascending norepinephrine pathways impaired in experimental hydrocephalus. *Japan J Pharmacol* 32:205-208, 1982
 37. Ellef SM, Schanl MD, Ligetti L, et al: Concurrent measurements of cerebral flow, sodium, lactate and high energy phosphate metabolism using ^{19}F , ^{23}Na , ^1H and ^{31}P nuclear magnetic resonance spectroscopy. *Magn Reson Med* 7:412-424, 1988
 38. Erencinska M, Silver IA: ATP and brain function. *J Cereb Blood Flow Metab* 9:219, 1989
 39. Fan KJ, Pezeshkpour G: Neurofibrillary tangles in association with congenital hydrocephalus. *J Natl Med Assoc* 79:1001-1003, 1987
 40. Flynn CJ, Faroqui AA, Horrocks LA: Ischemia and hypoxia. In: Siegel GJ, Agranoff BW, Albers RW, Molinoff PB (eds). *Basic neurochemistry. Molecular, cellular and medical aspects*. Raven Press, New York pp 783-795, 1989
 41. Galbreath E, Kim SJ, Brenner M, et al: Overexpression of TGF-beta 1 in the central nervous system of transgenic mice results in hydrocephalus. *J Neuropathol Exp Neurol* 54:339-349, 1995
 42. Gideon P, Thomsen F, Sorensen PS, et al: Increased self-diffusion of brain water in hydrocephalus measured by MR imaging. *Acta Radiol* 35:514-519, 1994
 43. Girard J: Gluconeogenesis in late fetal and early neonatal life. *Biol Neonate* 50:237-258, 1986
 44. Glees P, Voth D: Clinical and ultrastructural observations of maturing human frontal cortex. Part I (biopsy material hydrocephalic infants). *Neurosurg Rev* 11:273-278, 1988
 45. Glees P, Hasan M, Voth D, et al: Fine structural features of the cerebral microvasculature in hydrocephalic human infants: correlated clinical observations. *Neurosurg Rev* 12:315-321, 1989
 46. Glees P, Hasan M: Ultrastructure of human cerebral macroglia and microglia maturing and hydrocephalic frontal cortex. *Neurosurg Rev* 13:231-242, 1990
 47. Glees P, Voth D, Schwarz M: Ultrastructural observations on transendothelial transport from extracellular neuronal spaces towards the vascular lamina of cerebral capillaries of hydrocephalic human biopsies. *Eur J Pediatr Surg* 2, Suppl 1: 43, 1992
 48. Goh D, Minns RA, Pye SD, et al: Cerebral blood flow velocity changes after ventricular taps and ventriculoperitoneal shunting. *Child's Nerv Syst* 7:452-457, 1991
 49. Gould RM: Myelination development. In: Wiggins RC, Candless OW, Enna JJ (eds). *Developmental neurochemistry*. University of Texas Press, Austin pp 47-99, 1985
 50. Gylai L, Schnall M, McLaughlin AC, et al: Simultaneous ^{31}P and ^1H nuclear magnetic resonance studies of hypoxia and ischemia in the cat brain. *J Cereb Blood Flow Metab* 7:543-551, 1987
 51. Hale P, McAllister JP, Katz SD, et al: Improvement of cortical morphology in infantile hydrocephalic animals after ventriculoperitoneal shunt placement. *Neurosurgery* 31:1085-1096, 1992
 52. Hamilton PA, Hope P, Reynolds OR: Magnetic resonance spectroscopy. In: Levine MI, Benete MJ, Punt J (eds) *Fetal and neonatal neurology and neurosurgery*. Churchill Livingstone, 1988
 53. Harris NG, Jones HC, Williams SCR: MR imaging for measurements of ventricles and cerebral cortex in postnatal rats (H-Tx strain) with progressive inherited hydrocephalus. *Exp Neurol* 118:1-6, 1992
 54. Harris NG, Jones HC, McAllister JP: ^1H NMR spectroscopy of cerebral cortex in hydrocephalic H-Tx rats with and without shunt treatment. *Eur J Pediatr Surg* 5, suppl:52 (Abstract), 1995
 55. Harris NG, McAllister JP, Counaughton JM, et al: The effect of inherited hydrocephalus and shunt treatment on the

- cortical pyramidal cell dendrites in the infant H-Tx rat. *Exp Neurol* 141:269-79, 1996
56. Hidaka M, Matsumae M, Yamamura M, et al: Glucose metabolism and protective biochemical mechanisms in a rat brain affected by kaolin-induced hydrocephalus. *Child's Nerv Syst* 13:183-188, 1997
57. Hasan M, Glees P: Ultrastructural features of the human frontal cortex neurons of maturing and hydrocephalic cerebrum. *Arch Ital Anat Embriol* 95:17-26, 1990
58. Hassin GB: Hydrocephalus studies of the pathology and pathogenesis with remarks on the cerebrospinal fluid. *Arch Neurol Psychiatry* 24:1164-1186, 1932
59. Hawkins D, Bowers TM, Bannister CM, et al: The functional outcome of shunting H-Tx rat pups at different ages. *Eur J Pediatr Surg* 7 (suppl 1):31-34, 1997
60. Higashi K, Asahisa H, Ueda N, et al: Cerebral blood flow and metabolism in experimental hydrocephalus. *Neurol Res* 8:169-176; 1986, 1986
61. Hirsch JF: Consensus: long-term outcome in hydrocephalus. *Child's Nerv Syst* 10:64-69, 1994
62. Hochwald GM, Epstein F, Malhan C, et al: The relationship of compensated to decompensated hydrocephalus in the cat. *J Neurosurg* 39: 694-697, 1973
63. Holtzman D, McFarland EW, Jacobs D, et al: Maturational increase in mouse brain creatine kinase reaction rates shown by phosphorus magnetic resonance. *Dev Brain Res* 58:181-188, 1991
64. Hope PL, Cady EB, Tofts PS, et al: Cerebral energy metabolism studied with phosphorus NMR spectroscopy in normal and birth-asphyxiated infants. *Lancet* 2:366-370, 1984
65. Houkin K, Kwee IL, Nakada T: Persistent high lactate level as a sensitive MR spectroscopy indicator of Complete infarction. *J Neurosurg* 72:763-766, 1990
66. Hovda DA, Chugani HT, Villablanca JR, et al: Maturation of cerebral oxidative metabolism in the cat: a cytochrome oxidase histochemistry study. *J Cereb Blood Flow Metab* 12:1039-1048, 1992
67. Iacopino DG, Zaccone C, Molina D, et al: Intraoperative monitoring of cerebral blood flow during ventricular shunting in hydrocephalic pediatric patients. *Child's Nerv Syst* 11: 483-486, 1995
68. Inagawa T, Ishikawa S, Uozumi T: Homovanillic acid and 5-hydroxyindoleacetic acid in the ventricular CSF of comatose patients with obstructive hydrocephalus. *J Neurosurg* 52:635-641, 1980
69. Jones CT: The biochemical development of the fetus and neonate. Elsevier Biomedical Press, New York, 1982
70. Jones HC, Dack S, Ellis C: Morphological aspects of the development of hydrocephalus in a mouse mutant (SUMS/NP). *Acta Neuropathol* 72:268-276, 1987
71. Jones HC, Bucknall RM, Harris NG: The cerebral cortex in congenital hydrocephalus in the H-Tx rat: a quantitative light microscopy study. *Acta Neuropathol* 82:217-224, 1991
72. Jones HC, Richards HK, Bucknall RM, et al: Local cerebral blood flow in rats with congenital hydrocephalus. *J Cereb Blood Flow Metab* 13:531-534, 1993
73. Jones HC, Harris NG, Rocca JR, et al: Progressive tissue injury in infantile hydrocephalus and prevention/reversal with shunt treatment. *Neurol Res* 22:89-96, 2000
74. Kaiser GL, Wenger P, Jost A: Clinical, radiological and neurochemical follow-up in normal, hydrocephalic and hydrocephalic shunted rats of the H-Tx strain. *Eur J Pediatric Surg* 5, suppl: 42-43 (Abstract), 1995
75. Knuckey NW, Preston J, Palm D, et al: Hydrocephalus decreases chloride efflux from the choroid plexus epithelium. *Brain Res* 618:313-317, 1993
76. Kobayashi H, Hayashi M, Kawano H, et al: Phosphorus-31 magnetic resonance spectroscopy of cerebral ischemia in cats. *Neurosurgery* 27:240-246, 1990
77. Komatsu S, Nioka S, Yoshizaki K, et al: Cerebral energy metabolism measured in vivo by 31P NMR in middle cerebral artery occlusion in the cat—relation to severity of stroke. *J Cereb Blood Flow Metab* 7:557-562, 1987
78. Kovnar EH, Coxe WS, Volpe JJ: Normal neurologic development and marked reconstitution of cerebral mantle after postnatal treatment of intrauterine hydrocephalus. *Neurology* 34:840-841, 1984
79. Kriebel RM, Shah AB, McAllister JP: The microstructure of cortical neuropil before and after decompression in experimental infantile hydrocephalus. *Exp Neurol* 119:89-98, 1993
80. Kriebel RM, McAllister JP: Pathology of the hippocampus in experimental feline infantile hydrocephalus. *Neurol Res* 22:29-36, 2000
81. Kudo T, Tada K, Takeda M, et al: Learning impairment and microtubule associated protein 2 decrease in gerbils under chronic cerebral hypoperfusion. *Stroke* 21:1205-1209, 1990
82. Laptook AR, Hassan A, Peterson J, et al: Effects of repeated ischemia in cerebral blood flow and brain energy metabolism. *NMR Biomed* 1:74-79, 1988
83. Laptook AR, Corbett RJ, Uauy R, et al: Use of 31P magnetic resonance spectroscopy to characterize evolving brain damage after perinatal asphyxia. *Neurology* 39:709-712, 1989
84. Lawson B, Anday E, Guillet R, et al: Brain oxidative phosphorylation following alteration in head position in preterm and term neonates. *Pediatr Res* 22:302-305, 1987
85. Longatti PL, Canova G, Guida F, et al: The CSF myelin basic protein: A reliable marker of actual cerebral damage in hydrocephalus. *J Neurosurg Sci* 37:87-90, 1993
86. Longatti PL, Guida F, Agostini S, et al: The CSF myelin basic protein in pediatric hydrocephalus. *Child's Nerv Syst* 10: 96-98, 1994
87. Lumenta CB, Skotarczak U: Long-term follow-up in 233 patients with congenital hydrocephalus. *Child's Nerv Syst* 11:173-175, 1995
88. Lux WE, Hochwald GM, Sahar A et al: Periventricular water content. *Arch Neurol* 23:475-479, 1970
89. Malm J, Kristensen B, Ekstedt J, et al: CSF monoamines metabolites, cholinesterases and lactate in the adult hydrocephalus syndrome (normal pressure hydrocephalus) related to CSF hydrodynamic parameters. *J Neurol Neurosurg Psychiatry* 54:252-259, 1991
90. Mangano FT, McAllister JP, Jones HC, et al (1998): The microglial response to progressive hydrocephalus in a model of inherited aqueductal stenosis. *Neurol Res* 20:697-704, 1998
91. Manos P, Bryan GK, Edmond J: Creatine kinase activity in postnatal rat brain development and in cultured neurons, astrocytes and oligodendrocytes. *J Neurochem* 56:2101-2107, 1991
92. Massicotte EM, Buist R, Del Bigio MR: Altered diffusion and perfusion in hydrocephalic rat brain: a magnetic resonance imaging analysis. *J Neurosurg* 92:442-7, 2000

93. Matsumae M, Lorenzo AV, Black P: Measurements of intracranial compartment volumes in ventriculomegaly patients and volunteers assessed by MRI. *Eur J Pediatr Surg* 2, suppl 1: 34, 1992
94. McAllister JP, Maugans TA, Shah MV, et al: Neuronal effects of experimentally induced hydrocephalus in newborn rats. *J Neurosurg* 63:776-783, 1985
95. McAllister JP, Cohen MI, O'Mara KA, et al: Progression of experimental infantile hydrocephalus and effects of ventriculoperitoneal shunts: an analysis correlating magnetic resonance imaging with gross morphology. *Neurosurgery* 29:329-340, 1991
96. Mies G, Ishimaru S, Xie Y, et al: Ischemic thresholds of cerebral protein synthesis and energy state following middle cerebral artery occlusion in rat. *J Cereb Blood Flow Metab* 11: 753-761, 1991
97. Milhorat TH: Hydrocephalus historical notes, etiology and clinical diagnosis. In: Section of Pediatric Neurosurgery of the American Association of Neurological Surgeons (ed) *Pediatric neurosurgery. Surgery of the developing nervous system*. Grune & Stratton, New York pp 197-210, 1982
98. Minamikawa J, Kikuchi H, Ishikawa M, et al: High energy phosphate metabolism in congenital hydrocephalic rats. An in vivo ^{31}P magnetic resonance spectroscopy study. In: Matsumoto S, Tamaki N (eds) *Hydrocephalus: pathogenesis and treatment*. Springer-Verlag, New York pp 121-130, 1991
99. Miwa S, Inagaki C, Fujiwara M, et al: The activities of noradrenergic and dopaminergic neuron systems in experimental hydrocephalus. *J Neurosurg* 57:67-73, 1982
100. Miyake H, Eghwurdijakpor PO, Sakamoto T, et al: Catecholamine alterations in experimental hydrocephalus. *Child's Nerv Syst* 8:243-246, 1992
101. Miyazawa T, Wada M, Sato K: A quantitative Golgi study of cortical pyramidal neurons in congenitally hydrocephalic rats-HTX. *Child's Nerv Syst* 3:263-270, 1988
102. Miyazawa T, Sato K: Impairment of synaptogenesis and learning disability in HTX-rats with arrested shunt-dependent hydrocephalus. *Child's Nerv Syst* 7:121-8, 1991
103. Miyazawa T, Nishiye H, Sato K, et al: Cortical synaptogenesis in congenitally hydrocephalic HTX-rats using monoclonal anti-synaptic vesicle protein antibody. *Brain Dev* 14:75-79, 1992
104. Morell P, Quarles RH, Norton WT: Formation, structure and biochemistry of myelin. In: Siegel GJ, Agranoff BW, Albers RW, Molinoff PB (eds) *Basic neurochemistry. Molecular, cellular, and medical aspects*. Raven Press, New York pp 109-136, 1989
105. Mori K, Miyake H, Kurisaka M, et al: Immunohistochemical localisation of superoxide dismutase in congenital hydrocephalic rat brain. *Child's Nerv Syst* 9: 136-141, 1993
106. Nakada J, Oka N, Endo S, et al: Changes in the cerebral vascular bed in experimental hydrocephalus: an angiographic and histological study. *Acta Neurochir (Wien)* 114:43-50, 1992
107. Nakada T, Kwee IL, Suzuki N, et al: Intrauterine fetal brain NMR spectroscopy: ^1H and ^{31}P studies in rats. *Magn Reson Med* 12:172-180, 1989
108. Nehlig A, de Vasconcelos AP, Boyet S: Postnatal changes in local cerebral blood flow measured by the quantitative autoradiography [^{14}C] iodoantipyrine technique in freely moving rats. *J Cereb Blood Flow Metab* 9:579-588, 1989
109. Norwood WI, Ingwall JS, Norwood CR, et al: Developmental changes of creatine kinase metabolism in rat brain. *Am J Physiol* 244:205-210, 1983
110. O'Shea KS, Rheinheimer JST, D'Amato CJ, et al: Alterations in the neuroepithelial basal lamina in a neurological mutant with prenatal hydrocephalus. *J Neuropathol Exp Neurol* 47:507-515, 1988
111. Oi S, Ijichi A, Matsumoto S: Immunohistochemical evaluation of neuronal maturation in untreated fetal hydrocephalus. *Neurol Med Chir (Tokyo)* 29:989-994, 1989
112. Pettegrew JW, Panchalingam K, Withers G, et al: Changes in brain energy and phospholipid metabolism during development and aging in the Fischer 344 rat. *J Neuropathol Exp Neurol* 49:237-249, 1990
113. Pettegrew JW, Kopp SJ, Munshaw NJ, et al: ^{31}P nuclear magnetic resonance studies of phosphoglyceride metabolism in developing and degenerative brain: preliminary observations. *J Neuropathol Exp Neurol* 46:419-430, 1987
114. Pople IK: Doppler flow velocities in children with controlled hydrocephalus: reference values for diagnosis of blocked cerebrospinal fluid shunts. *Child's Nerv Syst* 8:124-125, 1992
115. Raimondi AJ: A unifying theory for the definition and classification of hydrocephalus. *Child's Nerv Syst* 10:2-12, 1994
116. Richards HK, Pickard JD, Punt J: Local cerebral glucose utilization in experimental chronic hydrocephalus in the rat. *Z Kinderchir* 59:606-611 (Abstract), 1985
117. Richards HK, Buchknall RM, Jones JC, et al: The uptake of [^{14}C] deoxyglucose into brain of young rats with inherited hydrocephalus. *Exp Neurol* 103:194-198, 1989
118. Riva D, Milani N, Giorgi C, et al: Intelligence outcome in children with shunted hydrocephalus of different etiology. *Child's Nerv Syst* 10:70-73, 1994
119. Roricht S, Meyer BU, Woiciechowsky C, et al: Callosal and corticospinal tract function in patients with hydrocephalus: a morphometric and transcranial magnetic stimulation study. *J Neurol* 245:280-8, 1998
120. Rowlatt U: The microscopic effects of ventricular dilatation without increase in head size. *J Neurosurg* 48:957-961, 1978
121. Rubin RC, Hochwald G, Liwnicz B, et al: The effect of severe hydrocephalus on size and number of brain cells. *Dev Med Child Neurol* 14:117-120, 1972
122. Rubin RC, Hochwald GM, Tiell M, et al: Hydrocephalus: I. histological and ultrastructural changes in the pre-shunted cortical mantle. *Surg Neurol* 5: 109-114, 1976
123. Rubin RC, Hochwald GM, Tiell M, et al: Hydrocephalus: II. cell number and size, and myelin content of the pre-shunted cerebral cortical mantle. *Surg Neurol* 5: 115-118, 1976
124. Rubin RC, Hochwald GM, Tiell M, et al: Hydrocephalus: III. reconstitution of the cerebral cortical mantle following ventricular shunting. *Surg Neurol* 5:179-183, 1976
125. Sada Y, Moriki T, Yamane T, et al: Immunohistochemical study on blood-brain barrier in congenitally hydrocephalic HTX rat brain. *Zentralbl Pathol* 140:289-298, 1994
126. Schmidt H, Siems WG, Grune T, et al: Concentration of purine compounds in the cerebrospinal fluid of infants suffering from sepsis, convulsions and hydrocephalus. *J Perinat Med* 23:167-174, 1995
127. Shirane R, Sato S, Sato K, et al: Cerebral blood flow and oxygen metabolism in infants with hydrocephalus. *Child's Nerv Syst* 8:118-123, 1992

128. Shoesmith CL, Buist R, Del Bigio MR: Magnetic resonance imaging study of extracellular fluid tracer movement in brains of immature rats with hydrocephalus. *Neurol Res* 22:111-6, 2000
129. Siesjo BK: Cerebral circulation and metabolism. *J Neurosurg* 60:883-908, 1984
130. Siesjo BK: Mechanisms of ischemic brain damage. *Crit Care Med* 16:954-963, 1988
131. Sokoloff L: Circulation and energy metabolism of the brain. In: Siegel GJ, Agranoff BW, Albers RW, Mohnhoff PB (eds) *Basic neurochemistry. Molecular, cellular and medical aspects*. Raven Press, New York pp 565-590, 1989
132. Suda K, Sato K, Miyazawa T, et al: Changes of synapse-related proteins (SVP-38 and drebrins) during development of brain in congenitally hydrocephalic HTX rats with and without early placement of ventriculoperitoneal shunt. *Pediatr Neurosurg* 20:50-56, 1994
133. Suda K, Sato K, Takeda N, et al: Early ventriculoperitoneal shunt-effects on learning ability and synaptogenesis of the brain in congenitally hydrocephalic HTX rats. *Child's Nerv Syst* 10:19-23, 1994
134. Sun GY, Foudin LL: Phospholipid composition and metabolism in the developing and aging nervous system. In: Eichberg J (ed) *Phospholipids in nervous tissues*. John Wiley & Sons, New York pp 79-134, 1985
135. Sutton LN, Wood JH, Brooks BR, et al: Cerebrospinal fluid myelin basic protein in hydrocephalus. *J Neurosurg* 59:467-470, 1983
136. Sutton LN, McLaughlin AC, Kemp W, et al: Effects of increased ICP on brain phosphocreatine and lactate by simultaneous ¹H and ³¹P NMR spectroscopy. *J Neurosurg* 67:381-386, 1987
137. Suzuki F, Handa J, Maeda T: Effects of congenital hydrocephalus on serotonergic input and barrel cytoarchitecture in the developing somatosensory cortex of rats. *Child's Nerv Syst* 8:18-24, 1992
138. Tada T, Kanaji M, Kobayashi S: Induction of communicating hydrocephalus in mice by intrathecal injection of human recombinant transforming growth factor-beta 1. *J Neuroimmunol* 50:153-158, 1994
139. Takano T, Mekata Y, Yamano T, et al: Early ependymal changes in experimental hydrocephalus after mumps virus inoculation in hamsters. *Acta Neuropathol* 85:521-525, 1993
140. Tamaki N, Yasuda M, Matsumoto S, et al: Cerebral energy metabolism in experimental hydrocephalus. *Child's Nerv Syst* 6:172-178, 1990
141. Tashiro Y, Drake JM, Chakrabortty S, et al: Functional injury of cholinergic, GABAergic and dopaminergic systems in the basal ganglia of adult rat with kaolin-induced hydrocephalus. *Brain Res* 770:45-52, 1997
142. Tashiro Y, Drake JM: Reversibility of functionally injured neurotransmitter system with shunt placement in hydrocephalic rats: implications for intellectual impairment in hydrocephalus. *J Neurosurg* 88:709-717, 1998
143. Tofts P, Wray S: Changes in brain phosphorus metabolites during the post-natal development of the rat. *J Physiol* 359:417-429, 1985
144. Tsutsumi K, Niwa M, Himeno A, et al: Alpha-natriuretic peptide binding sites in the rat choroid plexus are increased in the presence of hydrocephalus. *Neurosci Lett* 87: 93-98, 1988
145. Valk J, van der Knaap MS: Magnetic resonance of myelin, myelination and myelin disorders. Springer-Verlag, Berlin, 1989
146. van der Knaap MS, van der Grond J, van Rijn PC, et al: Age-dependent changes in localized proton and phosphorus MR spectroscopy of the brain. *Radiology* 176:509-515, 1990
147. Wehby-Grant MC, Olmstead CE, Peacock WJ, et al: Metabolic responses of the neonatal rabbit brain to hydrocephalus and shunting. *Pediatr Neurosurg* 24:79-91, 1996
148. Wiggins RC, McCandlers DW, Enna JJ: *Developmental Neurochemistry*. University of Texas Press, Austin, 1985
149. Williamson EC, Pearson HE, McAllister JP: Gliosis and ganglion cell death in the developing cat retina during hydrocephalus and after decompression. *Dev Brain Res* 70:47-52, 1992
150. Wright LC, McAllister JP, Katz SD, et al: Cytological and cytoarchitectural changes in the feline cerebral cortex during experimental infantile hydrocephalus. *Pediatr Neurosurg* 16:139-155, 1990
151. Yamada H, Yokota A, Furuta A, et al: Reconstitution of shunted mantle in experimental hydrocephalus. *J Neurosurg.* 76:856-862, 1992
152. Young RSK, Cowan BE, Petroff OAC, et al: In vivo ³¹P and in vitro ¹H nuclear magnetic resonance study of hypoglycemia during neonatal seizure. *Ann Neurol* 22:622-628, 1987

Modern Imaging of Pediatric Hydrocephalus

FRANCIS BRUNELLE

Definition of Hydrocephalus

Hydrocephalus is defined as an increased volume of intracranial CSF. It is usually but not always associated with an increase in intracranial pressure. CSF accumulates in the ventricles, which become enlarged, or around the periphery of the brain (so-called external hydrocephalus). In acute hydrocephalus the ventricles may not have time to dilate, while with chronic hydrocephalus the ventricles may be very large. A new equilibrium between reabsorption and production of CSF is then reached at a higher pressure.

Normal CSF Circulation

CSF is produced by the choroid plexuses of the lateral, third, and fourth ventricles at a rate of approximately 450 ml per day. To date no noninvasive technique is able to measure the exact production of CSF. Reabsorption occurs mainly at the periphery of the brain through the arachnoid villi. Other pathways of reabsorption are the lymphatics of the spinal nerve roots and the cerebral deep medullary veins. These pathways may play only a small role in the normal physiology of CSF but their role is more important when the major pathways are obstructed. The total volume of CSF depends on age, but the normal adult volume of 150 ml is reached by the age of 5 years. The normal volume of the lateral ventricles as measured by us does not exceed 12-15 ml. The third ventricle only contains 1 ml.

It is known from Duboulay's work that the CSF exhibits a systolic-diastolic pattern in the subarachnoid space of the lumbar spine. It is now possible with cine phase contrast MRI to display the movement of the CSF in the ventricles and in the subarachnoid spaces. The systolic expansion of the brain pushes the CSF [10, 15, 20] downward around the periphery of the brain from the surface of the cortex to the foramen magnum in the cervical region. From the lateral ven-

tricles the CSF flows into the third ventricle and through the aqueduct of Sylvius.

At that level the CSF flows at a speed of 2 cm/s. During diastole the pattern is reversed: CSF flows back through the foramen magnum from the upper cervical spine and from the fourth ventricle into the aqueduct of Sylvius. This to-and-fro oscillatory motion can be depicted qualitatively or quantitatively. The movement is also seen in the region of the cervical spine. The majority of the flow occurs in the premedullary space. However, flow also exists in the space posterior to the cord, albeit to a lesser degree. The brain also moves, and its movement can be measured by MRI. The pons shows a downward movement in the posterior fossa during systole and an upward movement during diastole. The permeability of the aqueduct of Sylvius can therefore be demonstrated by phase contrast MRI. If this technique is not available, a sagittal T2-weighted scan can be obtained. A flow void phenomenon is seen when CSF is flowing; it appears black in the more stationary CSF, which appears white.

Diagnosis of Hydrocephalus by Imaging

Skull X-Rays

The classic signs of hydrocephalus in children depend on the age of the patient; in fact, they depend on the presence of open sutures. The classic signs of hydrocephalus include the following on skull X-rays:

- Increased digital marking of the skull
- Widening of the sutures, beyond the normal maximum of 3 mm
After the age of 2 years they include:
- Increased digital marking
- Erosion of the dorsum sellae

In chronic hydrocephalus long interdigitations of the sutures are seen due to progressive enlargement

of the head during growth of the skull. Depending on the etiology, lytic lesions of the skull may be seen – in lymphoma, leukemia, and histiocytosis X – and specific changes such as those seen in achondroplasia may be found. Calcifications may also be seen; they may indicate a specific cause such as pineal teratoma.

Ultrasonography

Ultrasonography is the screening procedure of choice for hydrocephalus in patients under 18 months of age, while the anterior fontanelle is still open. It is also useful for follow-up studies of ventricular size after treatment and can be performed at the bedside. Normal ventricles are slit-like in young children. When dilated, the anterior aspect of the frontal horns is easily seen. Their lateral aspects are rounded. The size of the third ventricle is very difficult to assess by ultrasound, the fourth even more so. For this reason, the precise diagnosis and cause of hydrocephalus is rarely made by ultrasound alone.

Computed Tomography

The diagnosis of hydrocephalus is based on analysis of the size of the ventricles. However, an enlarged ventricular system does not necessarily mean hydrocephalus; it must be distinguished from atrophy. Many ratios and measurements have been published. The most popular is the Evans ratio, which is calculated using an axial section on CT scan [12]. This ventricular index is the ratio between the intraventricular diameter at the level of the frontal horn and the inner skull diameter at the same level. This ratio is very seldom used in clinical practice for many reasons, the most important being the fact that ventricular enlargement is not homogeneous. In hydrocephalus, ventricular enlargement occurs first at the level of the

occipital horns. Laplace's law tells us that the force is the product of pressure \times surface area; thus, when the intraventricular pressure rises, the force will be greatest at the level where the surface area is largest, i.e., the occipital horns. In clinical practice, the most important parameter by which to distinguish atrophy from hydrocephalus is the head circumference together with the change in ventricular size. In atrophy, ventricular size is usually stable, whereas in hydrocephalus the head circumference and the ventricular size both increase. In children with open sutures the diagnosis may be made clinically on the basis of increased head circumference. In older patients (after 2 or 3 years of age) hydrocephalus is usually associated with compression of the peripheral CSF spaces (subarachnoid spaces), but not always – in communicating hydrocephalus these spaces may be normal, and in so-called external hydrocephalus they are actually enlarged. Periventricular hypodensity can be seen as a consequence of transependymal reabsorption of CSF in active hydrocephalus.

Magnetic Resonance Imaging

MRI is the examination of choice for showing dilatation of the ventricular system and revealing the underlying cause of the hydrocephalus. On T1-weighted sagittal scans the third ventricle is dilated mainly in its sagittal dimensions. The inferior floor of the third ventricle tends to balloon downward and posteriorly towards the dorsum sellae. In addition, the posterior aspect of the third ventricle balloons backwards. The corpus callosum is elevated. On T2-weighted sequences the ventricles appear white. The periventricular regions may also appear white due to periventricular transependymal reabsorption of CSF (Fig. 1). Gadolinium injection on T1 images is only necessary when looking for tumor, subarachnoid metastases or meningitis, or ventriculitis.

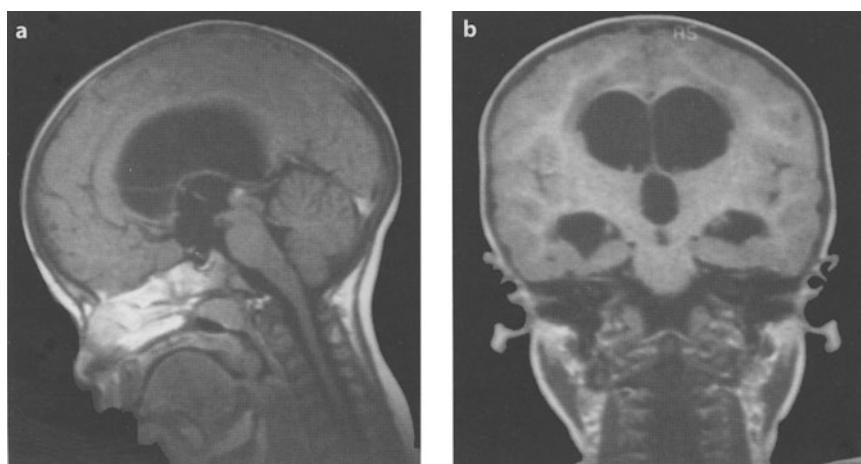


Fig. 1a,b. A 2-year-old girl with hydrocephalus secondary to aqueductal stenosis. **a** Sagittal, **b** coronal T1-weighted MRI scan. On T1 images, transependymal reabsorption is seen as a hypointense ribbon in the periphery of the ventricles

Postoperative Imaging

To assess ventricular size after shunting, CT scan alone is sufficient for follow-up. However, to assess the permeability of “internal shunts” such as third ventriculostomy or ventriculocystostomy, phase contrast MRI is needed. With phase contrast MRI, which is gated on the cardiac frequency, it is possible to assess the dynamics of CSF flow through these internal surgical shunts. For third ventriculostomy, a sagittal scan displays the movement of the CSF through the stoma [4, 22]. For ventriculocystostomy, imaging should be performed in the plane of the communication to visualize the CSF flow. When the aqueduct of Sylvius is compressed by a tumor, cyst, or vein of Galen aneurysm, cine phase contrast MRI can assess the reopening of the aqueduct after treatment for the cause of the obstruction [10].

Antenatal Diagnosis of Hydrocephalus

The most difficult task is to diagnose hydrocephalus antenatally, since ventricular dilatation is seen in both hydrocephalus and atrophy [8]. Measurement of the head circumference by MRI is essential. Assessment of biparietal diameter (BPD) is not accurate antenatally because the head of the fetus may be deformed: a scaphocephalic head may have a normal circumference and a small BPD. Normal measurements of the ventricles in the fetus have been published [29]. The largest diameter of the atrium should not exceed 9 mm. Biometric measurements in the fetus must be compared to those of an age-matched normal fetus in order to differentiate atrophy from hydrocephalus, as the normal morphology of the brain depends on gestational age: large ventricles in a large head are diagnostic of hydrocephalus, while in the presence of a small or even normal-sized head they are diagnostic of atrophy. Associated findings such as agenesis of the corpus callosum or hemorrhage may help the diagnosis. MRI is valuable in showing such associated malformations or hemorrhages [24].

Hydrocephalus and its Causes

Classically, the possible causes of hydrocephalus are divided up as follows:

- 1 Overproduction of CSF
 - 1.1 Choroid plexus papilloma
- 2 Obstruction of CSF pathways

- 2.1 Foramen of Monro
 - Glioependymal cysts
 - Colloid cysts
 - Gliomas of the fornix
 - Giant cell astrocytomas (tuberous sclerosis)
 - Choroid plexus tumor
 - Posthemorrhagic
 - Congenital
- 2.2 Third ventricle
 - Thalamic gliomas
 - Craniopharyngiomas
 - Optic pathway gliomas
- 2.3 Aqueduct of Sylvius
 - True obstruction
 - Diaphragm
 - Posthemorrhagic
 - Tectal tumor
 - Pineal tumor
 - Thalamic tumor
 - Vein of Galen vascular malformation
 - Incisural arachnoid cyst
 - Neurofibromatosis type 1
- 2.4 Fourth ventricle
 - Posterior fossa tumor
 - Medulloblastomas
 - Ependymomas
 - Astrocytomas
 - Choroid plexus tumors
 - Pontine tumor (rare)
 - Dandy-Walker
- 2.5 Foramen magnum
 - Chiari I malformation
 - Chiari II malformation
 - Osteochondrodysplasia (achondroplasia, etc.)
 - Upper cervical cord tumors
 - Arachnoid cysts
- 3 Nonobstructive hydrocephalus (communicating hydrocephalus)
 - Posthemorrhagic
 - Subarachnoid metastases (astrocytoma, medulloblastoma, leukemia)
 - Tuberculosis, meningitis
 - Increased venous pressure
 - Arteriovenous malformations
 - Stenosis of jugular foramen (osteochondrodysplasia, craniosynostosis)
 - Superior vena cava obstruction
- 4 External hydrocephalus
 - Post-traumatic
 - Superior vena cava obstruction
 - Idiopathic
- 5 Pseudotumor cerebri
- 6 Slit ventricle syndrome

Overproduction of CSF

Choroid plexus papillomas are intraventricular tumors. They may be benign or malignant. They are a source of overproduction of CSF, producing active hydrocephalus with massive ventricular enlargement and transepithelial CSF reabsorption. The hydrocephalus is cured after resection of the tumor. They are most often found in the lateral ventricles, but may occasionally be seen in the fourth ventricle. On CT, they appear as intraventricular masses that enhance homogeneously. They may contain one or several cysts. When they are large they are difficult to differentiate from a parenchymal tumor. They may be calcified. On MRI they are isointense lesions on T₁, heterogeneous on T₂, and enhance homogeneously. They are vascular lesions and can be embolized preoperatively. The differential diagnosis includes other intraventricular tumors:

- Choroid plexus carcinomas
- Intraventricular meningiomas
- Subependymal astrocytomas

The prognosis is good after surgery if the lesion is benign.

Obstructive Hydrocephalus

Isolated Lateral Hydrocephalus or Unilateral Ventricular Dilatation

Isolated lateral hydrocephalus is extremely rare and very difficult to differentiate from unilateral brain atrophy (Fig. 2) [14]. Even more confusing is the fact that unilateral ventricular dilatation due to atrophy can expand the cranial vault due to increased compliance of the brain on the abnormal side.

Causes include unilateral congenital atresia of the foramen of Monro or occlusion of this foramen due to tumor. CSF flow imaging can sometimes show occlusion of the foramen of Monro. Antenatal diagnosis by ultrasound has been described. Differentiation from unilateral atrophy is crucial as obviously the prognosis is quite different. Unilateral megaencephaly is a further differential diagnosis. In this latter case unilateral ventricular enlargement may be seen, but other features such as abnormal gyration, gray matter heterotopia, and calcification help to make the diagnosis. In older children another cause is the presence of a giant cell astrocytoma in the region of the foramen of Monro in a patient with tuberous sclerosis.

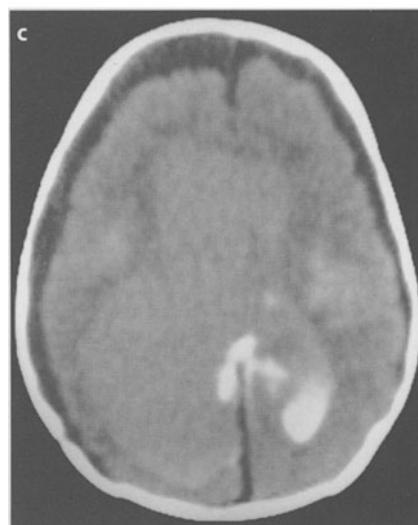
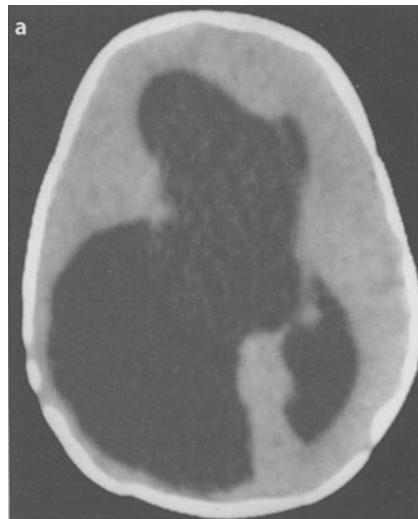


Fig. 2a-c. A 4-month-old girl. **a** Axial CT scan, **b** coronal T₁-weighted MRI (3D GRASS). Both images show dilatation of the right ventricle secondary to unilateral atresia of the foramen of Monro. **c** Same patient after endoscopic septostomy. CT scan with lumbar injection of contrast medium. Both ventricles have opacified, the left better than the right. Note the unopacified subdural collection

Obstruction of the Third Ventricle

Hydrocephalus due to obstruction of the third ventricle is rather rare as complete occlusion of the third ventricle by tumor is exceptional. Thalamic gliomas may completely occlude the third ventricle. More rarely, craniopharyngiomas or optic pathways gliomas may rupture and expand into the third ventricle and occlude the CSF pathways. Rare purely intraventricular tumors such as colloid cysts are another cause. More difficult to understand is the hydrocephalus that can be associated with supraoptic arachnoid cysts (Fig. 3). These cysts may be very large and push the floor of the third ventricle superiorly. The exact mechanism of the hydrocephalus is not completely understood. A valve mechanism filling the cyst during diastole and obstructing the CSF pathways during systole is one suggested hypothesis. In these cases we have demonstrated that the aqueduct of Sylvius is patent. Ventriculocystostomy between the third ventricle and the cyst may be performed; its patency can be assessed by cine phase contrast MRI.



Fig. 3. A 2-month-old baby girl with hydrocephalus and suprasellar cyst. Sagittal T1 MRI shows the suprasellar cyst pushing the third ventricle upward

Aqueduct Obstruction

Aqueductal obstruction can be easily diagnosed on MRI. The classical CT signs are dilatation of the lateral and third ventricles with a normal fourth ventricle. The ventricles are very large and the peripheral subarachnoid spaces compressed against the cranial vault. With MRI the diagnosis is readily made and the aqueduct permeability can be assessed. On sagittal T1-weighted images the lumen of the aqueduct can usually be seen in a normal

child. However, the MRI technique needs to be perfect: a thick parasagittal (more than 5 mm) MRI scan can fail to demonstrate the aqueduct lumen due to volume averaging. If it is not seen, a sagittal high-resolution (512 matrix) thin T2-weighted scan demonstrates the nature of the obstruction. In a normal child, the presence of flow in the aqueduct is responsible for a flow void phenomenon. The flow appears black on T2-weighted sequences although the CSF appears white. The normal speed of CSF at this level is 2 cm/s. When no flow is present, no void is seen and quantitative analysis of CSF movement shows an alternating rebound against the obstacle.

True Aqueductal Stenosis

MRI has shown that true aqueductal stenosis accounts for only 20% of patients with aqueductal obstruction. High-resolution MRI may show the nature of the obstruction, e.g., diaphragm or forking. The other 80% of cases of aqueductal obstruction result from periaqueductal tumors [2]. T1-weighted images with gadolinium contrast and T2-weighted images may be used to show small tumors in this vicinity. The exact nature and statistics of the tumor types are not known as biopsy is rarely performed in this region (Fig. 4). Surprisingly enough, even true obstructions of the aqueduct may not be revealed until later in childhood. Sagittal T2-weighted MRI is essential for preoperative analysis the shape of the third ventricle to assess whether third ventriculostomy is feasible. On such images a precise analysis of the anatomy of the third ventricle, the basilar artery, the prepontine cistern, and the clivus is mandatory. After surgery, the third ventriculostomy can be assessed by phase

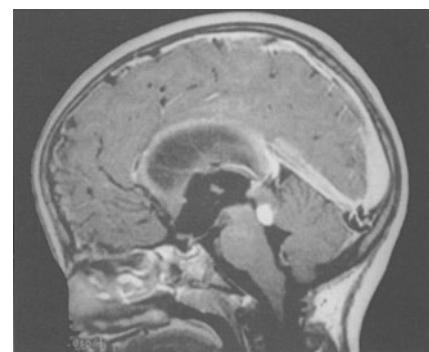


Fig. 4. A 9-year-old girl with hydrocephalus. MRI shows a small astrocytoma infiltrating the tectum. A nodule is enhancing

contrast MRI (Fig. 5). A sagittal scan can be obtained showing a to-and-fro movement of CSF through the ventriculostomy between the third ventricle and the prepontine spaces. Quantitative analysis may be performed on oblique scans perpendicular to the axis of the stoma. In such communications the speed of CSF flow is between 2 and 5 cm/s (Fig. 6). After surgical intervention, especially after performing an internal shunt, the ventricular size only slowly returns to normal. Peripheral redistribution of CSF occurs, re-expanding the peripheral CSF subarachnoid spaces, which become visible on CT or MRI.

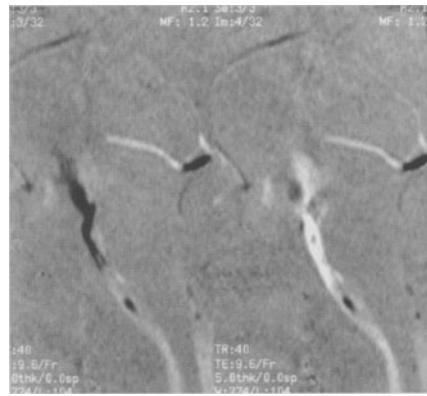


Fig. 5. An 11-year-old girl with aqueductal stenosis and ventriculostomy. Sagittal phase contrast cine MRI. Two images are displayed, during systole and diastole. Upward flow is black, downward flow is white. The ventriculostomy is patent, showing alternating black and white flow

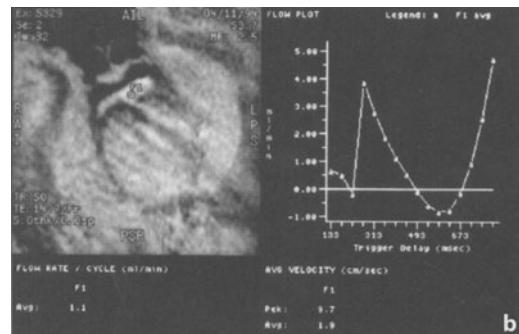
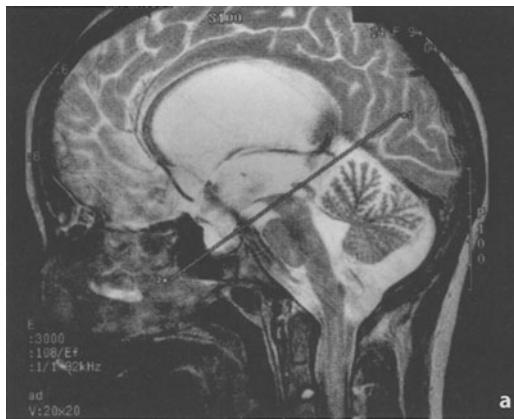


Fig. 6a, b. A 14-year-old boy with aqueductal stenosis treated with third ventriculostomy. **a** Sagittal T2-weighted MRI shows flow void in the region of the ventriculostomy. **b** Quantitative measurement of flow through the ventriculostomy proves the patency of the internal shunt

Congenital Aqueductal Stenosis

Congenital aqueductal stenosis is rare. It is difficult to diagnose on antenatal ultrasound alone as the aqueduct is impossible to image and the size of the fourth ventricle difficult to assess. Antenatal MRI allows one to diagnose aqueductal stenosis by showing the hydrocephalus in association with a normal-sized fourth ventricle and absence of the aqueductal lumen. This antenatal information has allowed us to organize rapid postnatal confirmation of the diagnosis and to instigate early treatment in one case (Fig. 7).



Fig. 7. Antenatal diagnosis of aqueductal stenosis at 37 weeks of gestation. Sagittal T2-weighted MRI sequence in utero shows ventricular dilatation and aqueductal stenosis. The foramen of Monro is seen as a black spot below the trigone

Posthemorrhagic Aqueductal Stenosis

Obstruction of the aqueduct can occur after intraventricular hemorrhage in prematurity (Fig. 8). It is then very often associated with massive dilatation of the occipital horn, probably due to white matter loss as a consequence of cerebral ischemia [5, 9].

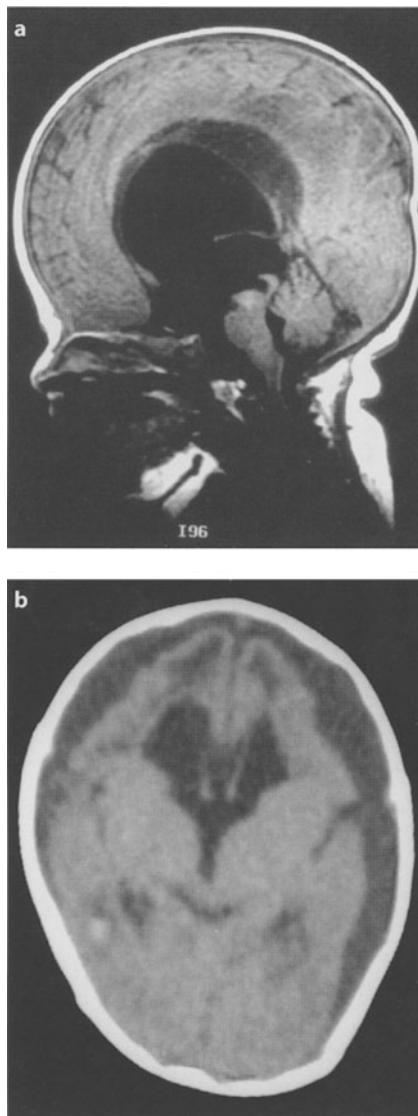


Fig. 8a, b. A 3-month-old premature baby with hydrocephalus. **a** Sagittal T1-weighted MRI shows massive ventricular dilatation. The aqueduct is obstructed at its distal end. **b** Same patient after shunting. The ventricles are smaller. Note the subdural effusion

Fourth Ventricle Obstruction

Fourth Ventricle Tumors

Medulloblastoma is the most common tumor of the fourth ventricle to cause hydrocephalus. Raised intracranial pressure is the most frequent presentation of this tumor. Other tumors such as ependymoma and cerebellar astrocytoma may also obstruct the fourth ventricle. The lateral and the third ventricles are massively dilated, and frequently this is associated with periventricular transependymal reabsorption of CSF. The aqueduct of Sylvius is not only patent but often wide open, as a consequence of the increased CSF pressure (Fig. 9). On T2-weighted images no flow is seen in the fourth ventricle. Third ventriculostomy may be performed as an emergency before the removal of the tumor. Sagittal MRI allows one to confirm the efficiency of the internal shunt. Phase contrast cine MRI demonstrates the alternating flow through the stoma. The ventricles rapidly return to normal size after shunting as is usually the case in acute hydrocephalus. As the normal CSF pathways are reopened after tumor removal, the ventriculostomy may close with no flow being seen through it.

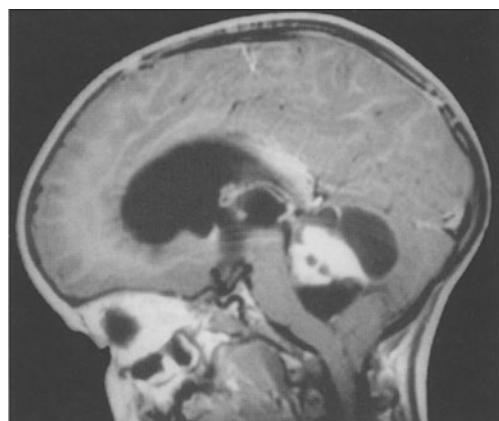


Fig. 9. A 12-year-old boy with hydrocephalus and posterior fossa astrocytoma. Sagittal T1-weighted MRI after gadolinium injection shows a cystic/solid tumor in the posterior fossa. The aqueduct is patent. Radiating hypointense streaks are seen anteriorly representing transependymal reabsorption of CSF

Dandy-Walker Malformation

About 50% of Dandy-Walker cysts (Fig. 10) are associated with hydrocephalus [17]. In our experience of Dandy-Walker syndrome diagnosed antenatally none of the cases showed hydrocephalus. This implies that the hydrocephalus develops after birth in most cases of Dandy-Walker syndrome. The diagnosis can be made by antenatal ultrasound, but the shape and size of the vermis is difficult to assess. Ultrasound shows a large cystic formation in the region of the posterior fossa; the position of the tentorium cerebelli is difficult to assess on ultrasound. Antenatal MRI is useful in showing not only the cyst but the partial or complete agenesis of the vermis (Fig. 11). In fact, the tentorium is elevated in both

Dandy-Walker syndrome and posterior fossa arachnoid cysts and cannot be used as a differential sign. T2-weighted sagittal MRI scans clearly show the dilated fourth ventricle, the agenesis of the vermis, and the position of the tentorium [3].

Postnatal MRI shows the following signs:

- Enlargement of the fourth ventricle
- Partial or complete agenesis of the vermis, best seen on T1-weighted sagittal and axial scans
- Elevation of the tentorium
- Callosal dysgenesis
- Gray matter heterotopia (rare)

After shunting of the fourth ventricle the two cerebellar hemispheres approach each other and may mimic a normal vermis on T1-weighted sagittal scans. Knowledge of the patient's past medical history therefore helps in making the diagnosis.

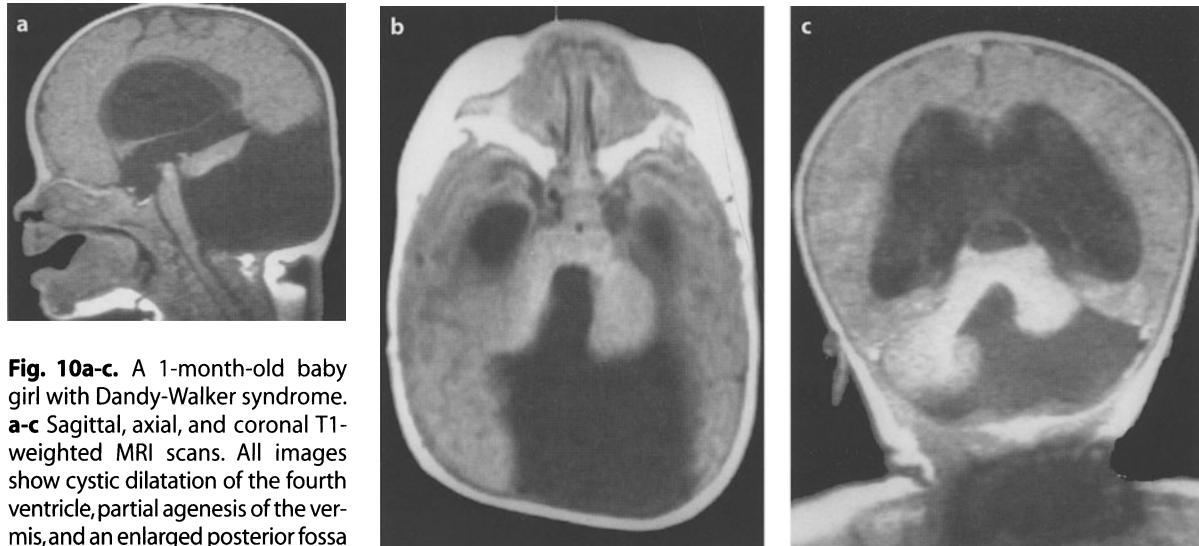


Fig. 10a-c. A 1-month-old baby girl with Dandy-Walker syndrome. a-c Sagittal, axial, and coronal T1-weighted MRI scans. All images show cystic dilatation of the fourth ventricle, partial agenesis of the vermis, and an enlarged posterior fossa with elevation of the tentorium

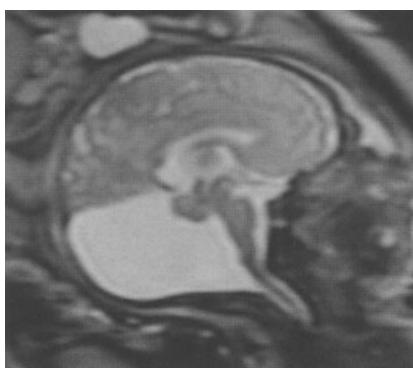


Fig. 11. Antenatal diagnosis of Dandy-Walker cyst. Sagittal T2-weighted image shows ventricular dilatation and fourth ventricular enlargement

Posterior Fossa Cysts

Posterior fossa arachnoid cysts (Fig. 12) can be distinguished from Dandy-Walker syndrome mainly because the vermis is complete and on sagittal T1-weighted scans the fourth ventricle is normal or even compressed anteriorly. The pons has moved against the clivus. These cysts are only rarely associated with hydrocephalus. They are very difficult to differentiate from an enlarged cisterna magna of the posterior fossa. The tentorium may also be elevated in both conditions. Even phase contrast cine MRI is unable to differentiate one from the other. The flow between the fourth ventricle and the cisterna magna can be slow, and

only metrizamide CT studies may show communication between the two compartments. However, these mega cisterna magna are probably compressive because they act as a CSF deadend. In other words, it is difficult if not impossible to differentiate a communicating arachnoid cyst from a mega cisterna magna.

Trapped (Isolated) Fourth Ventricle

After multiple shunts, hemorrhage or surgery the fourth ventricle may become isolated with complete obstruction of the aqueduct and of the CSF outlets of the fourth ventricle (Fig. 13) [7, 27]. Because the



Fig. 12a, b. A 5-year-old girl with hydrocephalus and posterior fossa cyst. **a** T2-weighted sagittal MRI shows the posterior fossa cyst and a flow void in the fourth ventricle. **b** Axial CT contrast-enhanced image shows nonopacification of the cyst whereas the ventricles are opacified

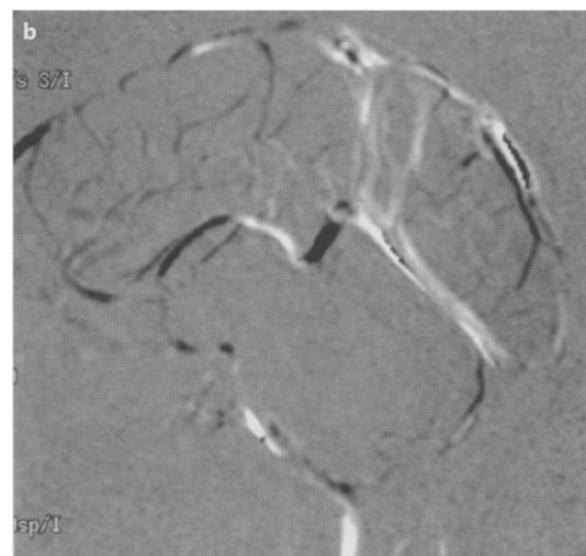


Fig. 13a, b. A 2-year-old baby boy with shunted hydrocephalus caused by premature intraventricular hemorrhage. Meningitis and a trapped fourth ventricle. Cine phase contrast sagittal MRI. No flow is seen either in the fourth ventricle or in the aqueduct

choroid plexus of the fourth ventricle is producing CSF and when the lateral ventricles are shunted above, the fourth ventricle becomes dilated and may be responsible for posterior fossa symptoms. The fourth ventricle appears rounded and dilated, and the vermis is pushed posteriorly and the pons anteriorly by the dilatation. The lateral ventricles are usually normal in size, as they are in most cases already shunted. These findings may be difficult to analyze in patients after posterior fossa surgery. Sagittal MRI scans are the best imaging modality to diagnose this complication.

Treatment is shunting or revision of the shunt of the fourth ventricle.

Foramen Magnum Obstruction

Although reabsorption of CSF occurs at the level of pacchionian granulations in the supratentorial compartment, it can happen that obstruction of the CSF spaces at the level of the foramen magnum or even in the upper cervical region may cause hydrocephalus. It is possible that obstruction of the normal compliance compartment represented by the upper cervical arachnoid spaces may change the hydrodynamics of CSF and lead to hydrocephalus.

Chiari I abnormality is due to engagement of the cerebellar tonsils in the foramen magnum. It may lead to syringomyelia (25%) or even hydrocephalus. In children the tonsils should not extend more than 5 mm below the foramen magnum. Chiari I abnormality can also be the consequence of hydrocephalus, posterior fossa tumor, craniosynostosis, or lumboperitoneal shunt. These other causes should be excluded before a Chiari I malformation is held responsible for hydrocephalus. Opening the bony and dural structures to recreate a cisterna magna is the usual treatment.

Chiari II malformation is a dysraphic state associated with spina bifida. Hydrocephalus is almost invariably associated with Chiari II malformation. Obstruction of the distorted aqueduct and/or of the foramen magnum are among the possible explanations. Hydrocephalus appears a few days after closure of the myelomeningocele. Most of these children are then shunted.

It is beyond the scope of this chapter to describe the features of Chiari II malformation.

Osteochondrodysplasias

A narrow foramen magnum can be observed in several osteochondrodysplasias [16, 28]. The most common and best known is achondroplasia (Fig. 14). This osseous disease is complicated by the fact that it is associated with obstruction of the cerebral venous return at the level of jugular foramen. Patients with achondroplasia present with enlarged heads. MRI shows dilated ventricles but also periventricular effusions (see "External Hydrocephalus" below). The pathophysiology of hydrocephalus is not clear. Very few patients with achondroplasia will require shunting.

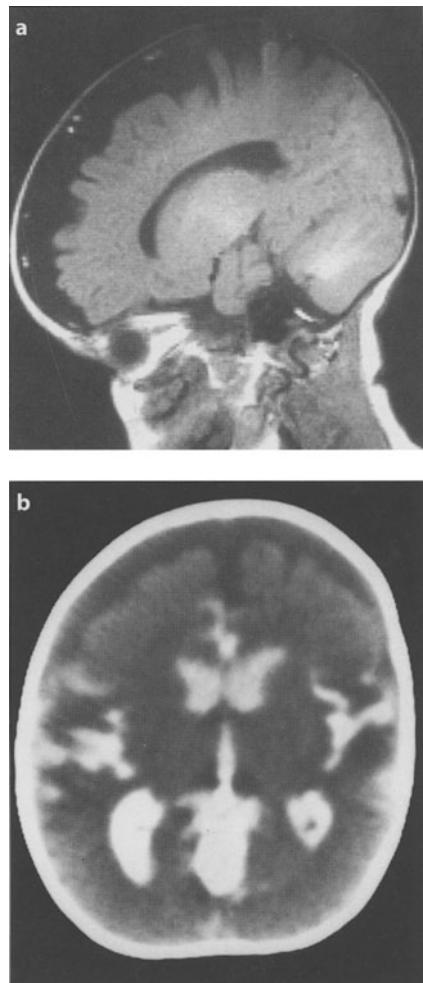


Fig. 14a, b. A 5-month-old patient with achondroplasia and "external hydrocephalus." **a** Parasagittal T1-weighted MRI shows a pericerebral effusion with apparent dilated "subarachnoid" spaces. **b** Axial CT scan after contrast injection in the lumbar subarachnoid spaces: the ventricles are opacified, as are the sylvian fissures, but not the anterior dilated "subarachnoid" spaces

Upper Cervical Cord Tumor

Tumors of the upper cervical cord may present with hydrocephalus, but the mechanism is not clearly understood. Increased protein content of CSF and bleeding may cause obstruction of the villi. A patient with idiopathic hydrocephalus should undergo upper cervical MRI to exclude tumor (Fig. 15) [25].

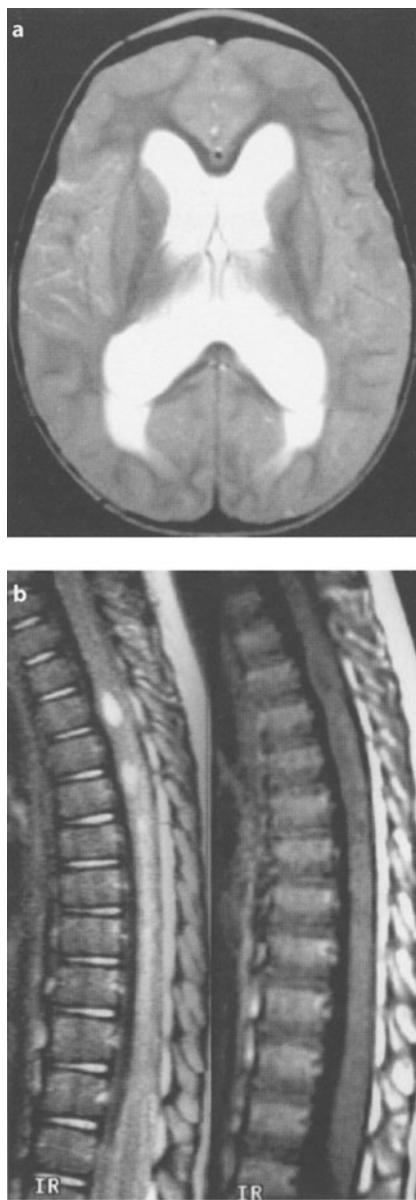


Fig. 15a, b. A 3-year-old boy with upper thoracic spinal cord tumor and hydrocephalus. **a** T2-weighted axial images show hydrocephalus and periventricular hyperintensity, representing transependymal reabsorption of CSF. **b** Same patient, sagittal T1-weighted MRI with and without contrast show the tumor in the upper dorsal spinal cord

Communicating Hydrocephalus

Hemorrhage

The most common cause of communicating hydrocephalus (accounting for 30% of hydrocephalus in children) is hemorrhage in the neonatal period, particularly in the premature infant (Fig. 16). Obstruction of the arachnoid villi leads to massive acute dilatation of the entire ventricular system. Peripheral subarachnoid spaces may be enlarged as well. Dilatation usually is predominant in the occipital region. The reason for this phenomenon is not clear, but white matter atrophy due to the often associated periventricular leukomalacia (PVML) in this setting may be responsible.

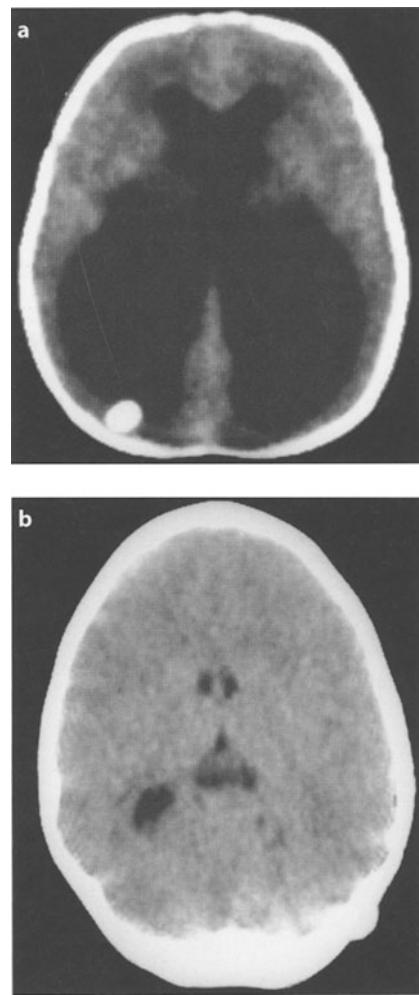


Fig. 16a, b. A 2-month-old baby premature girl with intraventricular hemorrhage. **a** CT scan at 2 months of age. Massive ventricular dilatation with cortical thinning. **b** Same patient at 2 years of age. The ventricles are narrow and the cortical mantle is normal

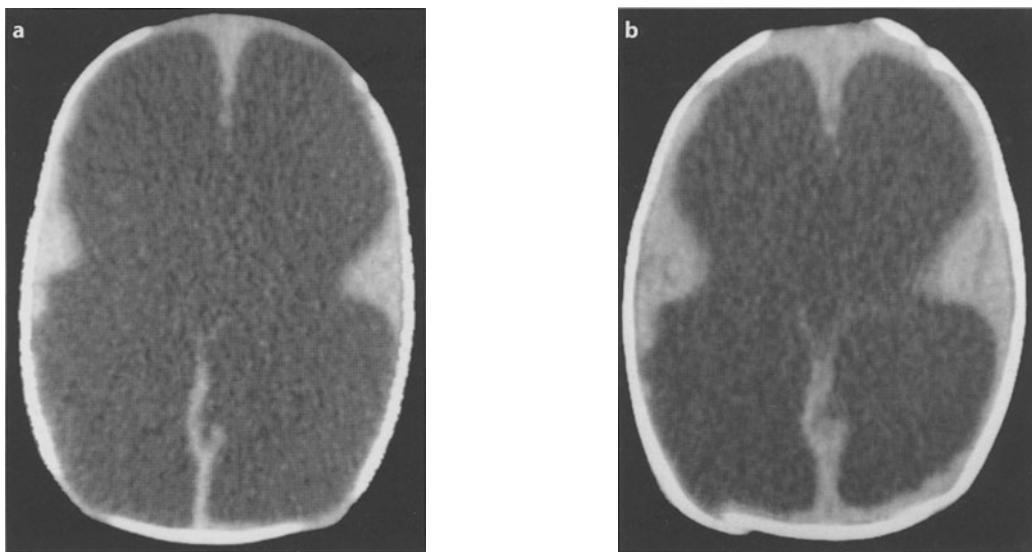


Fig. 17a, b. A 6-month-old premature baby with a maternofetal infection (*Enterobacter*). **a** Massive hydrocephalus with cortical mantle thinning. The sutures are widened. **b** Same patient after ventriculoperitoneal shunting. The ventricles are smaller, the cortex thicker, and the sutures overlapping

This hydrocephalus may resolve spontaneously. About one-third of these babies require shunting. The prognosis does not depend on hydrocephalus but rather on the degree of PVML and brain ischemia.

meningitis as well. CT or MRI shows diffuse enhancement of the subarachnoid spaces, and sometimes the ependyma of the ventricles (in cases of ventriculitis).

Metastases

Subarachnoid metastases may be responsible for hydrocephalus by obstructing the arachnoid villi [18]. Medulloblastomas but also benign astrocytomas may seed into the subarachnoid spaces. They are easily diagnosed using T1-weighted MRI after gadolinium injection. Enhancement of all the subarachnoid spaces is diagnostic of carcinomatous meningitis. This finding should be distinguished from the normal enhancement of the dura that occurs after surgery.

Meningitis

Hydrocephalus is very common in the acute phase of bacterial meningitis (Figs. 17, 18). Diffuse involvement of the subarachnoid spaces by tuberculosis or other form of granulomatous or fungal meningitis may cause hydrocephalus (Fig. 19). Hydrocephalus may be a sequel of other forms of



Fig. 18. A 3-month-old baby boy who had neonatal pneumococcal meningitis. CT scan shows ventricular dilatation associated with parenchymal loss and calcifications

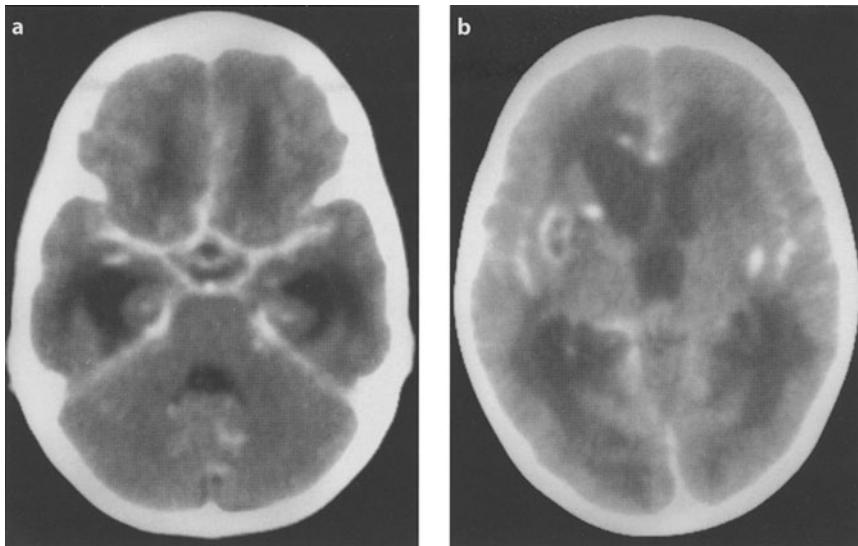


Fig. 19a, b. Hydrocephalus secondary to tuberculosis. Axial CT scan after contrast injection. Ventricular dilatation is seen as well as periventricular hypodensity. Cistern and basal ganglia enhancement is present

Increased Venous Pressure

Increased venous pressure may be responsible for hydrocephalus or also pseudotumor cerebri [26]. Increased venous pressure may have various causes, such as superior vena cava thrombosis (Fig. 20), jugular vein stenosis in achondroplasia, or arteriovenous malformation (AVM: parenchymal AVM, vein of Galen AVM). This condition is difficult to diagnose on CT or MRI alone. MR angiography can be useful in showing thrombosis of the superior vena cava in patients with multiple central venous

catheters. Obstruction at the level of the jugular foramen can be suspected when MR angiography shows not only stricture of the jugular vein at the level of the base of the skull, but also the presence of multiple collaterals. Definitive diagnosis depends upon angiography and direct measurement of the intracranial venous pressure.

External Hydrocephalus

Benign external hydrocephalus has been extensively described in the literature [26]. We prefer the term “benign pericerebral effusion” (Figs. 21–23). The exact anatomical location of the accumulation of fluid is still a source of controversy. The condition occurs in children under 2 years of age while the sutures are still open; it never happens in children with closed sutures. Patients present with increased head circumference and mild psychomotor retardation, often simply axial hypotonia. These effusions tend to stabilize spontaneously. When large they may be managed with a subdural-peritoneal shunt. In a previous study [1] we showed that after lumbar injection of contrast medium these pericerebral effusions almost invariably do not opacify, the underlying opacified subarachnoid spaces being seen to be compressed below the effusion. The origin of the effusions is not clear. In a few cases there is a clear-cut history of previous trauma and sometimes subarachnoid hemorrhage. Whether they are subdural or in compartmented subarachnoid spaces does not really matter, the treatment is the same: avoidance of shunting depending on the clinical setting.

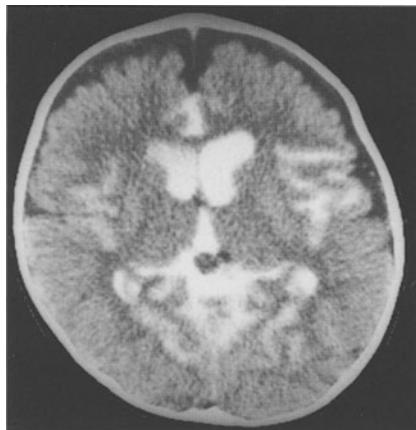


Fig. 20. A 1-year-old baby boy with superior vena cava thrombosis and external hydrocephalus. CT scan after lumbar injection of contrast. The anterior dilated spaces are not opacified whereas the ventricles and the sylvian fissures are



Fig. 21. Seizures and cranial trauma in a 6-month-old girl. So-called external hydrocephalus: actually chronic subdural effusion

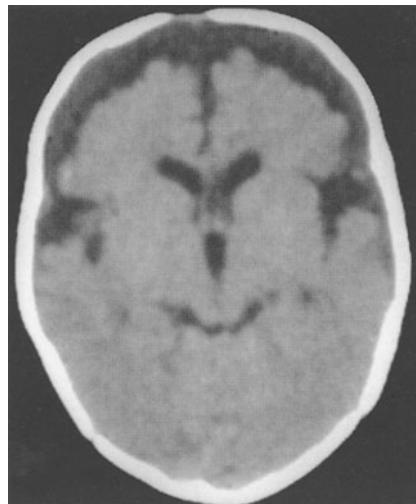


Fig. 22. A 4-month-old boy with acute dehydration. CT scan shows two pericerebral compartments: a dense subdural effusion and an isodense subarachnoid effusion

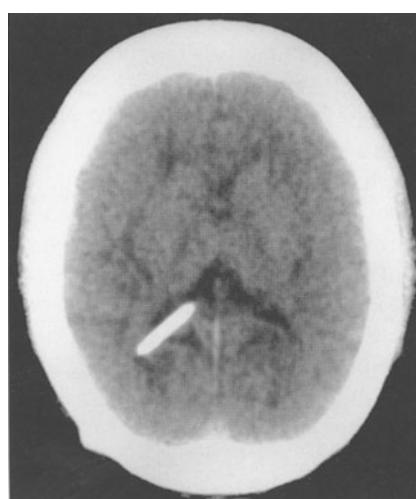


Fig. 23. Axial CT scan in a 28-year-old patient with shunted hydrocephalus. The ventricles are small, the skull is thickened

Pseudotumor Cerebri

Pseudotumor cerebri is defined by the presence of increased intracranial pressure with normal-sized ventricles [21]. It does not strictly belong in a discussion of hydrocephalus. This condition is associated with papilledema and carries the risk of optic nerve atrophy and blindness. Causes include:

- Metabolic: hyperthyroidism, hypercortisolism
- Drugs and toxic substances: antibiotics, indomethacin, vitamin A, pesticides
- Feeding following starvation
- AVM: reversible after embolization
- Jugular vein stenosis

Postoperative Imaging and Imaging of Complications

One of the important roles of imaging is to follow up patients with hydrocephalus after shunt placement. If a prosthesis is inserted, CT scan and plain films of the shunt are performed (thorax, abdomen). CT shows the location of the tip of the shunt and the size of the ventricles, and looks for subdural effusions. Plain films assess the continuity of the shunt from the skull to the abdomen. Bleeding can be observed on CT, usually coming from the choroid plexus, and usually of no clinical significance. After shunting ventricular size decreases, the pericerebral subarachnoid spaces reopen, and the periventricular edema resolves. In young patients, the cerebral mantle may re-expand. The sutures close and may become thin and dense on skull X-rays [parasutural sclerosis (Harwood-Nash)]. The thickness of the vault may increase in chronic shunted patients.

Shunt Malfunction

Malfunction of a shunt may result from:

- Obstruction of the intracranial tip by intraparenchymal impaction or choroid plexus colonization or infection
- Disconnection of the tube
- Obstruction in the abdominal cavity due to peritoneal adhesions. Local cystic fluid formation is seen by ultrasound [13].

Shunt Migration

The distal end of a ventriculocardiac shunt may migrate into the heart or pulmonary artery and the

distal end of a ventriculoperitoneal shunt into a hollow viscus (stomach, small bowel, rectum, colon, bladder).

Slit Ventricle Syndrome

The slit ventricle syndrome is a rare entity that occurs in shunted children with [11, 19, 23]:

- Closed sutures
- Small ventricles
- No pericerebral subarachnoid spaces

Any small increase of intracranial pressure (coughing, abdominal efforts) leads to headaches because the near-absence of subarachnoid spaces means that this increase in pressure and volume cannot be accommodated. CT or MRI shows normal-sized ventricles or even small "slit-like" ones with no peripheral subarachnoid spaces. After treatment the subarachnoid spaces return to normal.

References

1. Baraton J, Brunelle F, Pierre Kahn A, et al: Tomodensitometrie couplée à la cisternographie dans les épanchements chroniques péricérébraux de l'enfant. *Neurochirurgie* 35:395-400, 1989
2. Barkovich AJ, Newton TH: MR of aqueductal stenosis: evidence of a broad spectrum of tectal distortion. *AJNR Am J Neuroradiol* 10:471-476, 1989
3. Barkovich AJ, Kjos BO, Norman D, et al: Revised classification of posterior fossa cysts and cyst-like formations based on results of multiplanar MR imaging. *AJNR Am J Neuroradiol* 10:977-988, 1989
4. Bradley WG Jr, Whittemore AR, Kortman KE, et al: Marked cerebrospinal fluid void: indicator of successful shunt in patients with suspected normal-pressure hydrocephalus. *Radiology* 178:459-466, 1991
5. Brann BS, Qualls C, Papile L, et al: Measurement of progressive cerebral ventriculomegaly in infants after grades III and IV intraventricular hemorrhages. *J Paediatr* 117:615-621, 1990
6. Brinners S, Bodensteiner J: Benign subdural collections of infancy. *Pediatrics* 67:802-804, 1980
7. Coker SB, Anderson CL: Occluded fourth ventricle after multiple shunt revisions for hydrocephalus. *Paediatrics* 83:981-985, 1989
8. Drugen A, Krause B, Canady A, et al: The natural history of prenatally diagnosed cerebral ventriculomegaly. *JAMA* 261:1785-1788, 1989
9. Dykes FD, Dunbar B, Lazarra A, et al: Posthaemorrhagic hydrocephalus in high risk preterm infants: natural history, management and long term outcome. *J Paediatr* 114:611-618, 1989
10. Enzmann DR, Pelc NJ: Normal flow patterns of intracranial and spinal cerebrospinal fluid defined by phase contrast cine MR imaging. *Radiology* 178:467-474, 1991
11. Epstein F, Lapras C, Wisoff JH: Slit ventricle syndrome: etiology and treatment. *Pediatr Neurosci* 14:5-10, 1988
12. Evans WA: An encephalographic ratio for estimating ventricular enlargement and cerebral atrophy. *Arch Neurol Psychiatr* 47:931-937, 1942
13. Gaskill SJ, Marlin AE: Pseudocysts of the abdomen associated with ventriculoperitoneal shunts: a report of twelve cases and a review of the literature. *Pediatr Neurosci* 15:23-26, 1989
14. Gaston BM, Jones BE: Prenatal unilateral hydrocephalus. Atresia of the foramen of Monro. *Paediatr Radiol* 19:328-329, 1989
15. Greitz D, Franck A, Nordell B: On the pulsatile nature of intracranial and spinal CSF circulation demonstrated by MR imaging. *Acta Radiol* 34:1-8, 1993
16. Hecht JT, Butler IJ: Neurologic morbidity associated with achondroplasia. *J Child Neurol* 5:84-97, 1990
17. Hirsch JF, Pierre-Kahn A, Renier D, et al: The Dandy-Walker malformation: a review of 40 cases. *J Neurosurg* 61:515-522, 1984
18. Kochi M, Mihara Y, Takada A, et al: MRI of subarachnoid dissemination of medulloblastoma. *Neuroradiology* 33:264-267, 1991
19. Laurin RL, Olivi A: Slit ventricle syndrome review of 15 cases. *Paediatr Neurosci* 13:118-124, 1987
20. Martin AJ, Drake JM, Lemaire C, et al: Cerebrospinal fluid shunts: flow measurements with MR imaging. *Radiology* 173:243-247, 1989
21. Minns RA, Hamilton AH: Benign intracranial hypertension pseudo tumor cerebri. *Clin Dev Med* 113/114:400-425, 1991
22. Missir O, Dormont P, Pierot L: MR visualisation of CSF flow through a ventriculostomy. *Neuroradiology* 31:93-94, 1989
23. Oi S, Matsumoto S: Infantile hydrocephalus and the slit ventricle syndrome in early infancy. *Child's Nerv Syst* 3:145-150, 1987
24. Pattern RM, Mack LA, Fribert HJ: Unilateral hydrocephalus prenatal sonographic diagnosis. *AJR Am J Radiol* 156:359-363, 1991
25. Rifkinson-Mann S, Wisoff JH, Epstein F: The association of hydrocephalus with intramedullary spinal cord tumours: a series of 25 patients. *Neurosurgery* 27:749-754, 1990
26. Sainte-Rose C, Lacombe J, Pierre-Kahn A, et al: Intracranial venous sinus hypertension: cause or consequence of hydrocephalus in infants. *J Neurosurg* 60:727-736, 1984
27. Scotti G, Musgrave MA, Fitz CR, et al: The isolated fourth ventricle in children: CT and clinical review of 16 cases. *AJR Am J Radiol* 135:1233-1238, 1980
28. Steinbock P, Hall J, Flodmark O: Hydrocephalus in achondroplasia: the possible role of intracranial venous hypertension. *J Neurosurg* 71:42-48, 1989
29. Twickler DM, Reichel T, McIntire DD, Magee KP, Ramus RM: Fetal central nervous system ventricle and cisterna magna measurements by magnetic resonance imaging. *Am J Obstet Gynecol* 187:927-931, 2002

Classification and Definition of Hydrocephalus: Origin, Controversy, and Assignment of the Terminology

SHIZUO OI

Introduction

Since hydrocephalus is not a single pathological disease, but a pathophysiological condition of disturbed dynamics of the cerebrospinal fluid (CSF) with or without underlying disease, its classification is often complex and confused. There are numerous classifi-

cation categories, parameters, and criteria (Table 1). In each patient hydrocephalus can be given a classification, to which are added further individual qualifying parameters and variables, so that the full range of classified subtypes of hydrocephalus can be uncountable: congenital-fetal/progressive/high-pressure/non-communicating/idiopathic/macrocephalic/internal-triventricular hydrocephalus, etc.

Table 1. Classification of hydrocephalus. (Adapted from [85], p.686)

Entity involved	Parameter	Subtypes
Patient	Onset	Congenital/acquired Fetal/neonatal/infantile/child/adult/geriatric Acute/subacute/chronic
	Causes	Primary/secondary/idiopathic
	Underlying lesions	Dysgenetic/posthemorrhagic/post-SAH/post-IVH/postmeningitic/post-traumatic/ With brain tumor/spinal cord tumor/brain abscess/arachnoid cyst/cysticercosis, etc.
	Symptomatology	Macrocephalic/normocephalic/microcephalic Occult/symptomatic/overt Coma/stupor/dementia Hydrocephalus/parkinsonism complex, etc.
Hydrocephalus	Pathophysiology: – CSF circulation	Communicating/noncommunicating Nonobstructive/obstructive External/internal/interstitial Isolated compartments: UH/IFV/IRV/ICCD/DCH/DLFV, etc.
	– ICP dynamics	High/normal
	– Chronology	Slowly progressive/progressive/long-standing/arrested
Treatment	Postshunt	Shunt-dependent/shunt-independent Slit-like ventricle/slit ventricle syndrome, etc.

SAH, subarachnoid hemorrhage; *IVH*, intraventricular hemorrhage; *UH*, unilateral hydrocephalus; *IFV*, isolated fourth ventricle; *IRV*, isolated rhombencephalic ventricle; *ICCD*, isolated central canal dilatation; *DCH*, double-compartment hydrocephalus; *DLFV*, disproportionately large fourth ventricle

In this chapter, the current status of classification of hydrocephalus in representative subgroups (Table 2) is discussed, focusing on the

critical elements of confusing terminology and definitions in the individual hydrocephalus categories.

Table 2. Representative subgroups in the classification of hydrocephalus. (Adapted from [Oi S, 2003])

Congenital hydrocephalus	Acquired hydrocephalus
<i>Simple hydrocephalus</i> (hydrocephalus with congenital change limited in the CSF pathway)	<i>Acquired hydrocephalus</i> (hydrocephalus secondary to underlying lesion in the postnatal period)
Atresia of foramen of Monro	Tumor
Aqueductal stenosis	Posthemorrhagic
Maldevelopment of arachnoid granulation	Postinfectious
Others	Post-traumatic
<i>Dysgenetic hydrocephalus</i> (hydrocephalus associated with CNS dysgenesis)	Others
Hydranencephaly	<i>Postshunt hydrocephalus</i> (hydrocephalus after shunt placement)
Holoprosencephaly	Shunt-dependent
Dandy-Walker syndrome	Unilateral hydrocephalus
Dysraphism	Isolated fourth ventricle
Chiari malformation	Isolated rhombencephalic ventricle
Syringobulbia-myelia	Isolated central canal dilatation
Lissencephaly	
Arachnoid cyst, etc.	
Others	
<i>Secondary congenital hydrocephalus</i> (hydrocephalus secondary to underlying lesion in the fetal period)	
Tumor	
Posthemorrhagic	
Postinfectious	
Others	

Classification in Representative Subgroups of Hydrocephalus

Fetal Hydrocephalus and the Perspective Classification of Congenital Hydrocephalus (PCCH)

Concept

The neuroimaging techniques of ultrasonography [6, 9, 11, 14, 21, 26, 34, 38, 41, 52, 58, 66, 75, 80, 111, 112] and magnetic resonance imaging [22, 34, 76, 80, 111, 113] have enabled prenatal diagnosis of fetal hydrocephalus on the basis of morphology; however, its management remains a difficult challenge. No single category of hydrocephalus is an adequate predictor of the postnatal clinical features. Moreover, few of the presently available classification systems take into account the chronological changes in the hydrocephalic state from the fetal to the neonatal and infantile periods, or reflect the underlying developmental or embryological stages of the brain,

especially the neuronal maturation process. The prognosis may also depend on the progression of the hydrocephalus and the affected brain and on the degree of damage to the neuronal maturation process. For this reason, we have developed a new classification system for congenital hydrocephalus, the “Perspective Classification of Congenital Hydrocephalus” (PCCH) [79]. This classification is based on the stage, type, and clinical category of congenital hydrocephalus. Regarding the clinoembryological stages, each stage reflects both clinical and embryological developmental aspects of the neuronal maturation process in the hydrocephalic fetus or infant. The clinoembryological stages are as follows (Fig. 1).

Stage I occurs between 8 and 21 weeks’ gestation, which is the period of legally permissible termination of pregnancy in Japan. Cell proliferation is the main process in neuronal maturation.

Stage II extends from 22 to 31 weeks’ gestation, the period of intrauterine preservation of the fetus before pulmonary maturation is completed. Cell differentiation and migration are the main processes in neuronal maturation.

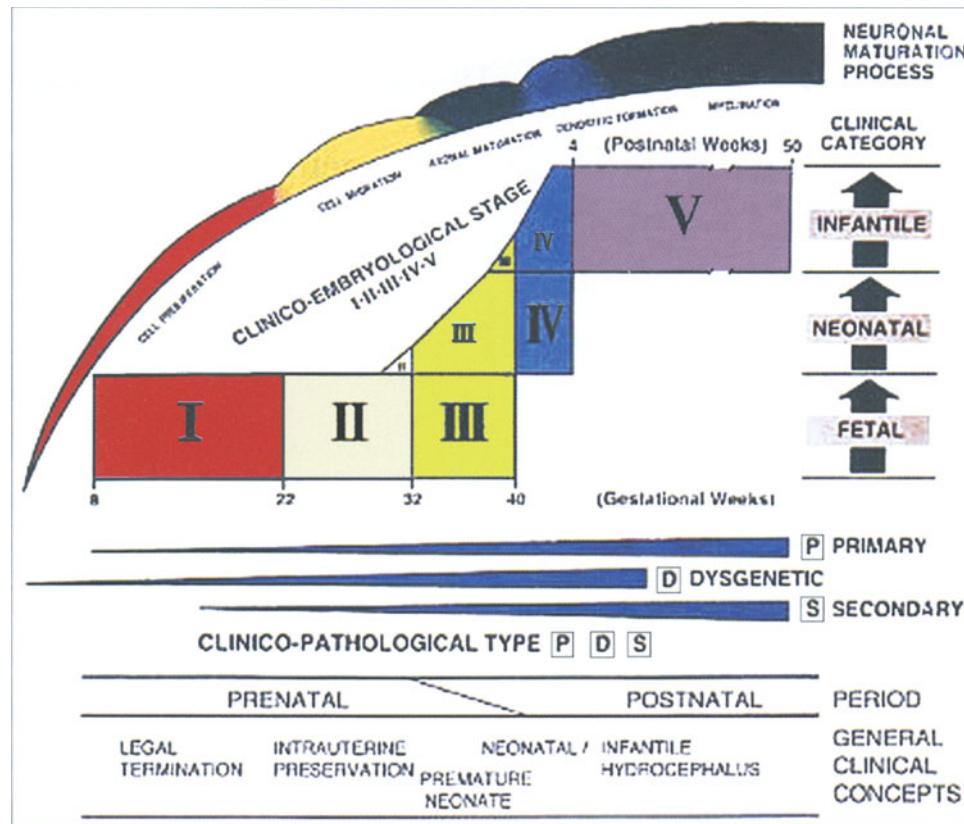


Fig. 1. Perspective classification of congenital hydrocephalus (PCCH). (From [79], p. 124, with permission)

Stage III extends from 32 to 40 weeks' gestation, a period of possible premature/preterm neonatal hydrocephalus, if delivery occurs. Axonal maturation is the main process in neuronal maturation.

Stage IV occurs between 0 and 4 weeks of postnatal age, the period of neonatal hydrocephalus. Dendritic maturation is the main process in neuronal maturation.

Stage V extends from 5 to 50 weeks of postnatal age, the period of infantile hydrocephalus. Myelination is the main process in neuronal maturation.

In each stage, individual conditions with differing features of hydrocephalus can be classified along with the embryological or developmental background of the affected brain and CSF circulation in each pathological type with subtypes. The clinicopathological subtypes are:

1. Primary hydrocephalus, including communicating or uncomplicated hydrocephalus, aqueductal stenosis, foraminal atresia, and others
2. Dysgenetic hydrocephalus, including hydrocephalus with spina bifida, bifid cranium, Dandy-Walker cyst, holoprosencephaly, hy-

dranencephaly, lissencephaly, congenital cyst, and others

3. Secondary hydrocephalus: hydrocephalus due to brain tumor, hemorrhage, or other vascular disease(s); infection; trauma; subdural fluid collection; and others

These conditions should be considered in relation to the standard clinical categories of fetal, neonatal, and infantile hydrocephalus, based on essential differences in their pathophysiological appearance, including the dynamics of intracranial pressure (ICP) and CSF circulation [80]. This classification should be applied when the diagnosis of hydrocephalus is made before any procedures have been performed.

Diagnostic Procedures for Morphology of Fetal Hydrocephalus

Ultrasonography is the first imaging technique to be used in cases where there is a possibility of fetal CNS malformation, to screen or regularly monitor the CNS malformation. The biparietal diameter (BPD) and the size of the lateral ventricle are evaluated if

these are found to be abnormal, and brain morphology is further analyzed. Magnetic resonance imaging is also performed to evaluate fetal brain and spinal cord morphology. Magnetic resonance imaging (0.5 or 1.5 T with multislice spin-echo partial saturation pulse sequence, TR 400–500 ms, TE 20–30 ms) is routinely used in these evaluations. The heavily T₂-weighted spin-echo sequence with reversal image (TR 4300 ms, TE 130 ms) is also used in our practice.

Magnetic resonance imaging may be superior to ultrasonography in demonstrating the CNS structures in one slice, such as a midline sagittal slice of the entire brain and spinal cord, whereas ultrasonography is advantageous in delineating these structures on continuous images in real time. For this reason, motion of the fetus is not a practical problem in ultrasonography, but it is necessary to piece together separate findings to demonstrate anatomical relationships or the overall state of the CNS. It is extremely useful to perform such imaging in patients with midline anomalies associated with hydrocephalus, such as spina bifida with Chiari malformation, encephalocele with herniated brain and deformed intracranial structure, Dandy-Walker syndrome with posterior fossa cyst/vermis dysgenesis and ventriculomegaly, or holoprosencephaly with monoventricular configuration and dorsal sac.

Our method of using heavily T₂-weighted imaging with a superconducting magnet is extremely useful technically and practically. The total imaging time does not exceed 90 s and sedation of the fetus is not necessary. Because the CSF space is delineated in white as an area with extremely high signal intensity, deformed or malformed brain parenchyma, which shows a slightly higher but nearly isointense signal on regular T₁-weighted images, is well demarcated. This seems to be the technique that best depicts underlying malformations in fetal hydrocephalus, including neural placode or meningocele sac and/or Chiari malformation in spina bifida, dorsal sac in holoprosencephaly, and agenesis of the corpus callosum.

Management of Fetal Hydrocephalus Based on the Classification

In our previous analysis of factors possibly affecting the postnatal outcome of 24 fetuses with hydrocephalus, the only significant factor was the length of time spent in utero after diagnosis of hydrocephalus [78]. However, further analysis performed using our new classification, PCCH, suggests that postnatal outcomes differ depending on the time of onset of the hydrocephalus, even within the same category or sub-

types [84, 85, 89, 109]. The IQ or DQ (development quotient) of patients whose hydrocephalus was diagnosed at PCCH stage III was higher than that of patients diagnosed at stage II in cases of primary hydrocephalus, and higher than that of patients with some types of dysgenetic hydrocephalus such as myeloschisis.

Intensive efforts have been made to identify the type(s) of fetal hydrocephalus that will cause irreversible damage if left untreated [39, 47, 78]. The data presented here imply that the neuronal maturation process could be affected by progression of ventriculomegaly during the period before pulmonary maturation, i.e., up to 32 weeks' gestational age (PCCH stage II). If the assumption presently justifying a surgical procedure to decompress such a progressive state of hydrocephalus at stage II is the irreversibility of the neuronal maturation, based on both clinical and experimental data, it is a matter of great concern how best to perform intracranial decompression in the fetus. Clewell and associates first attempted surgical treatment of fetal hydrocephalus in utero by using a technique of ventriculoamniotic shunt placement [56]. It is estimated that placement of ventriculoamniotic shunts for fetal hydrocephalus has been performed in more than 60 cases around the world [55, 56, 95]. However, the results reported by the cooperative study from the International Fetal Surgery Registry were disappointing [56, 95]. The authors investigated the pressure dynamics of fetal hydrocephalus in both clinical cases [80] and an experimental model. It is clear from those results that a fetus with hydrocephalus is extremely hypertensive, with a specific feature of high amniotic cavity pressure or uterine contraction pressure contributing to the circumferential pressure. The pressure gradient between the fetal ventricle and the amniotic cavity may not always be high enough to drain excessive fetal CSF via a ventriculoamniotic shunt. Although some improved techniques and instrumentation have been reported [11, 94, 106], a methodology affording more reliable and safer decompression for intrauterine fetal hydrocephalus needs to be established.

Experimental Models of Congenital Hydrocephalus and Comparable Clinical Forms [4, 84]

Findings in the numerous experimental models of congenital hydrocephalus may be clinically applicable to a variety of forms of hydrocephalus (Fig. 2). These include communicating hydrocephalus, aqueductal stenosis, Dandy-Walker syndrome, Chiari malformation, hydrocephalus due to congenital skull base deformity, hydromyelic hydrocephalus, and a number of others (Table 3).

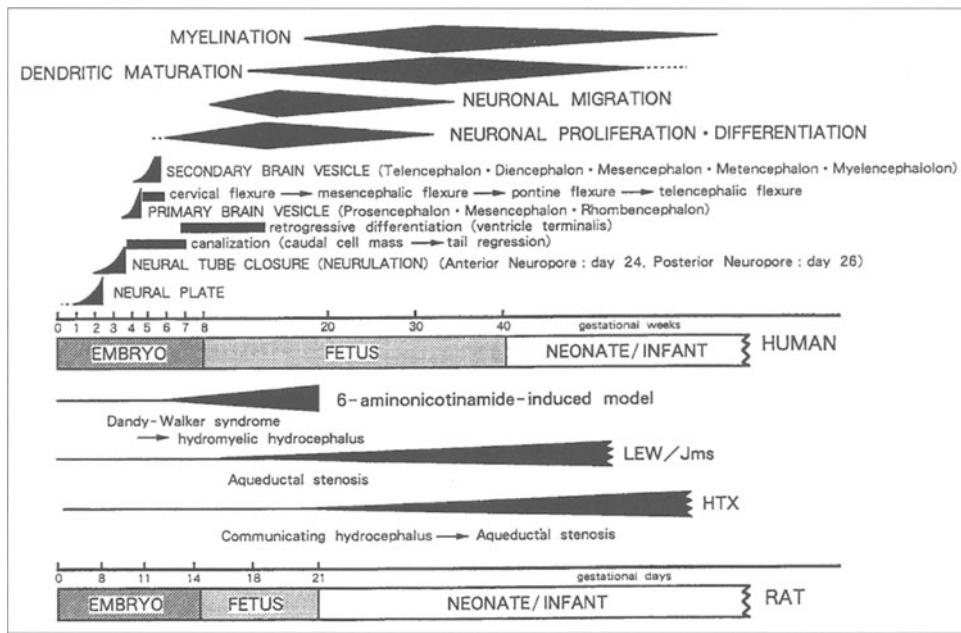


Fig. 2. Overview of the developmental periods of the neuronal maturation process in human set against similar data for the major experimental models of congenital hydrocephalus in the rat, together with the clinically comparable types of congenital hydrocephalus. (From [84], p. 300, with permission)

Table 3. Postnatal outcome in patients with fetal hydrocephalus according to PCCH stage and type.^a (Adapted from [85], p.691)

Clinicopathological type	Outcome (postnatal DQ/IQ) by clinoembryological stage			Total
	I (up to 21 weeks)	II (22-31 weeks)	III (32-40 weeks)	
Primary	n.a.	67.5 (35-100)	76.6 (20-132)	74.2 (20-132)
Dysgenetic	20	49.5 (20-114)	59.2 (20-120)	52.4 (20-120)
Dysgenetic with spina bifida aperta (myeloschisis)	n.a.	45.0 (20-80) ^b	81.3 (60-120) ^b	63.1 (20-120)
Secondary	n.a.	70, 15, 20	5, 20	26 (5-70)

n.a., not applicable. ^aIndividual DQ/IQ values are given for patients whose secondary hydrocephalus was diagnosed in stage II or III. Other values in table reflect the mean DQ/IQ values, with ranges provided parenthetically; ^bPostnatal outcome in patients with myeloschisis at stage II was significantly poorer than that of patients with myeloschisis at stage III ($p<0.1$)

Genetic Analysis: Not a Criterion of Classification for Congenital Hydrocephalus

There have been various types of gene abnormality in patients with congenital hydrocephalus [4, 78, 84, 85, 89, 109]. Classically, X-linked hydrocephalus [85] has been known as the only significant hereditary form of congenital hydrocephalus with aqueductal stenosis, which belongs to the simple type of congenital hydrocephalus. The recent genetic analysis series confirmed that an abnormal L1 mRNA located in Xq28 is the causative genopathy in X-linked aqueductal stenosis [4, 78, 84, 109]. However, it has also been recognized that this form of con-

genital hydrocephalus may have more than 20 different genotypes in the form of L1 gene anomaly with or without various cerebral dysgenetic lesions [89, 109]. The phenotype of a single form of dysgenetic hydrocephalus also has various forms of genotype.

These important findings show that abnormalities in genotype do not necessarily indicate the specific form of hydrocephalus, but may suggest the presence of a primarily arrested neuronal maturation process in the brain parenchyma itself. For example, even in a small entity of dysgenetic hydrocephalus, Dandy-Walker syndrome, various forms of genopathy have been reported [73, 87], such as Warburg syndrome, Joubert-Boltshauser syndrome,

Fraser cryptophthalmos, Coffin-Siris syndrome, oral-facial-digital syndrome II, Aicardi syndrome, Meckel-Gruber syndrome, Turner syndrome, and so on, as well as various types of chromosomal abnormalities including duplication of 17q, deletion of 6p24-25, trisomy 13, trisomy 18, 9qh+ heteromorphism, and others.

As to the classification of hydrocephalus, it should be emphasized that genetic analysis may be necessary to understand the associated primary brain dysgenesis but cannot be used for classification of hydrocephalus, that is, "disturbed CSF circulation".

Specific Forms of Hydrocephalus: Classification and Treatment Modalities

Isolated Compartments in Various Forms

We have previously reported that excess drainage of CSF via a ventricular shunt system will cause morphological changes in the CSF pathways [43] and possibly lead to isolation of compartments [64, 65, 67, 68, 71]. These phenomena produce a slit-like ventricle most commonly seen in young infants [65, 71] and occasionally lead to the slit ventricle syndrome [71]. The mechanism of development of an isolated ventricle after shunting is closely related to the presence of a slit-like ventricle [65]. The mechanism of obstruction at the foramen of Monro in isolated unilateral hydrocephalus [64] and that of aqueductal obstruction in isolated fourth ventricles [68] oc-

curred after shunt placement are essentially the same. Both occur in a previously communicating ventricular system, and in both cases reduction of the size of all ventricles is initially seen after shunting [64, 68]. Isolation then gradually develops and re-enlargement of the isolated compartment is observed. Dynamic studies of the CSF using metrizamide CT ventriculography have confirmed the presence of a one-way valve at either the foramen of Monro or the aqueduct [68], and pressure gradients (Fig. 3) between the compartments have also been recorded [64, 67, 68]. We suggest that similar isolation may occur after placement of a shunt in the lateral ventricle in cases of communicating holoneuronal canal dilatation. Various types of isolation (types I-IV) may then develop, depending upon the site of occlusion (Figs. 4, 5) [77]. Also, extracranial overdrainage of CSF via the shunt changes the ICP dynamics and produces a unique CSF circulatory disturbance (Fig. 3).

We have reported that excess drainage of CSF via a ventricular shunt system can cause morphological changes in the CSF pathways [67] and possibly lead to isolation of compartments [64, 65, 67, 77]. The obstruction at the foramen of Monro in isolated unilateral hydrocephalus (IUH) [64] and aqueductal obstruction in isolated fourth ventricle (IFV) [15, 67, 77] after shunt placement occurs in a previously communicating ventricular system, and in both cases a reduction in the size of all ventricles is seen initially after shunting [65, 77], with subsequent isolation and re-enlargement of the isolated compartment.

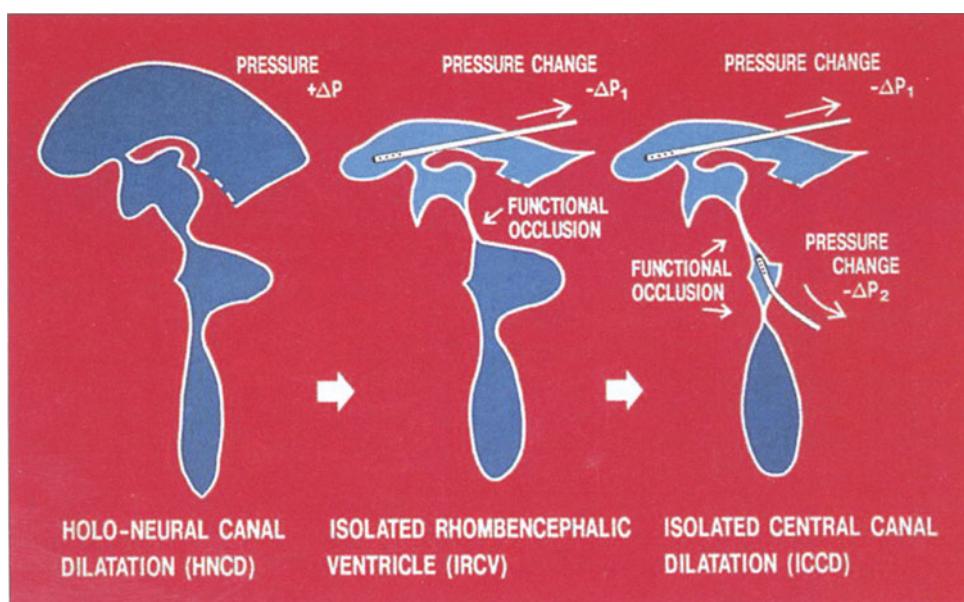


Fig.3. Development of isolated compartments after shunting in holoneuronal canal dilatation. The site of functional occlusion (either the aqueduct of Sylvius or the obex) may have a "valve" action by which the dilated compartment is isolated and develops a lower intraventricular pressure. (From [77], p.378, with permission)

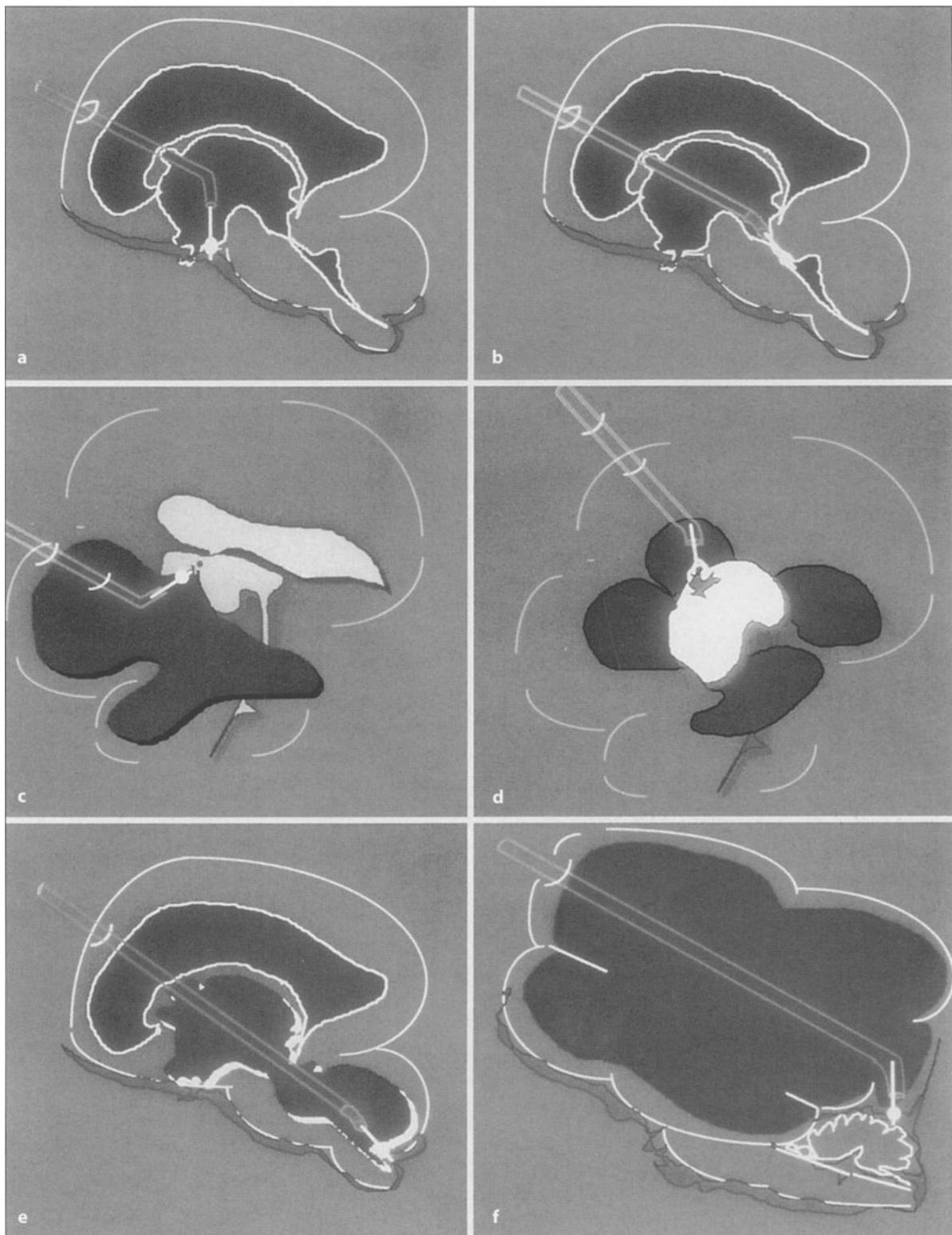


Fig. 4a-f. Neuroendoscopic procedures in various forms of noncommunicating hydrocephalus: **a** third ventriculostomy for long-standing overt ventriculomegaly in adult (LOVA), **b** aqueductal plasty (rostral approach) for LOVA, **c** foraminal plasty of foramen of Monro for isolated unilateral hydrocephalus (IUH), **d** cyst wall removal for isolated third ventriculomegaly, **e** fourth ventriculostomy for disproportionately large fourth ventricle, **f** dorsal sac ventriculostomy for dorsal sac in holoprosencephaly. (From [87], p. 58, with permission)

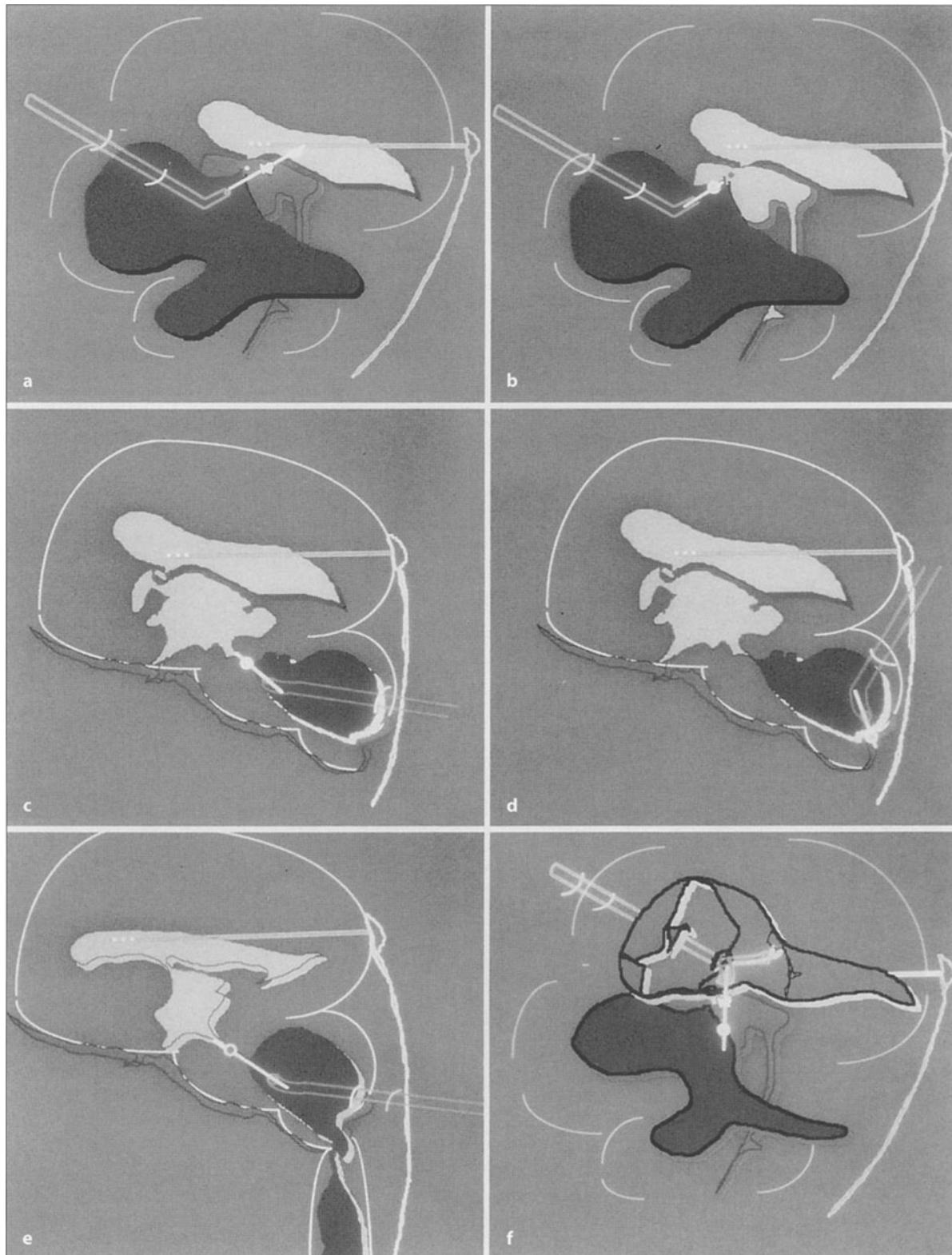


Fig. 5a-f. Neuroendoscopic procedures for various forms of postshunt isolated compartments: **a** septostomy for IUh, **b** foraminoplasty of foramen of Monro for IUh, **c** aqueductal plasty (caudal approach) for isolated fourth ventricle (IFV), **d** fourth ventriculostomy for IFV, **e** aqueductal plasty (caudal approach) for isolated rhombencephalic ventricle, **f** septal fenestration for loculated ventricle. (From [87], p.60, with permission)

External Hydrocephalus

Subdural fluid accumulation is commonly found in many clinical entities, such as meningitis – especially when caused by *Haemophilus influenzae* [25, 110] – trauma [13, 33, 114], familial megalencephaly [19], brain atrophy, idiopathic cases, and so on [98]. Therefore, it is logical to conclude that it would be improper to consider this pathoradiological or pathoanatomical finding as a single clinical entity and treat all cases in accordance with a standard therapeutic protocol. Since CT technology was introduced, numerous terms have been used to describe the CT findings of fluid accumulation over the cerebral convexity in infants. They include “external hydrocephalus” [96], “pseudohydrocephalus” [103], “benign subdural effusion” [102], “benign enlargement of subarachnoid spaces” [53], “benign communicating hydrocephalus” [46], and “subdural effusion secondary to ruptured subarachnoid spaces” [115]. That some infants do not remain in a “benign” condition is a problem we cannot ignore.

The following became clear after the investigation of CSF dynamics by quantitative analysis of metrizamide CT cisternography. There was a very slow and light fluid exchange between the subdural effusion and the adjacent subarachnoid space, which is a part of the major CSF pathway system (Fig. 6). There may be an increasing osmotic pressure gradient from the subarachnoid space to the subdural effusion, as suggested by the high protein concentration in the effusion [28, 98] (this was frequently observed in our patients as well). In some inflamma-

tory processes such as meningitis [25, 110], the exudates from and the permeability of the arachnoid membrane may be increased. The arachnoid membrane, which is the outer surface of the major CSF pathway, could be easily torn [40] in minor head injuries of infants, thereby permitting CSF leakage into the subdural space. In cases with an unknown etiology (which were the majority among our patients), there are various possible explanations for this pathoanatomical change in infants. It could be the result of a transient disproportion between CSF production and absorption. The arachnoid granulations are essentially morphologically immature prior to 3 months of age [116]. An overaccumulation of CSF could possibly pass through the arachnoid membrane by some mechanism, resulting in the formation of a subdural effusion. The most prominent gradient may exist on the line of the ventricle-subarachnoid space-subdural space and anterior fontanel, where a subdural effusion is most marked on CT. Consequently, we proposed a theory that the major CSF pathways could be impaired in this region (“regional destruction”) (Fig. 6) [73].

The authors do not deny that there can be fluid accumulation over the cerebral convexity in the pathophysiological entity known as “external hydrocephalus” [101], especially in the early phase of congenital communicating hydrocephalus. In fact, sometimes an exploratory craniotomy reveals a deep subarachnoid space but no significant subdural fluid accumulation [3]. This entity is a true part of hydrocephalus, and should be differentiated from a subdural effusion because it occurs in the major CSF pathways. An important problem, however, has been left unsolved. That is,

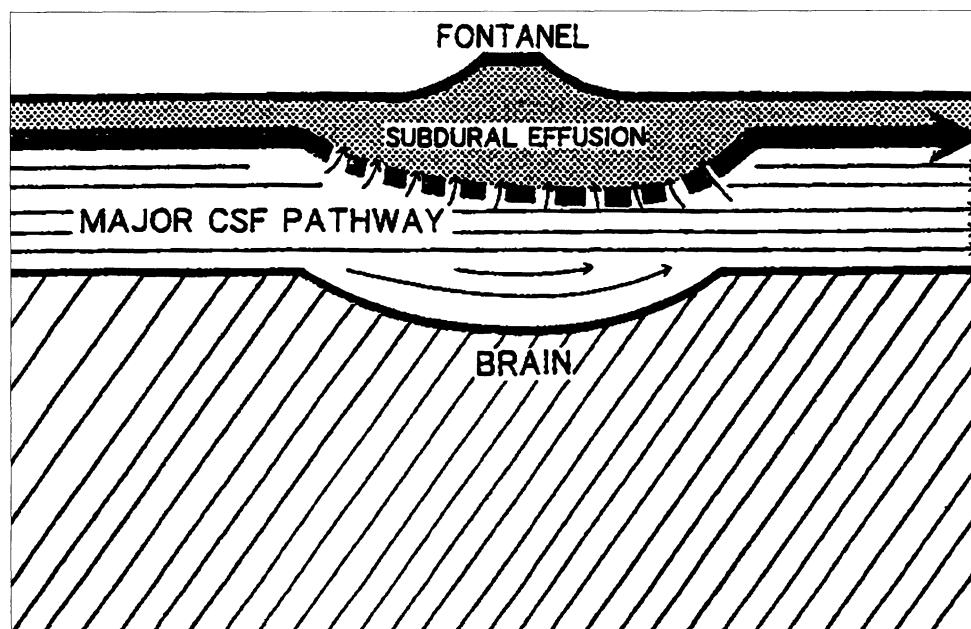


Fig. 6. Concept of “regional destruction of major CSF pathway” for infantile subdural effusion. (From [73], p. 15, with permission)

apart from those reports including direct observation during surgery [3], no other reports have clarified the exact anatomical location of the fluid accumulation, which simply appears as a low-density zone over the cerebral convexity on the CT scan. As a result of the present quantitative analysis of CSF dynamics, it is thought that there may be some interference by the subdural effusion on the CSF circulation in both the major and minor pathways, resulting in ventriculomegaly in some cases. Hypothetically, the pathoanatomical condition of "external hydrocephalus" may be due to delayed development or function of the arachnoid villi in the sagittal sinus [3]. During the fetal period, and to a certain extent in the newborn period, the CSF is absorbed mainly through the ventricular wall; the subarachnoid space subsequently develops as the main CSF pathway. Tsubokawa et al. [115] considered that poorly balanced CSF absorption during such a special transitional period of the CSF dynamics might be a pathogenetic factor for subdural effusion. They also proposed that subarachnoid effusion should be distinguished from subdural effusion in infants in spite of resulting in similar clinical signs [115].

Thus, an infantile subdural effusion should be considered to be a phenomenon of "regional breakdown of the major CSF pathways" and must be clearly distinguished from "external hydrocephalus". We strongly suggest that an infantile subdural effusion is mostly "benign", progressing uneventfully in some cases, and careful observation as well as a thorough understanding of the pathophysiological status are required to be able to decide whether surgery is necessary or not.

Post-traumatic Hydrocephalus [72]

Since severe forms of head trauma are always accompanied by brain parenchymal destruction, and injury to the blood vessels results in cellular damage and vasogenic edema, these morphological changes lead to altered tensile properties and ex vacuo dilatation [60, 72]. Ventricular dilatation, especially in the late post-traumatic stage, does not necessarily mean a hydrocephalic state. As mentioned before, inasmuch as hydrocephalus is defined as a condition with a disturbed CSF circulation, it is essential to determine the circulatory condition when a diagnosis of hydrocephalus has been made. We developed a quantitative analysis of CSF circulation in relation to the major and minor CSF pathways on computerised tomography cisternography (CTCG) [70]. It is also useful to determine whether post-traumatic ventriculomegaly is due to disturbed CSF circulation (hydrocephalus). In an acute post-traumatic stage, however, the presence of ventriculomegaly is sufficient for a diagnosis if there have been no episodes of CNS disorders in the past.

Continuous ICP monitoring is useful to find out whether the hydrocephalic state is progressive or arrested [119], particularly in the chronic phase. Intracranial pressure monitoring may also provide certain standards for shunt indication [35].

Acute hydrocephalus occurring in a massively swollen brain has a different pathomechanism: the CSF flow might be blocked in the early stage by obstruction of the CSF pathway [93], but ventricular dilatation cannot be ascertained because of the parenchymal swelling. As indicated in our previous study [35], the entire ICP remains high due to cerebral edema in the acute phase, just as the intraventricular CSF pressure does in the following stage. Wieser and Probst [120] emphasized that the important factors in the acute stages are increased CSF pressure, disturbed CSF dynamics, brain swelling, and vascular circulation disorders; parenchymal atrophy is the most important factor in the chronic stages. Symptomatically, these conditions may conceal one another. Whether the patient's symptoms between the acute and subacute stages are secondary to a primary injury, to increased CSF pressure, or a combination of the two, becomes a matter of great concern.

Progressive unilateral hydrocephalus with or without obstruction of the foramen of Monro could be classified into several categories [64]. Since a decompressive procedure is essential, and is usually performed on one side of the cranium with extreme caution in cases with severe head trauma and midline shift, the distribution of intracranial compliance will be asymmetrical and unbalanced postoperatively. If this condition occurs in infants, it will produce unilateral ventriculomegaly and hemicranial expansion together with communicating hydrocephalus. This type of hydrocephalus should be treated by placement of a shunt in the ipsilateral ventricle, to reduce the intraventricular pressure on that side [64]. By contrast, a cranioplasty procedure after a primary craniectomy in infants who have undergone a shunt placement for post-traumatic hydrocephalus may reduce intracranial compliance more than is physiologically required. As the incidence of postshunt slit ventricle is extremely high – 85.5% in our data [71] – the ICP dynamics at the time of shunt malfunction are sometimes quite significant [69]. We have experienced two cases of infants with severe forms of slit ventricle syndrome created by overreduction of the intracranial compliance [69]. One of them was a post-traumatic case.

In the relatively chronic hydrocephalic stage after a head injury, normal-pressure hydrocephalus is usually found, and this is generally accepted to be the more common form of post-traumatic hydrocephalus [29, 36, 54, 120]. Children, however, hardly ever reveal the characteristic triad of dementia, incontinence, and gait disturbance found in adult sufferers [1]. In order to predict the outcome of a shunting procedure, a diagnosis

of slowly progressive or arrested hydrocephalus is required, together with the demonstration of concomitant injuries to functional structures of the developing brain. We believe that both a quantitative evaluation of CSF circulation [42,70] and an analysis of ICP [120] are very valuable tools in the assessment of the progression of post-traumatic chronic hydrocephalus.

Chronology and Classification of Hydrocephalus in Adults

Concept of Hydrocephalus Chronology in Adult and Stages I-V 11

The term “normal-pressure hydrocephalus” (NPH) was first published by Hakim et al. in 1964 and 1965

[1,36A]. They defined this type of hydrocephalus as a new syndrome with such specific clinical features as treatable dementia, but named “normal-pressure” from the pathophysiological aspect. Today, with advances in continuous ICP monitoring and in dynamic analyses, it has become clear that the CSF pressure dynamics are not “normal” in this type of hydrocephalus (Table 4). After a literature analysis in respect of the pathophysiology (ICP dynamics and CSF dynamics, therapeutic problems), selection of the shunt system, and entity of “NPH”, the present author clarifies aspects of the confusion in the classification and terminology of hydrocephalus and presents a concept of “hydrocephalus chronology in adults” (HCA) (Fig. 7). The hydrocephalic state is classified into HCA stages I-V based on the symptomatological features in relation to the chronological changes in ICP dynamics. Because of a variety of ICP

Table 4. “True NPH”: definition and diagnostic criteria^a

Category	Definition
Concept	Pathophysiological entity of progressive hydrocephalus with normal range of ICP dynamics
Diagnostic criteria	<ol style="list-style-type: none"> Progressive ventriculomegaly with obliterated cortical sulci on CT/MRI Normal baseline pressure with or without pressure-wave-like elevation but essentially within normal range (0-18 cm H₂O) in continuous ICP measurement Clinical symptoms may or may not include dementia, urinary incontinence, gait disturbance, vegetative state, akinetic mutism, apathetic consciousness, and parkinsonism
Therapeutic specificity	Not treatable with a normal-pressure-range shunt system of over medium-pressure but only with low- or extremely-low-pressure-range shunt system, or by neuroendoscopic third ventriculostomy, if noncommunicating in type

^aUnderlying disease may or may not be clarified and should not be specific, if present. CSF dynamics may or may not be communicating in type and should not be specific. Diagnostic criteria 1+3 define “true NPH”

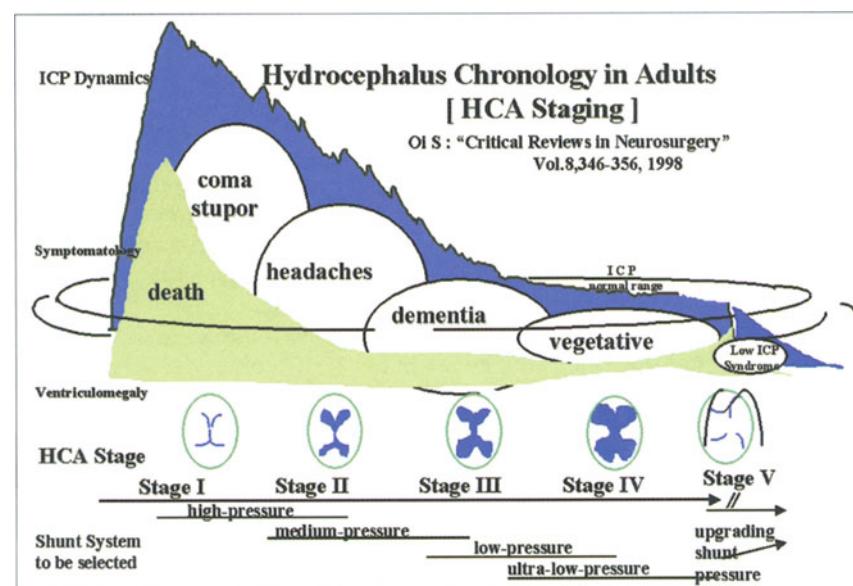


Fig. 7. Hydrocephalus chronology in adults (HCA) with the staging and shunt system to be selected. (From [86], p. 355, with permission)

Table 5. Concept, diagnostic criteria, and therapeutic specificity of hydrocephalic dementia^a

Category	Definition
Concept	Symptomatological entity of progressive hydrocephalus with clinical features of dementia
Diagnostic criteria	<ol style="list-style-type: none"> 1. Progressive ventriculomegaly with obliterated cortical sulci on CT/MRI 2. Clinical symptoms include dementia with or without headaches, gait disturbance, and urinary incontinence 3. Continuous ICP measurement may reveal various patterns of ICP dynamics and should not be specific
Therapeutic specificity	Treatable with shunt placement (but the effective shunt system depends on the individual pressure dynamics) or with neuroendoscopic third ventriculostomy, if noncommunicating in type

^a No underlying disease possibly causative of dementia should exist except for the hydrocephalus. CSF dynamics may or may not be communicating in type and should not be specific. Diagnostic criteria 1+2+3 define hydrocephalic dementia

dynamics recognized in NPH patients, a new term, “hydrocephalic dementia”, is proposed, since reference to the misleading pathophysiological aspect may cause confusion. It is also emphasized that the ICP dynamics are varied and change chronologically in this specific type of hydrocephalus (Table 5). The symptoms of the definitive triad of dementia, gait disturbance, and urinary incontinence are not specific to a certain kind of ICP dynamics, but may also be seen in the period of high ICP (HCA stage III). If “NPH” is defined strictly as “hydrocephalus with low baseline pressure, with pressure waves ranging mainly in the normal pressure range and treatable only using a low- or ultra-low-pressure shunt system, “true NPH” should be identified in late HCA stage III and stage IV. The symptoms may still include dementia, but may change to a vegetative state later on. The selection of shunt system, mainly in respect of the differential pressures, should be based on the specific ICP dynamics or HCA stage.

Problems in the Terminology of NPH

Since hydrocephalus is a clinicopathophysiological condition of disturbed CSF circulation secondary to a variety of underlying diseases or pathological lesions, problems in the terminology and classification remain. When Hakim et al. [1, 36A] defined NPH as a new syndrome with such specific clinical features as treatable dementia, they named it “normal-pressure” from the pathophysiological aspect. The discrepancy between the characteristics of the syndrome and the pathophysiological based term “normal-pressure hydrocephalus” is responsible for the confusion in the classification of hydrocephalus in the adult at the present time, over 30 years after it was first described.

The selection of shunt system to treat hydrocephalus should be made not uniformly but depending on the differences in pathophysiology in the pa-

tient population or on changes over time in the individual case. Since NPH is not a simple steady hydrocephalic state, the ICP and CSF dynamics are varied and change from one stage to another even in the same patient. In relatively early or acute stages of hydrocephalus, the compliance of the brain parenchyma is well preserved and the neuronal damage is reversible. Although the baseline pressure in the ICP dynamics is within normal limits, though in the relatively high-pressure range, the patient’s symptoms are typical, with the clinical triad of dementia, urinary incontinence, and gait disturbance, and frequent pressure pulses may be present in the continuous ICP monitoring record. Relatively high- or medium-pressure shunt systems may deal well with this stage of NPH. However, the selection of the shunt system becomes more significant in the late or chronic stage of NPH. The symptoms remain identical with the clinical triad, but the neuronal dysfunction is relatively long-standing and may not be reversible in a short period. The ICP dynamics may reveal a relatively low-pressure range as the baseline pressure and decreased compliance, but pressure waves are still present. If a medium-pressure shunt system is applied in this stage of NPH, a satisfactory result may not ensue. It is necessary to use a low- or ultra-low-pressure shunt system to remove the relatively small amount of excessive CSF, which is still a causative factor of the pressure waves. These pressure waves may not already be within the remarkably high-pressure range, but in a high range close to the normal level. Brain compliance will be reduced and CSF flow movement may not be so prominent. If these indices are present, NPH in this stage should be treated by the use of a low-pressure or sometimes an ultra-low-pressure shunt system.

Great confusion in the term “normal-pressure hydrocephalus” begins from this point. Some of the “NPH” cases are not normal even at the baseline pressure, and the majority of “NPH” cases have high pres-

sure. The terminological error should be firmly corrected in the classification of hydrocephalus. The term “normal-pressure hydrocephalus” should not be used except in those few cases in which the ICP dynamics suggest baseline pressure within the normal low-pressure range and pressure waves nearly within the normal-pressure range. This may be called “true NPH” in the strictly defined terminology of hydrocephalus based on the pathophysiological concept of ICP dynamics. The question then arises of how what we currently refer to as “NPH” should be defined? The terminology applied in this hydrocephalic syndrome with the clinical triad in adults should be based on the specific symptomatology. I hereby propose the term “hydrocephalic dementia” (see Table 5), on the basis of the original descriptions by Hakim et al.

Longstanding Overt Ventriculomegaly in Adult

The present author and colleagues have proposed a unique category of hydrocephalus in adults, namely, a long-term hydrocephalus, “longstanding overt ventriculomegaly in adult” (LOVA) [88]. Although its mechanism still remains unclear, patients with LOVA often suffer from a progressive course of hydrocephalus that continues into adulthood. The same authors also reported that the hydrocephalic state in LOVA is extremely difficult to treat with a shunt because of lost intracranial compliance.

Patients with LOVA in whom significant progressive symptoms of hydrocephalus had developed were first diagnosed as being hydrocephalic during adulthood [91]. In all patients, ventriculomegaly was prominent, involving the lateral and third ventricles as demonstrated on CT and/or magnetic resonance images. None of the patients had any known underlying disease or symptoms or signs, indicating that the

hydrocephalus had first occurred at birth or during infancy in accordance with neuroimaging findings of longstanding hydrocephalus. In this study, to prove this history objectively, the specific diagnostic criteria for LOVA included macrocephaly greater than two standard deviations in head circumference (57 cm in female and 58 cm in male patients), and/or neuroradiological evidence of a significantly expanded or destroyed sella turcica.

CSF dynamics change over time [19] under disturbed conditions. A large head is not necessarily indicative of hydrocephalic progression, even if it is accompanied by prominent ventriculomegaly, if CSF formation and absorption are well balanced [45, 61]. Arrested hydrocephalus [45, 119] is the opposite of progressive hydrocephalus. However, in our experience, arrested and progressive hydrocephalus do not remain constant, but sometimes change to other forms of hydrocephalus. Based on this concept, an individual’s hydrocephalic state may shift into a different or even the opposite subtype during certain periods. Arrested hydrocephalus does not always remain asymptomatic, but can change to a form of progressive hydrocephalus with active symptoms. LOVA is a chronological concept of hydrocephalus (Table 6). As described here, LOVA may be summarized as a complex entity with the following compatible subtypes:

1. Onset may be congenital in origin but becomes manifest during adulthood.
2. The underlying lesion is aqueductal stenosis.
3. Symptoms include macrocephaly, increased ICP symptoms, dementia, subnormal IQ, and others.
4. Pathophysiological characteristics include non-communicating CSF circulation and an ICP dynamics that mainly consists of high ICP.
5. The chronology is long-term and progressive
6. The hydrocephalus becomes arrested after shunt placement or ventriculostomy.

Table 6. Concept, diagnostic criteria, and treatment of longstanding ventriculomegaly in adults (LOVA)^a

Category	Definition
Concept	Chronological entity of progressive hydrocephalus with longstanding ventriculomegaly in adult, most likely starting from infancy
Diagnostic criteria	<ol style="list-style-type: none"> 1. Overt ventriculomegaly involving the lateral and third ventricles with obliterated cortical sulci on CT/MR imaging 2. Clinical symptoms include macrocephaly with or without subnormal IQ, headaches, dementia, gait disturbance, urinary incontinence, vegetative state, akinetic mutism, apathetic consciousness, and parkinsonism 3. Neuroimages may demonstrate expanded or destroyed sella turcica as evidence of longstanding ventriculomegaly
Therapeutic specificity	Treatable with shunt, but extremely delicate pressure control such as that provided by positive pressure ventilation is required: neuroendoscopic third ventriculostomy is mostly effective

^a Diagnostic criteria 1+2±3 define LOVA

Hydrocephalus Chronology and Selection of Shunt

The shunt valve, designed basically with different pressures ("low-medium-high") limits the range of the flow rate along with ICP. A CSF shunt flow rate of approximately 50 ml/h will be obtained when the ICP is around 90 mmH₂O with use of a low-pressure shunt system, 150 mmH₂O with a medium-pressure system, and 220 mmH₂O with a high-pressure system (OM-MAC Shunt System by S. Oi et al., Kaneka Medics, Tokyo, Japan). The shunt system should be selected not routinely at a single pressure, but the pressure chosen should depend upon the ICP dynamics in the individual case of hydrocephalic dementia. In the stage where the ICP level is relatively high, the shunt selected may be a medium-pressure system. In such ICP dynamics – usually during a relatively acute or subacute period in secondary hydrocephalus – the brain parenchymal compliance is well preserved and the withdrawal of small amounts of CSF by the shunt may normalize the high amplitude of pressure waves (HCA stage III). By contrast, a low- or ultra-low-pressure system may be necessary in the stage where ICP is relatively low. The compliance is lost and usually the pulse pressure is small in range, with relatively low baseline pressure. However, it may still be possible to reverse any injury to the neuronal function, which is affected by such small but significant pressure waves (late HCA stage III and HCA stage IV). In these stages, a shunt system should delete the pressure waves in the mildly abnormally high or even normal but relatively high ICP range in these cases. The medium-pressure shunt is not indicated in this stage of ICP dynamics.

The CSF shunt flow, however, is not steady in this condition but is largely dependent on the ICP dynamics. Theoretically, it would be expected that the CSF shunt flow is greater in patients treated with a low-pressure shunt system than in those treated with a high-pressure system. However, sometimes the reverse is true because of differences in the ICP dynamics among hydrocephalic patients (see Fig. 7). Although the patients with hydrocephalic dementia have the same symptoms – the triad of dementia, urinary incontinence, and gait disturbance – their ICP dynamics vary considerably. Even in a single patient they change over time. It must also be emphasized that in patients with hydrocephalic dementia, the therapeutic outcomes should be evaluated only when treatment was applied with the most suitable shunt system for the individual different ICP dynamics.

References

- Adams RD, Fisher CM, Hakim S, et al: Symptomatic occult hydrocephalus with normal cerebrospinal fluid pressure. *N Engl J Med* 273:117-126, 1965
- Aikawa H, Kobayashi S, Suzuki K: Aqueductal lesions in 6-aminonicotinamide-treated suckling mice. *Acta Neuropathol (Berl)* 71:243-250, 1986
- Anderson H, Elfverson J, Svendsen P: External hydrocephalus in infants. *Child's Brain* 11:398-402, 1984
- Babapour B, Oi S, Klekamp J, et al: Congenital hydrocephalus and associated hydronephrosis – a pathological study in experimental rat model. *Nervous System in Children* 27:243-249, 2002
- Bakey RA, Sweeney KM, Wood JH: Pathophysiology of cerebrospinal fluid in head injury. Part 1: Pathological changes in cerebrospinal fluid solute composition after traumatic injury. *Neurosurgery* 18:234-243, 1986
- Baxi L, Warren W, Collins MH, et al: Early detection of caudal regression syndrome with transvaginal scanning. *Obstet Gynecol* 75:486-489, 1990
- Berry RJ: The inheritance and pathogenesis of hydrocephalus-3 in the mouse. *J Pathol Bacteriol* 81:157-167, 1961
- Broit A, Sidman RJ: New mutant mouse with communicating hydrocephalus and secondary aqueductal stenosis. *Acta Neuropathol (Berl)* 21:316-331, 1972
- Bronstein M, Zimmer E, Gershoni-Baruch R, et al: First- and second-trimester diagnosis of fetal ocular defects and associated anomalies: report of eight cases. *Obstet Gynecol* 77:443-449, 1991
- Carton CA, Perry JH, Winter A, et al: Studies of hydrocephalus in C57 blank mice. *Trans Am Neurol Assoc* 81:147-149, 1956
- Clark SL, DeVore GR, Sabey PL: Prenatal diagnosis of cysts of the fetal choroid plexus. *Obstet Gynecol* 72:585-587, 1988
- Clark FH: Hydrocephalus: a hereditary character in the house mouse. *Proc Natl Acad Sci USA* 18:654-656, 1932
- Coheh I: Chronic subdural accumulations of cerebrospinal fluid after cranial trauma. Report of a case. *Arch Neurol Psychiatr* 18:709-723, 1927
- Comstock CH, Culp D, Gonzalez J, et al: Agenesis of the corpus callosum in the fetus: its evolution and significance. *J Ultrasound Med* 4:613-616, 1985
- D'Agostino AN, Kernohan JW, Brown JR: The Dandy-Walker syndrome. *J Neuropathol Exp Neurol* 22:450-470, 1963
- Dandy WE: Extirpation of the choroid plexus of the lateral ventricles in communicating hydrocephalus. *Ann Surg* 68:569-579, 1918
- Dandy WE: An operative procedure for hydrocephalus. *Bull Johns Hopkins Hosp* 33:189-190, 1922
- Davis L: Neurological surgery. Lea & Febiger, Philadelphia 1936
- Day RE, Schutt WH: Normal children with large heads: benign familial megalcephaly. *Arch Dis Child* 54:512-517, 1979
- Deol MS: The origin of the abnormalities of inner ear in Dreher mice. *J Embryol Exp Morphol* 12:727-733, 1964
- Depp R, Sabbagh RE, Brown JT, et al: Fetal surgery for hydrocephalus: successful in utero ventriculoamniotic shunt for Dandy-Walker syndrome. *Obstet Gynecol* 61:710-714, 1983

22. Dinh DH, Wright RM, Hanigan WC: The use of magnetic resonance imaging for the diagnosis of fetal intracranial anomalies. *Childs Nerv Syst* 6:212-215, 1990
23. Dohrmann GJ: Cervical spinal cord in experimental hydrocephalus. *J Neurosurg* 37:538-542, 1972
24. Faulhauer K, Donauer E: Experimental hydrocephalus and hydrosyringomyelia in the cat. Radiological findings. *Acta Neurochir (Wien)* 74:72-80, 1985
25. Feigin RD, Dodge PR: Bacterial meningitis: New concepts of pathophysiology and neurologic sequelae. *Pediatr Clin North Am* 23:541-556, 1976
26. Fernald E, Uvebrant P, von Wendt L: Overt hydrocephalus at birth - origin and outcome. *Child's Nerv Syst* 3:350-353, 1987
27. Gardner WJ: Hydrodynamic mechanism of syringomyelia: its relationship to myelocoele. *J Neursurg Psychiatry* 28:247-259, 1965
28. Gitlin D: Pathogenesis of subdural collections of fluid. *Pediatrics* 16:1345-1352, 1955
29. Granholm I, Svendgaard N: Hydrocephalus following traumatic head injuries. *Scand J Rehab Med* 4:31-34, 1972
30. Green MC: The developmental effects of congenital hydrocephalus (ch) in the mouse. *Dev Biol* 23:585-608, 1970
31. Grunberg H: Congenital hydrocephalus in the mouse: a case of spurious pleiotropism. *J Genet* 45:1-21, 1943
32. Gruneberg H: Two new mutant genes in the house mouse. *J Genet* 45:22-28, 1943
33. Gutierrez FA, McLone DG, Raimondi AJ: Physiology and a new treatment of chronic subdural hematoma in children. *Child's Brain* 5:216-232, 1979
34. Hanigan WC, Gibson J, Kleopoulos NJ, et al: Medical imaging of fetal ventriculomegaly. *J Neurosurg* 64:575-580, 1986
35. Hayashi M, Kabayashi H, Kawano H, et al: ICP patterns and isotope cisternography in patients with communicating hydrocephalus following rupture of intracranial aneurysm. *J Neurosurg* 62:220-226, 1985
36. Jensen F, Jensen FT: Acquired hydrocephalus I. A clinical analysis of 160 patients studied for hydrocephalus. *Acta Neurochir* 46:119-133, 1977
- 36A. Hakim S: Some observation on CSF pressure. Hydrocephalic syndrome in adults with "normal" CSF pressure: recognition of a new syndrome [Spanish]. Thesis no. 957, Javeriana University School of Medicine, Bogota, Colombia, 1964
37. Higashi K, Noda Y, Mufune H: Pathological studies on the brain of congenital hydrocephalic rats. *Shoni No Noshinkei* 12:1-9, 1987
38. Hill LM, Martin JG, Fries J, et al: The role of the transcerebellar view in the detection of fetal central nervous system anomaly. *Am J Obstet Gynecol* 164:1220-1224, 1991
39. Hirsch JF: Surgery of hydrocephalus: past, present and future. *Acta Neurochir (Wien)* 116:155-160, 1992
40. Hoff J, Bates E, Barnes B, et al: Traumatic subdural hygroma. *J Trauma* 13:870-876, 1973
41. Hoffman-Tretin JC, Horouptian DS, Koenigsberg M, et al: Lobar holoprosencephaly with hydrocephalus: antenatal demonstration and differential diagnosis. *J Ultrasound Med* 5:691-697, 1986
42. Johnston IH, Howman-Giles R, Whittle IR: The arrest of treated hydrocephalus in children. A radionuclide study. *J Neurosurg* 61:752-756, 1984
43. Kalter H: Experimental mammalian teratogenesis, a study of galactoflavin-induced hydrocephalus in mice. *J Morphol* 112:303-317, 1963
44. Kausch W: Die Behandlung des Hydrocephalus der kleinen Kinder. *Arch Klin Chir* 87:709-715, 1908
45. Kelley RI, et al: X-linked recessive aqueductal stenosis without macrocephaly. *Clin Genet* 33:390-394, 1988
46. Kendall B, Holland I: Benign communicating hydrocephalus in children. *Neuroradiology* 21:93-96, 1981
47. Kirkinen P, Serlo W, Jouppila P, et al: Long-term outcome of fetal hydrocephaly. *J Child Neurol* 11:189-192, 1996
48. Kohn DF, Chinookoswong N, Chou SM: A new model of congenital hydrocephalus in the rat. *Acta Neuropathol (Berl)* 54:211-218, 1981
49. Koyama T: Erzeugung von Missbildungen im Gehirn durch Methyl-Nitrose-Harnstoff und Äthyl-Nitrose-Harnstoff an SD-JCL Ratten. *Arch Jpn Chir* 39:233-254, 1970
50. Masters C, Alpers M, Kakulas B: Pathogenesis of reovirus type 1 hydrocephalus in mice. Significance of aqueductal changes. *Arch Neurol* 34:18-28, 1977
51. McGahan JP, Phillips HE: Ultrasonic evaluation of the size of the trigone of the fetal ventricle. *J Ultrasound Med* 2:315-319, 1983
52. McGahan JP, Haesslein HC, Meyers M, et al: Sonographic recognition of in utero intraventricular hemorrhage. *AJR Am J Roentgenol* 142:171-173, 1984
53. Ment LR, Cuncic CC, Geehr R: Benign enlargement of the subarachnoid spaces in the infant. *J Neurosurg* 54:504-508, 1981
54. Meyers CA, Levin HS, Eisenberg HM, et al: Early versus late lateral ventricular enlargement following closed head injury. *J Neurol Neurosurg Psychiatr* 46:1092-1097, 1983
55. Michejda M, Patronas N, Di Chiro G, et al: Fetal hydrocephalus. II. Amelioration of fetal porencephaly by in utero therapy in nonhuman primates. *JAMA* 251:2548-2552, 1984
56. Michejda M, Queenan JT, McCullough D: Present status of intrauterine treatment of hydrocephalus and its future. *Am J Obstet Gynecol* 155:873-882, 1986
57. Mixter WJ: Ventriculostomy and puncture of the floor of the third ventricle. Preliminary report of a case. *Boston Med Surg J* 188:277-278, 1923
58. Monteagudo A, Reuss ML, Timor-Tritsch IE: Imaging the fetal brain in the second and third trimesters using transvaginal sonography. *Obstet Gynecol* 77:27-32, 1991
59. Mori T: A study of the tellurium-induced experimental hydrocephalus. *Neuropathology* 6:355-365, 1985
60. Nevin NC: Neuropathological changes in the white matter following head injury. *J Neuropathol Exp Neurol* 26:66-84, 1967
61. Nishizaki T, Tamaki N, Nishida Y, et al: Bilateral internuclear ophthalmoplegia due to hydrocephalus: a case report. *Neurosurgery* 17:822-825, 1985
62. Nulsen FE, Spitz EB: Treatment of hydrocephalus by direct shunt from ventricle to jugular vein. *Surg Forum* 2:399-403, 1951
63. Ohba N: Formation of embryonic abnormalities of the mouse by a viral infection of mother animals. *Acta Pathol Jpn* 8:127-138, 1958
64. Oi S, Matsumoto S: Pathophysiology of nonneoplastic obstruction of the foramen of Monro and progressive unilateral hydrocephalus. *Neurosurgery* 17:891-896, 1985
65. Oi S, Matsumoto S: Slit ventricles as a cause of isolated ventricles after shunting. *Child's Nerv Syst* 1:189-193, 1985

66. Oi S, Yamada H, Sasaki K, et al: [Diagnosis and treatment of fetal hydrocephalus. Problems in evaluation of the hydrocephalic state and selection for intrauterine shunt procedure.] *Neurol Med Chir* 25:195-202, 1985 (Jpn)
67. Oi S, Matsumoto S: Isolated fourth ventricle. *J Pediatr Neurosci* 2:125-133, 1986
68. Oi S, Matsumoto S: Pathophysiology of aqueductal obstruction in isolated IV ventricle after shunting. *Child's Nerv Syst* 2:282-286, 1986
69. Oi S, Matsumoto S: Dynamic change in intracranial pressure in slit-like ventricles and isolated ventricles in childhood hydrocephalus after shunt placement. In: Ishii S (ed) *Hydrocephalus*. Excerpta Medica, Tokyo, pp 135-147, 1986
70. Oi S, Shose Y, Yamada H, et al: CSF dynamics in children. A quantitative analysis of the relativity of major and minor pathways of cerebrospinal fluid dynamics. *CT Kenkyu (Jpn)* 8:153-162, 1986
71. Oi S, Matsumoto S: Infantile hydrocephalus and the slit ventricle syndrome in early infancy. *Child's Nerv Syst* 3:145-150, 1987
72. Oi S, Matsumoto S: Post-traumatic hydrocephalus in children: pathophysiology and classification. *J Pediatr Neurosci* 3:133-147, 1987
73. Oi S, Matsumoto S: Natural history of subdural effusion in infants: prospective study of 87 cases. *J Pediatr Neurosci* 4:15-24, 1988
74. Oi S, Yamada Y, Matsumoto S: A prenatal CSF shunt procedure for fetal hydrocephalus, animal experimental model: pressure dynamics of intrauterine hydrocephalus and fetal ventriculo-mater peritoneal (FV-MP) shunt. *Shoni No Noshinke (Jpn)* 14:215-221, 1989
75. Oi S, Tamaki N, Matsumoto S, et al: Prenatal neuroimaging in fetal dysraphism. *Neurosonology* 3:90-96, 1990
76. Oi S, Tamaki N, Kondo T, et al: Massive congenital intracranial teratoma diagnosed in utero. *Child's Nerv Syst* 6:459-461, 1990
77. Oi S, Kudo H, Yamada H, et al: Hydromyelic hydrocephalus: correlation of hydromelia with various stages of hydrocephalus in postshunt isolated compartments. *J Neurosurg* 74:371-379, 1991
78. Oi S: Is the hydrocephalic state progressive to become irreversible during fetal life? *Surg Neurol* 37:66-68, 1992
79. Oi S, Sato S, Matsumoto S: A new classification of congenital hydrocephalus: perspective classification of congenital hydrocephalus (PCCH) and postnatal prognosis. Part 1. A proposal of a new classification of fetal/neonatal/infantile hydrocephalus based on neuronal maturation process and chronological changes. *Jpn J Neurosurg (Jpn)* 3:122-127, 1994
80. Oi S, Matsumoto S, Katayama K, et al: Pathophysiology and postnatal outcome of fetal hydrocephalus. *Child's Nerv Syst* 6:338-345, 1990
81. Oi S, Hidaka M, Matsuzawa K, et al: Intractable hydrocephalus in a form of progressive and irreversible "hydrocephalus-parkinsonism complex": A case report. *Curr Trends Hydrocephalus (Tokyo)* 5:43-49, 1995
82. Oi S: Recent advances in neuroendoscopic surgery: realistic indications and clinical achievement. *Crit Rev Neurosurg* 6:64-72, 1996
83. Oi S, Hidaka M, Togo K, et al: Neuro-endoscopic surgery, part 3: Characteristics of rigid, semi-rigid and flexible/steerable endoscopy: analysis in cadaver dissection, experimental animal model and clinical Application. *Curr Trends Hydrocephalus (Tokyo)* 5:57-66, 1996
84. Oi S, Yamada H, Sato O, Matsumoto S: experimental models of congenital hydrocephalus and comparable clinical problems in the fetal and neonatal periods. *Child's Nerv Syst* 12:292-302, 1996
85. Oi S, Honda Y, Hidaka M, et al: Intrauterine high-resolution magnetic resonance imaging in fetal hydrocephalus and prenatal estimation of postnatal outcomes with "perspective classification". *J Neurosurg* 88:685-694, 1998
86. Oi S: Hydrocephalus chronology in adults: confused state of the terminology. *Crit Rev Neurosurg* 8:346-356, 1998
87. Oi S, Hidaka M, Honda Y, et al: Neuroendoscopic surgery for specific forms of hydrocephalus. *Child's Nerv Syst* 15:56-68, 1999
88. Oi S, Shimoda M, Shibata M, et al: Pathophysiology of long-standing overt ventriculomegaly in adults (LOVA). *J Neurosurg* 92:933-940, 2000
89. Oi S, Babapour B, Klekamp J, et al: Prerequisites for fetal neurosurgery: management of central nervous system anomalies toward the 21st century. *Crit Rev Neurosurg* 9:252-261, 1999
90. Oi S, Matsumoto S: Morphological findings of postshunt slit-ventricle in experimental canine hydrocephalus: aspects of causative factor for isolated ventricles and slit ventricle syndrome. *Child's Nerv Syst* 2:179-184, 1986
91. Oi S, Sato O, Matsumoto S: Neurological and medico-social problems of spina bifida patients in adolescence and adulthood. *Child's Nerv Syst* 12:181-187, 1996
92. Oka K, Yamamoto M, Ikeda K, et al: Flexible endoneurosurgical therapy for aqueductal stenosis. *Neurosurgery* 33:236-243, 1993
93. Pedersen KK, Haase J: Isotope liquorgraphy in the demonstration of communicating obstructive hydrocephalus after severe cranial trauma. *Acta Neurol Scand* 49:10-30, 1973
94. Platt LD, DeVore GR: Modification of fetal intraventricular amniotic shunt. *Am J Gynecol* 152:1044-1045, 1985
95. Pretorius DH, Davis K, Manco-Johnson ML, et al: Clinical course of fetal hydrocephalus: 40 cases. *AJR Am J Roentgenol* 144:827-831, 1985
96. Pudenz RH, Russell FE, Hund AH: Ventriculoauriculostomy. A technique for shunting cerebrospinal fluid into the rigid auricle. Preliminary report. *J Neurosurg* 14:171-179, 1957
97. Putnam TJ: Treatment of hydrocephalus by endoscopic coagulation of the choroids plexus. Description of a new instrument and preliminary report of results. *N Engl J Med* 210:1373-1376, 1934
98. Rabe EF, Flynn RE, Dodge PR: Subdural collections of fluid in infants and children. A study of 62 patients with special reference to factors influencing prognosis and the efficacy of various forms of therapy. *Neurology* 18:559-570, 1968
99. Raimondi AJ, Bailey OT, McLone DG, et al: The pathophysiology and morphology of murine hydrocephalus in hydrocephalus 3 and Ch mutants. *Surg Neurol* 1:50-55, 1973
100. Raimondi AJ, Clark SJ, McLone DG: Pathogenesis of aqueductal occlusion in congenital murine hydrocephalus. *J Neurosurg* 45:66-77, 1976
101. Robertson WC Jr, Gomez MR: External hydrocephalus. *Arch Neurol* 35:541-544, 1978

102. Robertson WC Jr, Chun RWM, Orrison WW, et al: Benign subdural collections of infancy. *J Pediatr* 94:382-385, 1979
103. Sahar A: Pseudohydrocephalus-megalocephaly, increased intracranial pressure and widened subarachnoid space. *Neuropädiatrie* 9:130-131, 1978
104. Sasaki S, Goto H, Nagano H, et al: Congenital hydrocephalus revealed in the inbred rat. LEW/Jms. *Neurosurgery* 13:548-554, 1983
105. Sato K, Naomi N, Akira S, et al: Experimental production of myeloschisis, Chiari malformation type II, posterior fossa hydrocephalus and other malformations related to craniospinal dysraphism in rat fetuses by single intra-gastric administration of ethylenethiourea. *Child's Nerv Syst* 1:1-6, 1985
106. Saunders RL, Simmons GM, Edwards WH, et al: A cranial nail for fetal shunting. *Child's Nerv Syst* 1:185-187, 1985
107. Scarff JE: Third ventriculostomy as the rational treatment of obstructive hydrocephalus (abstract). *J Pediatr* 6:870-871, 1935
108. Scarff JE: The treatment of nonobstructive (communicating) hydrocephalus by endoscopic cauterization of the choid plexuses. *J Neurosurg* 33:1-18, 1970
109. Shinoda M, Hidaka M, Lindqvist E, et al: NGF, NT-3 and Trk C mRNAs, but not TrkA mRNA, are upregulated in the paraventricular structures in experimental hydrocephalus. *Child's Nerv Syst* 17:704-712, 2001
110. Smith MHD, Dormont RF, Prather GW: Subdural effusions complicating bacterial meningitis. *Pediatrics* 7:34-43, 1951
111. Takagi T, Hashimoto N, Togari H, et al: [Holoprosen- cephalia with Dandy-Walker cyst diagnosed in utero by MRI: report of a case]. *No To Hattatsu* 20:237-41 1988 (Jpn)
112. Takahashi Y, Tsutsumi H, Hashi K: Two cases of vein of Galen aneurysm in neonates: clinical problems and its treatment. *Shoni No Noshinkei* 15:253-260, 1990
113. Thickman D, Mintz M, Mennuti M, et al: MR imaging of cerebral abnormalities in utero. *J Comput Assist Tomogr* 8:1058-1061, 1984
114. Till K: Subdural haematoma and effusion in infancy. *Br Med J* 3:400-402, 1968
115. Tsubokawa T, Nakasuma S, Sato K: Effect of temporary subdural-peritoneal shunt on subdural effusion with subarachnoid effusion. *Child's Brain* 11:47-59, 1984
116. Turner L: The structure of arachnoid granulations with observation of their physiological and pathological significance. *Ann R Coll Surg* 29:237-264, 1961
117. Vries JK: An endoscopic technique for third ventriculostomy. *Surg Neurol* 9:165-168, 1978
118. Walker MK, Carey L, Blockmeyer DL: The neuronavigational 1.2-mm neuroview neuroendoscope. *Neurosurgery* 36:617-618, 1995
119. Whittle IR, Johnston I, Sesser M: Intracranial pressure changes in arrested hydrocephalus. *J Neurosurg* 62:77-82, 1985
120. Wieser HG, Probst C: Clinical observations on hydrocephalus with special regard to the posttraumatic malreabsorptive form. *J Neurol* 212:1-21, 1976
121. Yamada H, Oi S, Tamaki N, et al: Prenatal aqueductal stenosis as a cause of congenital hydrocephalus in the inbred rat. LEW/Jms. *Child's Nerv Syst* 8:394-398, 1992

Hydrocephalus: Intracranial Pressure, Myelination, and Neurodevelopment

PATRICK W. HANLO¹, ROB H.J.M. GOOSKENS² AND PETER W. VANDERTOP³

Introduction

The actual importance of hydrocephalus as a neurological disorder is severely underestimated. The incidence of congenital and infantile hydrocephalus is reported to be 0.48–0.81 per 1000 live births and stillbirths [7,17]. Cases of secondary hydrocephalus are seldom included in the incidence and prevalence figures.

Up to the present time, the treatment of childhood hydrocephalus is often not straightforward. In progressive hydrocephalus, cerebrospinal fluid (CSF) diversion is the treatment of choice, avoiding secondary cerebral damage by decreasing the raised intracranial pressure (ICP) and restoring intracranial dynamic balance. The evaluation of the rate at which the hydrocephalic process progresses, and defining the right indication and moment for surgical intervention, remains, however, a difficult task usually based on the most common clinical signs of raised ICP. Complications of shunt implantation, especially infection and dysfunction, are quite common, and can cause serious morbidity. Recent estimates suggest the proportion of treated hydrocephalic patients with persistent neurological deficits to be as high as 52%–78% [7,16,55]. Therefore, unnecessary shunt implantation should be avoided, and early detection of shunt malfunction is very important.

The distinction between hydrocephalus that will spontaneously compensate in due course, without causing significant cerebral damage, and slowly progressive hydrocephalus, with its associated risk of serious developmental deficit, is often hard to make. In this context, specific diagnostic tools might help us further to delineate the indication for surgical intervention in childhood hydrocephalus.

Several studies have shown that clinical symptoms of raised ICP in childhood hydrocephalus are non-specific and often unreliable [15, 28, 29, 31]. In patients with dubious neurological manifestations of progressive hydrocephalus, (non-invasive) ICP measurement

can provide valuable information on the intracranial dynamic situation [27].

Moreover, because the hydrocephalic process has possible pathological consequences for the periventricular brain tissue, it is just as important to investigate the effect of raised ICP on the developing brain. This can be done by studying not only the neurodevelopmental outcome of the patient, but also the effect of raised ICP on the process of myelination.

Myelination

Myelin is a complex membranous structure characteristic of nervous tissue forming sheaths around axons, and is produced by oligodendrocytes. Myelination is a major dynamic process in the developing brain, progressing rapidly after birth and reaching an advanced stage by the age of 2–3 years in most parts of the brain. The relationship between the progress of myelination and the functional maturity of the brain was discussed as early as the beginning of the last century [18, 19, 56, 57]. Flechsig [18, 19] showed that pathways and structures in the human nervous system become myelinated in a highly ordered sequence. Different fibres of corresponding functional systems become myelinated at the same time, and it was postulated that tracts in the nervous system become myelinated when they become functional. Therefore, Flechsig [18] stated that myelination is an expression of functional maturity of the brain. Later examinations by other investigators showed that, apart from the movements observed in early fetal life, there is a close relationship between myelination and acquisition of function [33, 50, 61].

All earlier studies on myelination in the nervous system are based on histological data. An important drawback of these studies is that they cannot be per-

¹ Department of Neurosurgery/Pediatric Neurosurgery; ²Child Neurology, University Medical Center Utrecht, The Netherlands; ³Department of Neurosurgery, University Hospital, Vrije Universiteit Amsterdam, The Netherlands

formed during life, and, therefore, longitudinal studies correlating the progress of myelination and neurodevelopment could not be carried out.

Delayed myelination has been investigated in a few histological and biochemical studies [4, 9, 11, 49, 59, 60]. Most of these studies are not concerned with the state of psychomotor development, and at best the comparison between myelination and development was only qualitative.

Magnetic Resonance Imaging and Myelination

Magnetic resonance imaging (MRI) provides a unique means of evaluating the progress of myelination *in vivo* [21, 36, 47, 53]. The advantage of MRI is that it allows delineation of the progress of cerebral myelination during life. Patterns of myelination in the normal developing brain have been extensively described in MRI studies and provide reliable references for the detection of delayed myelination [1, 2, 6, 24–38, 48, 53]. In the course of brain maturation typical changes appear in both T1- and T2-weighted images. Although signal intensity on images depends on a number of specific tissue variables, several studies have shown that signal intensity on MRI can be used as an indirect measure of increasing myelination.

Myelination of the central nervous system starts in the second trimester of gestation, commencing in the spinal nerve roots and the spinal cord. At the beginning of the third trimester of gestation, myelination starts in the brain stem. Soon thereafter myelin appears in the cerebellar white matter and in the posterior limb of the internal capsule. Histological investigations have revealed that, at birth, most of the cerebral white matter is still unmyelinated, while myelin is present in considerable amounts in the brain stem, cerebellar white matter and internal capsule, with extensions to the thalamus, basal nuclei and central part of the corona radiata [8, 30]. After birth, myelination spreads over the remainder of the brain following a certain pattern. In the first month after birth, myelination proceeds in the corona radiata towards the sensory cortex, and subsequently towards the motor cortex. After about 3 months the radiatio optica is largely myelinated, and soon thereafter myelination has advanced towards the parietal lobe. Myelination proceeds towards the occipital and frontal lobe from about the 4th month onwards, and from about the 5th–6th month onwards in the temporal direction as well. Reliable follow-up on the progression of myelination with MRI can be conducted at 1-month intervals. The major part of myelin deposition occurs dur-

ing the first 2 years of life. In the same period, swift changes occur in psychomotor development. Myelination is virtually completed in early adulthood [5].

Several authors have revealed patterns of delayed myelination on MRI, detected in children with developmental delay [20, 21, 37, 39]. However, developmental performance and the progress of myelination were not sufficiently quantified: only the presence or absence of delayed myelination and the presence or absence of developmental delay could be compared.

Very few studies have assessed the prognostic value of the progress of myelination for final neurodevelopmental outcome [21, 32, 58]. Most of these studies were concerned with hypoxic-ischaemic brain damage in preterm neonates, and the correlation between myelination and psychomotor development was not calculated quantitatively. Furthermore, the severity of the parenchymal damage is hard to quantify in infants with hypoxic-ischaemic lesions; damage to structures or processes in the brain other than myelination might have been responsible for psychomotor retardation. Guit et al. [26] found that the progression of myelination in the early postnatal period could to a certain extent predict functional outcome.

Hydrocephalus and Myelination

The process of myelin deposition can be affected by several intracranial disorders, including infantile hydrocephalus [10, 12, 13, 52]. Hydrocephalus can lead to deteriorating intracranial dynamics, with decreased intracranial compliance and cerebral perfusion pressure (CPP) [46]. In this context it has been suggested on the basis of transcranial Doppler investigations that raised intracranial pressure (ICP) can cause secondary ischaemic damage to the brain [41]. It is likely that the vulnerable process of myelination can be adversely affected by infantile hydrocephalus. Even demyelination has been identified as a common feature of the white matter pathology accompanying hydrocephalus [12, 22, 40, 44]. Increased myelin basic protein levels in the CSF of hydrocephalic patients confirm demyelination in severe ventriculomegaly [35].

Van der Knaap et al. [52] quantified the relationship between myelination as determined by MRI and neurodevelopmental testing in a homogeneous patient population of hydrocephalic infants. These patients differed only in the severity of their ventricular dilatation, and there was no focal parenchymal damage. Some patients had minor neurological deficits, caused only by the hydrocephalic disorder. An important advantage of this study was that the severity of hydrocephalus could be defined by calculating the

intracranial CSF volume using the MR technique. A highly significant correlation between myelination and neurodevelopmental performance was found ($r=0.80$). There was a tendency in patients with larger CSF volumes to show poorer neurodevelopmental performance and more severely delayed myelination. The correlation coefficients were negative, but none reached the level of significance. Since neither the progress of myelination nor neurodevelopmental performance was determined by the intracranial CSF volume, another factor was thought to affect brain maturation in these infants. The level and duration of raised ICP were considered to be potentially of importance with respect to parenchymal damage and delay of brain maturation in infantile hydrocephalus.

In a similar population of hydrocephalic infants, we reassessed the relationship between myelination (determined by MRI), psychomotor development (using the Bayley and McCarthy scales for neurodevelopmental testing, NDT), and ventricular dilatation [3, 54]. Moreover, we evaluated the correlation between non-invasive ICP measurements [anterior

fontanelle pressure (AFP) measurements] [43] and the variables mentioned previously [27]. In this study the ventricle-skull ratio (VSR) was used to assess the size of the ventricles as an indication of the severity of hydrocephalus on MRI. The VSR (maximum diameter of the frontal horns, plus the diameter of the ventricles at the level of the cella media, plus the maximum diameter of the occipital horns, over the maximum internal skull diameter) showed the highest correlation ($r=0.89$) with the actual intracranial CSF volume, as calculated by MR volume measurements [53]. We also found a highly significant correlation between myelination and psychomotor development ($r=0.80$), and a poor correlation between both these variables and the VSR (Fig. 1) [27]. The influence of the VSR on the correlation between myelination and psychomotor development was negligible. Apparently the degree of hydrocephalus is less important than the severity of parenchymal damage and the delay of normal brain maturation caused by raised ICP and mechanical distortion of the brain due to ventriculomegaly [12, 25, 37, 52, 27].

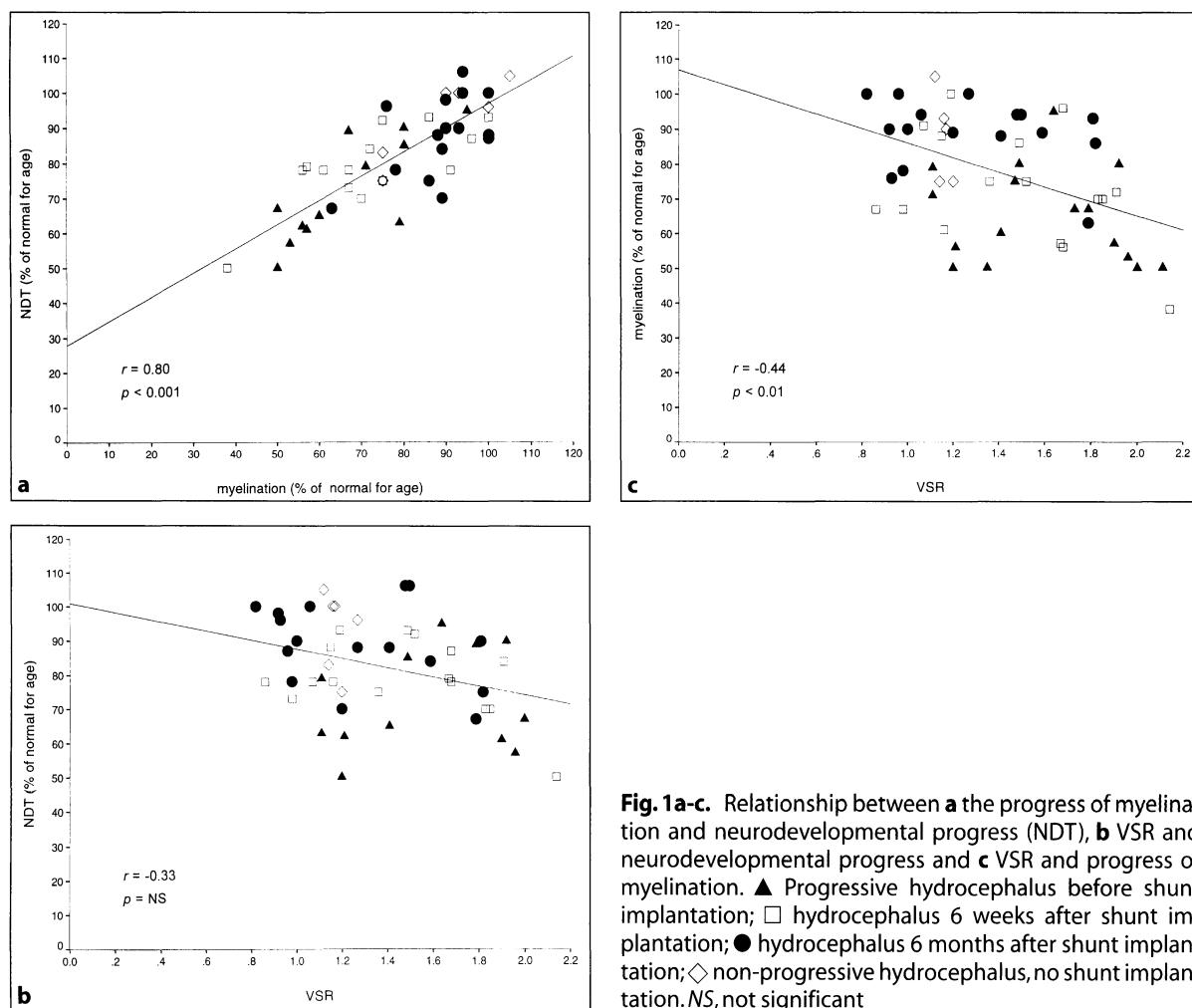


Fig. 1a-c. Relationship between **a** the progress of myelination and neurodevelopmental progress (NDT), **b** VSR and neurodevelopmental progress and **c** VSR and progress of myelination. ▲ Progressive hydrocephalus before implantation; □ hydrocephalus 6 weeks after shunt implantation; ● hydrocephalus 6 months after shunt implantation; ◇ non-progressive hydrocephalus, no shunt implantation. NS, not significant

In this study we also showed a poor correlation between mean AFP (ICP) and VSR (Fig. 2). A significant negative correlation, however, between mean AFP (ICP) and both myelination ($r=-0.67$) and psychomotor development ($r=-0.70$) was demonstrated (Fig. 2). From the correlation between mean AFP (ICP) and myelination, it can be concluded that it is plausible that the process of myelin deposition is adversely influenced by raised ICP and decreased intracranial compliance in hydrocephalic infants. This results in delayed myelination, and consequently in developmental delay.

Cerebral damage caused by progressive hydrocephalus is not entirely irreversible [52]. The magnitude of these pathological changes is mostly dependent on the age at which hydrocephalus develops and the duration of the hydrocephalic process combined with impaired cerebral blood flow. To what extent these changes can be prevented by CSF diversion has not been clearly defined. This

phenomenon of reversible white matter damage and compensatory myelination has also been described in in vitro studies [14]. In our studies we found that shunt implantation, with a concomitant decrease in ICP, improved the progress of myelination, sometimes even dramatically, towards normal for age (Fig. 3) [27]. This suggests that in these hydrocephalic infants, the delay in myelination can be reversible. As can be expected from the correlation between myelination and psychomotor development, similar findings were observed concerning psychomotor development. In most of the patients, it was not the initial pre-operative degree of myelination, but the progression of myelination after successful shunt implantation, that correlated with more long-term outcome (mean follow-up: 2.5 years). Persistent functional deficits in hydrocephalic patients are probably caused by irreversible neuronal and axonal damage [12].

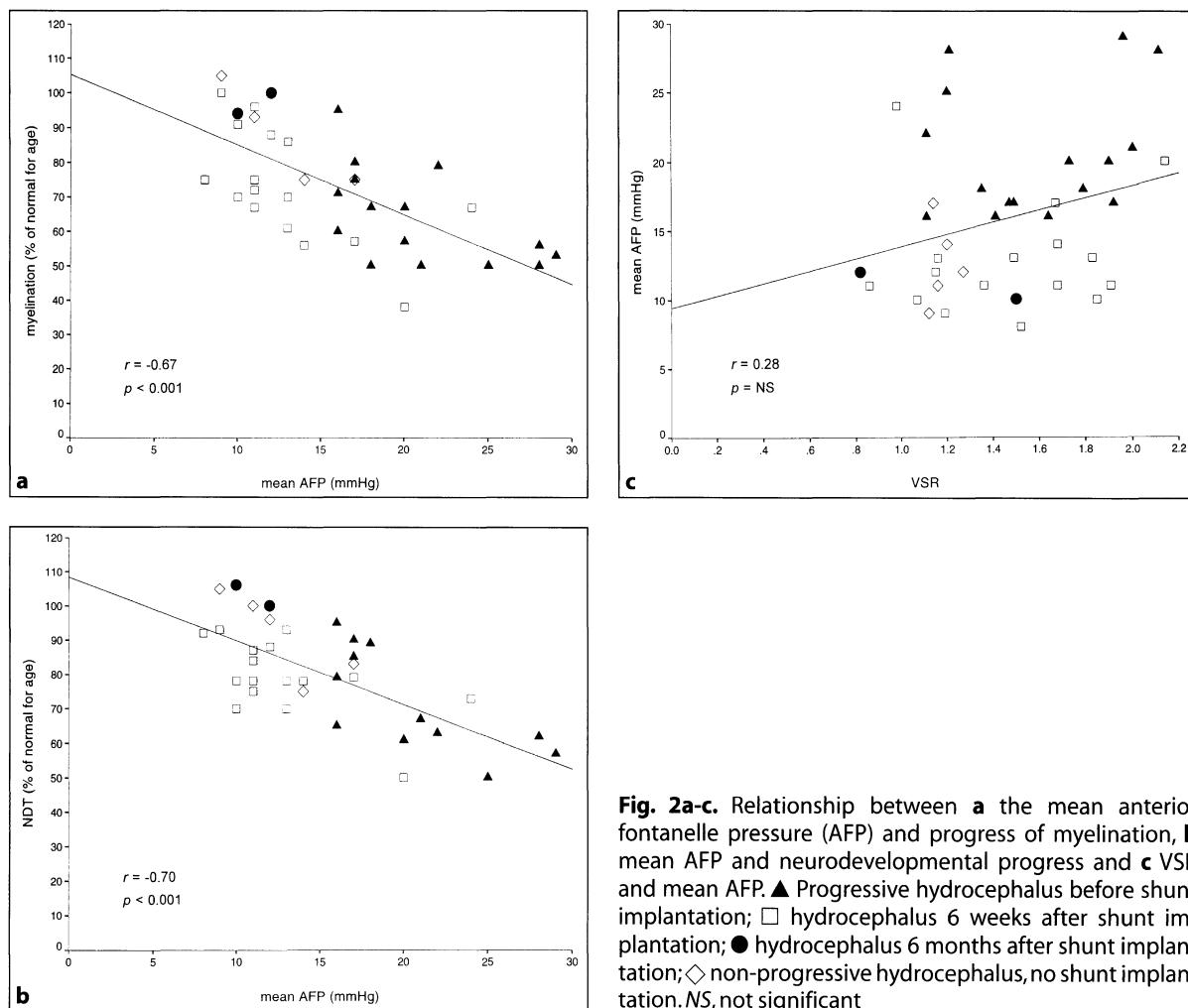


Fig. 2a-c. Relationship between **a** the mean anterior fontanelle pressure (AFP) and progress of myelination, **b** mean AFP and neurodevelopmental progress and **c** VSR and mean AFP. ▲ Progressive hydrocephalus before shunt implantation; □ hydrocephalus 6 weeks after shunt implantation; ● hydrocephalus 6 months after shunt implantation; ◇ non-progressive hydrocephalus, no shunt implantation. NS, not significant

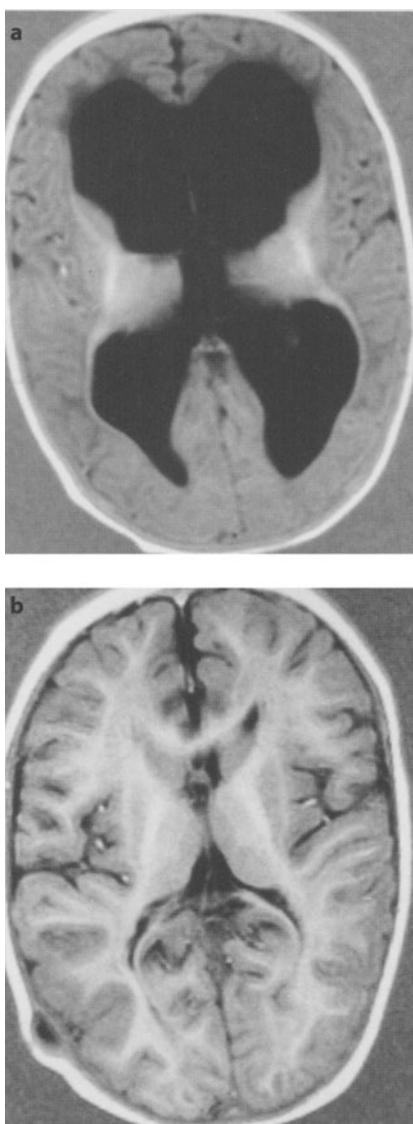


Fig. 3a, b. Myelination on MRI (inversion recovery) in shunted hydrocephalus: **a** preoperative myelination of 56% (percentage of normal for age); **b** 6 months postoperative myelination of 95%

It is clear that raised ICP cannot in itself account entirely for the delay in myelination and development found in hydrocephalic children. An important factor regarding the extent and reversibility of the secondary ischaemic insult to the brain in hydrocephalic infants [41] is probably the duration of increased ICP. In our previously mentioned study one patient had evidence of long-standing raised ICP and showed severely delayed myelination and psychomotor development in the preoperative period, which did not recover despite adequate shunt function. The

preoperative duration of raised ICP was not exactly known in the majority of our patients, because ICP was not measured repeatedly before operation, and clinical symptoms related to increased ICP are not very reliable. In addition to the duration of increased ICP, other features that might have a detrimental effect on brain myelination could be intermittent ICP changes, abnormal ICP waveform characteristics, decreased cerebral perfusion pressure and intracranial compliance. Metabolic changes in neonatal hydrocephalus can also lead to brain injury with delayed myelination [10].

Developing hydrocephalus in low-birth-weight infants, which can sometimes occur without macrocephaly or intraventricular haemorrhage, is not always associated with raised ICP [34]. A period of "clinically asymptomatic ventricular enlargement", which may last for several weeks, occurs in 35% of these neonates. In 65% of these infants, the hydrocephalic process arrests spontaneously, but often the ventricular size does not return to normal. Strictly this is not a posthaemorrhagic hydrocephalus, which is defined as progressive ventriculomegaly due to impaired CSF flow and/or absorption. The persisting ventriculomegaly ("hydrocephalus *ex vacuo*") in these infants is caused by extensive neonatal white matter damage ("periventricular malacia"), resulting in delayed myelination ("hypomyelination") in conjunction with loss of white matter tissue [34].

Furthermore, a close interdependency exists between neurons and myelin. A disorder affecting one of the two components inevitably leads to a disturbance of the other as well. Del Bigio [12] states that in hydrocephalus damage occurs to axons and myelin in the periventricular white matter. This damage appears to result from the combination of mechanical distortion of the brain and impaired cerebral blood flow due to increased ICP. It has been shown that neuronal maturation is delayed in fetal hydrocephalus, while in the fetal period myelination of the cerebral hemispheres has not yet begun [12, 42]. Therefore, it cannot be excluded that, at least in part, the delay in myelination is secondary to a delay in neuronal maturation in progressive hydrocephalus.

Conclusion

The effect of the duration of raised ICP on neurodevelopment is obviously difficult to quantify. The fact, however, that psychomotor development correlates well with the progress of myelination, and that ICP clearly shows significant correlation with both the progress of myelination and psychomotor develop-

ment, confirms that raised ICP is an important factor which negatively affects the progress of myelination in infantile hydrocephalus.

Little is known about the relationship between raised ICP and long-term outcome in children. The results of recent studies suggest, however, that there is a distinct correlation between ICP and neurodevelopmental outcome in hydrocephalic infants. The CSF volume or size of the ventricles seems to be less important regarding the progress of myelination and neurodevelopment in these infants.

A decrease in ICP leads to progress and recovery of myelination and an improvement in neurodevelopment. The treatment of patients with infantile hydrocephalus, therefore, may benefit from intensive non-invasive ICP monitoring, in order to prevent secondary brain parenchymal damage, which is expressed in delayed myelination. Further research to reveal other factors that may influence the process of myelination, in particular the duration of raised ICP, is necessary. The predictive value of the early progress of myelination for truly long-term outcome (school performance, fine motor skills) has yet to be established.

References

1. Barkovich AJ: Normal development of the neonatal and infant brain. In: Barkovich AJ (ed) *Pediatric neuroimaging*. Raven Press, New York, pp 5-34, 1990
2. Barkovich AJ, Kjos BO, Jackson DE, et al: Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology* 166: 173-180, 1988
3. Bayley N: *Bayley scales of infant development*. Psychological Corporation, New York, 1969
4. Benda CE: Mongolism. In: Minkler J (ed) *Pathology of the nervous system*. McGraw-Hill, New York, pp 1361-1371, 1971
5. Benes FM: Myelination of cortical hippocampal relays during late adolescence. *Schizophrenia Bull* 15: 585-593, 1989
6. Bird CR, Hedberg M, Drayer BP, et al: MR assessment of myelination in infants and children: usefulness of marker sites. *AJNR Am J Neuroradiol* 10: 731-740, 1989
7. Blackburn BL, Fineman RM: Epidemiology of congenital hydrocephalus in Utah, 1940-1979: Report of an iatrogenically related "epidemic". *Am J Med Genet* 52: 123, 1994
8. Brody BA, Kinney HC, Kloman AS, Gilles FH: Sequence of central nervous system myelination in human infancy. I. An autopsy study of myelination. *J Neuropathol Exp Neurol* 46: 283-301, 1987
9. Chase HP: The effects of intrauterine and postnatal undernutrition on normal brain development. *Ann NY Acad Sci* 205: 231-244, 1973
10. Chumas PD, Drake JM, Del Bigio MR, et al: Anaerobic glycolysis preceding white matter destruction in experimental neonatal hydrocephalus. *J Neurosurg* 80: 491-501, 1994
11. Damska M, Laure-Kamionowska M: Myelination as a parameter of normal and retarded brain maturation. *Brain Dev* 12: 214-220, 1990
12. Del Bigio MR: Neuropathological changes caused by hydrocephalus. *Acta Neuropathol* 85: 573-585, 1993
13. Del Bigio MR, Da Silva MC, Drake JM, et al: Acute and chronic cerebral white matter damage in neonatal hydrocephalus. *Can J Neurol Sci* 21: 299-305, 1994
14. Del Bigio MR, Kanfer JN, Zhang YW: Myelination delay in the cerebral white matter of immature rats with kaolin-induced hydrocephalus is reversible. *J Neuropathol Exp Neurol* 56: 1053-1066, 1997
15. Di Rocco C, Caldarelli M, Ceddia A: "Occult" hydrocephalus in children. *Child's Nerv Syst* 5: 71-75, 1989
16. Fennell E, Hagberg G, Hagberg B: Infantile hydrocephalus: the impact of enhanced preterm survival. *Acta Paediatr* 79: 1080-1086, 1990
17. Fennell E, Hagberg G, Hagberg B: Infantile hydrocephalus epidemiology: An indicator of enhanced survival. *Arch Dis Child Fetal Neonatal Ed* 70: 123-128, 1994
18. Flechsig P: Developmental (myelogenetic) localisation of the cerebral cortex in the human subject. *Lancet* 2: 1027-1029, 1901
19. Flechsig P: *Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage*. Thieme, Leipzig, 1920
20. Fletcher JM, McCauley SR, Brandt ME, et al: Regional brain tissue composition in children with hydrocephalus. Relationships with cognitive development. *Arch Neurol* 53, 549-557, 1996
21. Fujii Y, Konishi Y, Kuriyama M, et al: MRI assessment of myelination patterns in high risk infants. *Pediatr Neurol* 9: 194-197, 1993
22. Gadson DR, Variend S, Emery JL: The effect of hydrocephalus upon the myelination of the corpus callosum. *Eur J Pediatr Surg* 25: 311-317, 1978
23. Gadson DR, Variend S, Emery JL: Myelination of the corpus callosum. II. The effect of relief of hydrocephalus upon the processes of myelination. *Eur J Pediatr Surg* 28: 314-321, 1979
24. Grodd W: Normal and abnormal patterns of myelin development of the fetal and infantile human brain using magnetic resonance imaging. *Curr Opin Neurol Neurosurg* 6: 393-397, 1993
25. Guidetti B, Occhipinti E, Riccio A: Ventriculo-atrial shunt in 200 cases of non-tumoral hydrocephalus in children: remarks on the diagnostic criteria, postoperative complications and long-term results. *Acta Neurochir* 21: 295-308, 1969
26. Guit GL, Bor M van de, Ouden L den, et al: Prediction of neuro-developmental outcome in the preterm infant: MR-staged myelination compared with cranial US. *Radiology* 175: 107-109, 1990
27. Hanlo PW: Non-invasive intracranial pressure monitoring in infantile hydrocephalus and the relationship with transcranial Doppler, myelination and outcome. Thesis, Utrecht, The Netherlands, 1995
28. Hanlo PW, Gooskens RHJM, Faber JA, et al: Relationship between anterior fontanelle pressure measurements and clinical signs in infantile hydrocephalus. *Child's Nerv Syst* 12: 200-209, 1996
29. Kaiser AM, Whitelaw AGL: Intracranial pressure estimation by palpation of the anterior fontanelle. *Arch Dis Child* 62: 516-517, 1987
30. Kinney HC, Brody BA, Kloman AS, et al: Sequence of central nervous system myelination in human infancy. II. Pat-

- terns of myelination in autopsied infants. *J Neuropathol Exp Neurol* 47: 217-234, 1988
31. Kirkpatrick M, Engleman H, Minns RA: Symptoms and signs of progressive hydrocephalus. *Arch Dis Child* 64: 124-128, 1989
 32. Konishi Y, Hayakawa K, Kuriyama M, et al: Developmental features of the brain in preterm and fullterm infants on MR imaging. *Early Hum Dev* 34: 155-162, 1993
 33. Langworthy OR: Development of behavior patterns and myelination of the nervous system of the human fetus and infant. *Contrib Embryol Carnegie Inst* 24: 3-57, 1933
 34. Leviton A, Gilles F: Ventriculomegaly, delayed myelination, white matter hypoplasia, and periventricular leukomalacia: how are they related? *Pediatr Neurol* 15: 127-136, 1996
 35. Longatti PL, Canova G, Guida F, et al: The myelin basic protein: a reliable marker of actual cerebral damage in hydrocephalus. *J Neurosurg Sci* 37: 87-90, 1993
 36. Maezawa M, Seki T, Imura S, et al: Magnetic resonance signal intensity ratio of gray/white matter in children. Quantitative assessment in developing brain. *Brain Dev* 15: 198-204, 1993
 37. Maixner WJ, Morgan MK, Besser M, et al: Ventricular volume in infantile hydrocephalus and its relationship to intracranial pressure and cerebrospinal fluid clearance before and after treatment. A preliminary study. *Pediatr Neurosurg* 16: 191-196, 1991
 38. Martin E, Kikinis R, Zuerer M, et al: Developmental stages of human brain: an MR study. *J Comput Assist Tomogr* 12: 917-922, 1988
 39. Martin E, Boesch C, Zuerer M, et al: MR imaging of brain maturation in normal and developmentally handicapped children. *J Comput Assist Tomogr* 14: 685-692, 1990
 40. McAllister II JP, Chovan P: Neonatal hydrocephalus. Mechanisms and consequences. *Neurosurg Clin North Am* 9: 73-93, 1998
 41. Minns RA, Goh D, Pye SD, et al: A volume-blood flow velocity response (VFR) relationship derived from CSF compartment challenge as an index of progression of infantile hydrocephalus. In: Matsumoto S, Tamaki N (eds) *Hydrocephalus: pathogenesis and treatment*. Springer, Tokyo, Berlin Heidelberg, pp 270-278, 1991
 42. Oi S, Ijichi A, Matsumoto S: Immunohistochemical evaluation of neuronal maturation in untreated fetal hydrocephalus. *Neurol Med Chir* 29: 989-994, 1989
 43. Peters RJA, Hanlo PW, Gooskens RHJM, et al: Non-invasive ICP monitoring in infants: the Rotterdam Teletransducer revisited. *Child's Nerv Syst* 11: 207-213, 1995
 44. Rubin RC, Hochwald GM, Tiell M, et al: Hydrocephalus: I. Histological and ultrastructural changes in the pre-shunted cortical mantle. *Surg Neurol* 5: 109-114, 1976
 45. Rubin RC, Hochwald GM, Tiell M, et al: Hydrocephalus: II. Cell number and size, and myelin content of the pre-shunted cerebral cortical mantle. *Surg Neurol* 5: 115-118, 1976
 46. Sato H, Sato N, Tamaki N, et al: Threshold of cerebral perfusion pressure as a prognostic factor in hydrocephalus during infancy. *Child's Nerv Syst* 4: 274-278, 1988
 47. Squires LA, Krishnamoorthy KS, Natowicz MR: Delayed myelination in infants and young children: radiographic and clinical correlates. *J Child Neurol* 10: 100-104, 1995
 48. Staudt M, Schropp C, Staudt F, et al: Myelination of the brain in MRI: a staging system. *Pediatr Radiol* 23: 169-176, 1993
 49. Takashima S, Becker LE: Developmental neuropathology in bronchopulmonary dysplasia: alteration of glial fibrillary acidic protein and myelination. *Brain Dev* 6: 451-457, 1984
 50. Tilney F, Casamajor L: Myelinogeny as applied to the study of behavior. *Arch Neurol Psychiatry* 12: 1-66, 1924
 51. van der Knaap MS, Valk J: MR imaging of the various stages of normal myelination during the first year of life. *Neuroradiology* 31: 459-470, 1990
 52. van der Knaap MS, Valk J, Bakker CJ, et al: Myelination as an expression of the functional maturity of the brain. *Dev Med Child Neurol* 33: 849-857, 1991
 53. van der Knaap MS, Bakker CJ, Faber JA, et al: Comparison of skull circumference and linear measurements with CSF volume MR measurements in hydrocephalus. *J Comput Assist Tomogr* 16: 737-743, 1992
 54. van der Meulen BF, Smrkovsky M: Handleiding MOS 2.5-8.5, McCarthy Ontwikkelings Schalen. Swets and Zeitlinger, Lisse, 1986
 55. Villani R, Tomei G, Gaini SM, et al: Long-term outcome in aqueductal stenosis. *Child's Nerv Syst* 11: 180-185, 1995
 56. Vogt O: Quelques considérations générales sur la myelo-architecture du lobe frontal. *Rev Neurol* 20: 405-420, 1910
 57. Von Monakow C: Über die Projections- und die Associationszentren im Grosshirn. *Monatschr Psychiatrie* 8: 405-420, 1900
 58. Vries LS de, Dubowitz LMS, Pennock JM, et al: Extensive cystic leukomalacia: correlation of cranial ultrasound, magnetic resonance imaging and clinical findings in sequential studies. *Clin Radiol* 40: 158-166, 1989
 59. Wiggins RC: Myelin development and nutritional insufficiency. *Brain Res Rev* 4: 151-175; 1982
 60. Wisniewski KE, Schmidt-Sidor B: Postnatal delay of myelin formation in brains from Down syndrome infants and children. *Clin Neuropathol* 8: 55-62, 1989
 61. Yakovlev PI, Lecours AR: The myelogenetic cycles of regional maturation of the brain. In: Minkowski A (ed) *Regional development of the brain in early life*. Blackwell, Oxford, pp 3-70, 1967

Posthemorrhagic Hydrocephalus of Prematurity

FREDERICK A. BOOP

Introduction

While improvements in the resuscitation and management of the premature neonate have led to increased survival among very-low-birth-weight infants, brain damage related to intraventricular hemorrhage of prematurity (IVHP) continues to account for significant health care expenditure in the United States. It has been estimated that in 1992 dollars, \$7.4 billion was spent in caring for survivors of low birth weight within the United States. Although advances in neonatal care have markedly reduced the mortality of 24- to 28-week-gestation infants, a parallel reduction in the neurodevelopmental morbidity associated with survival has not been recognized [11].

Epidemiology

With approximately four million births occurring annually in the United States, it can be estimated that 50 000 very-low-birth-weight infants will be born yearly [49]. Studies from a decade ago anticipated that one-third to one-half of these infants would suffer IVHP; however, a number of factors have served to effectively lower the incidence of IVHP since that time [8, 32, 42]. More recent studies have demonstrated that, with current management, only 20%, or 10 000 infants in the United States, will suffer an IVH annually. Of those infants suffering an IVH, 20%-74%, depending upon the study, will go on to develop posthemorrhagic hydrocephalus [43]. Factors associated with the reduction in IVHP as well as management options for those infants developing PHH will be discussed below.

Pathophysiology of IVHP

Intracranial hemorrhage in the very-low-birth-weight infant most commonly occurs in the germi-

nal matrix (Fig. 1). This is a specialized tissue in the subependymal region of the developing brain located near the head of the caudate nucleus at the level of the foramen of Monro. In early gestation (10-20 weeks' gestation), the germinal matrix is the site of pluripotential neural stem cells giving rise to neuroblasts, which migrate along radial glia to their appropriate cortical layer. In the third trimester, however, these stem cells are primarily responsible for forming glioblasts, which will give rise to macroglia and oligodendrocytes. The germinal matrix remains well developed through approximately 34 weeks' gestation, then gradually involutes and is virtually gone by term. The germinal matrix vascular supply is comprised of large irregular vessels with a poorly developed basement membrane and little stromal support. These vessels serve as a watershed for the periventricular medullary veins and do not have much of an intima or media. Furthermore, in the developing brain, autoregulation is also just developing. Therefore, systemic alterations in blood pressure and blood flow may directly impact on these delicate vessels, resulting in hemorrhage [45].

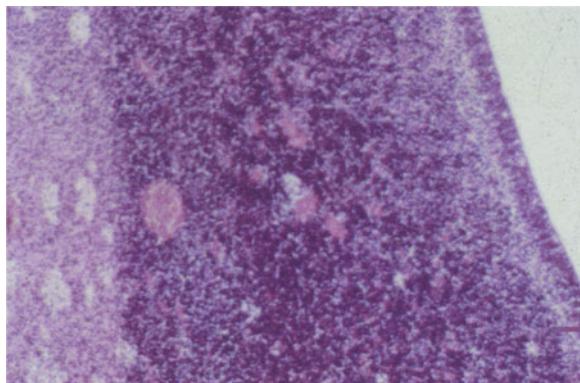


Fig. 1. Hemorrhage of the germinal zone

¹ Department of Neurosurgery/Pediatric Neurosurgery, Semmes-Murphy Clinic, Memphis, Tennessee, USA

A second area in which neonatal autoregulation is poorly developed is within the choroid plexus. Although hemorrhage within the choroid plexus accounts for only a small percentage of IVHP, it is a common site of origin for spontaneous hemorrhage within the brain of the *term* neonate [7].

When hemorrhage occurs within the germinal matrix, the tissue containing these neural stem cells is commonly destroyed. Destruction of the matrix, in turn, leads to cystic degeneration of the involved region of brain. The infarcted brain tissue is then replaced by a small cystic cavity lined with hemosiderin and gliosis [49].

In approximately 15% of infants suffering IVHP, a much larger area of hemorrhagic white matter infarction is seen. This is typically above and lateral to the lateral ventricle and is characteristically asymmetrical (Fig. 2). Two-thirds of these lesions will be unilateral. These lesions, termed “periventricular hemorrhagic infarction” (PHI), are often mistakenly thought

to represent direct extension of the intraventricular hemorrhage into the white matter. Careful pathological analysis has shown, however, that these fan-shaped hemorrhages closely follow the distribution of the periventricular medullary veins and represent, in fact, venous infarction of the periventricular white matter. These lesions are radiographically distinguishable from the less common secondary areas of periventricular leukomalacia (PVL) in that the PVL is usually symmetrical, nonhemorrhagic, and presumably secondary to periventricular white matter ischemia. In the case of PVL, the IVH is believed to cause distention of the lateral ventricles. Positron emission tomography studies of infants with IVH have demonstrated ischemia of the subventricular white matter tracts [46].

It has been postulated that PHI occurs when a germinal matrix hemorrhage or IVHP causes local mass effect, thus compressing the terminal veins near the venous angle. This, in turn, causes a secondary hemorrhagic venous infarction [17, 50]. This hypothesis is supported by the fact that the peak time for noting these periventricular hemorrhages is on the 4th postnatal day, a time during which 90% of IVHP have already occurred.

Another consequence of IVHP, and the subject of this chapter, is posthemorrhagic hydrocephalus (PHH). PHH has been presumed to develop as a consequence of the breakdown of blood products and cellular debris within the ventricular system. These blood products in turn cause chemical arachnoiditis and a fibrotic reaction within the ventricles and the arachnoid granulations, leading to granular ependymitis and adhesive arachnoiditis. Most commonly, this leads to hydrocephalus by scarring the posterior fossa subarachnoid spaces [50]. In some instances, this may also be of sufficient magnitude to obstruct the aqueduct of Sylvius or the arachnoid granulations (Fig. 3).

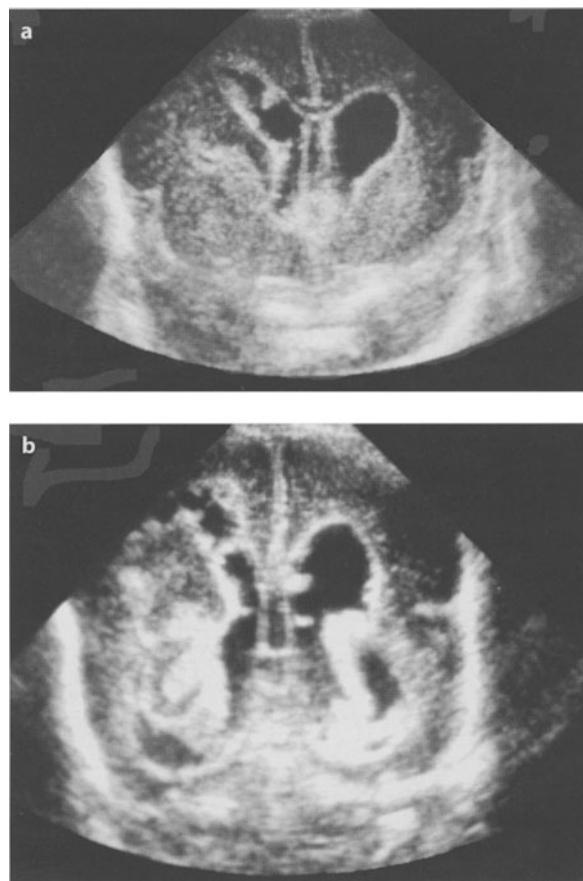


Fig. 2a, b. Transaxial view of the frontal horns of the lateral ventricle. Note clot within the ventricles with hemorrhagic infarction of the periventricular white matter (PHI) and marked hydrocephalus



Fig. 3. Posthemorrhagic hydrocephalus: note the clots in the ventricular systems and the obstruction of the aqueduct

Clinical Presentation

Most studies of IVHP agree that the incidence is highest in infants weighing less than 1500 g at birth. The lower the birth weight, the higher the likelihood of IVHP. Also, the lower the birth weight, the worse the hemorrhage is likely to be. Beverley et al. have shown that 50% of IVH will occur within the first 8 h after birth [4]. In many instances, IVH may be clinically silent. In view of this, some authors advocate routine head ultrasound studies in any infant born at less than 34 weeks' gestation [9], while others advocate ultrasound for any infant weighing less than 1500 g at birth. Clinical events suggestive of IVH may include a sudden alteration in vital signs, particularly if accompanied by bradycardia or apnea, a sudden unexplained drop in hematocrit, or neonatal seizures. A bulging fontanelle, separation of the sutures, or a rapidly increasing head circumference may suggest the development of acute hydrocephalus

[22]. When IVHP is suspected, repeat ultrasonography has been shown to be both sensitive and specific. Most centers use the grading scale of Papile, in which IVHP as seen on ultrasound is graded on a scale of I-IV [30]. A grade I hemorrhage is defined as a small bleed confined to the germinal matrix (Fig. 4). A grade II hemorrhage has extension into the ventricle (Fig. 5). A grade III hemorrhage is associated with dilatation of the ventricle (Fig. 6), and a grade IV hemorrhage not only shows ventriculomegaly, but involvement of the periventricular white matter (Fig. 2). This grading scale has been shown to be of prognostic significance for both mortality and neurodevelopmental outcome [33].

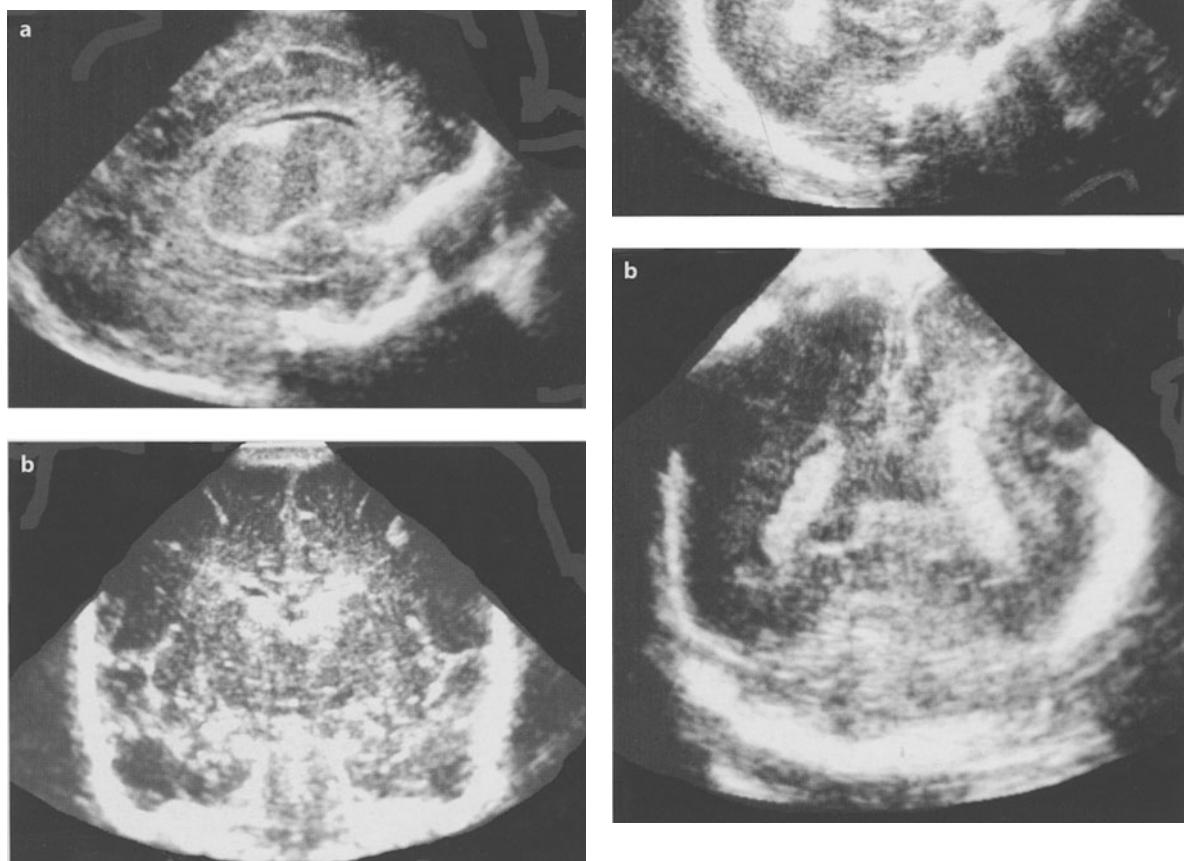


Fig. 4a, b. Right sagittal and coronal ultrasound images of a Papile grade I subependymal hemorrhage. Note hyperechoic signal in the region beneath the ventricle

Fig. 5a, b. Right sagittal and coronal ultrasound images of a Papile grade II intraventricular hemorrhage. Note extension of the hemorrhage through the ependyma and into the lateral ventricle. The ventricle remains small, without evidence of hydrocephalus

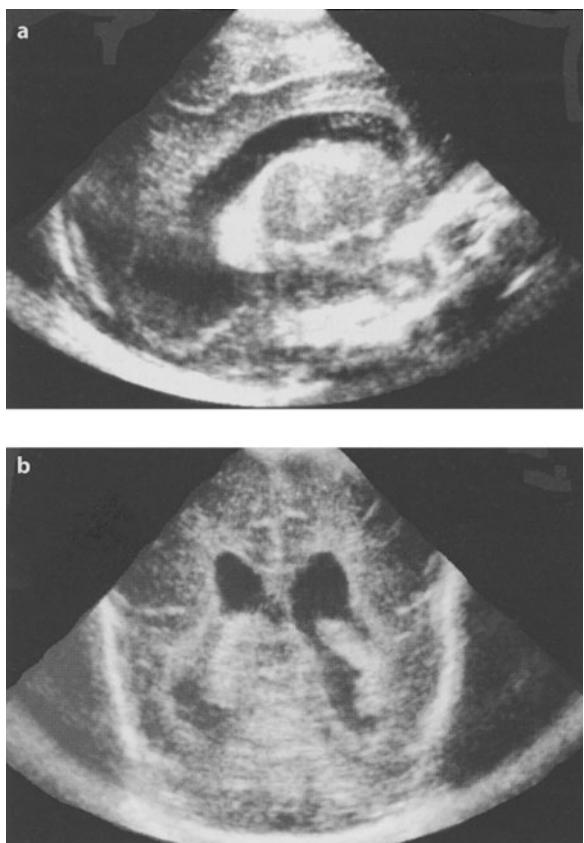


Fig. 6a, b. Right sagittal and coronal ultrasound images of a Papile grade III intraventricular hemorrhage. Note extension of the hemorrhage into the ventricle with the interval development of hydrocephalus

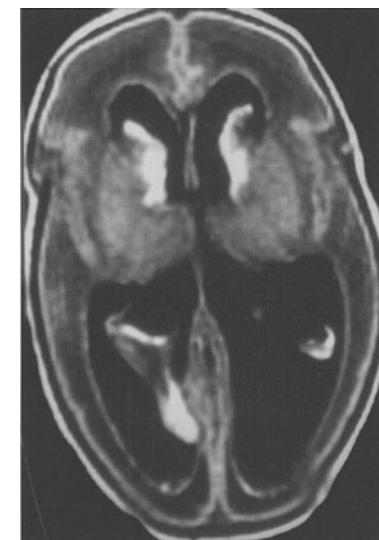


Fig. 7. MRI showing intraventricular hemorrhage and hydrocephalus

Among those infants suffering IVHP, the incidence of PHH is reported to vary from 25% to 74% (Fig. 7). As mentioned, the pooling of intraventricular blood and hemorrhagic debris within the ventricular system most commonly causes obliterative arachnoiditis of the posterior fossa, although obstruction of the aqueduct of Sylvius or of one foramen of Monro may also be seen [24]. When this occurs, the neonate will typically present with a rapidly increasing head circumference, lethargy, apnea, and bradycardia. Vomiting may be noted. When this occurs, intervention becomes necessary. By contrast, slow enlargement of the ventricles on follow-up ultrasound studies in the absence of a growing head or clinical symptoms of raised intracranial pressure may represent loss of brain volume from periventricular ischemia (Fig. 8). This may represent not necessarily progressive hydrocephalus, but an ex vacuo phenomenon that may require no intervention. Having said this, Volpe et al. have demonstrated on ultra-

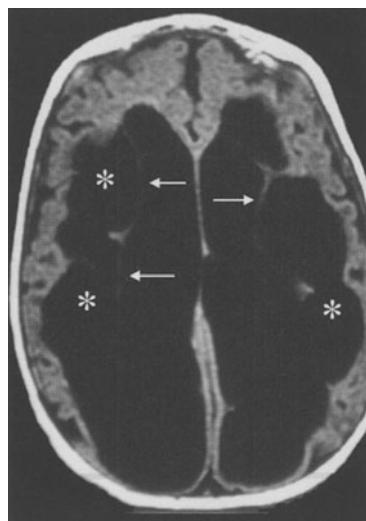


Fig. 8. Periventricular leukomalacia. Arrows show the ependymal layer, asterisks show the area of white matter damage

sound studies that ventricular enlargement generally precedes an increase in head growth in infants developing PHH [44]. Some authors have advocated recording flow velocities and the resistance to flow by transcranial Doppler ultrasonography as a means of monitoring cerebral perfusion pressure in these infants (Fig. 9) [6, 10, 35].

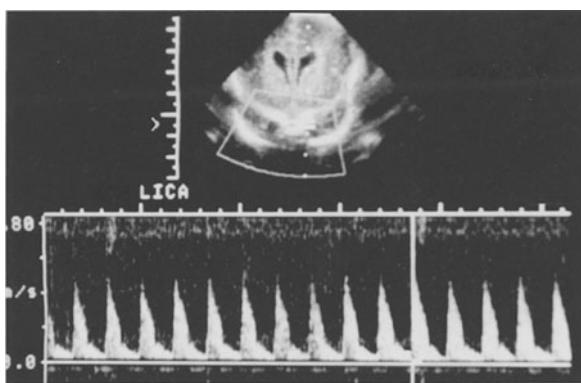


Fig. 9. Transcranial Doppler flow study of the left internal carotid artery (*LICA*) demonstrating flow velocity. The resistive index (RI) is the systolic flow minus the diastolic flow divided by the systolic flow times 100. This value correlates with cerebral perfusion pressure and usually declines steadily over the first few months of life. If the value is increasing, it supports the diagnosis of hydrocephalus

Reducing Risk

Volpe et al. have pointed out that since the most common association of IVHP is premature delivery, the most effective prevention strategy would be aimed at halting premature labor. Beyond this, a number of factors have been noted to impact upon the survival of the low-birth-weight infant. It has been noted, for example, that transportation of the premature infant in utero and the mother to a perinatal center specializing in high-risk deliveries is associated with a much lower incidence of IVHP than is seen in infants transported after delivery [47]. It has also been said that low forceps and cesarean section may reduce the incidence of IVH, although this has not been proven in randomized controlled trials. Nonetheless, prolonged labor and breech delivery are two factors clearly associated with increased risk to the premature infant.

Prenatal interventions may also influence the incidence of IVHP. Preterm infants exhibit 30%-60% of the normal adult level of vitamin K-dependent coagulation factors, and prenatal administration of intramuscular vitamin K to the mother has been shown to reduce the risk of hemorrhage. In one study, the incidence of IVHP in infants whose mothers had received vitamin K at least 4 h before delivery was 5%, compared to 33% in those infants whose mothers had not received the treatment [34].

Similarly, at least three prospective studies have looked at the prenatal administration of phenobarbital as a means of reducing IVHP. In the prospective, randomized trial of Morales and Koerten, which included 150 women, those infants of mothers who had

received phenobarbital had a 21% incidence of IVHP, versus 47% among those whose mothers had not. Of those in the phenobarbital group, 5% had severe bleeds, compared to 13% in the control group [26].

Stable xenon studies of the neonatal circulation have suggested that, in premature infants, autoregulation is poorly developed and the periventricular circulation is pressure-passive [20]. Because of this, alterations in systemic blood pressure and flow may be directly transmitted to the friable vessels within the germinal matrix. It is no wonder, then, that the three most notable factors predisposing to IVHP at parturition are birth trauma, hypoxemia, and hypercarbia [42]. Thus, the elimination of factors contributing to increases and fluctuations in cerebral blood flow have had a major impact on the reduction of IVHP. For example, the widespread use of surfactant has reduced the incidence of hyaline membrane disease and pulmonary hypertension, thus reducing the risk of IVHP. The study of Perlman et al. looked at blood pressure and flow variations in premature infants in relation to risk of hemorrhage. In this study of intubated premature neonates, those infants who were maintained on pancuronium were able to maintain a relatively steady blood pressure and flow. In this group, 7 out of 27 suffered IVHP. In the second group, infants who attempted to breathe in resistance to the ventilator demonstrated significant lability in their blood pressure, which, in the pressure-passive cerebral arterioles, is directly transmitted to the germinal matrix. In this group, 21 of 23 infants suffered IVH. This being the case, it is now recommended that premature infants be maintained on paralytics and sedation through the at-risk period (first 72 h following birth) [31].

Ethamsylate is a medication that has been shown in several prospective randomized controlled trials to reduce the risk of IVHP. The mechanism of action remains unclear. Ethamsylate has been shown to polymerize hyaluronic acid, which may promote platelet adherence or may strengthen the capillary basement membrane. It also has been shown to inhibit prostaglandin synthesis [47]. In the study of Ment et al., looking at the effects of ethamsylate on IVHP in the beagle puppy model, the drug was shown to reduce the incidence of IVHP on the basis of its effects upon cerebral blood flow [25]. In the clinical trial of Morgan et al., 70 infants were given ethamsylate and compared to a matched control group. In this study 26% of the treated group, compared to 51% of the control group, suffered IVHP, although there was no difference in the number of infants suffering severe IVHP [27]. In the study of Behrman, a similar decrease in IVHP was noted in the treated group. In this trial, only 10% of treated infants suffered severe IVHP, compared to 32% in the control group [2]. In the largest study, by Benson et

al., 162 treated infants and 168 control infants were followed, with a 24% incidence of IVHP in the treated group versus 36% in controls. Thus, these three studies have demonstrated safety and efficacy of ethamsylate in reducing the incidence of IVHP and severe IVHP in preterm infants [3].

Development of Hydrocephalus

Hydrocephalus can be defined as ventricular expansion due to an imbalance between the production and absorption of cerebrospinal fluid (CSF). From a practical standpoint, it is due to elevated intraventricular pressure and an increased amount of intracranial CSF. The likelihood of developing PHH is directly related to the severity of the preceding IVHP [39]. As mentioned above, the grading scale of Papile, which has now become widely adopted, offers prognostic implications both for the development of PHH and for developmental outcome [30, 33]. By definition, infants suffering a grade I or II hemorrhage do not have hydrocephalus. Of the grade III and IV infants, there appears to be wide variability in the incidence of shunt requirement, suggesting that the definition of progressive hydrocephalus may vary from one institution to another. For example, in the study of Levy et al., 72 preterm infants were followed from birth to 16 years of age. Of those, only 6 patients showed resolution of their hydrocephalus and were able successfully to avoid a shunt [18]. On the other hand, the study of Ment et al. followed 52 patients with IVH, 45% of whom demonstrated ventriculomegaly, but only 5 of whom required shunts for progressive symptoms [24]. Some of this controversy will, hopefully, be clarified below.

Pathophysiology of PHH

Pathological studies of infants with PHH suggest that ventriculomegaly may occur in nearly half of them, but that this may not necessarily represent a progressive pressure-related phenomenon. Ventricular dilatation may be an ex vacuo phenomenon related to loss of brain substance as a result of venous infarction or periventricular white matter ischemia. In those infants suffering hypoxic-ischemic encephalopathy (HIE), the loss of brain volume may be even more widespread [13]. In such instances one may see progressive ventricular enlargement on serial imaging studies, but this is a low-pressure phenomenon associated with a soft anterior fontanelle, overriding su-

tures, and failure of head growth. In some instances, the clinician may see a combination of volume loss and slowly progressive hydrocephalus, making it difficult to determine clinically whether to place a shunt or to follow the infant. The decision to place a shunt is not always straightforward. This may account for some of the variability in the incidence of shunting from one institution to the next [39].

PHH is generally defined by progressive ventriculomegaly associated with a full anterior fontanelle, separation of the cranial sutures, and an accelerated rate of head growth compared to published normative values. This may be associated with clinical symptoms of raised intracranial pressure such as vomiting, lethargy, and episodic apnea or bradycardia [22]. Studies of CSF flow in such infants suggest that, following IVHP, the most common cause of progressive hydrocephalus is obliterative arachnoiditis occurring in the posterior fossa and preventing CSF from circulating over the cerebellum to gain access to the arachnoid granulations. This would explain why, in most cases, the increased intracranial pressure and full fontanelle can be temporarily ameliorated with lumbar punctures [39]. In some infants, however, lumbar puncture is unsuccessful. It has thus been recognized that, in some instances, infants with PHH have developed an acquired aqueductal stenosis related to blood clot within the third ventricle and aqueduct. This has implications both for the immediate management of such an infant as well as for the long-term management of the hydrocephalus.

Treatment

Medical

Once progressive hydrocephalus is recognized in the infant suffering IVHP, treatment must be implemented. Although CSF diversion is effective, such surgery is generally not recommended immediately. First of all, in a certain percentage of infants, the hydrocephalus may be transient and may resolve as the intraventricular blood breaks down or is removed. In many instances, the infant is too unstable or physically too small to allow immediate placement of a ventriculoperitoneal (VP) shunt. In such cases, treating the infant by alternative methods is crucial.

A number of temporizing schemes have been attempted in these infants, including head wrapping, intravenous glycerol, isosorbide, and acetazolamide coupled with a loop diuretic. Of these, the combination of acetazolamide and furosemide has shown the

most promise [12]. The daily administration of acetazolamide and furosemide has been shown to decrease the rate of CSF production, thus controlling the hydrocephalus in some instances. In the study of Shinhar et al., for example, 49 infants with ventriculomegaly following IVHP were studied. Of these, 16 suffered PHH. Infants were treated with acetazolamide therapy initiated at a dose of 25 mg/kg per day and gradually increased to a maximum dose of 100 mg/kg per day. Furosemide was given simultaneously at a dose of 1 mg/kg per day. As the acetazolamide can cause acid-base disturbances, base replacement was initiated with a systemic alkalizing agent (Polycitra) at 8 mEq/kg per day. In this study, the authors felt that they were able to avoid shunts in 7 of the 16 infants with PHH [40].

Controversy remains over the value of serial lumbar punctures in the management of PHH [21, 30]. There is no doubt that serial lumbar punctures can temporarily control hydrocephalus in most infants. In the study of Kreusser et al., serial lumbar punctures were attempted in 16 infants and were successful in 12 but not so in 4 [16]. This suggests that in 4 of the 16 ventricular obstruction by the blood clot was present. Other studies, such as the prospective randomized controlled trial of Anwar et al., have supported lumbar punctures as a temporary management option but have shown no difference in the long-term development of PHH or the need for shunting in the treated group versus controls [1]. The prospective randomized controlled studies of the Ventriculomegaly Trial Group looked at neurodevelopmental outcome in neonates managed by serial lumbar punctures versus controls. These studies followed 157 infants for up to 30 months and found no difference in developmental outcomes between the groups and a 7% incidence of meningitis in the infants undergoing serial lumbar punctures. The group concluded that serial lumbar puncture cannot be recommended in the management of PHH [52, 53].

Surgical

One of the standard surgical techniques for managing PHH in the infant too small for a shunt has been by serial ventricular taps. For infants in whom the ventricles do not communicate with the lumbar theca, infants who are too unstable to tolerate a lateral decubitus position, or those in whom lumbar punctures are not feasible, ventricular taps are effective for the temporary control of PHH. With this technique, a 23-gauge butterfly needle is introduced into the lateral ventricle through the coronal suture at the level of the mid-pupillary line. Ten milliliters of CSF per kilo-

gram of body weight are usually withdrawn at each tap. Taps are repeated as often as necessary. The disadvantage of this technique is that it requires repeated perforations of the frontal cortex. To what degree this damages the cortex or predisposes to epilepsy and other complications is speculative [9].

To avoid repeated punctures of the brain, many authors advocate placement of a ventricular access device (VAD) with a prefixed ventricular catheter attached to a subcutaneous plastic reservoir that can be aspirated percutaneously on a long-term basis [23]. In the study of Hudgins et al., 149 infants with PHH were treated in this fashion. In this large series, 20% required revision, 15 for occlusion by clot, 9 for a trapped contralateral ventricle, and 7 for infection. The overall infection rate was 8%; in five infants with infections, the infection was cleared with a combination of systemic and intrathecal antibiotics. Eighty-eight percent of the infants in this study went on to require a VP shunt [15].

Most infants with a VAD may require taps once every 2-3 days. Occasionally an infant will become rapidly symptomatic and may require taps as often as twice daily. In such cases, some authors advocate the use of temporary external ventricular drainage (EVD) [51]. This has the added advantage of maintaining a constant intraventricular pressure, whereas temporary drainage alternates between very high and very low intraventricular pressure. In the study of Rhodes et al., 37 infants with PHH were managed with EVDs. These were placed at the bedside in the neonatal intensive care unit and maintained for an average of 21 days. Twenty-seven of the EVDs had to be replaced because of occlusion with clot. Ten percent of infants demonstrated apnea when the device was inserted, 8% experienced hemorrhage, and 6% developed ventriculitis. Although the mortality in this study was 27%, in no instance was death related to the EVD. Seventeen of the 27 survivors went on to require a VP shunt [38].

Studies of fibrinolytics in the management of IVHP have shown some promise. The experimental work of Pang et al., looking at the lysis of intraventricular clot in a canine model, demonstrated more rapid resolution of the hemorrhage and less ventriculomegaly in those animals receiving intraventricular urokinase as compared to control animals [28, 29]. Based upon this work, Hudgins et al. conducted a prospective trial of intraventricular urokinase in 18 preterm infants with VADs in place. The infants were divided into a low-dose and high-dose treatment group, both of which received intraventricular urokinase through the VAD twice daily for 7 days. No infant had a hemorrhagic complication during treatment, demonstrating the safety of the use of urokinase. The authors were able to demonstrate earlier resolution of

the intraventricular clot by the introduction of urokinase. Although the numbers were quite small, the infants receiving low-dose therapy had a significantly lower requirement for shunting than both the high-dose group and historical controls [14].

Another temporizing measure for PHH is the subgaleal shunt. In such instances, a VAD such as a Rickham reservoir is placed with the distal limb left open to drain into a large subgaleal pocket created at the time of placement of the device. The CSF under pressure drains through this stent, thus distending the scalp and allowing absorption of CSF by the galea. Some authors advocate placement of a low-pressure flushing device under the galea such that CSF can be pumped manually into the subgaleal pocket [36]. This technique has the advantage of maintaining a fairly constant and low intracranial pressure in most cases without requiring intermittent tapping. In those few infants in whom CSF production exceeds the absorptive capability of the subgaleal space, intermittent taps of the pocket may be required. In the study of Sklar et al., 62 infants were treated in this fashion. In this series, there was one treatment-related death and a 10% infection rate. Thirty-nine infants went on to require a permanent shunt [41].

VP Shunts

As has been shown in most of the studies on temporary measures to treat PHH, regardless of the method, somewhere between 10% and 35% of infants will show resolution of their hydrocephalus as their IVH resolves and as intraventricular protein and debris return to normal. In the majority of infants, however, the hydrocephalus appears long-lasting. Whether this relates to scarification of the arachnoid granulations, adhesive arachnoiditis of the posterior fossa, or obstruction at the level of the aqueduct of Sylvius depends upon the individual. Whichever is the case, when this occurs a more permanent treatment of the hydrocephalus is required. At nearly all centers, this means conversion of the temporary treatment to a VP shunt. Although CSF diversion to other body cavities may be necessary in specific instances, 90% of infants with persistent PHH will be treated with a VP shunt. This shunt has the advantage of longevity in that extra tubing can be placed within the peritoneum to allow for rapid growth in the first years of life. The peritoneum is also relatively forgiving in cases of infectious complications.

Controversy remains over the most appropriate time for placement of the VP shunt. Most pediatric neurosurgical centers would use temporary measures in the very-low-birth-weight infant (< 800 g)

until it is relatively certain that the infant is going to survive. Similarly, most will use temporary measures until certain that any systemic medical problems such as sepsis, pulmonary difficulties, or hemodynamic instability have been treated and that the child is medically stable enough to undergo a general anesthetic and the stress of surgery. Thirdly, it may be seen from the aforementioned studies that ventricular catheters placed in the presence of acute hemorrhage, whether for external ventricular drainage or for intermittent VAD taps, will occlude in 20%-60% of infants. Debate continues, however, as to when it is safe to place a shunt without an inordinate risk of malfunction. Most pediatric neurosurgeons will continue temporizing measures until the CSF protein is under 300 mg% and the CSF has turned from tea-colored to xanthochromic. Finally, debate continues over the appropriate size an infant must achieve prior to placement of a shunt. Many authors suggest the infant must weigh 1500 g before shunting. At Boston Children's Hospital the neurosurgeons prefer the infant to weigh 1750 g [9]. Others have reported no increased complications in placing shunts at 1000 g. Again, if two-thirds of the infant's total body weight is in the head, one might want to make sure there is enough subcutaneous tissue to tolerate the shunt tubing without erosion. We prefer to wait until the infant is at least 1400 g and the CSF protein is less than 500 mg% before placing a shunt. Definitive studies as to the optimal timing of shunt placement in this population remain outstanding.

Complications

Several studies have pointed out that the malfunction and infection rates for infants shunted within the first 6 months of life are higher than in older children and adults. In the study of Boynton et al., early shunting was attempted in the treatment of premature infants with PHH. The authors demonstrated an average of 4.2 shunt revisions per patient and a 50% infection rate. In this series, seven infants died, two from complications of shunt infection [5]. In a more recent review from our own institution, we found that the infection rate in infants shunted in the perinatal period was 13% compared to an overall shunt infection rate of 3.7%.

Outcome

A number of studies have examined the outcome following IVHP. In reviewing these studies, one must

realize that the field of neonatology has shown rapid advances such that there has been both a decline in the overall incidence of IVHP and an increase in survival for preterm infants. Despite this, however, there has been little improvement in the neurodevelopmental outcome of infants surviving IVHP. The outcome must therefore relate directly to two major factors: gestational age at birth and the degree of brain injury in the perinatal period (i.e., the severity of hemorrhage). Hack and Fanaroff examined the outcome of infants born weighing less than 750 g over a 6-year period. In this study, 8% of infants born at 23 weeks survived compared to 16% of those born at 24 weeks, 53% at 25 weeks, 63% at 26 weeks, and 72% at 27 weeks. Among the survivors who were followed to a corrected age of 20 months, 11 of 32 infants had moderate to severe neurodevelopmental impairment [11].

Boynton reported the neurodevelopmental outcome in 50 preterm infants who required a VP shunt for PHH. In the follow-up, 7 died, 28% had severe visual impairment, 24% had hearing impairment, 38% had seizure disorders, and 60% had multiple handicaps. In this review, a grade IV IVH and a history of neonatal seizures were the two factors predictive of a worse outcome [5].

In the review of Resch et al., 299 preterm infants suffering IVHP were observed over a 5-year period. Of this cohort, 23 infants died and 68 developed PHH. Of the surviving infants, 25% were normal at 5 years, 25% showed mild neurological impairment, 28% had moderate handicaps or mental retardation and 22% were severely affected. The requirement of a VP shunt in this series was a significant predictor of a worse developmental outcome, and those with a history of shunt infection or multiple shunt revisions fared particularly poorly [37].

More recently, Levy et al. reported a series of 76 infants with grade III or IV IVHP who required VP shunts for PHH. In this regression analysis, mortality was best predicted, in order of importance, by extent of IVHP, number of shunt revisions, and weight at birth. The factors that appeared to be the most important predictors of motor outcome included grade of hemorrhage, weight at birth, and presence of neonatal seizures. The grade of hemorrhage was also the most important predictor of cognitive outcome [18].

Leichty et al. looked at the timing of shunting in relation to developmental outcome in 16 infants. In those shunted before 6 weeks of age versus those shunted after 6 weeks, there was no difference in motor outcome at 1 year. In this study, 15/17 infants were abnormal at 1 year, with only 3 scoring above 90% on the Bayley psychomotor developmental index [19]. Given that the performance at 1 year predicts the outcome at 5 years, this is somewhat harrowing.

Conclusion

IVH in the premature newborn continues to be a major health care concern. It can be estimated that 50 000 low-birth-weight infants will be born in the United States this year alone. Improved neonatal resuscitation has clearly reduced the risk of IVHP, but 20% of these infants will suffer an IVH. Several studies have demonstrated that the outcome following IVHP is related to the severity of the hemorrhage and the age of the patient at birth. Volpe has also shown that the periventricular white matter destruction following IVHP is most commonly related to a secondary venous infarction rather than to direct extension of the IVHP itself. Of those infants suffering IVHP, 25%-30% will develop PHH. The likelihood of developing PHH is directly related to the severity of hemorrhage, with 55% of grade III and 80% of grade IV hemorrhages leading to PHH [48]. In this group of infants, the hydrocephalus will resolve in a significant number with either medical management or temporizing surgical procedures; however, at least 20% will require placement of a permanent shunt. Although significant progress has been achieved over the last two decades in reducing both the perinatal mortality and the incidence of IVHP, little improvement in the neurodevelopmental outcome has been accomplished for the infant with posthemorrhagic hydrocephalus.

References

1. Anwar M, Kadam S, Hiatt I, et al: Serial lumbar punctures in prevention of post-hemorrhagic hydrocephalus in preterm infants. *J Pediatr* 107: 446-450, 1985
2. Behrman RE: Preventing low birth weight: a pediatric perspective. *J Pediatr* 107:842-854, 1985
3. Benson JWT, Hayward C, Osborne JP, et al: Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birth weight infants. *Lancet* 1: 1297-1300, 1986
4. Beverley D, Chance G, Coates C: Intraventricular haemorrhage-timing of occurrence and relationship to perinatal events. *Br J Obstet Gynecol* 91: 1007-1013, 1984
5. Boynton B, Boynton C, Merritt A, et al: Ventriculoperitoneal shunts in low birth weight infants with intracranial hemorrhage: neurodevelopmental outcome. *Neurosurgery* 18: 141-145, 1986
6. Chadduck WM, Seibert JJ, McGowan TC, et al: Duplex pulsed doppler US versus intracranial pressure in the neonate: clinical and experimental studies. *Radiology* 171: 155-159, 1989
7. Donat J, Okazaki H, Kleinberg F, et al: Intraventricular hemorrhages in full-term and premature infants. *Mayo Clin Proc* 53:437-441, 1978
8. Fernal E, Hagberg G: Infantile hydrocephalus: declining prevalence in preterm infants. *Acta Paediatr* 87:392-396, 1998

9. Frim D, Scott M, Madsen J: Surgical management of neonatal hydrocephalus. *Neurosurg Neonate* 9: 105-110, 1998
10. Goh D, Minns R, Pye S, et al: Cerebral blood flow velocity changes after ventricular taps and ventriculoperitoneal shunting. *Child's Nerv Syst* 7: 452-457, 1991
11. Hack M, Fanaroff A: Outcomes of extremely-low-weight infants between 1982 and 1988. *N Engl J Med* 321: 1642-1647, 1989
12. Hansen A, Snyder E: Medical management of neonatal posthemorrhagic hydrocephalus. *Neurosurg Neonate* 9: 95-104, 1998
13. Hill A, Volpe J: Seizures, hypoxic-ischemic brain injury, and intraventricular hemorrhage in the newborn. *Ann Neurol* 10: 1091-1091, 1981
14. Hudgins R, Boydston W, et al: Intrathecal urokinase as a treatment for intraventricular hemorrhage in the preterm infant. *Pediatr Neurosurg* 26: 281-287, 1997
15. Hudgins R, Boydston W, Gilreath M: Treatment of posthemorrhagic hydrocephalus in the preterm infant with a ventricular access device. *Pediatr Neurosurg* 29: 309-313, 1998
16. Kreusser K, Tarby T, Kovnar E, et al: Serial lumbar punctures for at least temporary amelioration of neonatal posthemorrhagic hydrocephalus. *Pediatrics* 75: 719-724, 1985
17. Leech R, Kohnen P: Subependymal and intraventricular hemorrhages in the newborn. *Am J Pathol* 77: 465-475, 1974
18. Levy M, Masri L, McComb J: Outcome for preterm infants with germinal matrix hemorrhage and progressive hydrocephalus. *Neurosurgery* 41: 1111-1118, 1997
19. Liechty E, Bull M, Bryson C, et al: Developmental outcome of very low birth weight infants requiring ventriculoperitoneal shunts. *Child's Brain* 10: 340-349, 1983
20. Lou HC, Lassen NA, Friis-Hansen B: Impaired autoregulation of cerebral blood flow in the distressed newborn infant. *J Pediatr* 94: 118-121, 1979
21. Mantovani J, Pasternak J, et al: Failure of daily lumbar punctures to prevent the development of hydrocephalus following intraventricular hemorrhage. *J Pediatr* 97: 278-281, 1980
22. Marlin A, Gaskill S: The etiology and management of hydrocephalus in the preterm infant. In: Scott RM (ed) *Hydrocephalus*. Baltimore, Williams & Wilkins, pp 67-78, 1990 (Concepts in neurosurgery, vol 3)
23. McComb J, Ramos A, Platzker A, et al: Management of hydrocephalus secondary to intraventricular hemorrhage in the preterm infant with a subcutaneous ventricular catheter reservoir. *Neurosurgery* 13: 295-300, 1983
24. Ment L, Duncan C, Scott D, et al: Posthemorrhagic hydrocephalus. *J Neurosurg* 60: 343-347, 1984
25. Ment LR, Steward WB, Duncan CC: Beagle puppy model of intraventricular hemorrhage: ethamsylate studies. *Prostaglandins* 27: 2245-2256, 1984
26. Morales WJ, Koerten J: Prevention of intraventricular hemorrhage in very low birth weight infants by maternally administered phenobarbital. *Obstet Gynecol* 68: 295-299, 1986
27. Morgan MEI, Benson JWT, Cooke RWI: Ethamsylate reduces the incidence of periventricular haemorrhage in very low birth weight babies. *Lancet* 2: 830-831, 1981
28. Pang D, Sclabassi RJ, Horton JA: Lysis of intraventricular clot with urokinase in a canine model. 1. Canine intraventricular blood cast model. *Neurosurgery* 19: 540-546, 1986
29. Pang D, Sclabassi RJ, Horton JA: Lysis of intraventricular clot with urokinase in a canine model. 2. In vivo safety study of intraventricular urokinase. *Neurosurgery* 19: 547-552, 1986
30. Papile L, Burstein J, Burstein R, et al: Posthemorrhagic hydrocephalus in low-birth-weight infants: Treatment by serial lumbar punctures. *J Pediatr* 97: 273-277, 1980
31. Perlman JM, McMenamin JB, Volpe JJ: Fluctuating cerebral blood flow velocity in respiratory distress syndrome. *N Engl J Med* 1983;309: 204-209
32. Philip A, Allan W, Tito A, et al: Intraventricular hemorrhage in preterm infants: declining incidence in the 1980s. *Pediatrics* 84: 797-801, 1989
33. Pinto-Martin J, Riolo S, et al: Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in a low birth weight population. *Pediatrics* 5: 249-254, 1995
34. Pomerance JJ, Teal JG, Gogolok JF, et al: Maternally administered antenatal vitamin K: Effect on neonatal prothrombin activity, partial thromboplastin time, and intraventricular hemorrhage. *Obstet Gynecol* 70: 235-241, 1987
35. Quinn M, Ando Y, Levene M: Cerebral arterial and venous flow-velocity measurements in post-haemorrhagic ventricular dilatation and hydrocephalus. *Dev Med Child Neurol* 34: 863-869, 1992
36. Rahman S, Teo C, Morris W, et al: Ventriculosubgaleal shunt: a treatment option for progressive posthemorrhagic hydrocephalus. *Child's Nerv Syst* 11: 650-654, 1995
37. Resch B, Gedermann A, et al: Neurodevelopmental outcome of hydrocephalus following intra-/periventricular hemorrhage in preterm infants: short- and long-term results. *Child's Nerv Syst* 12: 27-33, 1996
38. Rhodes T, Edwards W, Saunders R, et al: External ventricular drainage for initial treatment of neonatal posthemorrhagic hydrocephalus: Surgical and neurodevelopmental outcome. *Pediatr Neurosci* 13: 255-262, 1987
39. Roland E, Hill A: Intraventricular hemorrhage and posthemorrhagic hydrocephalus: current and potential future interventions. *Clin Perinatol* 1: 589-605, 1997
40. Shinnar S, Gammon K, et al: Management of hydrocephalus in infancy: use of acetazolamide and furosemide to avoid cerebrospinal fluid shunts. *J Pediatr* 107: 31-37, 1985
41. Sklar F, Adegbite A, Shapiro K, et al: Ventriculosubgaleal shunts: management of posthemorrhagic hydrocephalus in premature infants. *Pediatr Neurosurg* 18: 263-265, 1992
42. Szymonowicz W, Yu V, Walker A, et al: Reduction in periventricular haemorrhage in preterm infants. *Arch Dis Child* 61: 661-665, 1986
43. Van de Bor, et al: Incidence and prediction of periventricular - intraventricular hemorrhage in very preterm infants. *J Perinat Med* 15: 333-339, 1987
44. Volpe J, Pasternak J, Allan W: Ventricular dilation preceding rapid head growth following neonatal intracranial hemorrhage. *Am J Dis Child* 131: 1212-1215, 1977
45. Volpe JJ: Intraventricular hemorrhage in the premature infant - current concepts. Part I. *Ann Neurol* 25: 3-11, 1989
46. Volpe J, Herscovitch P, et al: Positron emission tomography in the newborn: extensive impairment of regional cerebral blood flow with intraventricular hemorrhage and hemorrhagic intracerebral involvement. *Pediatrics* 72: 589-601, 1983
47. Volpe JJ: Intraventricular hemorrhage in the premature infant - current concepts. Part II. *Ann Neurol* 25: 109-116, 1989

48. Volpe JJ: Intracranial hemorrhage: germinal matrix-intraventricular hemorrhage of the premature infant. In: Volpe JJ (eds) *Neurology of the newborn*. Philadelphia, Saunders, 1995
49. Volpe J: Brain injury in the premature infant – from pathogenesis to prevention. *Brain Dev* 19: 519-537, 1997
50. Weller R, Shulman K: Infantile hydrocephalus: clinical, histological, and ultrastructural study of brain damage. *J Neurosurg* 36: 255-265, 1972
51. Weninger M, Salzer H, Pollak A, et al: External ventricular drainage for treatment of rapidly progressive posthemorrhagic hydrocephalus. *Neurosurgery* 31: 52-58, 1992
52. Whitelaw A, et al: Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation. *Arch Dis Child* 65: 3-10, 1990
53. Whitelaw A, et al: Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation: results at 30 months. *Arch Dis Child* 70: F129-F136, 1994

Hydrocephalus with Myelomeningocele

SPYROS SGOUROS

Epidemiology

The incidence of myelomeningocele ranges between 0.2 and 2 per 1000 live births, with regional and racial variations [11]. The overall incidence of myelomeningocele has declined significantly in the last two decades, due to improved maternal nutrition during pregnancy with addition of folic acid and wider availability of prenatal diagnosis and therapeutic termination of pregnancy. The exact incidence of hydrocephalus in myelomeningocele is not known. In a significant proportion of patients hydrocephalus is absent at birth but develops in the first few weeks or months of life, indicating that there is a spectrum of manifestation [11]. Hydrocephalus is seen in postnatal neuroimaging obtained prior to closure of the defect in 15%–25% of children with myelomeningocele [11, 12], but in most surgical series the proportion of patients with myelomeningocele who require shunting reaches up to 80%–90% (although inevitably there must be some sample bias in such series) [41, 59]. No obvious correlation between the level of the lesion and the presence of hydrocephalus has been shown [41, 59].

Natural History

In the 1960s, before shunting became established, these patients had a poor prognosis; the majority were not offered treatment, and only 20% of non-operated children with hydrocephalus and myelomeningocele reached adulthood, with poor intellectual outcome [23, 30, 57, 70]. After the introduction of shunting, outcomes improved. In a review of a cohort of patients treated in the 1970s for spina bifida aperta, it was noted that 52% of the pa-

tients were alive at 20 years [23]. Most of the deaths occurred in the 1st year of life, mostly due to renal and respiratory problems associated with the spina bifida. Only a few of the deaths were related to hydrocephalus. In a similar recent review of children treated in the 1980s, only 27% had died, most of them in the first year of life, from causes not related to hydrocephalus but to the spina bifida [59]. The life expectancy of children with myelomeningocele has been calculated as 40 years [13], but it should be borne in mind that modern intensive management of these patients has been pursued only for the last 45 years [56]. Of interest is that a recent study of long-term outcome noticed a higher mortality rate among shunted children with hydrocephalus and myelomeningocele than among non-shunted children [13]. The difference was assumed to be due to shunt-related complications, and the authors suggested that efforts should be directed towards delaying shunting as much as possible or considering third ventriculostomy as an alternative. There continues to be a small risk of mortality for these patients even throughout adulthood. In a recent survey of adults with spina bifida, 6% of patients died due to shunt-related problems or after cranivertebral decompression for Chiari malformation [35].

Pathophysiology

A variety of factors are implicated in the pathogenesis of hydrocephalus in children with myelomeningocele. The Chiari type II malformation, aqueduct stenosis, anomalous venous drainage, the open myelomeningocele and the presence of other CNS malformations all contribute to the development of hydrocephalus.

Role of Chiari Malformation

In the context of the Chiari type II malformation there is extensive deformity of the posterior fossa and its structures. The brain stem has abnormal disposition with respect to the midbrain and the tentorial hiatus, the posterior fossa is smaller in capacity than normal [43], the fourth ventricle is caudally displaced, and there is significant prolapse of the cerebellar tonsils through the foramen magnum [46]. The vertical translocation of the brain stem causes increased resistance of CSF flow through the tentorial hiatus. The crowding of the foramen magnum leads to occlusion of the outlets of the fourth ventricle. The small volume of the posterior fossa in conjunction with the very abnormal tilt of the tentorium and the cerebellar prolapse causes increased tension inside the posterior fossa, which leads to increased resistance to the venous outflow through the sigmoid sinuses and venous hypertension. This creates an element of “communicating” hydrocephalus. The vertical translocation of the brain stem functionally compounds any anatomical aqueduct stenosis. It is difficult to ascertain which of all these factors is the most important in the pathogenesis of hydrocephalus, as they are all interlinked.

Role of Aqueduct Stenosis

Aqueduct stenosis of variable degree is present in patients with myelomeningocele and Chiari II malformation. In neuroimaging obtained early after birth in severe cases, a large third and a small fourth ventricle are often seen, indicating aqueduct stenosis (Fig. 1). In detailed radiological and cadaveric studies of patients with myelomeningocele and Chiari II malformation, the midbrain was found to be deformed in the majority of patients [44]. The tectal plate was deformed craniocaudally and ventrodorsally, in a beak-like configuration, so that the aqueduct was progressively angulated to the point that in severe cases it had assumed a V-shape pointing dorsally [44]. This, combined with the crowding of the tentorial hiatus, creates a functional obstruction. The fourth ventricle was elongated and smaller than normal and the third ventricle dilated, although not as much as in typical aqueduct stenosis [45]. While aqueduct stenosis contributes to the pathogenesis of hydrocephalus, the remaining CSF pathways are deformed and abnormal. This is in contrast to typical isolated aqueduct stenosis, and probably contributes to the low

success rate of third ventriculostomy when performed as primary treatment for hydrocephalus early in life.

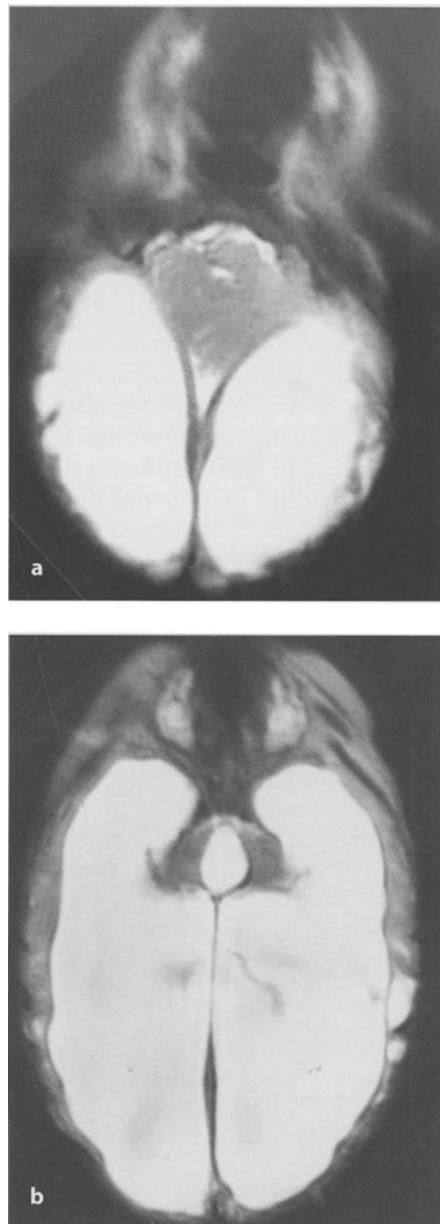


Fig. 1a, b. Neuroimaging of a 1-month-old girl born with thoracic myelomeningocele and hydrocephalus. The initial decision was against active treatment, as she was considered to be too severely affected and it was believed that she would not survive. Having survived for 1 month, she was subsequently offered surgical treatment. **a** Axial T2-weighted MRI scan showing a very small fourth ventricle, grossly dilated lateral ventricles and very thin cortical mantle. **b** Axial T2-weighted MRI scan showing a dilated third ventricle and lateral ventricles with very attenuated cortical mantle. These appearances strongly suggest severe aqueduct stenosis

Role of Venous Abnormalities in the Posterior Fossa

During the last two decades the role of venous hypertension in the pathogenesis of hydrocephalus has been increasingly recognized [1]. In the presence of Chiari II malformation, the small posterior fossa volume and the abnormal anatomical disposition of the structures within it, as well as the crowding of the foramen magnum due to the cerebellar herniation, lead to compression of the sigmoid sinuses, which in turn leads to venous hypertension. In addition, compression of the deep venous drainage system (internal cerebral veins) due to the deformation of the midbrain [44] can further contribute to venous hypertension [1]. On the other hand, treatment of the hydrocephalus with a ventricular shunt does not necessarily improve the venous hypertension, as it does not address its original cause, which is the venous compression on the midbrain and the posterior fossa. Reduction of the CSF pressure with shunting results in accumulation of interstitial fluid in brain structures due to the venous hypertension, and contributes to deterioration of aqueduct stenosis due to interstitial oedema [1]. This situation is often seen in shunted patients who present later on with blocked shunt and improve with third ventriculostomy.

Role of Closure of the Myelomeningocele in the Development of Hydrocephalus

While it is certain that development of hydrocephalus is related temporally to the closure of the myelomeningocele, it is not clear whether this is a causative relationship, or whether simply closure of the neural sac precipitates and accelerates the inevitable. In immediate postnatal imaging hydrocephalus is seen only in 15%–25% of children with myelomeningocele [11], but in a significant proportion of the remaining children, hydrocephalus develops in the first few weeks of life after closure of the defect. A small proportion of patients with open myelomeningocele deteriorate dramatically after closure of the defect. The mechanism behind that deterioration is multifactorial. A significant role is played by impaction of hindbrain hernia. Hindbrain hernia is present in a very high proportion – almost all – of the children born with open myelomeningocele [61]. The development of hindbrain hernia during gestation is considered to be due to the progressive caudal migration of the hindbrain in association with the low pressure

conditions that the open myelomeningocele creates in the spine. Progressive cerebellar prolapse also exacerbates the anatomical deformity of the midbrain, which is implicated in the formation of aqueduct stenosis and further impacts on the already compromised venous drainage of the sigmoid sinuses. It is known that the incidence of *in utero* ventriculomegaly is greater after 24 weeks' gestation, indicating a progressive deterioration [2]. Prior to and during surgical repair of the myelomeningocele in the first few days of life, loss of CSF results in even further deterioration of the hindbrain hernia and the associated hydrocephalus. This can lead to acute neurological deterioration due to a combination of raised intracranial pressure related to the ventriculomegaly, and acute bulbar dysfunction due to compression of the brain stem in the region of the foramen magnum. The neurological state usually improves after ventricular shunting [12].

Of interest is that in a small number of children who had intrauterine repair of myelomeningocele, the incidence of hydrocephalus was decreased in comparison to historical controls who had "traditional" treatment, from 91% to 59% [7, 65]. The same group noted that the incidence of hindbrain hernia present at birth in the group of children who had intrauterine closure of the myelomeningocele was considerably lower than in historical controls [66]. Hence they postulated that the lower incidence of hydrocephalus was due to the absence of the obstructing effect of the hindbrain hernia at the level of the foramen magnum to the flow of CSF [7, 65]. In another study of intrauterine closure of myelomeningocele, only one of the nine surviving patients required ventriculoperitoneal shunt, and two others were being considered for a shunt [61]. Similarly, in this group of patients a lower than expected rate of hindbrain herniation was observed. While no long-term follow up is available of these children who underwent intrauterine closure of myelomeningocele, it seems that early closure of the open sac may reduce the incidence of hydrocephalus. It may be oversimplistic to assume that this is only due to the lack of the obstructing effect of hindbrain hernia: it is almost certain that a variety of factors are implicated. The different anatomical disposition of the posterior fossa structures in such patients almost certainly leads to improved flow through the aqueduct, improved compliance of CSF flow around the brain stem and the tentorial hiatus and lower venous outflow pressure in comparison to patients born with open myelomeningocele. These factors may be far more important than the obstruction at the foramen

men magnum in isolation, considering that in patients with Chiari I malformation the incidence of hydrocephalus is much lower than in patients with Chiari II.

Role of Other CNS Malformations

Neural tube defects are the commonest group of congenital malformations seen in post-mortem examinations, accounting for up to 45% of deaths related to CNS malformation [48]. In the context of bifid cranium and spina bifida, cervical meningocele/myelomeningocele is occasionally associated with various forms of encephalocele, in which parts of the cerebellum are prolapsing through the occipital cranial defect. Such cases constitute very severe forms of dysraphism, with a high incidence of hydrocephalus and a very poor prognosis.

Specific Clinical Manifestations

As with other forms of infantile hydrocephalus, children with myelomeningocele can develop enlarging head with bulging fontanelle, enlarged scalp veins, macrocrania, suture diastasis and positive "crack-pot" sign. If left untreated they develop "sunset" eyes, recurrent vomiting and later respiratory arrest. The particular consideration in children with myelomeningocele, though, is the presence of hindbrain hernia in the context of the Arnold-Chiari malformation, which can cause clinical symptoms of bulbar palsy early, and can remain unnoticed by inexperienced observers. Poor feeding, recurrent vomiting, poor sucking, generally subdued behaviour with poor crying, high pitched cry or stridor due to vocal cord paralysis, episodes of apnoea and recurrent aspiration – often manifesting with recurrent pneumonia – can all be manifestations of brain stem dysfunction due to hindbrain hernia, aggravated by ventricular dilatation. Lastly, persistent CSF leak from the repaired spinal wound almost invariably indicates active hydrocephalus, even if the ventricular size is only modestly enlarged and the anterior fontanelle is not bulging.

Radiology

Most children born with myelomeningocele will have undergone in utero ultrasound scans, which provide information on the state of the ventricular system. Even if these scans are available, it is important to obtain neuroimaging soon after birth, to assess the state of the ventricular system and of the hindbrain. Magnetic resonance imaging (MRI) remains the ideal medium, as it shows in good detail the ventricles, the aqueduct and the hindbrain. Drawbacks remain the inconsistent availability of MR scanners and the technical difficulties of obtaining MR scans in such a newborn baby. Sedation is usually not indicated due to the potential problems of bulbar dysfunction and intracranial hypertension, and the babies do not stay immobile for long periods of time. As a result, the quality of images is often poor due to movement artefacts. In such circumstances, CT scan will provide enough information on the state of the ventricular system, and assist in deciding on the need for ventricular shunt.

There is a very high incidence of hindbrain hernia – almost all patients born with open myelomeningocele have it to some degree. In up to 15%–20% there is marked hydrocephalus, and in a further 20% there is moderate ventriculomegaly [67]. The third ventricle is moderately dilated in most cases [45] (Fig. 1). The lateral ventricles have a characteristic appearance in almost all patients: the occipital horns are more dilated than the frontal horns, and the long axis of the lateral ventricles tend to be parallel [67] (Fig. 2). A contributing factor may be the partial or complete absence of the falx in almost all patients with myelomeningocele and hydrocephalus, and absence of the septum pellucidum in a very high proportion of these patients [45]. It has been postulated that the defects are part of a wider neurodevelopmental defect affecting the cerebrum, as the shape of the ventricular system resembles more the fetal configuration than that of normal newborns [3, 67]. MRI shows well the hindbrain hernia and the small posterior fossa and the midbrain deformity and kinking of the aqueduct, which is often poorly visualized [47, 68].

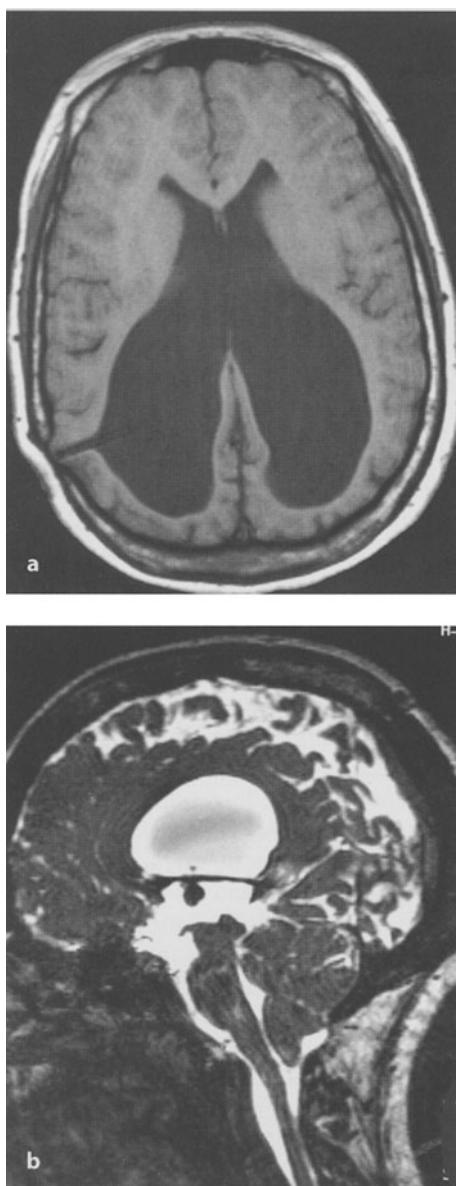


Fig. 2a, b. MRI scans of a 14-year-old girl with thoracic myelomeningocele and shunted hydrocephalus, who presented with symptoms indicative of shunt malfunction. **a** Axial T1-weighted MRI scan showing the typical ventricular configuration of patients with myelomeningocele-related hydrocephalus. Small frontal horns and large occipital horns are seen. The shunt catheter is seen in the right parietal region. **b** Sagittal CISS (constructive interference in the steady state) scan showing absence of high signal in the region of the aqueduct, indicating non-patency

Treatment

Children with a clinical picture of active hydrocephalus, and with significant ventriculomegaly, often with evidence of periventricular lucency indicat-

ing raised CSF pressure in the ventricular system, will need treatment early in life. In contrast, children with mild or moderate ventriculomegaly and head circumference within the normal centiles may not need shunting at first, and an observation policy can be adopted for the first few months of life, while monitoring of the head circumference and repeat ultrasound or MRI will help decide whether they will finally require shunting. Surgical treatment of hydrocephalus in the majority of cases consists of insertion of a ventricular shunt. The most favourite distal site remains the peritoneum, although for difficult cases with other co-existing abdominal problems there are other options such as the right atrium, the gall bladder, the ureter or the bladder. In practice, the overwhelming majority of shunts nowadays are ventriculoperitoneal. As in other forms of hydrocephalus, shunts require continuous careful monitoring, as at 10 years, up to 80% of them have required revision because of some form of failure [53]. While shunted hydrocephalic children with myelomeningocele have largely similar outcomes to children with other types of hydrocephalus [8, 26, 29, 31, 37, 55, 60], several studies have highlighted the higher infection rate in the early months after shunt insertion, thought to be related to CSF contamination from the open myelomeningocele [8, 17, 34, 36, 38, 40, 52, 60]. Emphasis should be placed on the need to perform closure of the defect as soon as possible after birth, to avoid CSF infection.

It should be noted that children with myelomeningocele may have increased risk of developing secondary craniosynostosis following shunt insertion [32]. While this may happen in the context of shunt overdrainage, it has been postulated that the presence of myelomeningocele results in a state of reduced content of CSF of the entire neuraxis, which results in reduced drive for brain development, which in turn results in early suture closure [32].

Another consideration particular to myelomeningocele-related hydrocephalus is the relationship between hydrocephalus and scoliosis, which is present in a very high proportion of these patients, as well as syringomyelia, which is seen infrequently in these patients. It has been observed that scoliosis deteriorates in the presence of untreated hydrocephalus, and improves following successful shunting [18, 20]. The underlying mechanism is not fully understood, but it is postulated that active hydrocephalus exacerbates the compressive effect of the hindbrain hernia on the descending pathways at the craniocervical junction, inducing neuromuscular balance on the already compromised spine from the bifid deformity.

In patients with syringomyelia, a common mode of presentation of shunt obstruction is deteriora-

tion of syringomyelia, which improves after shunt revision (Fig. 3).

Timing of the Shunt

When treating children who unequivocally require shunting soon after birth, the common dilemma that neurosurgeons face is whether to perform shunting at the time of the surgical closure of the myelomeningocele, or whether to defer it for a few days or weeks. Arguments in favour of delayed shunting are shorter anaesthetic time for the operation of myelomeningocele closure for a neonate who is only a few days old and possibly through the physiological jaundice period, and a theoretically lower shunt infection rate. Arguments in favour of simultaneous shunting are a lower complication rate from the spinal wound in the form of CSF leak and shunt infection and improved chances of better development by reducing intracranial hypertension early. In series where the two methods have been compared, the conclusion reached was that simultaneous shunting was associated with a lower complication rate from shunt infection and overall better outcome [16, 40, 47]. Certainly, it appears that simultaneous shunting decreases the incidence of CSF leak from the repaired spina bifida wound, and protects against CSF infection. Indeed, one of the signs of oncoming hydrocephalus after closure of myelomeningocele is persistent CSF leak. Whenever feasible, simultaneous shunting and closure of myelomeningocele should be preferred. In children with open myelomeningocele in whom there has been delay in closure of the defect, there is the risk that CSF infection may already have taken place. In such circumstances, CSF microbiological testing should be performed, and if CSF infection is present, external ventricular drainage should be employed for a week to 10 days in conjunction with antibiotic treatment, until the CSF infection is controlled and a shunt can be inserted.

Surgical Pitfalls Specific to Shunt Surgery in Myelomeningocele

In cases where shunting is performed simultaneously with myelomeningocele closure, additional precautions to maintain sterility of the surgical fields should be exercised. Some authors advocate placement of the child in some form of “park bench” position, which would allow both operations to take place without repositioning of the patient [22]. While this proposition is attractive, if the surgeon is

not familiar with this position it may actually complicate both procedures by not giving optimal access for either. In everyday clinical practice, most neurosurgeons prefer to close the myelomeningocele first with the child prone, and subsequently turn the child on his or her back for the shunt placement, while adequately protecting the newly repaired spinal wound with ample padding. This adds less than 1 h to the operating time [47].

Role of Third Ventriculostomy

Third ventriculostomy has been employed recently in the treatment of hydrocephalus of children with myelomeningocele. When used as a primary method of treatment, the reported success ranges around 30% [27, 28, 64]. It is difficult to regard this as a definitive outcome standard, as all studies have only small numbers of patients. One possible explanation for the low success rate is the fact that most patients who require treatment for the first time are infants or neonates, who are known to have lower success rate of third ventriculostomy than older children. Certainly, if on MRI examination there is clear evidence of aqueduct stenosis, the prognosis of third ventriculostomy is more favourable and the procedure may be recommended. In the presence of a patent aqueduct, verified on dynamic sequences, shunting is probably a safer option. Often in clinical practice the quality of the MR images is poor due to movement artefact and it is difficult to reach a categorical conclusion on the state of patency of the aqueduct.

When third ventriculostomy is used in children who have already been shunted and present with shunt malfunction at an older age, the reported success rate is considerably higher, ranging from 50% to 80% [6, 64]. A high proportion of these children have a significant degree of aqueduct stenosis. In such patients it is strongly recommended that MRI examination include dynamic sequences to investigate fully CSF flow through the aqueduct. In the author's experience, three patients who presented with blocked shunts and responded well to endoscopy had apparently patent aqueduct on ordinary T1- and T2-weighted sequences, but on dynamic MRI it was clear that there was no flow through the aqueduct (Fig. 2). In such circumstances, following third ventriculostomy, and especially if the shunt has been removed, it is advisable that an external ventricular drain be employed for the first few days, to allow emergency decompression if the third ventriculostomy does not function adequately and the patient deteriorates rapidly.

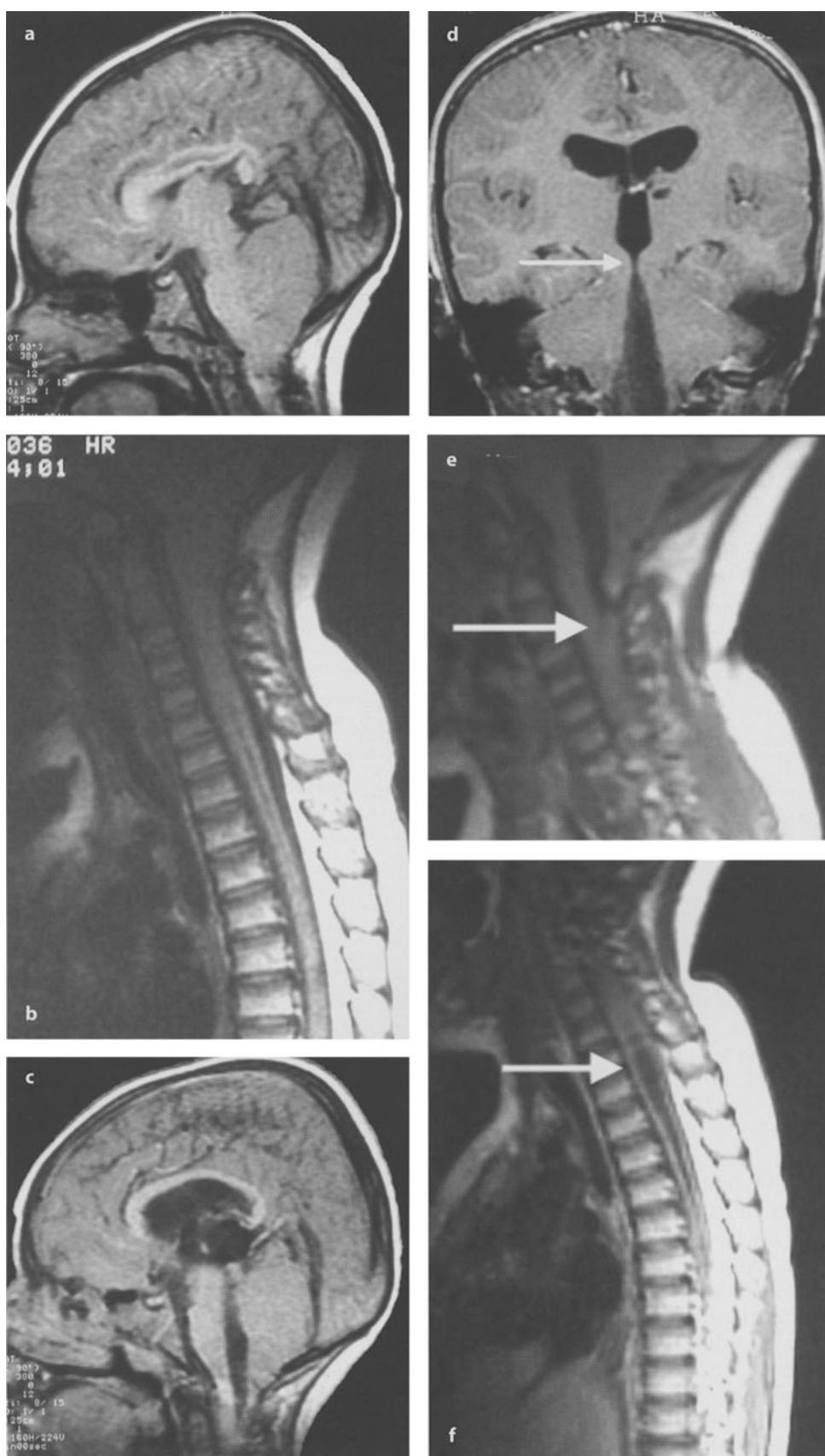


Fig. 3a-f. A 6-year-old boy affected by myelomeningocele and hydrocephalus, shunted at birth. Follow-up images show slit-like ventricles, Arnold-Chiari malformation, small posterior fossa (a) and a tiny syringomyelic cavity at cervical level (b). During shunt malfunction ventricles are dilated (c), the cerebral aqueduct is clearly patent (d, arrow), and the fourth ventricle becomes visible as well as the communication at the level of the obex (e) with the syringomyelic cavity (f) that develops at the cervical level. The only symptom presented was severe back pain. Shunt revision resolved the symptoms, and the ventricles and the syringomyelic cavity disappeared

Whenever third ventriculostomy is contemplated in children with myelomeningocele, the surgeon should have in mind that the ventricular anatomy is often unusual or abnormal, making the procedure more difficult. Often the floor of the third ventricle is thicker and more difficult to penetrate, the size of the third ventricle is smaller than in children with aqueduct stenosis, or there is absence of the septum pellucidum, which can lead to disorientation of an inexperienced operator. In general, inexperienced operators should avoid endoscopic third ventriculostomy in children with hydrocephalus due to myelomeningocele.

"Arrested" Hydrocephalus in Myelomeningocele: Does It Exist?

The issue of "arrested" hydrocephalus remains controversial. The situation is further compounded by the often erratic use of the term "compensated" hydrocephalus, to indicate hydrocephalus adequately treated. Several studies have analysed the intellectual state of children with myelomeningocele and presumed "arrested" hydrocephalus that has not been shunted. In series published before shunting was widely used, a large number of untreated hydrocephalics were considered to have "arrested" hydrocephalus [30, 70, 72]. Intellectual outcome in such patients was invariably subnormal, in contrast to shunted hydrocephalic patients. In contrast, two recent studies have found that a large proportion of non-shunted children have normal IQ [9, 19], and in one study non-shunted children had better average IQ than shunted hydrocephalic children [9]. It is difficult to ascertain whether the population profile of studies performed in two fundamentally different eras are comparable. To add to the debate, it has been demonstrated that in a proportion of non-shunted children or children who have had shunts but have been asymptomatic for years, intellectual decline can evolve in a very slow insidious manner, and will only be ascertained by serial IQ and psychometric testing [21, 39]. In a recent study, a high incidence of intracranial hypertension was found among such patients with untreated hydrocephalus and myelomeningocele [24]. In such cases, shunting (or shunt revision if they have a shunt which has not been revised for years) has been shown to improve IQ and overall performance [39].

Older children or young adults are sometimes seen with the typically shaped ventricles of hydrocephalus due to spina bifida in whom the ventricles do not appear to be under tension, there is no periventricular lucency and there is absence of

symptoms such as headache, drowsiness, diplopia or bulbar features, suggesting active hydrocephalus (Figs. 4, 5). If they have never been shunted, serial monitoring with intelligence and psychometric

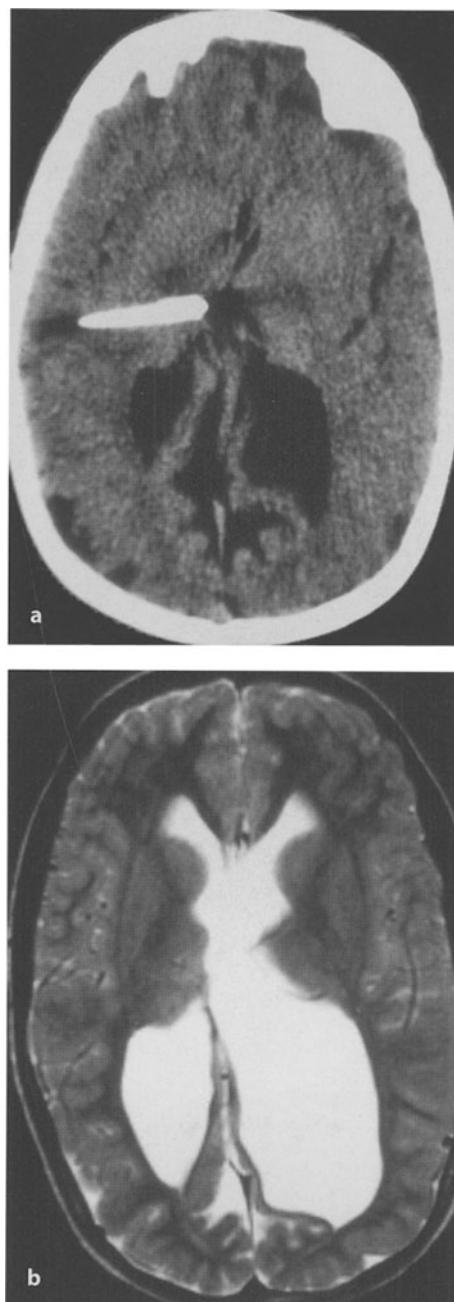


Fig. 4a, b. Girl affected by myelomeningocele and hydrocephalus, shunted at birth in a developing country. **a** CT scan at the age of 9 years: the proximal catheter is in the right thalamus, ventricles are small. **b** Follow-up MRI at the age of 11 years: the shunt is blocked, the ventricles are dilated, the patient has no signs or symptoms of intracranial hypertension. The parents refused any treatment. Two years later the patient was readmitted with severe epilepsy that resolved following shunt revision

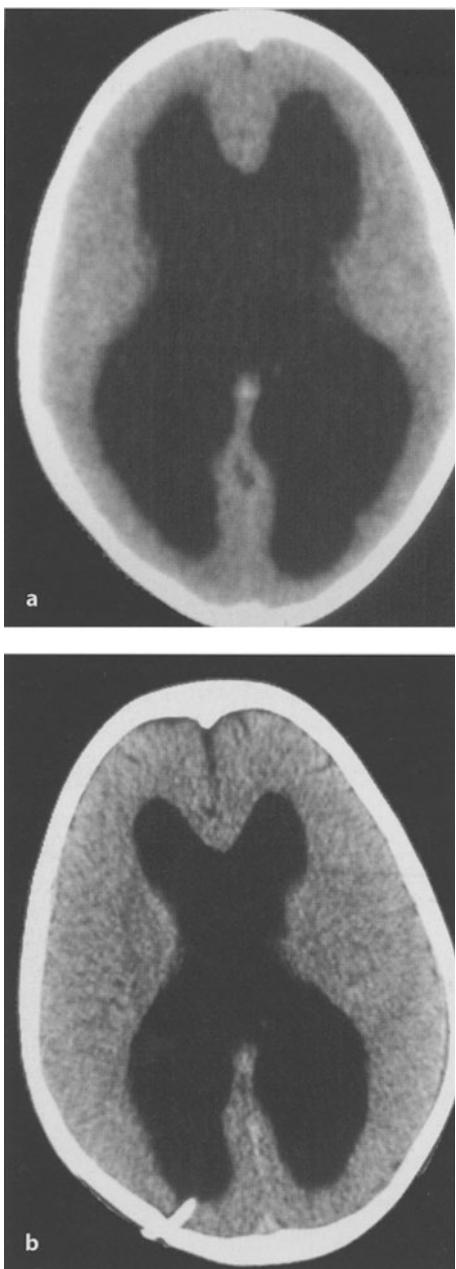


Fig.5a, b. A 7-year-old girl affected by myelomeningocele and hydrocephalus. Shunted at birth, her shunt was removed at the age of 2 months because of shunt infection and never re-implanted because the hydrocephalus was considered to be "arrested". She was admitted at the age of 7 years with macrocrania, papilloedema and mildly delayed psychomotor development. MRI showed hydrocephalus (a). Significant radiological and clinical improvement was observed after ventriculoperitoneal shunt (b)

testing should be undertaken. Absence of clinical symptoms and stability on psychometric testing should discourage the neurosurgeon from contemplating shunting solely on the basis of radiological

appearances, having in mind the high risk of bilateral subdural haematomas that such patients have. If they have been shunted in the past, caution should be exercised in considering any intervention on the shunt. Because shunts may be disconnected or appear not to have been working for years, it is tempting to regard the situation as "compensated" hydrocephalus and choose to remove the shunt, especially if it is causing local discomfort in the neck. However, shunts that have been implanted for years have acquired a tube of strong fibrous tissue surrounding them along their entire length. Even though the tube may appear fractured on radiographs, CSF is crossing the gap, guided by the encircling fibrous tube. Such shunts are actually functioning, and any attempt to remove them without instituting any alternative means of CSF drainage, such as third ventriculostomy, may prove lethal. In contrast, if either subtle symptoms or clear measured intellectual decline is present, treatment should be offered. In such cases, those who have not been shunted should be shunted, and those with shunts should have their shunts revised. The diagnosis of "compensated" or "arrested" hydrocephalus is only acceptable when the possibility of "symptomatic" hydrocephalus has been discarded. If in doubt, invasive intracranial pressure monitoring should be employed to clarify the situation.

Influence of Hydrocephalus in the Psychomotor Development of Patients with Myelomeningocele

With improved management of hydrocephalus, the main determining factor of the long-term outcome of children born with spina bifida aperta will be the level of spinal cord damage [23]. Several studies have shown that the worst prognosis, as far as motor outcome is concerned, is associated with thoracic lesions, whereas cervical and lumbar lesions have a better outcome, with patients usually ending up independently mobile [41]. Children with myelomeningocele without hydrocephalus have normal intelligence [9, 38]. For children with myelomeningocele and hydrocephalus, mental and intellectual outcome is dictated by the management of hydrocephalus. In the 1960s, before shunting had become an established technique, these patients were considered at birth as having a poor prognosis, to the extent that often treatment was not offered at all in the presence of open myelomeningocele [23, 25, 30, 50, 57, 70]. With the establishment of

ventricular shunting, a higher proportion of children received treatment, and outcomes improved after the 1970s. With careful and systematic treatment and follow-up, the social and educational outcome of the surviving spina bifida patients is similar to that of any other group of surviving hydrocephalic individuals that reach adulthood, making allowance for the associated physical disabilities owing to the associated paraplegia of the spina bifida [23, 55]. Several studies have demonstrated that at least 50%–70% of such patients can attain an IQ over 80, which is considered normal [14, 33, 41, 58, 59, 69, 72]. On detailed neuropsychological testing performance IQ has been shown to be worse than verbal IQ, as in children with other types of hydrocephalus [9, 42, 51, 69, 71]. Comparing different causes of hydrocephalus, myelomeningocele patients have at least as good IQs as patients with aqueduct stenosis [10, 51].

Several factors have been found to have a negative influence on the intellectual outcome of children with myelomeningocele and hydrocephalus: high lesion, poor mobility, shunt revisions, shunt infection and epilepsy [4, 10, 38, 51, 62]. The incidence of epilepsy in hydrocephalic children with myelomeningocele varies among different studies between 7% and 47% [5, 54, 55, 63] – no worse than for other types of hydrocephalus (the worst being post-meningitic and post-haemorrhagic hydrocephalus). In the absence of any other congenital brain abnormality, epilepsy does not seem to affect this group of children any worse than those with other types of hydrocephalus. A consideration specific to hydrocephalus related to myelomeningocele is the observation of a high incidence of precocious puberty among female patients, up to 16% [15, 49]. The potential mechanism has not been identified. Hypothalamic dysfunction due to congenital deformity of the midbrain has been postulated. One study identified correlation between the presence of a period of intracranial hypertension in the perinatal period and the development of precocious puberty [49]. Precocious puberty does not appear to have any impact on intellectual development.

References

1. Andeweg J: Intracranial venous pressures, hydrocephalus and effects of cerebrospinal fluid shunts. *Child's Nerv Syst* 5: 318–323, 1989
2. Babcock CJ, Goldstein RB, Barth RA, et al: Prevalence of ventriculomegaly in association with myelomeningocele: correlation with gestational age and severity of posterior fossa deformity. *Radiology* 190: 703–707, 1994
3. Bannister CM, Russell SA, Rimmer S: Pre-natal brain development of fetuses with a myelomeningocele. *Eur J Pediatr Surg* 8 Suppl 1: 15–17, 1998
4. Bier JA, Morales Y, Liebling J, et al: Medical and social factors associated with cognitive outcome in individuals with myelomeningocele. *Dev Med Child Neurol* 39: 263–266, 1997
5. Bourgeois M, Sainte-Rose C, Cinalli G, et al: Epilepsy in children with shunted hydrocephalus. *J Neurosurg* 90: 274–281, 1999
6. Brockmeyer D, Abtin K, Carey L, Walker ML: Endoscopic third ventriculostomy: an outcome analysis. *Pediatr Neurosurg* 28: 236–240, 1998
7. Bruner JP, Tulipan N, Paschall RL, et al: Fetal surgery for myelomeningocele and the incidence of shunt-dependent hydrocephalus. *JAMA* 282(19): 1819–1825, 1999
8. Caldarelli M, Di Rocco C, La Marca F: Shunt complications in the first postoperative year in children with meningomyelocele. *Childs Nerv Syst* 12: 748–754, 1996
9. Casari EF, Fantino AG: A longitudinal study of cognitive abilities and achievement status of children with myelomeningocele and their relationship with clinical types. *Eur J Pediatr Surg* 8 Suppl 1: 52–54, 1998
10. Dennis M, Fitz CR, Netley CT, et al: The intelligence of hydrocephalic children. *Arch Neurol* 38: 607–615, 1981
11. Dias MS: Myelomeningocele. In: Choux M, Di Rocco C, Hockley A, Walker M (eds) *Pediatric neurosurgery*. Churchill Livingstone, pp 33–59, 1999
12. Dias MS, McLone DG: Hydrocephalus in the child with dysraphism. *Neurosurg Clin N Am* 4: 715–726, 1993
13. Dillon CM, Davis BE, Duguay S, et al: Longevity of patients born with myelomeningocele. *Eur J Pediatr Surg Suppl* 1: 33–34, 2000
14. Donders J, Canady AI, Rourke BP: Psychometric intelligence after infantile hydrocephalus. *Childs Nerv Syst* 6: 148–154, 1990
15. Elias ER, Sadeghi-Nejad A: Precocious puberty in girls with myelodysplasia. *Pediatrics* 93: 521–522, 1994
16. Epstein NE, Rosenthal AD, Zito J, Osipoff M: Shunt placement and myelomeningocele repair: simultaneous vs. sequential shunting. *Childs Nerv Syst* 1: 145–147, 1985
17. Gamache FW: Treatment of hydrocephalus in patients with meningomyelocele or encephalocele: a recent series. *Childs Nerv Syst* 11: 487–488, 1995
18. Geiger F, Parsch D, Carstens C: Complications of scoliosis surgery in children with myelomeningocele. *Eur Spine J* 8: 22–26, 1999
19. Hagberg B: The sequelae of spontaneously arrested infantile hydrocephalus. *Develop Med Child Neurol* 4: 583–587, 1962
20. Hall P, Lindseth R, Campbell R, et al: Scoliosis and hydrocephalus in myelocle patients. The effect of ventricular shunting. *J Neurosurg* 50: 174–178, 1979
21. Hammond MK, Milhorat TH, Baron IS: Normal pressure hydrocephalus in patients with myelomeningocele. *Dev Med Child Neurol Suppl* 37: 55–68, 1976
22. Hubballah MY, Hoffman HJ: Early repair of myelomeningocele and simultaneous insertion of ventriculoperitoneal shunt: technique and result. *Neurosurgery* 20: 21–23, 1987
23. Hunt GM, Poulton A: Open spina bifida: a complete cohort reviewed 25 years after closure. *Dev Med Child Neurol* 37: 19–29, 1995

24. Iborra J, Pages E, Cuxart A, et al: Increased intracranial pressure in myelomeningocele (MMC) patients never shunted: results of a prospective preliminary study. *Spinal Cord* 38: 495-497, 2000
25. Jansen J: A retrospective analysis 21 to 35 years after birth of hydrocephalic patients born from 1946 to 1955. An overall description of the material and the criteria used. *Acta Neurol Scand* 71: 436-447, 1985
26. Jamjoom AB, Khalaf NF, Mohammed AA, et al: Factors affecting the outcome of foetal hydrocephaly. *Acta Neurochir (Wien)* 140: 1121-1125, 1998
27. Jones RFC, Kwok BCT, Stening WA, Vonau M: The current status of endoscopic third ventriculostomy in the management of non-communicating hydrocephalus. *Minim Invas Neurosurg* 37: 28-36, 1994
28. Jones RFC, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26: 86-92, 1990
29. Keucher TR, Mealey J: Long-term results after ventriculoatrial and ventriculoperitoneal shunting for infantile hydrocephalus. *J Neurosurg* 50: 179-186, 1979
30. Laurence KM, Coates S: The natural history of hydrocephalus. Detailed analysis of 182 unoperated cases. *Arch Dis Child* 37: 345-362, 1962
31. Lorber J: When is a shunt no longer necessary? An investigation of 300 patients with hydrocephalus and meningomyelocele: 11-22 year follow-up. *Z Kinderchir* 34: 327-329, 1981
32. Martinez-Lage JF, Poza M, Lluch T: Craniosynostosis in neural tube defects: a theory on its pathogenesis. *Surg Neurol* 46: 465-469, 1996
33. McCullough DC, Balzer-Martin LA: Current prognosis in overt neonatal hydrocephalus. *J Neurosurg* 57: 378-383, 1982
34. McCullough DC, Johnson DL: Myelomeningocele repair: technical considerations and complications. 1988. *Pediatr Neurosurg* 21: 83-89; discussion 90, 1994
35. McDonnell GV, McCann JP: Why do adults with spina bifida and hydrocephalus die? A clinic-based study. *Eur J Pediatr Surg* 10 Suppl 1: 31-32, 2000
36. McLone DG: Care of the neonate with a myelomeningocele. *Neurosurg Clin N Am* 9: 111-120, 1998
37. McLone DG: Continuing concepts in the management of spina bifida. *Pediatr Neurosurg* 18: 254-256, 1992
38. McLone DG, Czyzewski D, Raimondi A, Sommers R: Central nervous system infections as a limiting factor in the intelligence of children with meningomyelocele. *Pediatrics* 70: 338-342, 1982
39. McLone DC, Partington MD: An approach to the management of arrested and compensated hydrocephalus. *Pediatr Neurosurg* 19: 101-103, 1993
40. Miller PD, Pollack IF, Pang D, Albright AL: Comparison of simultaneous versus delayed ventriculoperitoneal shunt insertion in children undergoing myelomeningocele repair. *J Child Neurol* 11: 370-372, 1996
41. Mirzai H, Ersahin Y, Mutluer S, Kayahan A: Outcome of patients with meningomyelocele: the Ege University experience. *Childs Nerv Syst* 14: 120-123, 1998
42. Morrow JD, Wachs TD: Infants with myelomeningocele: visual recognition memory and sensorimotor abilities. *Dev Med Child Neurol* 34: 488-498, 1992
43. Naidich TP, Pudlowski RM, Naidich JB, et al: Computed tomographic signs of the Chiari II malformation Part I: Skull and dura partitions. *Radiology* 134: 65-71, 1980
44. Naidich TP, Pudlowski RM, Naidich JB: Computed tomographic signs of Chiari II malformation II: Midbrain and cerebellum. *Radiology* 134: 391-398, 1980
45. Naidich TP, Pudlowski RM, Naidich JB: Computed tomographic signs of the Chiari II malformation III: Ventricles and cisterns. *Radiology* 134: 657-663, 1980
46. Naidich TP, McLone DG, Fulling KH: The Chiari II malformation: Part IV. The hindbrain deformity. *Neuroradiology* 25: 179-197, 1983
47. Parent AD, McMillan T: Contemporaneous shunting with repair of myelomeningocele. *Pediatr Neurosurg* 22: 132-135; discussion 136, 1995
48. Pinar H, Tatevosyants N, Singer DB: Central nervous system malformations in a perinatal/neonatal autopsy series. *Pediatr Dev Pathol* 1: 42-48, 1998
49. Proos LA, Dahl M, Ahlsten G, et al: Increased perinatal intracranial pressure and prediction of early puberty in girls with myelomeningocele. *Arch Dis Child* 75: 42-45, 1996
50. Ransohoff J, Mathews ES: Neurosurgical management of patients with spina bifida and myelomeningocele. *Med Clin North Am* 53: 493-496, 1969
51. Riva D, Milani N, Giorgi C, et al: Intelligence outcome in children with shunted hydrocephalus of different etiology. *Childs Nerv Syst* 10: 70-73, 1994
52. Rolle U, Grafe G: About the rate of shunt complications in patients with hydrocephalus and myelomeningocele. *Eur J Pediatr Surg* 9 Suppl 1: 51-52, 1999
53. Sainte-Rose C, Piatt JH, Renier D, et al: Mechanical complications of shunts. *Pediatr Neurosurg* 17: 2-9, 1991
54. Saukkonen A-L, Serlo W, von Wendt L: Epilepsy in hydrocephalic children. *Act Paediatr Scand* 79: 212-218, 1990
55. Sgouros S, Malucci CL, Walsh AR, Hockley AD: Long term complications of hydrocephalus. *Pediatr Neurosurg* 23: 127-132, 1995
56. Shurtliff DB: 44 years experience with management of myelomeningocele: presidential address, society for research into hydrocephalus and spina bifida. *Eur J Pediatr Surg* 10 Suppl 1: 5-8, 2000
57. Shurtliff DB, Foltz EL, Loeser JD: Hydrocephalus. A definition of its progression and relationship to intellectual function, diagnosis and complications. *Am J Dis Child* 125: 688-693, 1973
58. Steinbok P: Dysraphic lesions of the cervical spinal cord. *Neurosurg Clin N Am* 6: 367-376, 1995
59. Steinbok P, Irvine B, Cochrane DD, Irwin BJ: Long-term outcome and complications of children born with meningomyelocele. *Childs Nerv Syst* 8: 92-96, 1992
60. Strahl EW, Dückting M, Nahser C, Nau HE: Long-term follow-up studies in hydrocephalus patients with spina bifida or encephalocele. *Adv Neurosurg* 8: 247-251, 1980
61. Sutton LN, Adzick NS, Bilaniuk LT, et al: Improvement in hindbrain herniation demonstrated by serial fetal magnetic resonance imaging following fetal surgery for myelomeningocele. *JAMA* 282: 1826-1831, 1999
62. Swank M, Dias L: Myelomeningocele: a review of the orthopaedic aspects of 206 patients treated from birth with no selection criteria. *Dev Med Child Neurol* 34: 1047-1052, 1992
63. Talwar D, Baldwin MA, Horbatt CI: Epilepsy in children with meningomyelocele. *Pediatr Neurol* 13: 29-32, 1995
64. Teo C, Jones R: Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25: 57-63, 1996

65. Tulipan N, Bruner JP, Hernanz-Schulman M, et al: Effect of intrauterine myelomeningocele repair on central nervous system structure and function. *Pediatr Neurosurg* 31: 183-188, 1999
66. Tulipan N, Hernanz-Schulman M, Bruner JP: Reduced hindbrain herniation after intrauterine myelomeningocele repair: A report of four cases. *Pediatr Neurosurg* 29: 274-278, 1998
67. Van Roost D, Solymosi L, Funke K: A characteristic ventricular shape in myelomeningocele-associated hydrocephalus? A CT stereology study. *Neuroradiology* 37: 412-417, 1995
68. Vogl D, Ring-Mrozik E, Baierl P, et al: Magnetic resonance imaging in children suffering spina bifida. *Z Kinderchir* 42 (Suppl I): 60-64, 1987
69. Wassing HE, Siebelink BM, Luyendijk W: Handedness and progressive hydrocephalus in spina bifida patients. *Dev Med Child Neurol* 35: 788-797, 1993
70. Yashon D: Prognosis in infantile Hydrocephalus; past and present. *J Neurosurg* 20: 105-111, 1963
71. Yeates KO, Enrike BG, Loss N, et al: Verbal learning and memory in children with myelomeningocele. *J Pediatr Psychol* 20: 801-815, 1995
72. Young HF, Nulsen FE, Weiss MH, Thomas P: The relationship of intelligence and cerebral mantle in treated infantile hydrocephalus. *Pediatrics* 52: 38-44, 1973

Benign Pericerebral Collections in Children

SPYROS SGOUROS AND CHRISTOS TOLIAS

Introduction

Excess extracerebral accumulation of CSF over the brain and under the arachnoid matter in infants was first described by Dandy, who introduced the term “external hydrocephalus”, indicating that CSF is collecting in a site external to the brain itself [14]. The plethora of terminology used in the past for extracerebral collections has been confusing and reflected the poor knowledge of the condition. Terms such as “benign subarachnoid collections of childhood”, “benign enlargement of the subarachnoid spaces”, “external hydrocephalus”, “widened subarachnoid space”, “subdural haematoma” (collection of blood), “subdural effusion” (collection of proteinaceous fluid) and “subdural hygroma” (collection of CSF) have all been used to describe extracerebral collections. Most of these terms predate the discovery of computed tomography (CT) and derive their origin from the clinical observations of the fluid recovered during subdural taps. Several early clinical series included patients with subarachnoid and subdural collections, contributing to the confusion over management and outcome issues [8]. A clear distinction should be made between benign pericerebral collections of CSF, previously called “external hydrocephalus”, and subdural collections. The wider use of CT in the 1980s and magnetic resonance imaging (MRI) in the 1990s has contributed significantly to differentiating between the two conditions. In the former, excess CSF is accumulating underneath the arachnoidea mater, whereas in the latter excess fluid – usually altered blood mixed with CSF – is accumulating between the arachnoid and the dura mater. The clinical presentation of the two conditions can be similar with progressive enlargement of the head, but the natural history is often different and consequently the management differs. For subarachnoid collections of CSF the term “benign pericerebral collections”

probably reflects the anatomical basis of CSF distribution and the natural history of the condition better, and is therefore to be preferred.

Incidence of Benign Pericerebral Collections

The incidence of benign pericerebral collections among infants is unknown. It appears to be more common in boys. Apart from the absence of any population-based studies, an additional problem associated with the diagnosis of the condition is the lack of clear definition of what constitutes a pericerebral collection in an infant. It is established that in normal neonates and infants the subarachnoid spaces are wider than in older children, and this may persist for up to the 1st year of life [21, 42]. It is not clear, though, when the normal prominent subarachnoid spaces become benign pericerebral collections of CSF. In most published series the diagnosis is made on the basis of disproportionate enlargement of the frontoparietal subarachnoid spaces on CT or MRI, without any attempt to quantify that enlargement. Differentiation from cerebral atrophy is equally unclear and has usually been based on the presence on non-increasing head circumference, associated with a uniform enlargement of subarachnoid spaces.

Pathophysiology of Benign Pericerebral Collections

The pathophysiology of benign pericerebral collections is not well defined. Many authors regard this condition as a variation of the normal growth pat-

tern. Following clinical and radiological observations a view has been proposed that at birth the subarachnoid spaces are normal, they can enlarge in the first few months of life when sutures are open, and gradually the collections fade away until they have disappeared by the time the sutures are closed [28]. It is conceivable that the redistribution of CSF in the first few months of life is associated with the direct exposure of the intracranial cavity to the atmospheric pressure through the open fontanelles. Another view postulates that anatomical or functional obstruction at the level of the arachnoid villae causes accumulation of CSF and dilatation of the subarachnoid spaces [9]. It has not been established, though, why the enlargement of the subarachnoid spaces is seen in the frontal and parietal regions. One can only postulate that it is a gravity-related phenomenon, as it is seen mostly in neonates and infants, who spent most time in the horizontal position, being unable to walk as yet. The term "external hydrocephalus" has always caused confusion with the true hydrocephalus. Intracranial CSF pressure has been measured in children with benign pericerebral CSF collections and has been found to be normal [35].

Clinical Features of Benign Pericerebral Collections

Clinical presentation can be with progressive enlargement of the head in the first few months of life, disproportionate to the remaining body growth. The head circumference usually crosses the centiles and often climbs well over the 95th parallel [2, 12, 28, 30, 33, 34, 48], although pericerebral collections have been observed in children with normal head circumference who underwent a CT scan for some other reason. Indeed, in a series of 67 children with widened subarachnoid spaces only 22% had macrocrania [36]. In another series of 63 patients, none had increased head circumference [35]. A significant proportion of children (20%) with benign pericerebral collections have been born prematurely [1]. In a large proportion of patients, up to 88%, a history of macrocrania among parents has been described [1, 48]. A history of abnormal delivery is reported on some occasions [35, 48]. Normal development is usually reported by the parents, although some developmental delay has been reported in up to 25% of children [1, 35]. Features of intracranial hypertension are usually absent both in the history and on examination. In the majority of patients no predisposing cause can be

identified for the CSF collections. In a small proportion of patients other associated conditions co-exist, such as epilepsy or a variety of genetic syndromes, such as achondroplasia, craniosynostosis, Beckwith syndrome, Soto syndrome, Goldenhar syndrome, Weaver syndrome and others, most of which can be associated with various forms of developmental delay and should be considered when advising parents on long-term prognosis.

Neuroradiological Findings

Before the development of modern digital imaging, a typical investigative approach to children with enlarging head circumference would be the performance of diagnostic subdural taps, followed by subdurography, radionuclide scan, air ventriculography or encephalography as appropriate [18, 39]. Technological progress in the field of radiology has made invasive techniques obsolete, which in turn lead to a lower threshold of investigation, resulting in more children undergoing imaging and in consequence a clearer knowledge of the condition. Diagnosis can be made with ultrasound imaging [13, 15, 44], but the methods of choice are CT and MRI. Ultrasound is available more readily to community paediatricians and can be used as a first quick measure in the investigation of a child with an enlarging head, excluding large space-occupying lesions. It can demonstrate clearly the deeper position of the cortical surface, and the widened subarachnoid spaces and interhemispheric fissure [44]. It can differentiate between subarachnoid and subdural collections. In a study comparing ultrasound and MR findings in seven children – four with benign pericerebral CSF collections and three with subdural collections – it was noted that in all cases ultrasound could differentiate between the two pathologies correctly [15]. The use of a 10-MHz probe was particularly helpful in identifying different components of the collections. The combined use of colour-Doppler imaging has also been reported as useful in discriminating between the two conditions [13]. The positive cortical vein sign has been described: colour-coded veins are seen crossing subarachnoid fluid collections at the cerebral convexities [13]. This sign was regarded as pathognomonic in a comparative study of 18 patients: concordance of diagnosis was seen in all patients when ultrasound and MR imaging were compared [13]. While the non-invasive nature of ultrasonography is appealing, the end-result is operator-dependent, which can be a problem when appropriate expertise is not available.

A more reliable and objective modality is the CT scan, which shows a considerable amount of CSF over the convexity of the brain parenchyma, usually more prominent in the frontal and parietal regions, and an enlarged interhemispheric fissure anteriorly (Fig. 1a). In the majority of patients (80%) the collections are bilateral [25, 36]. Mild or even moderate ventriculomegaly has been observed in up to 70% of the patients, but ventricles are normal in up to 30% of the patients [12]. Contrast-enhanced CT can help differentiate subarachnoid from subdural collections by the position of enhancing cortical blood vessels: in subarachnoid collections the vessels are seen traversing the collection, whereas in subdural collections the vessels are seen compressed on the cortical surface of the brain. In addition, subdural collections often are of greater density than CSF [22, 25, 28, 32, 33-36, 48]. The collections can be classified as to extent according to whether they occupy a frontal disposition only, or whether they extend and separate the anterior interhemispheric fissure, or whether in addition they dilate the cortical sulci as well (grade I, II and III or convexity-falk-sulcus type, respectively) [32, 36].

CT scan is not always reliable [30], and imaging in the brow-down position has been employed to enhance the detection rate. In cases where CT cannot resolve the difference between a subarachnoid collection and an isodense subdural one, MRI scan can significantly help to differentiate between the two conditions, in particular when a combination

of T1-, T2-weighted and proton density sequences are employed [4, 50]. In subarachnoid collections the fluid has an intensity similar to that of CSF, the vessels that cross the subarachnoid space are clearly seen as flow voids within the extracerebral collection, and the collected fluid follows the brain parenchyma in the sulci, often splaying them open (Fig. 1 b, c). In subdural collections the fluid has an intensity greater than that of CSF, no flow voids attributable to blood vessels are seen within the collections, the cerebral sulci are compressed and the arachnoid membrane is often clearly seen as a separate structure [4, 15, 22, 48] (Fig. 2). It is not unusual to have coexistence of subarachnoid and subdural collections, which can vary in appearance between the two sides of the head [32, 34].

An important issue is differentiation from cerebral atrophy. This issue is more important in children who have an apparent degree of developmental delay, and some other potential cause of cerebral atrophy. Differentiation between the two conditions has a significant bearing on prognosis. Radiological criteria for differentiation between the two conditions are not very rigid. Cerebral atrophy is usually diagnosed in children with normal or low head circumference for age, whose scans show a uniform enlargement of subarachnoid spaces, with wide dilatation of cortical sulci in all regions of the brain, and an element of ex vacuo ventriculomegaly. Sometimes, though, differentiation between pericerebral CSF collections and cerebral atrophy is not easy.

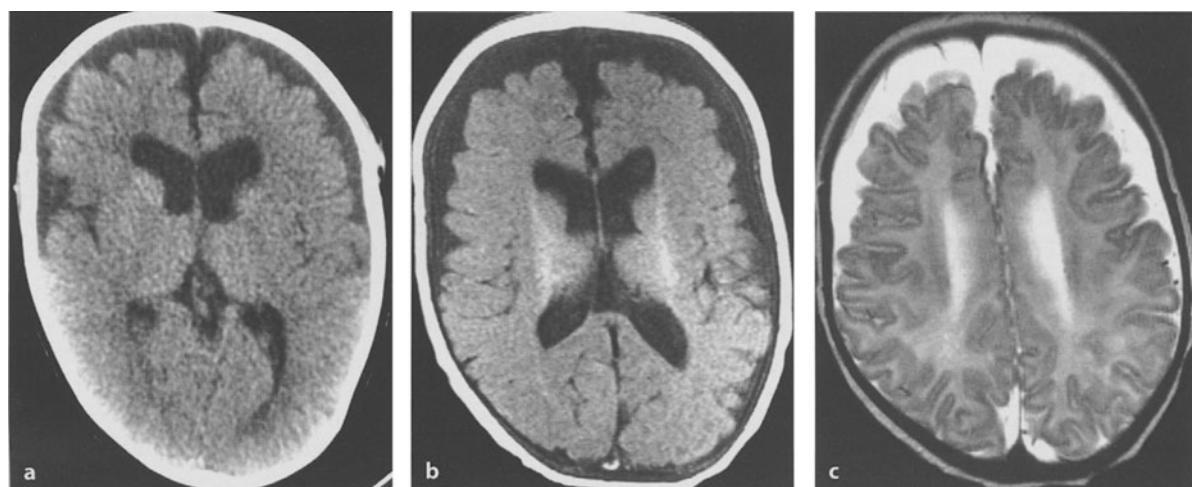


Fig. 1a-c. Benign pericerebral collections. **a** CT scan of a 4-month-old boy who presented with macrocephaly and seizures. Enlarged subarachnoid spaces are seen in the frontal regions. The anterior interhemispheric and right sylvian fissures are splayed open. Mild ventriculomegaly is present. **b** T1-weighted MRI scan, showing signal intensity in the pericerebral collections similar to ventricular CSF. The fluid of the collections "enters" the sulci, splaying them open. **c** T2-weighted MRI scan, showing clear signal voids from cortical veins, traversing the collections from the dura to the surface of the brain

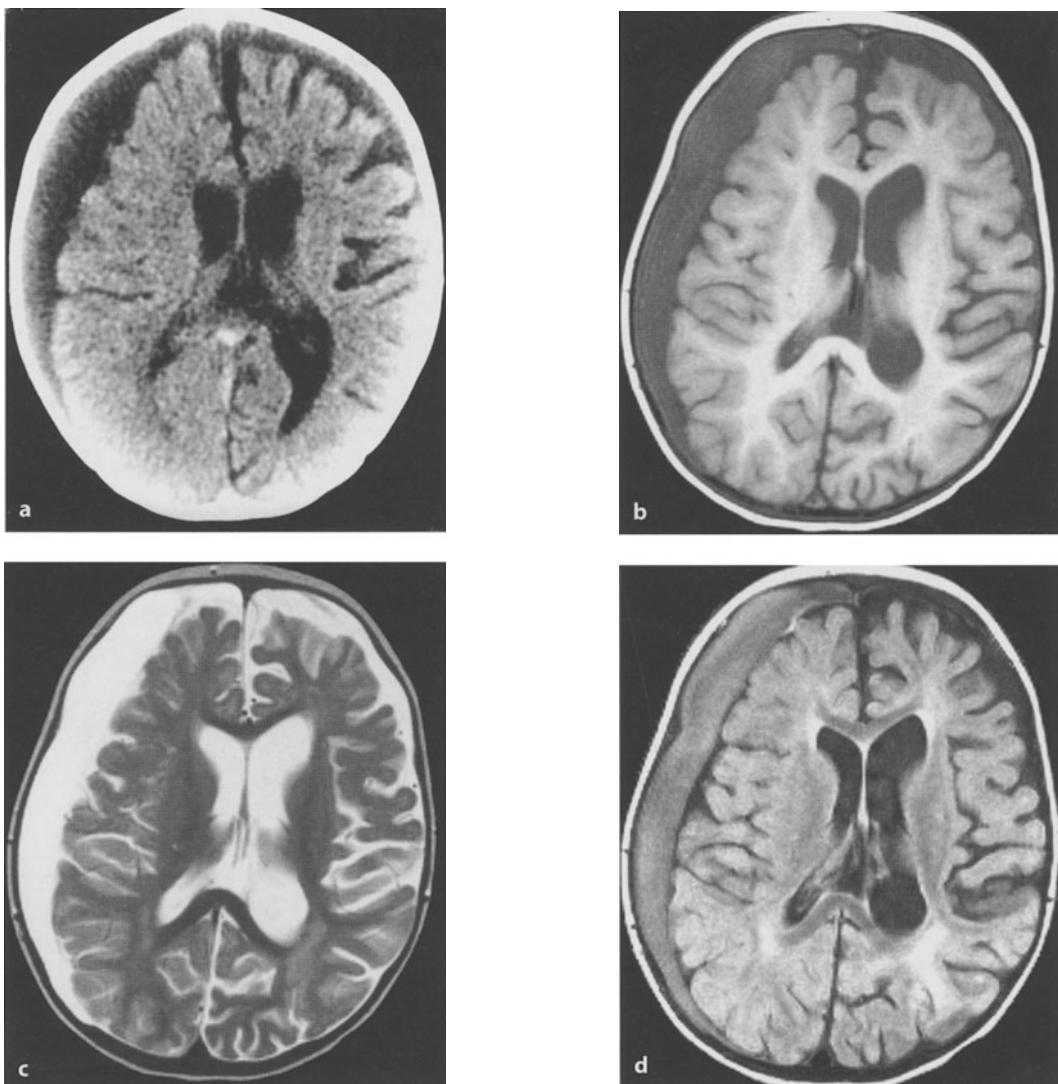


Fig. 2a-d. Subdural collections. **a** CT scan of a 10-month-old girl who had received anti-coagulation medication for heart surgery for several months. There is a collection overlying the convexity of the right hemisphere, compressing the underlying cortex. The signal is of mixed density. The ventricular cavities are slightly dilated. **b** T1-weighted MRI scan showing the right convexity collection. The signal intensity inside the collection is higher than that of the ventricular CSF. The collection does not enter the sulci but compresses them. The subarachnoid space appears separate underneath the collection, as a lower-intensity signal inside the sulci. On the left side the subarachnoid spaces are prominent over the frontal pole. **c** T2-weighted MRI scan, showing the right subdural collection. There are no signal-void blood vessels traversing the collection. In contrast, in the region of the left frontal pole there are vessels traversing the subarachnoid space, from the dura to the cortical surface. **d** Proton-density MRI scan, showing clearly the difference in signal intensity between the right subdural collection and the enlarged subarachnoid spaces on the left frontal region

Natural History of Benign Pericerebral Collections

Differentiation between benign subarachnoid CSF collection and subdural collection is important from the management point of view: the former requires no surgical treatment, the latter some form

of drainage. The outcome of benign subarachnoid collections is usually good without any surgical treatment: most children develop well, the head enlargement tends to arrest by 15–18 months and in most cases the collections disappear by 2 years of age. In a small proportion of children subtle motor developmental dysfunction can be identified with detailed testing [41]. In a study of 74 megalen-

cephalic children, one-third of them showed some form of delay, but there was no difference between children with normal and those with enlarged subarachnoid spaces [23]. There were some early reports of surgical drainage of subarachnoid collections, which invariably came to the conclusion that surgical drainage was unnecessary [2]. Several publications reported stabilization and even reduction of head circumference following conservative treatment and observation, and overall good developmental outcome [25, 28, 33, 36]. The evolution of the radiological appearance of the collections has been investigated with serial imaging: in a good proportion of children the collections remain unchanged, and in a significant proportion they decrease in size or disappear entirely [1, 36, 48]. Occasionally a corresponding decrease in ventricular size is observed [12, 36]. In a small proportion of patients poor outcome has been reported in association with coexisting epilepsy and in the presence of history of traumatic delivery [33, 35]. The view has been expressed that in the presence of marked ventricular enlargement a ventriculoperitoneal shunt should be inserted [48]. In most cases with marked ventriculomegaly the primary pathology is hydrocephalus, and differentiation is helped by the presence of periventricular lucency on CT scan, indicating increased tension inside the ventricular system.

Benign Pericerebral Collections and Subdural Haematoma

Subdural haematoma in infants following trauma or meningitis was first described by Ingraham and Matson, respectively, in their classic publications from the 1940s [19, 26]. Under normal circumstances in older children and adults, dura and arachnoid are in contact and the subdural space is collapsed, containing only a minute amount of CSF – less than 1 ml in total [49]. For reasons not entirely clear, at the two ends of the life spectrum – very young and very old – it is possible to have accumulation of fluid between these two membranes, giving rise to subdural collection. It has been suggested that the underlying pathophysiological mechanism leading to the formation of subdural collection includes regional breakdown of the arachnoid membrane [37], which allows accumulation of fluid – CSF and/or blood – in the space between dura and arachnoid. It has been postulated that an episode of hypoxia in the perinatal period may contribute to the immaturity leading to arach-

noid tear [39].

The incidence, cause and natural history of subdural collections in children is not well described at present, and is often a great source of anxiety when seen in the context of suspected non-accidental injury in very young children [16]. Apart from suspected shaking, other common causes include meningitis and complication of ventricular shunting. In a large proportion of children, usually in the first few months of life, no cause for the subdural collections is found and they are called spontaneous or idiopathic. For such cases there is still debate whether the cause is unrecognized shaking injury or birth trauma. There is increasing evidence that normal labour – in the absence of any form of instrumentation – can be potentially the cause of subdural haematomas seen in children during the first few months of life. In a large survey of nearly 5000 CT scans, 87 children were found with subdural collections, giving an approximate incidence of 1.5 per 1000 living infants [39]. Such a study inevitably would miss all the children who were never imaged, for a variety of reasons such as absence of severe symptoms or poor access to health services. The young age of these patients (70% less than 12 months, 90% less than 9 months of age) may indicate that the cause of the subdural collections could be found in the perinatal period [31, 39, 40]. In a large study of 600 000 live births, normal labour was found to be associated with various forms of intracranial haemorrhage in as many as 1 per 1900 live births [46]. The issue has particular medicolegal connotations in view of the child protection issues involved, but unfortunately conclusive evidence is still lacking. The incidence of subdural collection after meningitis can be as high as 10%-50% [26, 43]. Subdural collections have been reported in association with a variety of conditions including coagulopathy, vitamin K deficiency, leukaemia, central venous sinus thrombosis, otitis media, Kawasaki disease and juvenile xanthogranuloma.

A clear distinction should be made between traumatic acute subdural haematoma and chronic infantile subdural collections. Acute subdural haematoma due to direct trauma or extreme acceleration/deceleration injury largely follows the pathological process known from adult head injury and almost always has associated brain damage in the form of diffuse axonal injury, brain swelling and petechial haemorrhages in deep brain structures. Chronic infantile subdural collections, on the other hand, have an entirely different pathological process. The suggested mechanism of formation of an arachnoid tear, which enables CSF and blood from the subarachnoid space to gain access into the subdural space, probably

applies to the majority of cases of subdural collections. This arachnoid tear can happen spontaneously due to immaturity in very young children, or due to some form of “trauma” such as shaking or sudden decompression of the ventricular system during shunting, which leads to collapse of the cortical surface. Such trauma can cause rupture of the draining cortical veins.

There is an association between benign pericerebral subarachnoid CSF collections and subdural collections. Clinical studies have reported a higher incidence of subdural haematoma in children with pre-existing benign subarachnoid collections and development of spontaneous idiopathic subdural collections in children who were under surveillance for benign pericerebral collections [20, 23, 34]. We have also encountered children with the combination of unilateral subdural collection and a contralateral benign pericerebral CSF collection. All these observations probably support the theory of an arachnoid tear. In cases of subdural effusions associated with meningitis it is less clear how the fluid gains access to the subdural space. A potential mechanism is formation of inflammatory thrombophlebitis of extracerebral draining veins secondary to the infection, leading to exudate release which dissects the subdural space open [17, 43, 49].

The clinical presentation varies depending on the cause of the subdural collection. In idiopathic cases, usually there is no episode of acute deterioration, but rather a slowly progressive head enlargement, sometimes associated with motor and other neurodevelopmental delay. In post-meningitic cases, there is the history of previous infection and a subsequent history of head enlargement associated with progressive clinical deterioration showing in such forms as irritability, poor feeding pattern, progressive deterioration of level of consciousness and often continuing epilepsy [17, 26, 43]. In cases associated with one of the other causative conditions, the pattern is similar, without the history of the infective illness. In the case of shaking injury there is usually a well-defined description of rapid clinical deterioration of level of consciousness soon after injury [16]. The history of injury, though, is usually not volunteered by the parents or carers. In children in the first few months of life the condition manifests with irritability and change in the way they “handle”, followed soon by progressive lethargy and loss of consciousness. Often, in cases of repeated child abuse a history of failure to thrive is present. It is increasingly believed that in the context of non-accidental injury, shaking alone is not enough to cause the subdural collection, but impact is needed in addition [16].

Diagnosis is made with CT and MRI. On CT scan there are low-density collections over the convexity of the brain parenchyma, usually with a density higher than that of ventricular CSF (Fig. 2a). Not uncommonly, because of the different densities between CSF and subdural fluid, the level of the arachnoid layer can be traced circumferentially around the brain. The subdural collections do not enter the sulci. In 70% of cases the collections are bilateral, but in a minority are unilateral only [24, 29, 39, 40, 47, 48]. In approximately half of the patients the collections are less than 7 mm in thickness [39]. In most cases the collections are in the frontoparietal regions and the anterior interhemispheric fissure (70%) [20, 39]. In a significant proportion there is a degree of ventricular dilatation [20]. Coexistence of subdural and subarachnoid collections is well described [20, 34]. It is difficult to establish whether the presence of ventricular dilatation and subarachnoid collections predisposes to formation of subdural haematoma, or whether the presence of subdural haematoma causes a degree of impairment of CSF absorption. In cases of similar densities of fluid in the subdural and subarachnoid space, such as in an isodense subdural collection, CT scan may not be able to differentiate between benign subarachnoid and subdural collections. In such cases MRI scan differentiates very well between the two in all cases, given a combination of T1-weighted, T2-weighted and proton density sequences, as discussed already [4, 15, 22, 48] (Fig. 2 b, c, d). The differentiation between haematoma, effusion and hygroma is not always easy. In a minority of cases, fresh high-density fluid – presumed blood – is seen in the subdural space. In most cases, though, it is not easy to have a conclusive view on the composition of the subdural fluid from the radiological appearance. In any case, the composition of the subdural fluid – fresh blood, altered blood or proteinaceous CSF – is probably of very little consequence from the clinical management point of view. In cases of acute non-accidental head injury there are often other signs indicating the severity of the impact, such as subarachnoid haemorrhage, brain swelling or hypoxic damage with reversal sign in the basal ganglia [16]. In cases of repeated episodes of haemorrhage or infection, layers of old low-density fluid and new high-density fluid can be seen. Dating the subdural haemorrhages is particularly important in the context of suspected non-accidental injury, and in most cases this is neither easy nor precise.

The management of subdural collections is controversial. Reports in the literature support six different modalities: conservative management (no surgery, observation alone), repeated subdural taps, burr hole drainage, external subdural

drainage, subdural shunting, and craniotomy with open drainage. Several studies report spontaneous resolution of the subdural collections without any surgical treatment [31, 38, 45]. Unilateral subdural collections and bilateral collections with a thickness less than 7 mm on CT scan may have better chance of resolving spontaneously [39] (Fig. 3). In

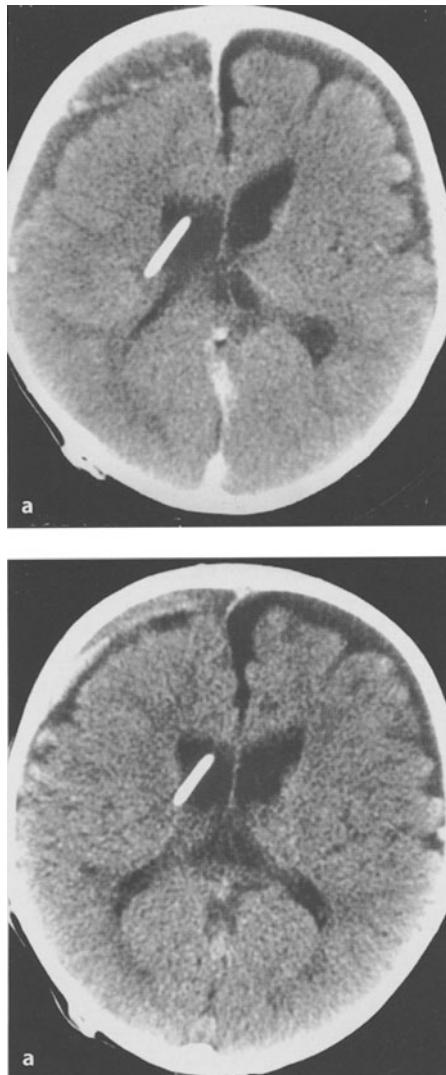


Fig. 3a, b. Subdural collection after ventriculoperitoneal shunting. Spontaneous resolution without surgical intervention. **a** CT scan of an 18-month-old child, shunted for hydrocephalus. A month after the operation he presented with a focal seizure. There was a right frontal subdural haematoma. The underlying cerebral hemisphere was compressed and distorted. **b** Following a 2-month period of observation without surgical intervention, repeat CT scan showed partial resolution of the subdural collection. The mass effect on the underlying cerebral hemisphere had resolved and the brain had a more normal disposition

cases of progressive head enlargement or clinical evidence of raised intracranial pressure, other studies describe resolution of the subdural collections following repeated subdural taps, which can take up to 17 taps over a period of 2 months [6, 10, 17, 27, 43]. In a high proportion of patients (up to 40%), repeated subdural taps fail to control the size of the subdural collections, and other forms of surgical intervention are required [3, 45]. Burr hole drainage has been employed, but does not seem to confer any additional advantage over the repeated subdural taps, and has been found to be associated with a high infection rate as well as a high failure rate, necessitating subsequent shunting [17, 27, 45]. External subdural drainage has been employed [11]. It has the advantage of not committing the patient to a permanent shunt, but the disadvantages of external drains, including mechanical and infective complications. The quickest and most effective method of eliminating the subdural collections appears to be the surgical insertion of a subdural-peritoneal shunt. Although invasive, it has a reported success rate in eliminating subdural collections as judged by CT scan of 80%-100% [24, 40, 45, 47] (Fig. 4). Unilateral shunt controls bilateral collections sufficiently [5, 7, 24, 40]. In most cases an unvalved shunt is sufficient [24, 40]. Subdural shunts, though, have a reported obstruction rate of up to 14% and an infection rate of 5% [24, 29, 40, 47]. Some surgeons prefer to remove the subdural shunts after a period of 3-6 months, to avoid long-term problems with the implanted shunt material, although this is not a universally accepted practice. This subjects the child to a second operation, and leaving the shunt behind either by choice or due to parental preference could be seen as a perfectly acceptable course. Craniotomy is reserved for complicated cases where repeat episodes of haemorrhage or infection have caused formation of membranes in the subdural space with entrapped loculated collections [6, 17, 26, 45].

Outcome following drainage of the subdural collections is good in general. Any associated condition such as meningitis, bleeding diathesis, epilepsy or other rare syndromes influence outcome. Non-accidental child abuse cases have a poorer outcome due to the often associated ischaemic brain injury. Following drainage of the subdural collections, it has been observed on serial CT scanning that initially the subdural collection decreases in size and subarachnoid CSF spaces enlarge, and subsequently the situation returns to normal, with complete resolution of the subdural collections and return of the configuration of the pericerebral subarachnoid spaces to normal [32].

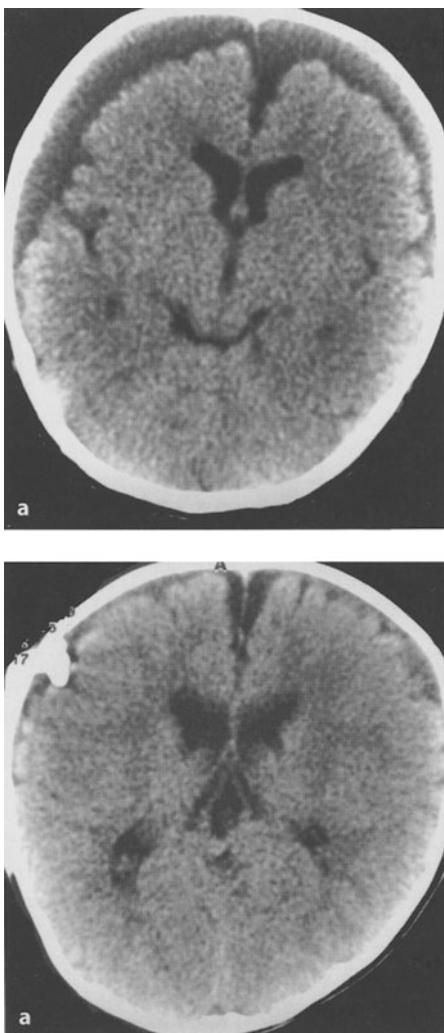


Fig. 4a, b. Surgical treatment of subdural collection with subdural-peritoneal shunt. **a** CT scan of a 5-month-old boy presenting with increasing head circumference. Bilateral subdural collections are present. The fluid of the collections has higher density than the underlying subarachnoid CSF, which creates a circumferential black halo around the brain. **b** CT scan obtained 4 months after insertion of a subdural-peritoneal shunt. The subdural collections had resolved completely. The subdural shunt was removed shortly afterwards

References

1. Alvarez LA, Maytal J, Shinnar S: Idiopathic external hydrocephalus: natural history and relationship to benign familial macrocephaly. *Pediatrics* 77: 901-907, 1986
2. Andersson H, Elfverson J, Svendsen P: External hydrocephalus in infants. *Child's Brain* 11: 398-402, 1984
3. Aoki N: Chronic subdural hematoma in infancy. Clinical analysis of 30 cases in the CT era. *J Neurosurg* 73: 201-205, 1990
4. Aoki N: Extracerebral fluid collections in infancy: role of magnetic resonance imaging in differentiation between subdural effusion and subarachnoid space enlargement. *J Neurosurg* 81: 20-23, 1994
5. Aoki N, Masuzawa H: Bilateral chronic subdural hematomas without communication between the hematoma cavities: treatment with unilateral subdural-peritoneal shunt. *Neurosurgery* 22: 911-913, 1988
6. Aoki N, Masuzawa H: Infantile acute subdural hematoma. Clinical analysis of 26 cases. *J Neurosurg* 61: 273-280, 1984
7. Aoki N, Miztani H, Masuzawa H: Unilateral subdural-peritoneal shunting for bilateral chronic subdural hematomas in infancy. *J Neurosurg* 63: 134-137, 1985
8. Baraton J, Brunelle F, Pierre Kahn A, et al: [X-ray computed tomography coupled with cisternography in chronic pericerebral effusions in young children] *Neurochirurgie* 35: 395-400, 411, 1989
9. Barlow CF: CSF dynamics in hydrocephalus, with special attention to external hydrocephalus. *Brain Dev* 6: 119-127, 1984
10. Briner S, Bodensteiner J: Bening subdural collections of infancy. *Pediatrics* 67: 802-804, 1981
11. Brotchi J, Bonnal J: Surgical treatment of subdural effusions in infants. *Acta Neurochir* 33: 59-67, 1976
12. Carolan PL, McLaurin RL, Towbin RB, Egelhoff JC: Benign extra-axial collection of infancy. *Pediatr Neurosci* 12: 140-144, 1986
13. Chen CY, Chou TY, Zimmerman RA, et al: Pericerebral fluid collection: differentiation of enlarged subarachnoid spaces from subdural collections with color doppler US. *Radiology* 201: 389-392, 1996
14. Dandy WE, Blackfan KD: Internal hydrocephalus: an experimental clinical and pathological study. *Am J Dis Child* 8: 406-482, 1914
15. De Vries LS, Smet M, Ceulemans B, et al: The role of high resolution ultrasound and MRI in the investigation of infants with macrocephaly. *Neuropediatrics* 21: 72-75, 1990
16. Duhaime AC, Gennarelli TA, Thibault LE, et al: The shaken baby syndrome: a clinical, pathological and biomechanical study. *J Neurosurg* 66: 409-415, 1987
17. Goodman JM, Mealey J: Postmeningitic subdural effusions: the syndrome and its management. *J Neurosurg* 30: 658-663, 1969
18. Harwood-Nash DC, Fitz CR: Large heads and ventricles in infants. *Radiol Clin North Am* 13: 199-224, 1975
19. Ingraham FD, Matson DD: Subdural hematoma in infancy. *J Pediatr* 24: 1-37, 1944
20. Kapila A, Rice B, Spies WG, et al: Enlarged cerebrospinal fluid spaces in infants with subdural hematomas. *Radiology* 142: 669-672, 1982
21. Kleinman PK, Zito JL, Davidson RI, Raftopoulos V: The subarachnoid spaces in children: normal variations in size. *Radiology* 147: 455-457, 1983
22. Kuzma BB, Goodman JM: Differentiating external hydrocephalus from chronic subdural hematoma. *Surg Neurol* 50: 86-88, 1988
23. Laubscher B, Deonna T, Uske A, van Melle G: Preimitive megalecephaly in children: natural history, medium term prognosis with special reference to external hydrocephalus. *Eur J Pediatr* 149: 502-507, 1990
24. Litofsky NS, Raffel C, McComb JG: Management of symptomatic chronic extra-axial fluid collections in pediatric patients. *Neurosurgery* 31: 445-450, 1992

25. Maytal J, Alvarez LA, Elkin CM, Shinnar S: External hydrocephalus: radiologic spectrum and differentiation from cerebral atrophy. *AJNR* 8: 271-278, 1987
26. McKay RJ, Ingraham FD, Matson DD: Subdural fluid complicating bacterial meningitis. *JAMA* 152: 387-391, 1953
27. McLaurin RL, Issacs E, Lewis HP: Results of nonoperative treatment in 15 cases of infantile subdural hematoma. *J Neurosurg* 34: 753-759, 1971
28. Ment LR, Duncan CC, Geehr R: Benign enlargement of the subarachnoid spaces in the infant. *J Neurosurg* 54: 504-508, 1981
29. Mircevski M, Boyadziev I, Mircevska D, Davkov S: Surgical treatment of acute subdural hygroma in children. *Childs Nerv Syst* 2: 314-316, 1986
30. Modic MT, Kaufman B, Bonstelle CT, et al: Megalencephaly and hypodense extracerebral fluid collections. *Radiology* 141: 92-100, 1981
31. Mori K, Handa H, Itoh M, Okuno T: Benign subdural effusion in infants. *J Comput Assist Tomogr* 4: 466-471, 1980
32. Morota N, Sakamoto K, Kobayashi N, et al: Infantile subdural fluid collection: diagnosis and post-operative course. *Childs Nerv Syst* 11: 459-466, 1995
33. Nickel RE, Galenstein JS: Developmental prognosis of infants with benign enlargement of the subarachnoid spaces. *Dev Med Child Neurol* 29: 181-186, 1987
34. Nishimura K, Mori K, Sakamoto T, Fujiwara K: Management of subarachnoid fluid collection in infants based on a long-term follow-up study. *Acta Neurochir (Wien)* 138: 179-184, 1996
35. Nogueira GJ, Zaglul HF: Hypodense extracerebral images on computed tomography in children. "External hydrocephalus": a misnomer? *Childs Nerv Syst* 7: 336-341, 1991
36. Odita JC: The widened frontal subarachnoid space. A CT comparative study between macrocephalic, microcephalic and normocephalic infants and children. *Childs Nerv Syst* 8: 36-39, 1992
37. Oi S, Matsumoto S: Natural history of subdural effusion in infants. Prospective study of 87 cases. *J Pediatr Neuropediatr* 4: 15-24, 1988
38. Robertson WC, Chun RWM, Ormison WW, Sackett JF: Bening subdural collections of infancy. *J Pediatr* 94: 382-385, 1979
39. Rothenberger A, Brandl H: Subdural effusions in children under two years - clinical and computer tomographic data. *Neuropediatrics* 11: 139-150, 1980
40. Sakka L, Cinalli G, Sainte-Rose C, et al: Subduro-peritoneal shunting in children. *Childs Nerv Syst* 13: 487 (abstract), 1997
41. Sandler AD, Knudsen MW, Brown TT, Christian RM Jr.: Neurodevelopmental dysfunction among nonreferred children with idiopathic megalencephaly. *J Pediatr* 131: 320-324, 1997
42. Shapiro R, Galloway SJ, Shapiro MD: Minimal asymmetry of the brain: a normal variant. *AJR* 147: 753-756, 1986
43. Syrigiannopoulos GA, Nelson JD, McCracken GH: Subdural collections of fluid in acute bacterial meningitis : a review of 136 cases. *Pediatr Infect Dis* 5: 343-352, 1986
44. Trounce JQ, De Vries L, Levene MI: External hydrocephalus-diagnosis by ultrasound. *Br J Radiol* 58: 415-417, 1985
45. Tolias C, Sgouros S, Walsh AR, Hockley AD: Outcome of surgical treatment for subdural collections in infants. In press *Pediatr Neurosurg* 33: 194-197, 2000
46. Towner D, Castro MA, Eby-Wilkens E, Gilbert WM: Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 341: 1709-1714, 1999
47. Vinchon M, Noulet N, Soto-Ares G, et al: Subduroperitoneal drainage for subdural hematomas in infants: results in 244 cases. *J Neurosurg* 95: 248-254, 2001
48. Wilms G, Vanderschueren G, Demaerel PH, et al: CT and MR in infants with pericerebral collections and macrocephaly: benign enlargement of the subarachnoid spaces versus subdural collections. *AJNR* 14: 855-860, 1993
49. Winston KR, Arnholz D: Extracerebral fluid collections. In: Albright L, Pollack I, Adelson D (eds) *Principles and practice of pediatric neurosurgery*, Thieme, New York, pp 261-269, 1999
50. Young IR, Bydder GM, Hall AS, et al: Extracerebral collections: recognition by NMR imaging. *AJNR* 4: 833-834, 1983

Hydrocephalus in Pediatric Patients with Posterior Fossa Tumours

CHRISTIAN SAINTE-ROSE

Introduction

The management of hydrocephalus associated with posterior fossa tumours in children has always been problematic: whilst the majority of patients will not require permanent CSF diversion, those patients who do so appear to suffer a stormier postoperative course [15] and are subject to the well-recognized problems associated with these devices. Although in the past it was often appropriate to shunt all these patients pre-operatively [2], technological advances in and changes in the availability of neuroimaging have allowed earlier diagnosis. Consequently, most paediatric neurosurgeons today use a combination of corticosteroids, early surgery and external ventricular drainage where necessary. In the literature, approximately one-third of patients overall will eventually require a shunt [15]. The factors associated with shunt placement have been retrospectively analysed [6, 15] and include young age (<10 years), midline tumours, incomplete tumour resection, CSF infection and persistent pseudomeningocele.

Internal CSF diversion is appealing given the obstructive nature of the hydrocephalus associated with these tumours [5, 11]. Despite this, third ventriculostomy remains under-utilized because of a number of concerns. Although the obstructive hydrocephalus may be controlled prior to tumour resection, there is a paucity of literature regarding the site of interference of CSF dynamics after tumour removal, making the long-term efficacy of the procedure unknown. More importantly, there is the question of safety in performing a third ventriculostomy in the presence of a large posterior fossa mass. On the other hand, the recent introduction of a protocol proposing high-dose chemotherapy before posterior fossa surgery in high-risk medulloblastomas raises the problem of curing the hydrocephalus before the onset of the chemotherapy.

This paper reports the findings of a study with the aim of addressing some of these issues.

Materials and Methods

Two hundred and six patients with posterior fossa tumours were admitted to the Paediatric Neurosurgical Department at the Hôpital Necker-Enfants Malades between 1 October 1993 and 31 December 1997. Ten patients in whom shunts had been inserted at the referring hospital were excluded from the present study. Of the remaining 196 patients, 186 underwent open posterior fossa surgery with the intention of gross tumour removal. The remaining ten patients underwent assessment and/or biopsy.

These patients, although not randomized, fell into three groups. In the first group (group A) the patients presented symptoms and/or signs of intracranial hypertension with ventricular dilatation on initial CT scan or MRI. In these patients an endoscopic third ventriculostomy was performed on admission according to the technique previously described [21]. Tumour surgery was then performed when convenient. In the second group (group B) the patients presented similarly to those in group A, but in these patients third ventriculostomy was not performed prior to posterior fossa surgery, mainly on the basis of personal surgical preference among the five staff neurosurgeons of the Department of Paediatric Neurosurgery. These patients were treated in a "conventional" fashion (steroids, early surgery, and ventricular drainage when needed). Group C consisted of those patients who had had no evidence of ventricular dilatation on initial CT scan.

The hospital records and imaging studies of the 196 patients were retrospectively reviewed with special attention paid to age, treatment of hydrocephalus (both type and timing of treatment), complications associated with treatment of hydrocephalus, operative position, site of tumour (midline, brainstem, involving the fourth ventricle, hemispheric or cerebellomedullary angle), extent of tumour resection at the time of posterior fossa surgery (complete, subtotal,

partial, biopsy), tumour pathology, postoperative course (CSF leak, pseudomeningocele and treatment), follow-up and shunt insertion or removal during the follow-up period.

On imaging studies the degree of ventricular dilatation was assessed and graded as normal, mild, moderate or severe by the same clinician who reviewed the initial CT scan. All patients underwent an MRI prior to the performance of third ventriculostomy or tumour removal. The site of the tumour and any evidence of metastatic disease were documented. All patients underwent a CT scan with and without contrast within 24 h of tumour removal which was used to grade the degree of tumour resection. Complete and subtotal resection showed no areas of contrast enhancement, whereas resection was considered as partial if areas of contrast enhancement were seen on the postoperative CT scan. In the initial phase of the study, patients undergoing third ventriculostomy were examined using cine MRI both before and after tumour surgery.

Results

Group A

There were 67 patients in group A. Their mean age at presentation was 6.6 years (median 5.7 years) (Table 1). Imaging studies confirmed severe ventricular di-

latation in 60% of the cases (Table 2). In addition 16 patients (23.8%) had evidence of metastatic spread. By definition, all the patients in group A had their hydrocephalus treated by an initial third ventriculostomy. There were no deaths and no permanent morbidity associated with this procedure. Four patients suffered immediate transient complications. One patient suffered a perioperative episode of presumed "upward herniation" requiring immediate posterior fossa tumour removal, with complete recovery. One had an incomplete third ventriculostomy that was repeated 2 days later with resultant clinical resolution. In the other two patients third ventriculostomy had to be aborted due to poor visibility. Thus 65 patients had a technically successful preliminary third ventriculostomy. All but one, i.e. 98%, had immediate symptomatic resolution. The mean time from ventriculostomy to posterior fossa surgery was 40 days (median 4 days, range 0-1703 days).

Most of the tumours in group A were midline. The details of location, pathology and extent of tumour resection are shown in Tables 3, 4 and 5. All except one underwent an attempt at gross total resection. Fifty-five patients underwent surgery in the sitting position, the remaining being operated upon in the ventral decubitus position. No substitute dural graft was used. The details of the postoperative complications are shown in Table 6. The mean follow-up was 786 days (median 661 days, range 1-2003 days).

Four patients ultimately required the implantation of a ventriculoperitoneal shunt for progressive hydrocephalus. One of these shunts was placed 19 days after

Table 1. Patient data in the three groups

	Group A	Group B	Group C
Mean age at presentation (years)	6.6	7.0	7.8
Age range at presentation	46 days-15 1 years	121 days-15 3 years	1.1 years-16 years
Percentage with metastases at presentation	24	19	11

Table 2. Severity of hydrocephalus at presentation in the three groups

	Group A (%)	Group B (%)	Group C (%)
Normal ventricles	0	0	100
Mild	9	26	
Moderate	31	38	
Severe	60	26	

Table 3. Tumour location in the three groups

	Group A (%)	Group B (%)	Group C (%)
Midline	67	56	21
Cerebellar hemisphere	14	23	32
Brainstem	9	12	30
Cerebellopontine angle	10	9	17

Table 4. Tumour histologies in the three groups

	Group A (%)	Group B (%)	Group C (%)
Medulloblastoma	46	35	13
Ependymoma	24	11	42
Astrocytoma	21	39	42
Ganglioglioma	3	0	2
Cavernoma	1	2	3
PNET	3	6	2
Meningioma	1	0	2
Other	1	7	19

PNET, primitive neuroectodermal tumour

Table 5. Extent of surgical resection in the three groups

	Group A (%)	Group B (%)	Group C (%)
Total	51	61	68
Subtotal	37	26	19
Partial	7	6	11
Biopsy	4	7	2

Table 6. Postoperative complications in the three groups

	Group A	Group B	Group C
Number of patients with postoperative complications	17/67 (25%)	31/82 (38%)	9/47 (19%)
Wound dehiscence (CSF leak)	8 (3)	12 (5)	5 (1)
Subdural collection (transient subdural shunt)	4 (2)	4 (1)	1 (1)
Pseudomeningocele (external lumbar drainage)	8 (2)	22 (5)	7 (4)
Epidural haematoma	1	5	1
Death	0	2	1

posterior fossa surgery because of postoperative signs of intracranial hypertension and the personal preference of the on-call surgeon. In another patient enrolled in a clinical trial of presurgical chemotherapy a shunt was inserted 21 days after third ventriculostomy. The remaining two patients had their shunts inserted 83 and 432 days respectively after posterior fossa surgery because of rapidly progressive subarachnoid seeding of their primary tumour. Of the four patients one had three episodes of shunt failure associated with dorsal mesencephalic dysfunction. A new endoscopic third ventriculostomy was performed. The stoma was found to be obstructed, was re-opened and the shunt removed.

Thirteen patients had tumour recurrence (10 in the posterior fossa, 2 as intracranial seeding, 1 as lumbar seeding). Only the two with intracranial seeding required a ventriculoperitoneal shunt (as mentioned above). One patient with a local recurrence of a posterior fossa ependymoma 4 years after preoperative third ventriculostomy, complete tumour removal and chemotherapy had the recurrence completely excised. He subsequently presented with increasing ventricular size, pseudomeningocele and gait disturbance whilst undergoing radiotherapy 8 months later. Cine MRI showed no flow through the stoma. Endoscopic third ventriculostomy was subsequently performed whereupon the stoma was found to be obstructed and was re-opened, with complete radiological and clinical resolution.

Group B

There were 82 patients in group B. The mean age at surgery was 7 years (median 6.3 years) (Table 1). On imaging studies, hydrocephalus was designated as moderate in 38% and severe in 26% of their cases (Table 2). Sixteen patients (19%) had evidence of metastatic spread.

The majority of the tumours in group B were midline. The details of localization, pathology and extent of resection are shown in Tables 3, 4 and 5 respectively. Seventy-six patients underwent an attempt at gross total resection, which was achieved in 71. Six patients underwent a biopsy only. The mean follow-up was 744 days (median 624 days, range 1-1697 days).

Sixty-six patients were operated upon in the sitting position, the remaining being operated in the ventral decubitus position. No substitute dural graft was used. External ventricular drainage was used in nine patients prior to tumour removal, in six at the time of surgery and in six patients in the postoperative period. Five patients required emergency evacuation of an extradural haematoma. Three of these were at the

site of the external ventricular drain and two occurred in the posterior fossa. All of these patients had been operated upon in the sitting position. Two patients died in the early postoperative period: one from acute intracranial hypertension 48 h after incomplete removal of a fourth ventricular medulloblastoma. The second was operated upon after an emergency external ventricular drainage failed to reverse the bilateral mydriasis present on admission. This patient died in the immediate postoperative period. The details of the operative complications are shown in Table 6.

Twenty-two patients (26.8%) presented symptoms and signs of intracranial hypertension with radiological evidence of active hydrocephalus following posterior fossa tumour surgery. In 16 patients the resection was considered to have been radiologically complete. The extent of surgical resection was not statistically significant in predicting the incidence of postoperative hydrocephalus ($p>0.02$). In 18 patients the hydrocephalus was diagnosed within 2 months of surgery. In the four patients in whom the development of hydrocephalus was delayed (6, 7, 7 and 28 months respectively), this occurred in the context of local recurrence or of subarachnoid seeding.

Sixteen patients were treated with a ventriculoperitoneal shunt at a mean of 107 days (median 20 days, range 10-845 days) after posterior fossa surgery. In two patients third ventriculostomy was performed for shunt malfunction, curing the hydrocephalus and allowing definitive removal of the shunt 5 months and 2 years respectively after shunt implantation.

In the remaining six patients the postoperative hydrocephalus was treated by endoscopic third ventriculostomy a mean of 16 days (median 7 days, range 3-42 days) after posterior fossa surgery. Two patients had evidence of tumour spread in the subarachnoid spaces at the time of third ventriculostomy. In all cases complete resolution of hydrocephalus was observed following the procedure and the patients remained symptom-free with a mean follow-up of 1.4 years.

Group C

There were 47 patients in group C, with a mean age at surgery of 7.8 years. The patients had no hydrocephalus on admission, the tumour being located in most cases in the cerebellar hemispheres or in the brain stem (Tables 2 and 3). Forty-six patients underwent an attempt at gross total removal; in one other biopsy alone was performed. The results of surgical resection are shown in Table 5. No exogenous dural substitute was used. One patient died of a sudden, un-

explained cardiac arrest 6 days after partial removal of a fourth ventricular medulloblastoma. The details of the operative complications are shown in Table 6. The mean follow-up was 756 days (median 638, range 1-1650 days).

Two patients (4.2%) presented symptoms and signs of intracranial hypertension with radiological evidence of active hydrocephalus 3 and 5 months respectively after posterior fossa surgery. They were treated with endoscopic third ventriculostomy and remained symptom-free with a mean follow-up of 2 years. No ventriculoperitoneal shunt was inserted postoperatively in this group.

Analysis of Results

Group A had significantly worse hydrocephalus than group B on admission ($p<0.01, \chi^2$). Despite there being no significant difference between groups A and B for all the other risk factors examined, group B patients presented a significantly higher incidence of postoperative hydrocephalus requiring surgical treatment ($p=0.001$) and had significantly more ventriculoperitoneal shunts inserted during the study period ($p<0.02$, Fisher's exact test). We observed fewer immediate postoperative complications in group A than in group B: 25% and 38% respectively. We observed (but were not able to quantify) a smoother postoperative course and a faster recovery, particularly in tumours adhering to the brain stem, in group A than in group B.

Discussion

The association of posterior fossa tumours with hydrocephalus, each a potentially lethal condition [19, 24], necessitates urgent surgical treatment in these seriously ill children. In the 1960s, when children presented in a poor clinical state due to a delayed diagnosis [15], the routine use of preoperative shunting [1, 10] significantly reduced the overall morbidity and mortality [2].

Improvements in the availability and in the types of neuroimaging now allow markedly earlier diagnosis. This, coupled with a growing awareness of "common" complications associated with ventricular shunting and rarer complications more specific to this patient population (such as upward herniation, tumour haemorrhage and peritoneal seeding of the intracranial tumour), caused neurosurgeons to question the need for routine shunt insertion [8, 9, 14, 16]. The result was a move towards a more ex-

pectant policy, with patients being treated with corticosteroids, early surgery and external ventricular drainage when needed [17, 20, 23]. Although theoretically appealing, this protocol was not without concern. External ventricular drainage used in this setting was not without risk both from the point of view of infection (4.9% according to Schmid and Seiler [22]) and from the risk of upward herniation or haemorrhage, with five patients in the present series developing intracranial haematoma subsequent to ventricular drainage, all of which required surgical evacuation. Of more concern, the more recent studies of this protocol have shown that ultimately 17%-40% of children [6, 7, 15, 18, 19, 22] with posterior fossa tumours have uncontrolled hydrocephalus and require shunt insertion during the postoperative period, with Culley et al. [6] and Lee et al. [15] reporting that this predominantly occurred within the first postoperative month. In adopting this expectant policy, those patients who ultimately require a shunt are placed at risk of intracranial hypertension, increased rate of CSF leak and pseudomeningocele formation [6, 15], prolonged hospitalization and a higher incidence of pseudobulbar palsy [15]. In the recent years, the implementation at our institution of a protocol requiring high-dose chemotherapy before posterior fossa surgery for patients affected by medulloblastomas with CSF spread at admission, raised the problem of curing the hydrocephalus before tumour removal. In these patients the treatment of hydrocephalus is a real challenge since any need for re-operation related to shunt failure during the phase of bone marrow transplant represents a life-threatening situation. For all these patients, arguably, we must do better.

Consequently, several authors have attempted to identify through retrospective analysis [6, 7, 15] those patients most at risk of requiring a shunt postoperatively and have identified several possible factors. Younger age at diagnosis has been shown to be significant by most [3, 6, 15, 18] but not all authors [7]. The severity of hydrocephalus prior to tumour surgery seems to be a predictor of shunt requirement in patients with medulloblastoma [15], but not in those with other histology [7, 18]. Midline localization [6, 15], incomplete tumour removal [6], the use of substitute dural grafts during closure [6], and higher Chang stages in medulloblastoma patients [15] are also considered by several to be significant risk factors for postoperative shunts. By contrast, tumour size and the use of external ventricular drainage [6] do not appear to have a direct prognostic effect [22].

In the present series, despite the lack of randomization, group A and group B patients were similar for all the above positive risk factors. In addition, group A patients had significantly more hydrocephalus on admis-

sion. Group C was, by definition, different. The rate of shunt insertion (16/82; 19.5%) in group B was in keeping with that found in the literature and would have been even higher if all the patients with postoperative hydrocephalus had been implanted with a ventriculoperitoneal shunt (six patients having been treated with third ventriculostomy). Patients in groups A and C presented a significantly lower rate of postoperative hydrocephalus. For group C, this probably means that in the present study it is possible to define retrospectively a group of patients with posterior fossa tumours without hydrocephalus on admission who are at low risk of postoperative hydrocephalus. Of more interest are those patients in group A in whom it is apparent that endoscopic third ventriculostomy had a curative effect on intracranial hypertension preoperatively and conceivably a prophylactic effect in the prevention of the development of hydrocephalus postoperatively. This is plausible when one considers the pathophysiology of hydrocephalus in these patients.

Preoperatively the development of hydrocephalus relates to the nature and localization of these tumours. Tumours arising from within the fourth ventricle fill and obstruct the ventricular cavity and its foraminal outlets. Cerebellar hemisphere tumours, on the other hand, induce severe anatomical distortion of the fourth ventricle with subsequent occlusion of the CSF pathways. Subarachnoid seeding may be present at diagnosis in patients with malignant tumours, favouring impairment of the subarachnoid pathways.

Logically, complete removal of the tumour re-establishes communication between the fourth ventricular cavity and the subarachnoid spaces, restoring a physiological CSF circulation and allowing resolution of hydrocephalus. Nevertheless, in the immediate postoperative period, an acute increase of resistance in the CSF circulation and resulting intracranial hypertension may be induced by two factors, the surgical subarachnoid haemorrhage, and the presence of cerebellar swelling. Later on, one-fourth to one-third of the patients remain hydrocephalic. The success rate of third ventriculostomy reported in this series confirmed the obstructive nature of these cases of post-operative hydrocephalus. The secondary development of adhesions at the level of the fourth ventricle outlets and the adjacent cisterns may permanently alter CSF hydrodynamics. This hypothesis matches with the higher frequency of postoperative hydrocephalus after the vermis has been split and the cisterna magna opened in order to gain access to the tumour. Finally, hydrocephalus may develop several months or years following the primary surgery, at the time of a local recurrence or of subarachnoid spread.

The obstructive nature of hydrocephalus in posterior fossa tumours, localized to the level of the fourth ventricular outlets both pre- and postoperatively, pro-

vides the rational basis for the curative effect of endoscopic third ventriculostomy. The significant reduction in the rate of postoperative hydrocephalus seen in our patients who underwent preliminary third ventriculostomy compared to those whose hydrocephalus was controlled perioperatively by ventricular drainage suggests that an additional prophylactic effect was in evidence. Preoperative normalization of CSF hydrodynamics seems to reduce the risk of occurrence of permanent postoperative impairment of the CSF circulation.

Rationally, third ventriculostomy would appear to be the procedure of choice in the postoperative control of hydrocephalus in patients with posterior fossa tumours. Yet there is a noticeable lack of information regarding this in the literature. Jones et al. [12] reported on the use of third ventriculostomy in the postoperative period in 2 patients – one procedure being performed 3 days after surgery for recurrent medulloblastoma, which was successful, and the second 3 years after excision of an ependymoma and radiotherapy, which proved technically impossible to perform due to haemorrhage.

In the present series endoscopic third ventriculostomy was performed in eight cases following posterior fossa surgery (6 in group B, 2 in group C) and successfully managed to control the hydrocephalus in all cases, even in the presence of subarachnoid seeding of the tumour, evident at the time of the procedure. A further three patients who had undergone postoperative shunting and who subsequently had episodes of shunt malfunction were able to have had their hydrocephalus successfully treated by third ventriculostomy [4].

The low morbidity and mortality associated with this technique reaffirm its validity as an alternative to ventricular shunting in these individuals. What remains controversial, however, is the employment of third ventriculostomy prior to posterior fossa tumour surgery in patients presenting with hydrocephalus. The concept, however, is not new.

In the past, third ventriculostomy has been used intermittently in the management of hydrocephalus associated with posterior fossa lesions [12, 13]. Jones et al. in 1987 appear to have been the first to have tried endoscopic third ventriculostomy prior to posterior fossa tumour removal, reporting on one patient with a medulloblastoma in whom the procedure was performed 6 days prior to tumour removal. Although the intracranial hypertension was successfully controlled, the patient had increased ataxia [12]. We did not see this phenomenon in any of our patients. Hopf et al. [11] have recently reported 17 cases of endoscopic third ventriculostomy in patients affected by posterior fossa neoplasms, with the hydrocephalus being successfully managed in 13 of them

(76%). No details were given on the modality or the timing of failure [11].

What makes the present series unique has been the systematic application of third ventriculostomy in a series of patients prior to definitive posterior fossa surgery. This protocol was instituted in an attempt to reduce the not insignificant rate of postoperative hydrocephalus with its associated significant morbidity, both from the point of view of the uncontrolled intracranial hypertension and from the morbidity associated with ventricular shunting. However, having instituted this protocol, it became apparent that a proportion of patients underwent an "unnecessary" procedure. Can this be justified?

Firstly, in our study third ventriculostomy appeared to be safe. There was no mortality associated with our technique and only four cases of transient morbidity, three of which were technical failures. Only one patient was neurologically worse following the procedure—the cause of which we can only speculate as being the result of upward herniation which resolved with immediate posterior fossa decompression. The procedure, using atraumatic balloon dilatation and slow irrigation when required [21], was technically no more difficult than that for congenital aqueduct stenosis. Theoretically, the tumour bulk may displace the brain stem forward and obliterate the interpeduncular cistern, thus making third ventriculostomy impossible. Although initially wary of this, we have not found this to be a problem in our experience. In fact, posterior fossa tumours tend to elevate the brain stem at the same time as pushing it forward. This means that the floor of the third ventricle is displaced largely above the posterior clinoid, thus making room for the fenestration (Fig. 1).

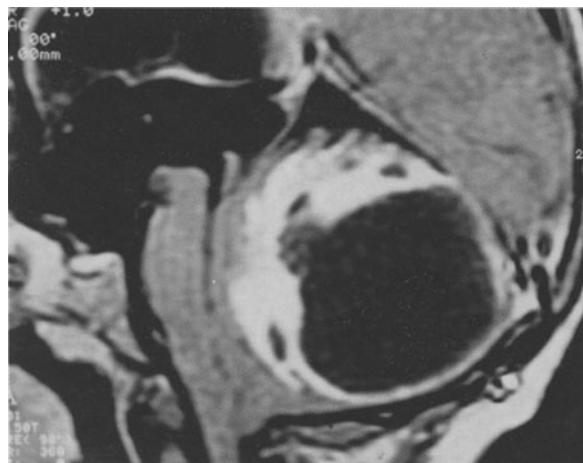


Fig. 1. Brain stem displacement induced by a posterior fossa tumour. The brain stem is pushed forward on the clivus but also upward by the tumour, elevating the posterior part of the floor of the third ventricle

Secondly, the preoperative control of the hydrocephalus may in fact provide benefit to these patients. The improved morbidity and mortality seen in the earlier studies after the introduction of ventricular drainage without doubt reflect the poor clinical state of the child at diagnosis [2]. However, given the smoother postoperative course seen in our patients treated with preliminary third ventriculostomy and the reduction in postoperative complications, the management of the hydrocephalus itself may be contributory.

Third ventriculostomy in our series was a safe technique and is a valid alternative in the treatment of postoperative hydrocephalus. Further, when used prior to posterior fossa tumour removal it reduces the risk of postoperative hydrocephalus and in so doing may lead to a reduction in morbidity and mortality among these patients.

Conclusion

The results from this retrospective study on a significant number of patients show that endoscopic third ventriculostomy is a feasible and safe method of treating hydrocephalus associated with posterior fossa tumours. When performed before posterior fossa surgery it had both a curative effect on intracranial hypertension before tumour removal and a prophylactic effect by preventing the development of hydrocephalus after tumour removal. When performed after posterior fossa surgery it cured the hydrocephalus in all cases. The significantly lower incidence of postoperative hydrocephalus in the group treated by third ventriculostomy prior to tumour removal is highly encouraging compared to that seen in our conventionally treated group and in the literature, and offers a consistent base for future prospective controlled studies to confirm these findings.

References

1. Abraham J, Chandy J: Ventriculo-atrial shunt in the management of posterior fossa tumours. Preliminary report. *J Neurosurg* 20: 252-253, 1963
2. Albright L, Reigel DH: Management of hydrocephalus secondary to posterior fossa tumours. *J Neurosurg* 46: 52-55, 1977
3. Allen JC, Epstein F: Medulloblastoma and other primary malignant neuroectodermal tumours of the CNS. The effects of patients' age and extent of disease on prognosis. *J Neurosurg* 57:446-451, 1982
4. Cinalli G, Salazar C, Yada JZ, et al: The role of third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43: 323- 329, 1998

5. Cinalli G, Sainte-Rose C, Chumas P, et al: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *Journal of Neurosurgery* 90:448-454, 1999
6. Culley DJ, Berger MS, Shaw D, et al: An analysis of factors determining the need for ventriculoperitoneal shunts after posterior fossa tumour surgery in children. *Neurosurgery* 34:402-408, 1994
7. Dias MS, Albright AL: Management of hydrocephalus complicating childhood posterior fossa tumours. *Pediatr Neurosci* 15: 283-290, 1989
8. Epstein F, Murali R: Pediatric posterior fossa tumours: Hazards of the 'preoperative' shunt. *Neurosurgery* 3: 348-350, 1978
9. Forrest DM, Cooper DG: Complications of ventriculo-atrial shunts. A review of 455 cases. *J Neurosurg* 29: 506-512, 1968
10. Hekmatpanah J, Mullan S: Ventriculo-caval shunt in the management of posterior fossa tumours. *J Neurosurg* 26:609-613, 1967
11. Hopf NJ, Grunert P, Fries G, et al: Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 44:795-806, 1999
12. Jones RF, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26: 86-92, 1990
13. Kelly PJ, Goerss S, Kall BA, et al: Computed tomography-based stereotactic third ventriculostomy: Technical note. *Neurosurgery* 18:791-794, 1986
14. Keucher TR, Mealy J: Long-term results after ventriculoatrial and ventriculoperitoneal shunting for infantile hydrocephalus. *J Neurosurg* 50:179-186, 1979
15. Lee M, Wisoff JH, Abbott R, et al: Management of hydrocephalus in children with medulloblastoma: Prognostic factors for shunting. *Pediatr Neurosurg* 20: 240-247, 1994
16. McLaurin RL: Disadvantages of the preoperative shunt in posterior fossa tumours. *Clin Neurosurg* 30: 286-294, 1983
17. Muszynski CA, Laurent JP, Cheek WR: Effects of ventricular drainage and dural closure on cerebrospinal fluid leaks after posterior fossa tumour surgery. *Pediatr Neurosurg* 21: 227-231, 1994
18. Papo I, Caruselli G, Luongo A: External ventricular drainage in the management of posterior fossa tumours in children and adolescents. *Neurosurgery* 10: 13-15, 1982
19. Raimondi AJ, Tomita T: Hydrocephalus and infratentorial tumours. *J Neurosurg* 55: 174-182, 1981
20. Rappaport ZH, Shalit MN: Perioperative external ventricular drainage in obstructive hydrocephalus secondary to infratentorial brain tumours. *Acta Neurochir* 96: 118-121, 1989
21. Sainte-Rose C: Third ventriculostomy. In: Manwaring KH, Crone K (eds) *Neuroendoscopy*, vol 1. New York, Mary Ann Liebert pp 47-62, 1992.
22. Schmid UD, Seiler RW: Management of obstructive hydrocephalus secondary to posterior fossa tumours by steroids and subcutaneous ventricular catheter reservoir. *J Neurosurg* 65: 649-653, 1986
23. Shalit MN, Ben Ari Y, Eynan N: The management of obstructive hydrocephalus by the use of external continuous ventricular drainage. *Acta Neurochir (Wien)* 47: 161-172, 1979
24. Stein BM, Tenner MS, Fraser RA: Hydrocephalus following removal of cerebellar astrocytomas in children. *J Neurosurg* 36: 763-768, 1972

Treatment of Hydrocephalus in Suprasellar Lesions

VITALY SIOMIN, SHLOMI CONSTANTINI

Hydrocephalus may become a major complicating factor in patients with suprasellar tumors. The differential diagnosis of suprasellar tumors that may potentially cause hydrocephalus is replete with various pathologies. Some tumors are more frequently associated with hydrocephalus (e.g., craniopharyngioma, optic pathway glioma), while others only occasionally cause it (e.g., germ cell tumor, pituitary adenoma, epidermoid cyst, and metastases). As hydrocephalus due to suprasellar tumors is primarily a pediatric neurosurgical problem, this chapter will be dedicated mostly to the management of hydrocephalus in pediatric patients with craniopharyngiomas and optic pathways gliomas (OPG).

masses with hydrocephalus and midbrain compression. Germ cell tumors may infiltrate the hypothalamus or disseminate to involve the third ventricle. Parasellar germinomas rarely present with hydrocephalus [14].

In addition to tumors, suprasellar *arachnoid cysts* may cause hydrocephalus. They are relatively rare and represent 6%-20% of all intracranial arachnoid cysts. Up to 90% of the reported suprasellar arachnoid cysts have occurred in children [15].

The focus of this chapter will primarily be on the management of hydrocephalus in craniopharyngioma and OPG patients. Other suprasellar lesions causing hydrocephalus will be addressed briefly.

Incidence of Hydrocephalus in Suprasellar Lesions

Craniopharyngiomas comprise 10% of pediatric brain tumors and constitute at least one-third of pediatric sellar-chiasmatic lesions. Hydrocephalus is found in up to 30% of craniopharyngioma patients upon presentation. OPG comprise about 10% of pediatric brain tumors. Up to 55% of patients with OPG at some point develop hydrocephalus that requires surgical intervention.

Another common tumor in the sellar region is *pituitary adenoma*. Only 5% of pituitary adenomas become large enough to obstruct CSF flow. Therefore, although large pituitary adenomas causing hydrocephalus have been described in the literature [23], they are relatively uncommon in pediatric clinical practice.

The vast majority of *germ cell tumors* arise along the midline from the suprasellar cistern (37%) to the pineal gland (48%), and an additional 6% involve both sites (Fig. 1). Nongerminomatous germ cell tumors present as posterior third ventricular

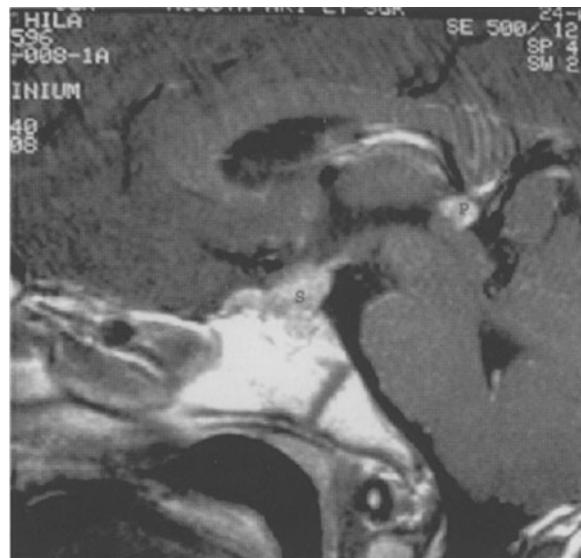


Fig. 1. Germ cell tumor arising in both the suprasellar cistern (S) and the pineal area (P) may cause hydrocephalus by obstructing the CSF flow at both the inlet and outlet of the third ventricle

Pathophysiology of Hydrocephalus in Suprasellar Tumors

Patients with suprasellar tumors usually develop an obstructive type of hydrocephalus. Only 20% of craniopharyngiomas are restricted to the sellar region. The rest of the tumors grow in various directions, compressing surrounding structures. Their anatomic proximity to the major CSF pathways may result in compression of various parts of the ventricular system. Hydrocephalus may, thus, result from obstruction at the following levels: (1) the basal cisterns, (2) invasion and obstruction of the inlet and outlet of the third ventricle, (3) occlusion of the foramina of Monro, and, rarely, (4) posterior displacement of the brainstem with occlusion of the sylvian aqueduct.

In most patients with OPG, hydrocephalus is obstructive in nature as well. In some patients, however, an “absorptive” component may be present. The latter is supported, although indirectly, by some well-documented cases of aresorptive ascites following ventriculoperitoneal shunting (VPS). Although obstruction is overwhelmingly the leading pathophysiological mechanism of hydrocephalus development in patients with OPG, absorption impairment should not be ignored, as it may give a clue to the causes of treatment failure in some patients.

Clinical Manifestations

Since both craniopharyngiomas and OPG are relatively slow-growing tumors, they may reach a significant size before causing any symptoms, particularly in children. Once the CSF flow becomes obstructed, the patients start having signs of increased intracranial pressure (ICP). Most commonly children with craniopharyngioma present with headaches (80%), nausea and vomiting (60%), visual loss due to papilledema or direct pressure on the optic pathways (40%), short stature due to endocrinological deficiencies (30%), and mentation disturbances (5%).

Patients with large OPG present with signs of raised ICP, similarly to craniopharyngiomas. However, they have endocrinological problems less frequently than patients with craniopharyngioma. Hydrocephalic infants may develop craniomegaly with bulging fontanel.

Notably, children with hydrocephalus that manifests with visual disturbances alone can remain undiagnosed for long periods of time. One of our patients,

a 14-year-old boy with a giant OPG with nearly complete visual loss on one side and a major visual field cut on the other, was a very good student at school, and able to read, write, and watch TV. Such a notable tolerance of significant visual loss in children may lead to development of severe long-standing hydrocephalus with marked anatomical distortions and compression of brain (Fig. 2). A high index of suspicion is, therefore, necessary in the approach to such nonspecific symptoms as headache, nausea, and vomiting in children.

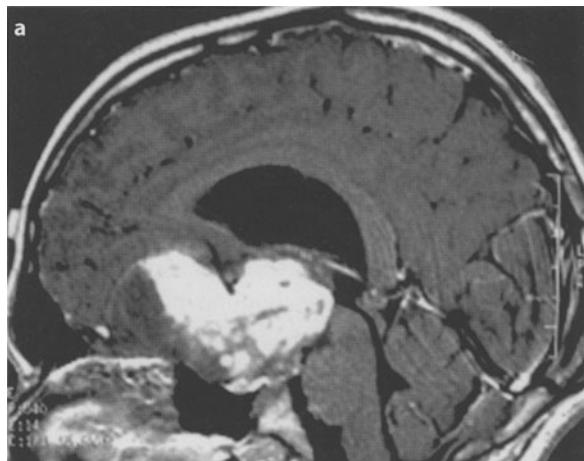


Fig. 2a, b. A large chiasmatic glioma in a 14-year-old patient with nearly complete visual loss on the left side and a major visual field cut on the right. Despite these abnormalities, he was a very good student at school, and able to read, write, and watch TV. **a** Sagittal and **b** coronal views after injection of gadolinium. The third ventricle is filled with the tumor. Marked ventriculomegaly is seen

Patients with hydrocephalus due to suprasellar arachnoid cysts manifest with signs of raised ICP (60%), ataxia (60%), macrocephaly (70%), reduced visual acuity (20%-30%), seizures (30%), and developmental delay (30%). Head bobbing is considered a pathognomonic symptom of suprasellar arachnoid cysts, but occurs in only 10% of patients. One of our patients was diagnosed as having a suprasellar arachnoid cyst in utero. The rapid increase in head circumference due to obstructive hydrocephalus required endoscopic fenestration of the lesion.

Radiological Findings

The images should be carefully studied to elucidate two issues crucially important in the management of hydrocephalus in patients with suprasellar tumors: (1) the nature and extent of the tumor, and (2) the changes in the anatomy of the ventricular system and the subarachnoid space.

Craniopharyngiomas causing hydrocephalus are usually large lesions that either extend into the third ventricle or arise within it. On CT, craniopharyngiomas typically appear as a heterogeneous mass confined to the suprasellar cistern. They usually contain hypodense cysts as well as calcifications. The latter are seen in 50%-80% of patients. Interestingly, calcifications are visible even on plain X-rays in 85% of children and in 40% of adults, making this finding the most characteristic feature of craniopharyngioma. Contrast enhancement occurs in the soft tissue components of the mass or in the cyst wall. MRI is more helpful in visualization of various constituents of the tumor, as well as for studying the relationships with surrounding anatomical structures (Fig. 3). Typically, a cyst of high or low intensity on the T1-weighted images can be seen. Low-intensity cysts are usually compatible with the presence of thin serous fluid or keratin. High-intensity thick fluid is most frequently due to the presence of hemorrhagic products and/or high protein content. Calcifications within the tumor may present as dark spots of signal dropout. The rule of thumb is that a large calcified cystic mass in the suprasellar lesion most likely represents a craniopharyngioma.

In patients with OPG the imaging invariably reveals focal or diffuse thickening of the visual pathways. CT usually demonstrates lesions enhancing with contrast. Calcifications are very uncommon. MRI is markedly superior to CT in visualization of the OPG. The enlargement of the optic pathways is usual-

ly isointense on T1-weighted images, while on T2 the signal intensity is higher than that of the intact nerve. OPG often extend from the optic nerve to as far as the optic radiations. MRI is, therefore, a mandatory tool in evaluation and staging of such OPG, often obviating the need for biopsy for histological diagnosis.

Suprasellar arachnoid cysts appear on CT as nonenhancing hypodense lesions, which may be often mistaken for an enlarged third ventricle. Both T1- and T2-weighted MRI sequences have signal characteristics of cystic fluid.

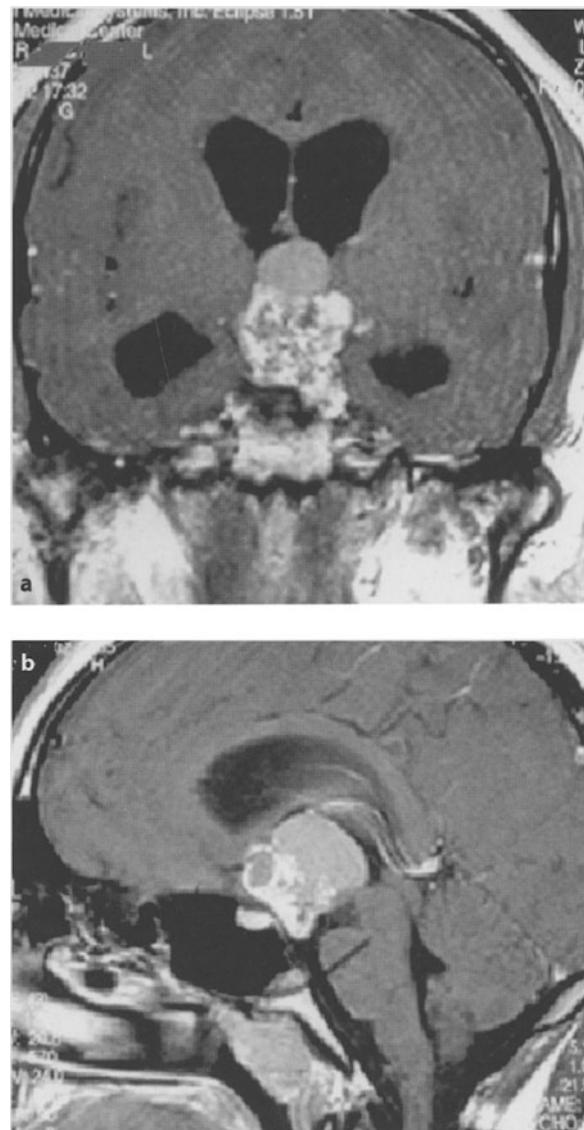


Fig. 3a, b. Craniopharyngioma. **a** Sagittal and **b** coronal T1-weighted images after administration of gadolinium. The tumor extends into the third ventricle causing obstruction of the CSF flow

Hydrocephalus itself does not have any peculiar features on imaging in the presence of a suprasellar tumor. A ventriculomegaly above the obstruction is usually seen along with a normal-looking fourth ventricle. Ventricular asymmetry, patency of the foramina of Monro and the width of the third ventricle should be noted. Periventricular low density on CT and a high-intensity signal on T₂-weighted MRI are suggestive of transependymal absorption of CSF.

Careful radiological evaluation is an extremely important tool in developing the treatment strategy, particularly when it comes to deciding about the priorities of treatment (e.g., tumor, cyst, or the hydrocephalus itself), timing, and the technicalities (e.g., shunt or endoscopy).

Tumor Removal and the Role of Hydrocephalus

Many strategic surgical approaches to craniopharyngioma and OPG have been described, including subfrontal, pterional, subtemporal, transcallosal, transsphenoidal, and transoral. It should be noted that both lesions recur quite frequently. In one series of craniopharyngiomas, a nearly 30% recurrence rate was observed in patients in whom total excision was thought to have been achieved [11]. The situation is similar with OPG. These patients have less than 60% 10-year relapse-free survival [13]. OPG carries even worse prognosis in children younger than 5 years, particularly in infants [22]. Five-year tumor progression rate in craniopharyngiomas ranges from 15% in those with total removal to 75% in those with partial removal, despite the use of surgery, chemotherapy, and irradiation [21].

The role of ventricular dilatation in tumor surgery is dubious. It actually depends on the approach to the lesion. Most authors consider it helpful in an interhemispheric transcallosal or transcortical transventricular approach. It is less helpful in subfrontal and trans-sylvian approaches, as more significant brain retraction is required in the presence of ventriculomegaly. Pre- or intraoperative CSF diversion may be helpful.

Management of Hydrocephalus in Suprasellar Tumors

The management of hydrocephalus in patients with suprasellar tumors depends on three main issues: (1) the size and configuration of the ventricular system,

(2) the extent and the level of compression by the tumor, and (3) whether the compression is caused by cystic or solid component (Fig. 4).

Shunt or Endoscopy?

The answer is both. The “reformation” in hydrocephalus treatment after the introduction and wide acceptance of endoscopic techniques led to “declaration of war” on shunts with an overwhelming desire to substitute the “bad” hardware for “more physiological,” endoscopic solutions. Shunts still play an important role in providing an immediate decrease in intracranial pressure, facilitating exposure and dissection of the tumor. On the other hand, endoscopy (particularly septostomy in unilateral hydrocephalus) often becomes an essential treatment modality. Hydrocephalus management in this group of patients should be balanced and should use the optimal combinations of shunting, endoscopy, and stereotaxy and image guidance.

Before or After Tumor Surgery?

Control of hydrocephalus prior to tumor surgery allows the surgeon to avoid damaging the brain en route to the lesion. In addition, surgery performed on a brain stressed by marked hydrocephalus may lead to poorer results. Resolution of the hydrocephalus and the subsequent decrease of intracranial pressure may lead to some recovery of the neural tissue. For instance, the optic nerves can then probably tolerate surgery better. In addition, we believe that after CSF diversion, the tumor surgery often becomes an elective issue, allowing more balanced and careful treatment planning.

Most authors, however, do not advocate initial shunting or endoscopy. In some 80% of patients with craniopharyngioma and 70% of those with OPG, the hydrocephalus may be cured after tumor surgery. Apparently, the placement of a foreign body with its potential sequelae of shunt failure (rate of 40%-60% in the first 5 years), shunt dependency, and the agony of multiple revisions is probably unnecessary in the majority of primary tumors of the sellar area. Similarly, endoscopic procedures, although rendered relatively safe, carry a 1%-2% risk of significant complications and a 30% risk of failure at long-term follow-up [5, 8]. In addition, shunting prior to tumor surgery may be associated with a higher risk of intratumoral bleeding [20].

This is not the case for recurrent tumors. Cystic craniopharyngiomas are often hard to control with irradiation, local aspiration, endoscopic fenestra-

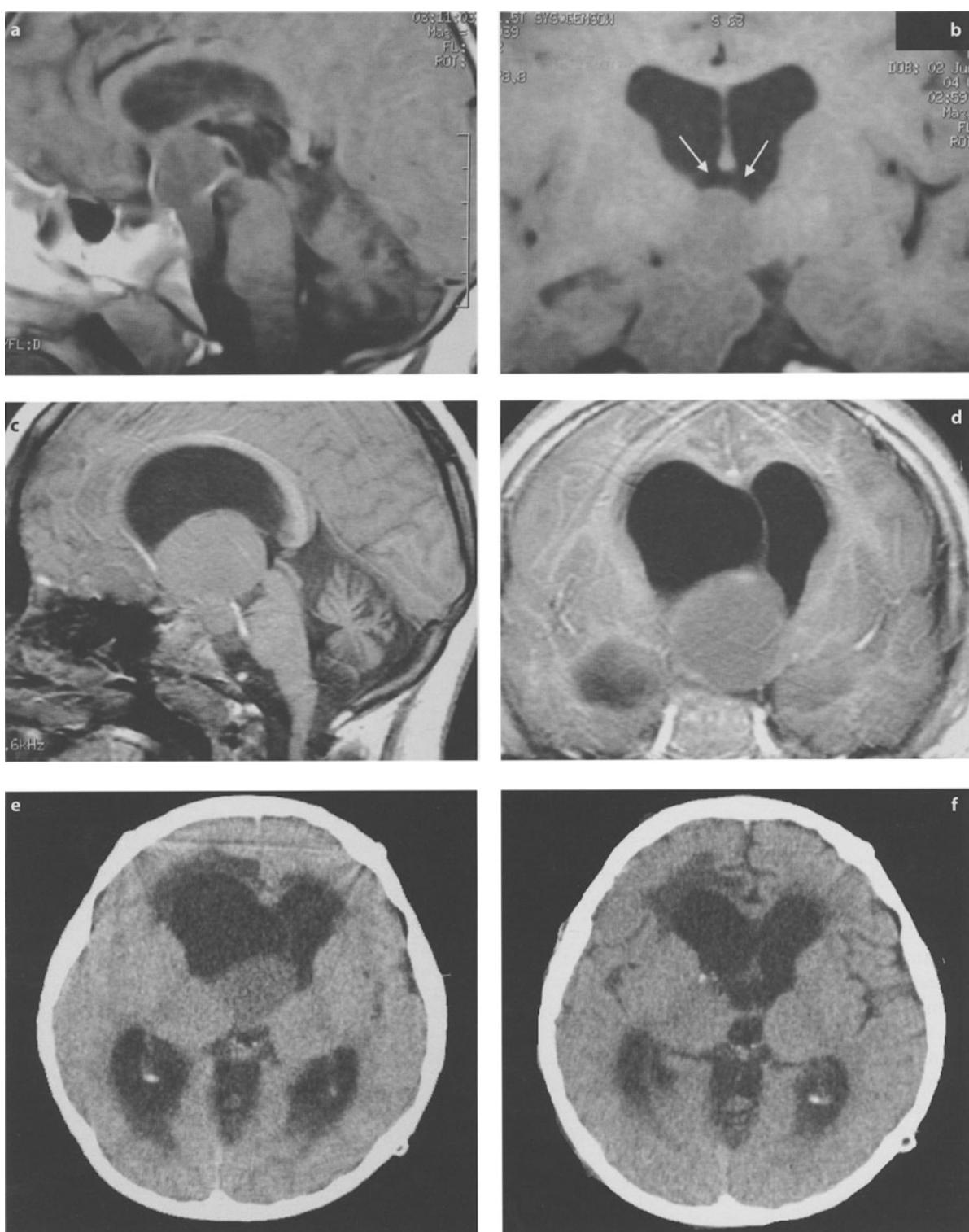


Fig. 4a-f. Recurrence of cystic craniopharyngioma: **a** Sagittal and **b** coronal T1-weighted images 4 months following incomplete removal of the lesion in another department. The tumor cyst is regrowing, but the posterosuperior part of the third ventricle and the two foramina of Monro (arrow) are free. Three months later, the volume of the cyst has increased, filling the third ventricle (**c**) and occluding both foramina of Monro (**d**), the right one before the left one, inducing asymmetric hydrocephalus. **e, f** CT scan at the time of **c** and **d** (**e**) and following endoscopic fenestration and aspiration of cyst fluid (**f**). This maneuver is always sufficient to resolve hydrocephalus before tumor removal

tion, and injections of bleomycin. In such patients, shunting of dilated ventricles becomes more practical.

With regard to OPG, 40% of patients have their hydrocephalus controlled following tumor removal. The remaining 60% eventually require ventriculoperitoneal shunt placement. A common complication following ventriculoperitoneal shunt placement in children with OPG is the development of ascites [10]. In such cases placement of a ventriculoatrial shunt, either in the first place or after ventriculoperitoneal shunt failure, has been advocated.

Although chiasmatic gliomas are commonly joined with hypothalamic gliomas, the latter are clearly different with regard to both the pathophysiology of hydrocephalus and the surgical approach. Not infrequently, in low-grade astrocytomas, the tumor growth is limited to the cavity of the third ventricle, causing its complete obstruction with minimal, if any, involvement of visual pathways. Such lesions are commonly approached surgically in an attempt to remove the tumor and open the upper and posterior parts of the third ventricle for normal CSF drainage.

In sum, currently there are no reliable predictors of the response of hydrocephalus to treatment. Since hydrocephalus will be controlled in a substantial number of patients after tumor surgery, it should be tried first, reserving endoscopy and shunting for the failures.

Shunting

Hydrocephalus

Since shunting of hydrocephalus is nowadays most commonly performed after tumor removal, it is essentially no different from the shunting of communicating hydrocephalus. Shunt placement prior to tumor surgery is very infrequently performed, for reasons stated in the previous section. In such cases bilateral shunts or Y-type shunts should certainly be discouraged, as associated with the introduction of unreliable complexity and unnecessary foreign material. Alternatively, septum pellucidotomy followed by shunting of one of the lateral ventricles is more appropriate. An endoscopic biopsy can be added. Much thought should be given to the planning of the skin incision and burr hole placement in cases when surgery is anticipated in the future. This can be facilitated by the use of neuronavigation to select the most appropriate surgical trajectories and burr hole sites, as well as considering possible craniotomy flaps at the initial stages of planning.

Postoperative Recurrent CSF Collections

Occasionally, recurrent CSF collections may develop in either subgaleal or subdural spaces, particularly after base-of-skull approaches in patients with OPG, due to extensive soft tissue stripping and, possibly, high protein content, immune reaction, or tumor spread. These collections should be shunted if they become symptomatic or cause significant mass effect on imaging. Ventriculoperitoneal, subdural-peritoneal, or subgaleal-peritoneal shunts are usually used, depending on the primary location of the collection. We have not found any of these types of shunting superior to others.

Septostomy

Septostomy (septum pellucidotomy) is essentially performed when drainage of CSF from either of the lateral ventricles is blocked. This may be due to blockage at the foramina of Monro, leading to either (1) asymmetrical hydrocephalus, if one of the foramina is blocked, or (2) symmetrical hydrocephalus, when there is no flow through either foramen. In the first case, septostomy may be performed alone, aiming at bypassing the blocked foramen of Monro by restoring free passage of CSF to the contralateral ventricle. In the second case, if tumor surgery or endoscopic procedure fail to eliminate obstruction of CSF outflow, septostomy should be performed prior to ventriculoperitoneal shunt placement in one of the ventricles. Septostomy generally is a relatively easy and highly successful procedure in this patient group.

Management of Tumor Cysts

Stereotactic Drainage

A ventricular catheter can be placed in a large tumor cyst and attached to the subcutaneous Ommaya reservoir. Both stereotactic guidance and neuronavigation techniques as well as placement under direct vision via craniotomy or endoscopy may be used. The indications for intracystic catheter placement include the following: (1) huge cystic lesions that cannot be totally resected, (2) primarily cystic lesion in minimally symptomatic patients, (3) recurrent cysts.

Notably, multiple cysts can be treated with multiple catheter placements.

Such an access to the cyst allows aspiration of the fluid if the cyst compresses surrounding structures, and intracystic chemotherapy with bleomycin. This technique, originally described by Takahashi et al. [19] leads to volumetric reduction of tumor cyst and stabilization of visual function in 57%-72% of patients. Cavalheiro et al. described disappearance of intratumoral calcifications in a patient treated with intracystic bleomycin [4].

Intracystic catheter placement is a sound alternative to direct microsurgical approach [17]. Its major advantages lie in avoidance of some endocrinological and neuropsychological impairments associated with open surgery. In recurrent tumors catheter placement becomes a treatment of choice.

Endoscopic Drainage

Endoscopic drainage of tumor cysts is technically feasible (Fig. 4e, f), but may have limitations in both craniopharyngioma and ONG and is therefore rarely used. Single drainage of the cystic cavity almost never produces a sustained effect, as the cysts tend invariably to reaccumulate. Fenestration of the cyst and inspection of it with the endoscope leads to continuous spillage of its highly proteinaceous contents into the ventricles by establishing communication between the cyst lined with secreting tumor cells, and the ventricles. The consequences of this have not been studied well, but are known to be associated with the morbidity of chemical ventriculitis [16]. Endoscopic equipment, however, can be used in endoscopically assisted surgery of lesions in the suprasellar area as well as in the ventricular system.

Management of Hydrocephalus in Suprasellar Arachnoid Cysts

Of note, only the minority of suprasellar arachnoid cysts need to be treated; the overwhelming majority will benefit from simple watching. If suprasellar arachnoid cysts become clinically significant, they can be managed by (1) craniotomy and open fenestration/resection, (2) endoscopic fenestration/resection, and (3) cystoperitoneal shunt placement.

For suprasellar arachnoid cysts associated with hydrocephalus a transcallosal approach has been most widely recommended. The goal of surgery is to achieve communication between the cyst and the ventricles. The success rate of craniotomy in suprasel-

lar arachnoid cysts ranges from 33% to 76%. Open surgery for cyst fenestration and resection may, like any other craniotomy, be potentially associated with the risk of seizures, postoperative neurological deficit, and hemorrhage.

Endoscopic procedures have become popular [15]. They involve fenestration and removal of the cyst membranes, preferably with ventriculostomy of the floor of the third ventricle [6]. The success rate in some series reached 89% [12]. The advantage of adding third ventriculostomy to the cyst fenestration is in establishing an extra conduit of communication between the ventricles and the subarachnoid space.

Management of Hydrocephalus in Germ Cell Tumors

In patients with germ cell tumors, endoscopic biopsy may become the single most significant intervention, as its results determine further treatment in a major way [1]. Germ cell tumors usually demonstrate dramatic response to radiation therapy with subsequent resolution of hydrocephalus. It is, therefore, important to start with an endoscopic procedure combined with biopsy. This approach obviates the need for either shunting (i.e., foreign body placement), or major surgery [7].

In some patients with marked hydrocephalus temporary ventricular drainage can be placed and emergency radiotherapy started [3]. The ventriculostomy may be removed after the germinoma shrinks and the obstruction to CSF flow is eliminated.

Pitfalls and Complications of the Treatment of Hydrocephalus in Suprasellar Tumors

Complications in this group of patients, whether undergoing open surgery or endoscopy, are not very different from those reported in more general series. All preventable complications occurring in patients undergoing surgical treatment of hydrocephalus due to suprasellar lesions can occur at any stage of treatment and are due to the following main reasons: preoperative misjudgment, intraoperative difficulties, or failure to monitor the patient appropriately postoperatively.

Preoperative misjudgment most commonly occurs (1) when the surgeon decides to be overly radical, trying to remove the lesion at any cost; (2) when the de-

sire to “utilize technology” leads to the performing of complex, risky, and lengthy advanced endoscopic procedures where simple shunting would be more justified; and (3) when the surgeon fails to appreciate the complexity of the anatomy of the suprasellar area, the extent of the lesion, and the involvement of the surrounding structures.

Intraoperative complications (e.g., bleeding, damage to surrounding structures) are primarily associated with difficulties in orientation [9, 18], particularly in the case of large arachnoid cysts. Orientation may be facilitated to some extent by the use of neuronavigation, although intraoperative brain shift may diminish its value and reliability in arachnoid cysts and, to a lesser extent, in suprasellar tumors. Optical control, on the other hand, is a valuable tool to evaluate the degree of inaccuracy of the neuronavigation during surgery.

Postoperative ICP monitoring may often be essential to identify features correlating with the failure of hydrocephalus treatment [2]. Traditional neuroimaging techniques have several limitations in assessing the success of the procedure, mostly in the early post-operative period. Indeed, a decrease in the ventricular size is often minimal and not visible before 3–4 weeks. MRI, which can detect the presence of a flow void signal through the third ventricle floor, has been reported to have a significantly high incidence of false positive findings. Therefore, after complex endoscopic procedures the present authors very frequently use ICP monitoring. A combination of both the intraparenchymal fiberoptic probe and an external ventricular drain is probably the safest. The main reason for “double monitoring” is the possibility of ICP monitoring for relatively long periods of time after the removal of a ventriculostomy. In situations where there is no clear need for external ventricular drainage but ICP monitoring is still desirable, we do not hesitate to use the intraparenchymal monitoring only, as it carries a markedly lower infection rate than ventriculostomy.

References

1. Abdulla J, Caemaert J: Endoscopic management of craniopharyngiomas: a review of 3 cases. *Minim Invasive Neurosurg* 38(2): 79–84, 1995
2. Bellotti A, Rapana A, Iaccarino C, Schonauer M: Intracranial pressure monitoring after endoscopic third ventriculostomy: an effective method to manage the ‘adaptation period’. *Clin Neurol Neurosurg* 103: 223–227, 2001
3. Buatti JM, Friedman WA: Temporary ventricular drainage and emergency radiotherapy in the management of hydrocephalus associated with germinoma. *J Neurosurg* 96: 1020–1022, 2002
4. Cavalheiro S, Sparapani FV, Franco JO, et al: Use of bleomycin in intratumoral chemotherapy for cystic craniopharyngioma. Case report. *J Neurosurg* 84: 124–126, 1996
5. Cinalli G, Sainte-Rose C, Chumas P, et al: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90: 448–454, 1999
6. Choi JU, Kim DS, Huh R: Endoscopic approach to arachnoid cyst. *Childs Nerv Syst* 15: 285–291, 1999
7. Ellenbogen RG, Moores LE: Endoscopic management of a pineal and suprasellar germinoma with associated hydrocephalus: technical case report. *Minim Invasive Neurosurg* 40: 13–15, 1997
8. Fukuhara T, Vorster SJ, Luciano MG: Risk factors for failure of endoscopic third ventriculostomy for obstructive hydrocephalus. *Neurosurgery* 46: 1100–1109; discussion 1109–1111, 2000
9. Gaab MR, Schroeder HW: Neuroendoscopic approach to intraventricular lesions. *J Neurosurg* 88: 496–505, 1998
10. Gil Z, Beni-Adani L, Siomin V, et al: Ascites following ventriculoperitoneal shunting in children with chiasmatic-hypothalamic glioma. *Childs Nerv Syst* 17: 395–398, 2001
11. Hoffman HJ, De Silva M, Humphreys RP, et al: Aggressive surgical management of craniopharyngiomas in children. *J Neurosurg* 76: 47–52, 1992
12. Hopf NJ, Perneczky A: Endoscopic neurosurgery and endoscope-assisted microneurosurgery for the treatment of intracranial cysts. *Neurosurgery* 43: 1330–1336; discussion 1336–1337, 1998
13. Jenkin D, Anyalfi S, Becker L, et al: Optic glioma in children: surveillance, resection, or irradiation? *Int J Radiat Oncol Biol Phys* 25(2): 215–225, 1993
14. Jennings MT, Gelman R, Hochberg F: Intracranial germ-cell tumors: natural history and pathogenesis. *J Neurosurg* 63: 155–167, 1985
15. Kirolos RW, Javadpour M, May P, Mallucci C: Endoscopic treatment of suprasellar and third ventricle-related arachnoid cysts. *Childs Nerv Syst* 17: 713–718, 2001
16. Kulkarni V, Daniel RT, Pranatartiharan R: Spontaneous intraventricular rupture of craniopharyngioma cyst. *Surg Neurol* 54: 249–253; discussion 253, 2000
17. Nakamizo A, Inamura T, Nishio S, et al: Neuroendoscopic treatment of cystic craniopharyngioma in the third ventricle. *Minim Invasive Neurosurg* 44: 85–87, 2001
18. Schroeder HW, Gaab MR, Niendorf WR: Neuroendoscopic approach to arachnoid cysts. *J Neurosurg* 85: 293–298, 1996
19. Takahashi H, Nakazawa S, Shimura T: Evaluation of post-operative intratumoral injection of bleomycin for craniopharyngioma in children. *J Neurosurg* 62: 120–127, 1985
20. Umansky F, Kluger Y, Gomori M, Constantini S: Traumatic intratumoral hemorrhage after ventriculo-peritoneal shunt. *Childs Nerv Syst* 4: 310–331, 1988
21. Van Effenterre R, Boch AL: Craniopharyngioma in adults and children: a study of 122 surgical cases. *J Neurosurg* 97: 3–11, 2002
22. Wisoff JH, Abbott R, Epstein F: Surgical management of exophytic chiasmatic-hypothalamic tumors of childhood. *J Neurosurg* 73: 661–667, 1990
23. Zikel OM, Atkinson JL, Hurley DL: Prolactinoma manifesting with symptomatic hydrocephalus. *Mayo Clin Proc* 74: 475–477, 1999

Hydrocephalus and Colloid Cysts

PHILIPPE DECQ¹, CAROLINE LE GUERINEL¹, LAURENT SAKKA¹, CHRISTO CHRISTOV⁴, PIERRE BRUGIÈRES², STÉPHANE PALFI¹, ELIANE MELON³ AND JEAN-PAUL NGUYEN¹

Introduction

Colloid cysts represent approximately 1% of all intracranial neoplasms [6, 12, 54, 173]. The preferential localization of these lesions to the anterior part of the third ventricle explains why these lesions appear primarily with obstructive biventricular hydrocephalus, the obstruction sitting on the level of the foramina of Monro. The natural history of these histologically benign tumors has not been clearly elucidated. Some colloid cysts are asymptomatic and can be followed for several years without any radiological changes [22, 30]. In contrast to this, some cysts have been reported to induce precipitous neurological decline [22, 25, 97], and they can also be a possible cause of sudden death due to acute obstruction of cerebrospinal fluid (CSF) pathways [3, 9, 20, 99, 139, 144].

The majority of cysts reported in the neurosurgical literature were symptomatic and were therefore treated. Current opinion is that symptomatic colloid cysts should be treated. The treatment of asymptomatic colloid cysts without ventricular enlargement remains controversial.

Since Dandy's description of the surgical approach to colloid cysts in the 1930s [31], several surgical modalities have been proposed. They may be divided in two categories: open surgical removal techniques and percutaneous aspiration procedures. The surgical removal of colloid cysts can be performed by transcortical-transventricular microsurgery [133, 136], transcallosal microsurgery [7, 103], or, more recently, by stereotactic microsurgical craniotomy [2, 21, 88, 116].

Simple cyst aspiration was first described in 1975 [52]. Stereotactic aspiration was subsequently reported to be a safe procedure [18, 85, 113, 118, 137]. However, recurrence following cyst aspiration appears to be not uncommon [104]. Simple shunting of CSF without any treatment of the cyst has also been described [29,

30], but carries a risk of insidious growth of the cyst, sometimes up to considerable dimensions. Endoscopy is the most recent technique. Publications are accumulating to show the major role of this new approach in the management of these lesions [1, 11, 28, 33, 34, 38, 41, 49, 58, 81, 97, 104, 112, 133, 138, 172]. By its very nature, endoscopy cannot offer as complete a removal as the microsurgical techniques. Nevertheless, this technique could constitute a valuable alternative, combining the advantages of a percutaneous technique with the possibility of "doing more than" a simple aspiration. The development of endoscopic instrumentation allows not only aspiration of the cyst, but also wide opening of the cyst wall and coagulation of all the visible parts of the cyst capsule.

This chapter reviews the clinical and radiological symptomatology of colloid cysts of the third ventricle, dominated, once again, by hydrocephalus, before discussing their surgical management focusing on the endoscopic procedure.

Epidemiology

General Features

Colloid cysts are histologically benign tumors that comprise between 0.5% and 1% of cerebral brain neoplasms [104]. This corresponds to approximately 15% of the tumors of the third ventricle [74]. A study undertaken in Finland over a 14-year period made it possible to establish an incidence of 3.2 new cases per one million head of population per annum, that is to say about 2% of all cerebral tumors [59]. The average age at the time of the diagnosis is approximately 48 years, ranging from 37 to 57 years in series comprising more than 30 patients [59, 79, 118]. Colloid cysts are rarely diagnosed in children. A general review of 1994

¹ Service de Neurochirurgie; ² Service de Neuroradiologie; ³ Département d'Anesthésie-Réanimation; ⁴ Inserm U421 Neuroplasticité et Thérapeutique, Hôpital Henri Mondor, Créteil, France

reports 3 cases out of 1400 patients presenting a cerebral tumor at the Sick Children's Hospital of Toronto from 1952 to 1992 [99]. There are 34 cases of colloid cysts reported in the literature from 1933 to 1994 among patients younger than 18 years.

Mortality

Coincidental colloid cysts have a very low risk of mortality, although currently it remains difficult to quantify. Among patients with symptomatic colloid cysts, a study by Buttner et al. in 1997 reports 98 sudden deaths occurring between a few hours and 17 years after the appearance of the symptoms [20]. A study of 11 000 medicolegal autopsies performed in 1980 reports 19 sudden deaths related to undiagnosed cerebral tumors which included only 1 case of colloid cyst [9]. In a large review of the literature from 1858 to 1994 carried out by Hernesniemi and Lievo [59] on 1167 cases of colloid cysts, mortality was 11% among the 856 operated patients. However, these were heterogeneous populations collected over a long period of time with many sources of bias. Among the 34 pediatric cases listed by MacDonald et al. in 1994, there were 8 deaths occurring a very variable time after the appearance of the symptoms (1 day, 1-2 weeks, 7 months). Two children died after lumbar puncture [99]. Familial cases have been reported, isolated or in association with other anomalies [4, 15, 71, 103, 122, 162, 163], supporting the assumption of genetic factors in this type of lesion. An association with several other malformations has been reported [17, 19, 35, 42, 82, 127, 129, 148].

Pathology

Histology

Colloid cysts are lined by a single to pseudostratified epithelial layer that may, however, show considerable differences from case to case and from one area to another within a specimen. In some cases the lining consists almost exclusively of a layer of flat to cuboidal cells [100, 92], while in others the epithelium is taller (columnar), the pseudostratification is more pronounced, and even true multilayering with formation of secondary lumina may occur [94]. Scattered goblet cells are easily found. Well-preserved, adequately sampled specimens may display the full spectrum of epithelial appearances neighboring denuded zones where the epithelium is altogether absent. The epithe-

lium invariably resides on a basal membrane that separates it from a thin connective tissue capsule that is sometimes covered by choroid plexus to which the outer surface of the cyst may be intimately adherent [92]. The amorphous, strongly eosinophilic and PAS-positive cyst content consists of cell debris, occasional inflammatory cells and lipid droplets, strands and streaks of degenerated nucleic acids and phospholipids [134]. The colloid cyst can present xanthogranulomatous change [53, 107, 153] that is probably secondary to hemorrhage in the colloid cysts [153] and not to degeneration of epithelial cells that have invaded the fibrous capsule, as originally proposed [149]. The importance of this rare morphological pattern lies in the fact that open surgery rather than stereotactic aspiration is indicated in the treatment of xanthogranulomas that both clinically and radiologically mimic pure colloid cysts [153]. Furthermore, in at least one case a xanthogranuloma of the third ventricle has been associated with a life-threatening hemorrhage [155].

Electron Microscopy

Numerous detailed electron microscopic studies have been devoted to the fine structure of colloid cysts (for review see [91, 109]). Six cell types have been identified [44, 95, 106, 107, 168]: ciliated and nonciliated columnar/cuboidal cells with glandular differentiation, goblet cells, cuboidal cells with squamous differentiation, basal cells, and intermediate forms [66, 91]. Rare cells with neuroendocrine-type granules were also documented in one meticulous study [66]. The ultrastructural characteristics of colloid cysts present features that closely resemble those of respiratory epithelium [5, 44, 61, 62, 64, 66, 80, 91], or, for that matter, the epithelium lining other maldevelopmental cysts of the central nervous system, such as enterogenous cysts [60, 63, 64, 65, 106, 114, 123], bronchogenic cysts [69, 126], or Rathke's cleft cysts [91, 146].

Immunohistochemistry

The lining of colloid cysts has been consistently found positive for cytokeratins and epithelial membrane antigen (EMA), negative for glial fibrillary acidic protein (GFAP), prealbumin, neurofilament, and neuron-specific enolase [27, 73, 90, 92] and, with rare exceptions [73, 100, 117], negative for S-100 protein [27, 73, 90, 92, 98, 100, 142, 145, 156, 159]. Different antigens have been isolated in some cases (carcinoembryonic antigen, secretory component and Clara cell antigen, tissue peptide antigen, and glutathione S-transferase

pi-isoenzyme) [73, 92, 100, 145, 156]. Some reports have shown both low- and high-molecular-weight cytokeratin expression [27, 90, 92, 156, 158]. This antigen profile of colloid cysts favors a nonneuroectodermal origin with a high degree of similarity to respiratory tract epithelium [92, 156] and to enterogenous cysts and Rathke's cleft cysts of the central nervous system [48, 92, 100].

Histogenesis

Like so many other domains of "the Borderland of embryology and pathology" (R.A.Willis), the embryopathogenesis of colloid cysts is poorly understood. To analyze it exhaustively would require a review of early neural embryogenesis and of the theories on the embryopathogenesis of enterogenous cysts and Rathke's cleft cysts, a task that clearly exceeds the scope of this chapter. For detailed information the reader is referred to some excellent recent reviews of these topics [14, 36, 48, 55, 56, 94, 110, 147]. The contention that colloid cysts arise from ectopic foregut endoderm [151] is in accord with most available morphological data and is, therefore, accepted by most authorities [91, 94, 109, 130]. Colloid cysts are thought to arise in the transverse cerebral fold and to secondarily attain the third ventricle as a result of a downward growth. Historically, a neuroectodermal origin of colloid cysts has been proposed [8, 29, 63, 68, 84, 98, 124, 147, 150], but nowadays these theories have practically no proponents.

Pathophysiology

The clinical signs of colloid cysts of the third ventricle are mainly related to hydrocephalus due to the occlusion of the foramen of Monro. However, the cyst can also by itself injure the surrounding structures, directly by a mass effect mechanism or indirectly by injury of the vascular elements. This is supported by the crowdedness of this anatomical area, a quasi-virtual ventricular cavity in the normal state, rich in vessels and eloquent neurological structures.

Hydrocephalus

The growth of colloid cysts can induce hydrocephalus, generally biventricular, by blockage of the CSF flow through one or both foramina of Monro. Colloid cysts may produce increased intracranial pressure by intermittent obstruction of the passage

of the CSF at the level of the interventricular foramen, acting like the legger of a bell as historically described by Dandy in 1933. In a substantial proportion of cases, head movement or position changes can precipitate, exacerbate, or even relieve the headache [170]. Among patients presenting with a colloid cyst of the third ventricle, numerous clinical signs are classically related to hydrocephalus: headaches, mental deterioration with memory disorders, somnolence, psychiatric troubles, nausea, vomiting, oculomotor disturbances, walking difficulties, and others. In fact, the presence of these clinical symptoms without hydrocephalus suggests that the colloid cyst could by itself induce these disorders: direct mass effect on the surrounding structures (fornix, thalamus, diencephalic vegetative centers) or indirectly by arterial or, especially, venous compression. We will further see that the post-operative complications (lesion of these structures) can reproduce some of the clinical signs presented by the patients. Lobosky reported three patients without hydrocephalus who complained of significant psychiatric troubles and memory disorders which significantly improved after removal of the colloid cyst. The mass effect on the diencephalic structures, the fornix, and the vessels was noted during surgery [22]. In addition, recent studies demonstrate an overvaluation of the so-called positional headaches in the "historical" publications [31]. Camacho et al., in a study of 1989, report only 2 patients with such positional headaches out of 84 patients with a colloid cyst inducing headaches. It seems to append rarely [22].

The problem of sudden death, classically described in the pathology of the third ventricle, goes back to the pre-CT era. Actually, this type of death seems to follow a prodromic phase where the not very specific clinical signs are underestimated. In a review of the literature published in 1997 collecting 98 cases of deaths known as sudden, Buttner et al. found only two cases of death that occurred very acutely [20]. In such cases, the death can be related to acute hydrocephalus with tonsillar hernia, or to a reflex mechanism involving the cardiovascular system.

Neurological Symptoms not Related to Hydrocephalus

An original observation of Faris and Terrence in 1989 [40] reports the history of a patient who complained for 1 year about intermittent gustatory and olfactory disorders. The CT scan during a symptomatic period showed a colloid cyst without hydrocephalus. Surgical removal allowed total resolution of the symptoms

over a period of 14 months. Camacho reported a patient without hydrocephalus complaining about memory and emotional disorders, probably following damage to the fornix [22].

Clinical Presentation

Headaches are the most common symptom of colloid cyst. In a review of the literature from 1858 to 1994 [59] that covered 939 patients, headaches clearly represented the most frequent symptom, occurring in 72% of the patients. In recent series including more than 15 patients, [21, 33, 59, 81, 88, 103, 170], headaches were present on average in from 65% [91] to 100% [170] of the cases. It lasted usually a very short time, less than 30 min [78]. The location is variable, typically bifrontal or generalized. The pain is severe and intense, and throbbing or achy in quality. It typically begins abruptly, lasts minutes to days, and ceases abruptly. Later, the headaches become more frequent and are often accompanied by other symptoms. In a substantial proportion of cases, head movement or position changes can precipitate, exacerbate, or relieve the headache. Vomiting is common, but dizziness and tinnitus may also occur. Dysautonomic symptoms occasionally accompany the headache: abdominal pain, tachycardia, hyperthermia, bradycardia or sweating. Visual disturbances such as flashes of light can occur during attacks [170]. This type of headache must be regarded as an alarm mandating brain imaging. Death can indeed occur after a few hours, generally after a phase of deterioration [139]. Nausea and vomiting may occur in 32% of the patients [59]; their incidence varies between 12.5% [104] and 37% [59] in recent series. Neurological deterioration occurs in 21% of the cases [59] and between 3% and 44% [104] of the patients in recent series. Visual troubles occur in 21% of the cases [59], varying from diminishing of visual acuity [21, 88] to papilledema [21], diplopia [33, 21, 50], or photophobia [21].

The study of Hernesniemi and Lievo reports on 22% of patients presenting with neurological deterioration, change of personality or simulating a psychiatric affection [59]. In a series of 37 patients, Mathiesen et al. [103] report a normal pressure hydrocephalus syndrome revealing a colloid cyst in 6 patients. Memory disorders can be found without clinical signs of hydrocephalus. This type of clinical presentation would appear more readily in the young subject [103]. Psychiatric disorders can reveal a colloid cyst: mental aberration, progressive dementia [160], hallucinations, modifications of the personality

with apparent schizophrenia [160], melancholia [160], or agitation with aggressiveness [75] – all these symptoms regressing after the removal of the cyst. Olfactory and gustatory hallucinations have been reported in a 46-year-old patient, disappearing after removal of the cyst [40].

CSF leakage could reveal a colloid cyst of the third ventricle. The mechanism of the leak remains unclear. Such cysts occur in patients without a history of cranial trauma. Surgical cure of the cyst allows progressive resolution of the leakage [77].

Colloid cyst is a very rare pathology in children. According to a retrospective study of MacDonald et al. in 1994, 3 cases were reported among 1400 cerebral tumors in a pediatric population [99]. The revealing symptoms are, as in adults, headaches with nausea and vomiting, which can mimic gastroenteritis and delay the diagnosis [144]. Sometimes signs of intracranial hypertension may occur with papillary edema, diplopia, and increased cranial circumference due to the hydrocephalus [99]. Drop attacks and dementia are exceptional [99]. Sudden death is also exceptional, just as in adults, generally preceded by headaches for days or months [9, 99, 139].

Sudden Death

In the majority of the cases, death follows one symptomatic period. This period lasts rarely less than 24 h [139]. However, sometimes death occurs without any premonitory sign [3]. Particular circumstances of occurrence are reported in the literature, e.g., following cranial trauma [167], after an airplane flight [20], or precipitated by diagnostic procedures such as lumbar puncture [122, 139].

Neuroradiology

Computed Tomography

On CT, colloid cysts usually appear as well-defined, round or oval, hyperdense masses in the anterior third ventricle at the foramen of Monro. On precontrast scans these masses are hyperintense relative to brain in approximately two-thirds of cases, isointense in one-third, and rarely hypointense [2, 21, 33, 46, 99, 104]. They generally do not show contrast enhancement, or, less commonly, show mild to moderate enhancement [143]. A ring-like pattern of enhancement has been also reported [143].

Maeder et al. [101] analyzed colloid cyst contents and found no significant difference in the amounts of various element concentrations (calcium, iron, and others) between hypodense and hyperdense cysts, but did find a correlation between increased density and high cholesterol content. A difference in anatomic structure due to a difference in the state of hydration with increased electron density is a possible explanation for the hyperdense central portion of the cyst. CT reveals and quantifies the hydrocephalus, present (according to series) in between 70% [88] and 100% of the cases [1, 2]. Active hydrocephalus is easily diagnosed by the signs of periventricular resorption of the CSF appearing in the form of periventricular hypodensities. Finally, a hyperdense CT appearance is predictive of high viscosity and therefore difficulty of cyst aspiration, especially in large cysts [85].

Magnetic Resonance Imaging

Colloid cysts have a varied appearance on MRI but are usually homogeneously hyperintense on T1-weighted images and hypointense on T2-weighted images. Often the central portion of the cyst becomes hypointense on T2-weighted images. Postcontrast rim enhancement is occasionally observed. Despite these differences in imaging characteristics, no histological variations were observed between the central and the outer portion of the cysts. It is proposed that the observed differences could be attributed to differences in state of hydration between the portions of the cyst [161]. Another study, comparing MRI and chemical analysis, found that the high signal intensity on T1-weighted images seemed to roughly follow the concentration of cholesterol within the cyst [101]. From a surgical point of view, Kondziolka and Lunsford did not find a correlation between MRI and the density of the cyst [85]. More recently, a study by El Khoury et al. on 19 colloid cysts operated on endoscopically shows for the first time a correlation between hypointensity on T2-weighted images and significantly increased viscosity of the cyst contents. Hyperintensity on T2-weighted images may predict surgical difficulties for cyst aspiration either in stereotactic conditions or endoscopically [39].

Management of Colloid Cysts

The first attempt to remove a colloid cyst was performed by Dandy through a posterior transcallosal approach, similar to that used to approach the pineal

gland. Later Dandy improved this technique and in 1930 proposed a transcortical transventricular approach.

Observation

A recent study [131] retrospectively reviewed 162 colloid cysts diagnosed between 1974 and 1998. It was suggested that patients harboring asymptomatic colloid cysts can be managed safely with clinical observation and serial neuroimaging. Fortytwo percent of the cysts in this series remained asymptomatic for a mean follow-up of 79 months. Only 8% of the patients developed cyst-related symptoms and could be therefore surgically treated. It was hypothesized that patients become symptomatic only when the cyst enlarges rapidly, causing CSF obstruction and increased intracranial pressure. Some cysts enlarge more gradually, allowing the patient to accommodate the cyst without any obstruction of the CSF flow. In these cases, if the cyst stops growing, even if the ventricles are enlarged, the patient may not require surgery [131]. In the opinion of Kondziolka and Lunsford, asymptomatic colloid cysts of less than 5 mm in diameter can be observed. Cysts that are more than 5 mm in diameter should be operated on whether they are symptomatic or not [87].

Shunting

Colloid cyst symptoms are usually related to hydrocephalus, sometimes with an acute presentation. The risk of death due to a benign tumor has led to a consensus that all symptomatic colloid cysts should be treated, and one of the simplest methods is to implant a shunt [30]. However, shunting is not very satisfactory for several reasons:

1. Bilateral obstruction of the foramen of Monro requires a bilateral ventricular catheter or a unilateral ventricular catheter associated with septum pellucidum fenestration
2. Shunts are susceptible to malfunction which may lead to severe symptoms in such non-communicating hydrocephalus
3. This non-curative treatment may lead to insidious growth of the cyst to considerable dimensions, causing irreversible memory disturbances

For all of the above reasons, we do not think that simple shunting is a valuable treatment for colloid cysts. However, Hattab et al. [57] reported 6 patients followed for up to 14 years after a shunt implantation without any clinical complication.

The treatment of hydrocephalus may also induce modifications of the cyst itself, as exceptionally reported by Kachhara et al. [76]. They reported the case of a 13-year-old boy admitted with a history of headaches, vomiting, and diplopia. A right ventriculoperitoneal shunt was inserted and the patient's condition returned to normal. The CT follow-up 2 weeks later showed that the ventricles were reduced in size. The colloid cyst had also decreased in size and had changed from a low-density appearance to a homogeneously denser appearance. The patient underwent removal of the cyst through a transcallosal approach. The cyst was said to have low water content and could be evacuated only with dissectors. The excised cyst showed no pathological evidence of hemorrhage. It was presumed that the changes were due to extraction of water from the cyst following shunt diversion.

Stereotactic Aspiration

Aspiration without resection was initially described as a therapeutic technique by Gutierrez-Larra et al. [52] in 1975. Bosch et al. were the first to describe stereotactic aspiration, which they used in four patients [18]. Stereotactic aspiration is a valuable surgical method for colloid cysts and probably the least traumatic, its success depending upon two main factors:

1. The viscosity of the cyst content, which can be assessed by the CT features. The preoperative CT scan appearance of a hypodense or isodense cyst predicts low viscosity, which correlates favorably with successful stereotactic aspiration. Unfortunately, approximately 70% of colloid cysts are hyperdense, which is predictive of high viscosity and therefore difficulty of cyst aspiration, especially in large cysts [33].
2. The size of the cyst. Small cysts are associated with unsuccessful aspiration, due to the difficulty of puncturing the cyst, which slides away from the probe [33].

Stereotactic aspiration can also lead to a risk of recurrence, sometimes after a long period of time more than 6 years) [15, 33, 38, 42, 45]. Recurrence is actually not surprising as the cyst capsule is left relatively undamaged during aspiration and is able to regrow. Stereotactic aspiration should probably be chosen for colloid cysts with low-viscosity contents so far as this can be determined preoperatively. However, the stereotactic needle can be exchanged with advantage for an endoscope introduced the same way. A review of the recent literature [85, 103, 118, 128] shows that total evacuation of the cyst by stereotactic puncture is possible in less than one-

third of the cases. Sometimes late recurrences appear in more than 17% of the cases. Forty-seven percent of the patients undergo aspiration several times.

Stereotactic puncture may induce or worsen memory disorders in 7% of cases. These disorders can be explained by injury to the fornix or septal veins directly from the tip of the probe or due to traction on the cyst during aspiration. Rarely, hemorrhage may occur [128].

Endoscopic Management

Direct visualization of a colloid cyst using a modern rigid endoscope was performed for the first time by Guiot in 1963, who was the first to use an endoscope with an external light source [51]. In 1983, Powell et al. [133] reported a series of 6 cases, three of which were successfully treated using a rigid endoscope. In 1988, Auer et al. [11] reported endoscopic aspiration and coagulation in one case. Other cases have been subsequently reported [28, 38, 97, 104]. At the present time, there are a large number of reports of colloid cyst treated endoscopically [1, 11, 28, 33, 34, 41, 49, 58, 81, 97, 103, 112, 133, 138, 172]. By its very nature, endoscopy cannot offer such complete removal as the microsurgical techniques. Nevertheless, this technique could constitute a valuable alternative, combining the advantages of a percutaneous technique with the possibility of "doing more than" simple aspiration. The development of endoscopic instrumentation allows not only aspiration of the cyst, but also wide opening of the cyst wall and coagulation of all the visible parts of the cyst capsule. In few selected cases, endoscopy allows complete removal of the cyst.

The Endoscopic Instrumentarium

There are different types of endoscope than can be used for colloid cysts. The endoscope we personally use is a rigid neuroendoscope with an oval sheath (5.2 mm-3.5 mm OD or 4 mm-7 mm OD) especially designed to best serve neurosurgical purposes (Decq Neuro-endoscope, Karl Storz, Tuttlingen, Germany). An articulated arm secured to the table fixes the neuroendoscope in the desired position. The neuroendoscope is long enough to allow stereotactic guidance when necessary (Fig. 1). Its instrumental channel (1.7 mm ID for the medium sheath and 3 mm ID for the larger sheath) allows the introduction of microscissors, microforceps, coagulating probes, puncture needles, and aspirating cannulas (Fig. 2).

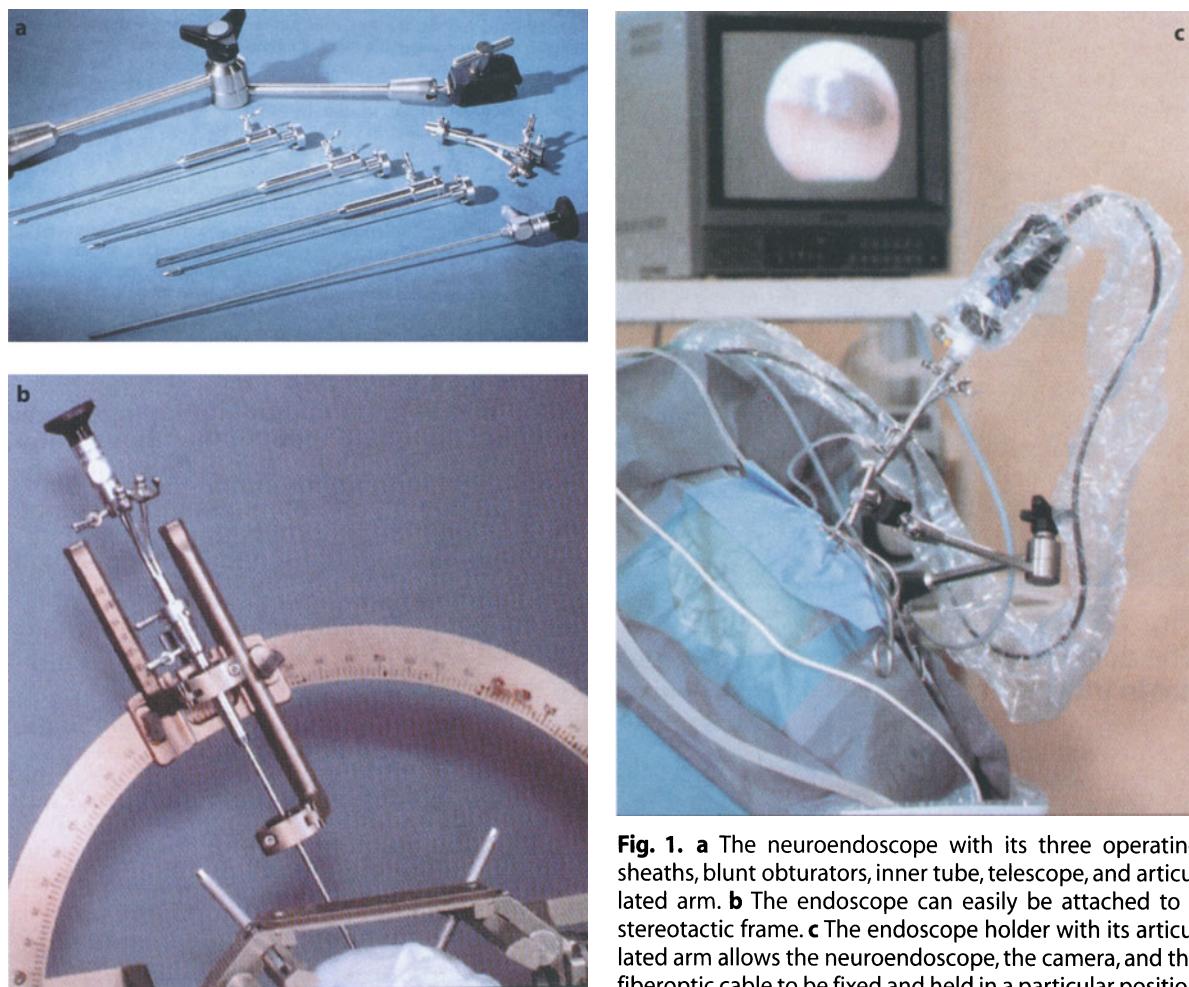


Fig. 1. **a** The neuroendoscope with its three operating sheaths, blunt obturators, inner tube, telescope, and articulated arm. **b** The endoscope can easily be attached to a stereotactic frame. **c** The endoscope holder with its articulated arm allows the neuroendoscope, the camera, and the fiberoptic cable to be fixed and held in a particular position

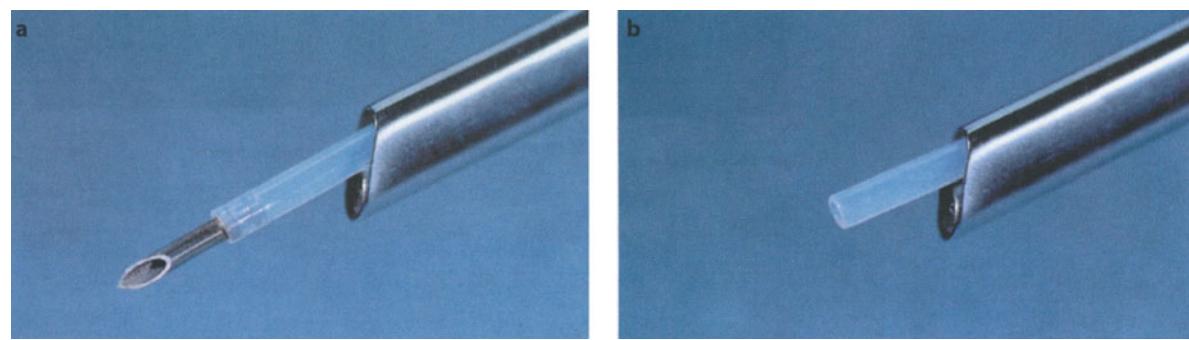


Fig. 2. **a** Puncture needle, **b** suction cannula

Endoscopic Procedure

The procedure is performed under endotracheal general anesthesia. A 4-cm linear skin incision is made parallel to the midline, 4 cm laterally and 4 cm in front of the coronal suture. A 1-cm diameter

burr hole is performed in a routine fashion. The dura is incised and the neuroendoscope is introduced into the lateral ventricle. Stereotactic guidance of the neuroendoscope was performed in two patients whose ventricles were not large enough to allow safe freehand-guided introduction of the neuroen-

doscope. In all other patients, the neuroendoscope is introduced into the ventricle under freehand guidance. The 30° telescope is backward oriented to observe the foramen of Monro and its posterior part. The frontal horn of the lateral ventricle and the foramen of Monro are inspected. The colloid cyst is identified, filling the foramen (Fig. 3a), adhering to the choroid plexus, and inserted on the roof of the third ventricle. The cyst wall is coagulated and then punctured with a puncture needle (Fig. 3b,c). The colloid material is often very viscous and initial aspiration is often unsuccessful. With microscissors and forceps, the cyst wall is opened as widely as possible, facilitating aspiration of the colloid material with aspirating probes (Fig. 3d). The cyst is progressively emptied and all the visible cyst wall is coagulated. When possible, the neuroendoscope is advanced inside the cyst to coagulate its inner surface. At the end of the procedure, all of the posterior part of the third ventricle is inspected. The residual cyst wall is coagulated on the choroid plexus situated on the roof of the ventricle, just behind the posterior wall of the foramen of Monro (Fig. 3e). In some cases, posterior puncture of the cyst is required through the most prominent and translucent distended part of the septum behind the foramen of Monro. Septum pellucidum fenestration

is not required. Third ventriculostomy may be easily performed when required (as we did in four patients with posteriorly implanted cysts). Intermittent irrigation with saline solution is performed when necessary to maintain the quality of vision. The neuroendoscope is then withdrawn. A small piece of gelfoam is placed in the cortical chimney. Bone powder is carefully replaced in the burr hole and the wound is closed in a routine fashion. In comatose patients, an external drainage should be placed in emergency, followed 2 or 3 days later by the endoscopic procedure.

As emphasized by Lewis et al. [97], endoscopic management of colloid cyst requires experience with endoscopic techniques. We began to perform such surgery after performing more than 100 endoscopic procedures, during which we learned how to move the neuroendoscope inside the ventricular cavities and to manipulate the instruments. Three simple instruments are very useful for this surgery. A puncture cannula with a transparent sheath is the most convenient instrument to puncture the cyst and to observe the colloid material. An aspirating cannula, as large as possible, is used to progressively aspirate the colloid material. Biopsy forceps and rongeurs are of no help at this stage. Shrinkage and coagulation of the cyst wall could be simply performed with a monopolar co-

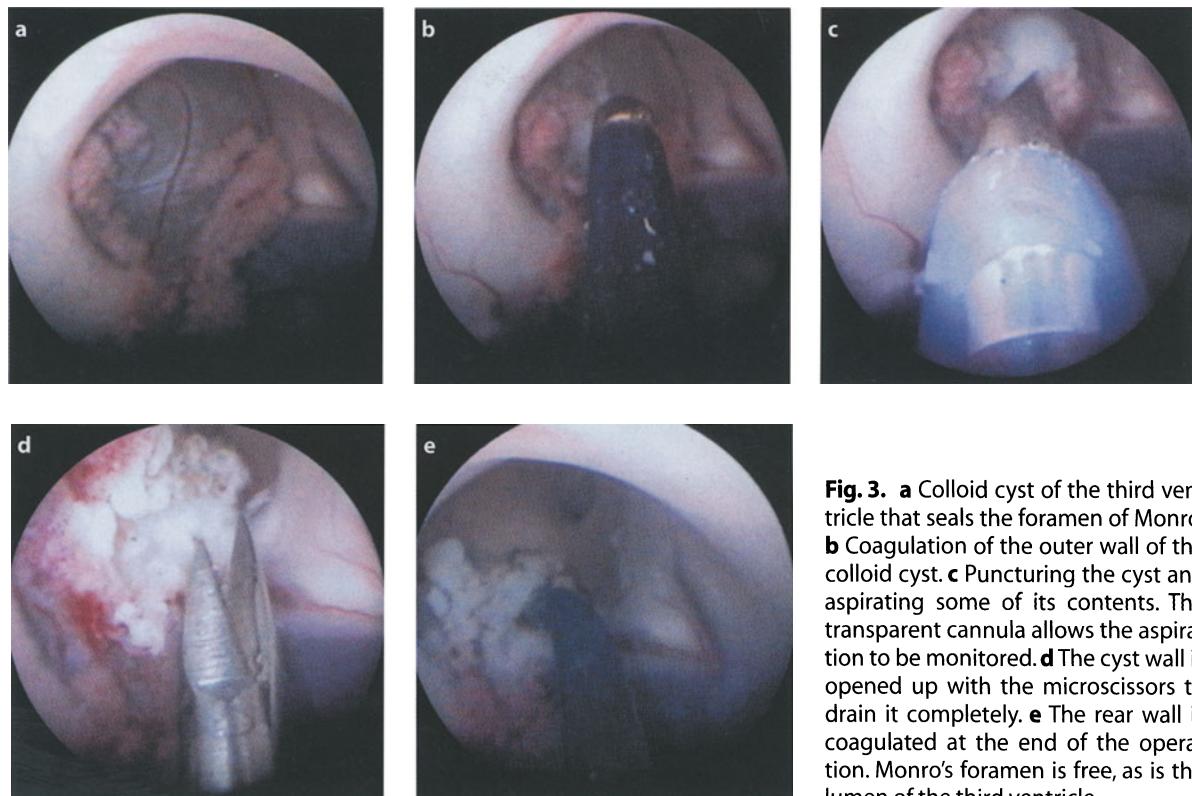


Fig. 3. **a** Colloid cyst of the third ventricle that seals the foramen of Monro. **b** Coagulation of the outer wall of the colloid cyst. **c** Puncturing the cyst and aspirating some of its contents. The transparent cannula allows the aspiration to be monitored. **d** The cyst wall is opened up with the microscissors to drain it completely. **e** The rear wall is coagulated at the end of the operation. Monro's foramen is free, as is the lumen of the third ventricle

agulating probe. In our experience, using a laser probe is no better than electrocoagulation.

The main criticisms regarding endoscopy are the following:

1. The manipulation of the endoscopic sheath may lead to more damage to the fornix around the foramen of Monro than a microsurgical approach. The risk, in our opinion, is strongly correlated to operator experience. When we began with endoscopy, performing third ventriculostomies, we sometimes caused a little fornix contusion, fortunately without any clinical manifestation. With time we learned how to manipulate the endoscope slowly and anticipate the trajectory of the sheath and the instruments, avoiding any significant fornix damage.
2. Excessive electrocoagulation may induce thermal injuries. Thermal injury may be induced by too high laser energy, as reported by Lewis et al. [97]. We never encounter this complication with monopolar coagulation combined with intermittent irrigation to cool the CSF.
3. Most of all, endoscopy allows only the use of small and limited instruments in one working channel with limited orientation compared with a microsurgical procedure using rigid, hand-held and diversified conventional microsurgical instruments in a limited but larger field.
4. The last problem is the question of the safety of the remnants left in place, which are made of coagulated cyst wall widely opened into the ventricular cavities. Longer follow-up studies will provide the answer to this.

Endoscopy allows treatment of the cyst in approximately two-thirds of cases [33, 81], or at least its disappearance on postoperative MRI. Approximately 12% of patients are reoperated on, by endoscopy in 5% of cases and by an open approach in 7% of the cases [1, 33, 34, 81, 138]. Postoperative memory disorders are not exceptional, being noted in more than 8% of the cases. Five percent of cases need shunting. The recurrences appear in 3% of cases after approximately 1 [34] to 4 years [1], depending on the series.

The results of our series were as follows: from January 1994 to June 1999, 23 patients underwent endoscopic surgery for colloid cysts of the third ventricle. The diagnosis was confirmed histologically in every case. There were 16 male and 7 female patients ranging in age from 20 to 76 years (mean 38.2 years). Presenting symptoms were most frequently intermittent headache (18 patients), followed by nausea (10 patients), short-term memory loss (7 patients), coma (3 patients), gait disturbance (3 patients), blurred vision (7 patients), and mental status changes (6 patients). One patient had had a

ventriculoatrial shunt placed at another institution 8 years before and had undergone two unsuccessful stereotactic aspirations. The duration of the symptoms from onset to presentation for medical advice ranged from 8 days to 10 years (mean 75 weeks). All patients had ventriculomegaly (Evans index ranging from 0.36 to 0.57, mean 0.44) except for the previously shunted patient. The cyst diameter ranged from 4 to 50 mm (mean 20 mm) (Fig. 4). The average follow-up was 24 months (range: 1 to 48 months). Operating time ranged from 60 to 240 min (mean 89 min) depending on the viscosity of the colloid material, the diameter of the foramen of Monro, and the exact position of the cyst. Depending on the radiological appearance, the procedure was carried out through a right (14 patients) or left (9 patients) precoronal burr hole. There was one case of bacterial meningitis successfully treated by antibiotics and four cases of "aseptic" meningitis (pleiocytosis without any identified organism). A tiny contusion of the column of the fornix was noted in five patients without any related clinical symptoms. All patients were relieved of the pre-operative symptoms except for two of the seven patients with memory disturbances, who still had a remaining deficit. One patient who had suffered from short-term memory deficit for more than 1 year was unchanged. The deficit appeared progressively in this previously shunted patient with insidious growth of his tumor. The other patient was improved but still had disabling short-term memory disturbances. No patient required ventricular shunting for hydrocephalus. Ventriculomegaly decreased postoperatively (postoperative Evans index ranged from 0.30 to 0.42 with an average of 0.36; statistically significant difference on paired Student t-test, $p=0.0001$) (Fig. 5). One patient suffered a postoperative seizure during the follow-up period, 2 weeks after surgery. Fifteen of the 23 patients (65%) were free of any residual cyst on postoperative MRI (Figs. 4-6). One radiological recurrence was observed 1 year after surgery, but the patient remains stable without any clinical symptoms up to now with a follow-up of 4 years. Postoperative MRI showed a small remnant of the cyst in six patients, with clinical recovery. In three patients, the remnant disappeared during the follow-up period (Fig. 7). In the other three patients the remnant diminished progressively. The remaining two patients had a large and too posteriorly implanted cyst. All visible parts of the cyst were treated and the third ventricular lumen was free of any CSF obstacle. However, on the postoperative MRI, we realized that only approximately the half of the cyst had been evacuated, with residual cyst on the roof of the third ventricle.

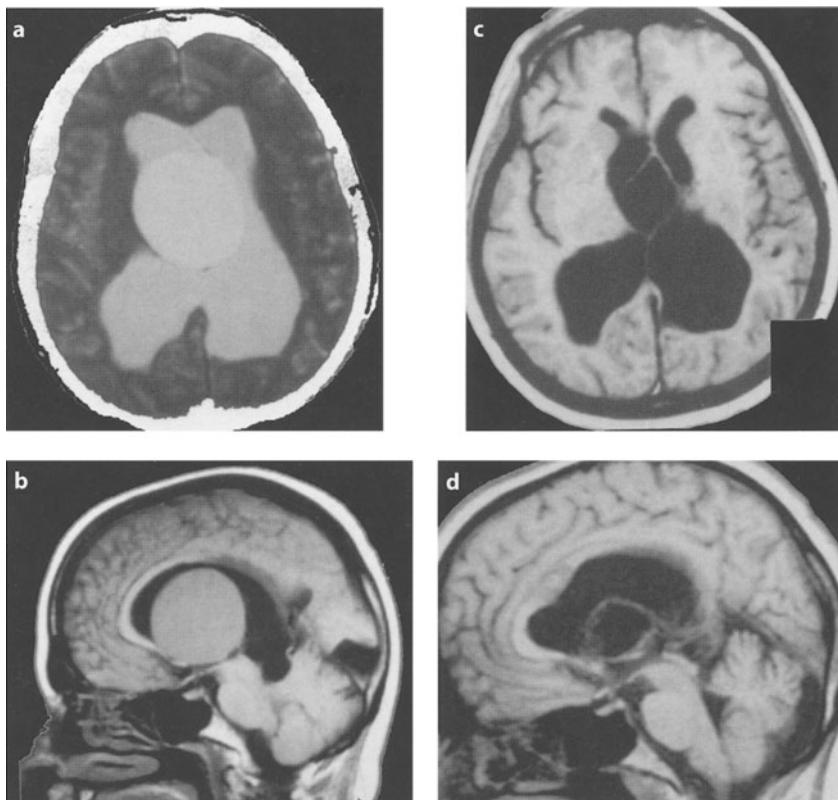


Fig. 4. The largest colloid cyst of our series. Preoperative MRI: **a** axial, **b** sagittal views. Postoperative MRI (at 1 year): **c** axial and **d** sagittal views

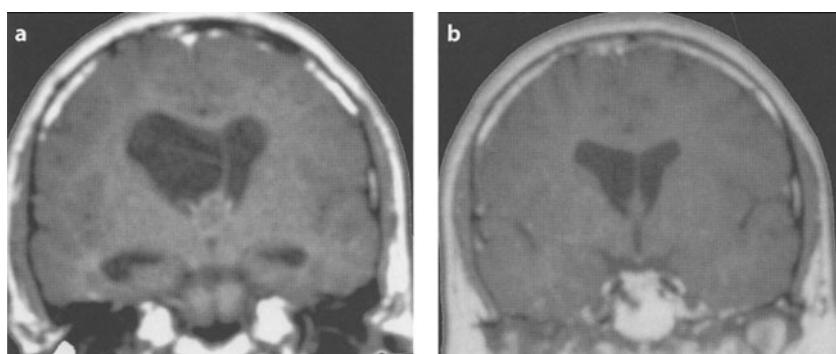


Fig. 5a, b. Ventriculomegaly decreased after endoscopic removal of colloid cysts. **a** Preoperative and **b** postoperative (at 2.5 years) MRI, coronal sections

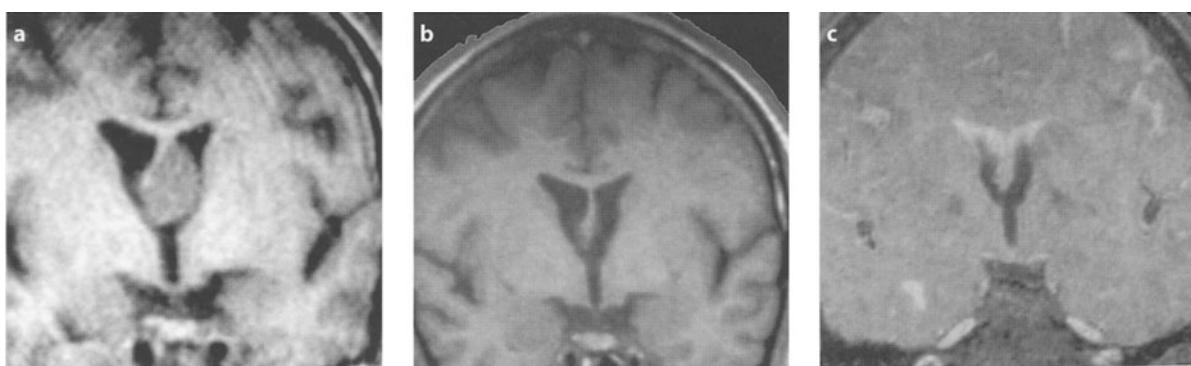


Fig. 6. **a** Preoperative MRI (coronal view) of a colloid cyst that developed mainly in the left lateral ventricle. **b** Coronal T2-weighted MRI 1.5 years postoperatively show that no remnant can be observed. **c** Coronal MRI flow sequence (FISP) shows both foramina of Monro to be free of any obstruction

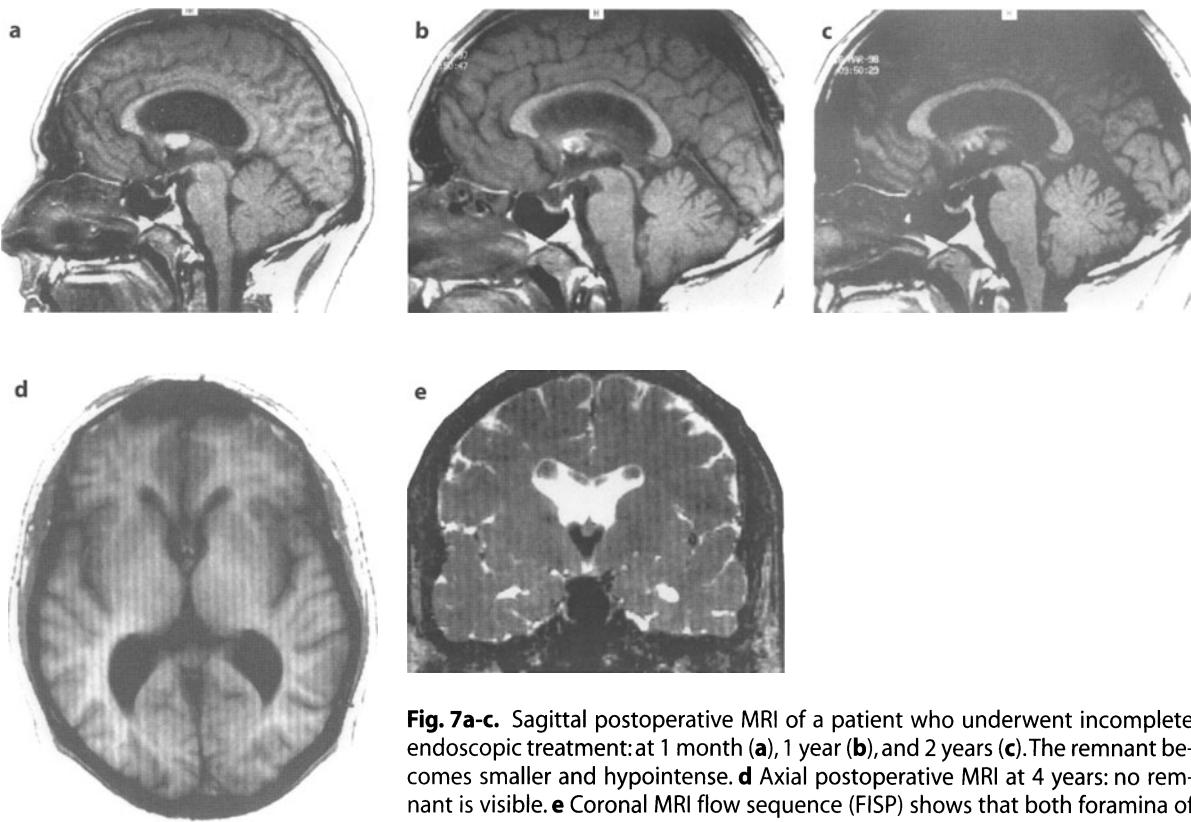


Fig. 7a-c. Sagittal postoperative MRI of a patient who underwent incomplete endoscopic treatment: at 1 month (a), 1 year (b), and 2 years (c). The remnant becomes smaller and hypointense. **d** Axial postoperative MRI at 4 years: no remnant is visible. **e** Coronal MRI flow sequence (FISP) shows that both foramina of Monro are free of any obstruction

Open Surgical Removal

Open surgical removal is the gold standard in the treatment of colloid cyst of the third ventricle. This is the only method, at the present time, which can remove the cyst and ensure definitive cure of this benign tumor. Since the initial report by Dandy in 1933, using a transcortical-transventricular approach [31], two surgical approaches have been routinely used:

1. The transcortical-transventricular approach, [21, 88, 116], which may be difficult in patients with small ventricles. The principal complication classically reported for this approach is the occurrence of postoperative epilepsy in from 0 to 5% of cases [2, 21, 46, 88]. Reinterventions are necessary [2, 21, 46, 88] in approximately 13% of the patients: ventricular shunting for persistent hydrocephalus (70%), or drainage of subdural or subcutaneous CSF collections (30%).
2. The transcallosal approach, which avoids any cortical incision and provides natural planes for dissection to the anterior part of the third ventricle through a callosal section [6, 7, 97, 103]. This approach allows access to the midline via the septum and directly to the attachment of the tumor. However, complications may also occur with this ap-

proach, such as venous infarction (bridging vein damage) or damage to the fornices [7, 97, 103]. The transcallosal approach, not passing through the cortex, is supposed to reduce the risk of epilepsy. Hernesniemi and Lievo [59] do not report any epilepsy among the 31 patients operated on through this approach. In fact, however, retraction of the cortex and venous damage may potentially lead to epilepsy. According to Gokalp et al. [46], therefore, the risk of epilepsy after both approaches is identical, close to 5%. Other complications have been reported: traumatic aneurysm of the pericallosal artery [152], superior longitudinal sinus thrombosis [43], diffuse subarachnoid hemorrhage [169], transient left hemiparesis [46], and a case of disconnection syndrome. The bilateral retraction of the gyrus cingularis can lead to mutism [135].

Total resection is not always achieved with either technique, only in 88% of the cases. A small remnant of the cyst wall may sometimes be left attached to the fornix or a thalamostriate vein [21, 88].

The memory disorders are a well-known complication of the open approaches, occurring in approximately 4% of cases. They are related to lesions of the fornix [70] and occur in various circumstances: division of the columns of the fornix during the transcal-

losal approach [2], lesions of the boundaries of the foramen of Monro, and lesions of the septal veins. Hernesniemi and Lievo [59] report 1 case among 31 patients, Villani et al. [164] 2 among 34 patients. The memory deficits relate to recent memory and generally transient [70, 164].

Conclusion

There is a consensus that all symptomatic colloid cysts should be treated. According to recent publications, it seems that asymptomatic colloid cysts can be observed with serial imaging. The quality of the results reported in endoscopic series with a very low morbidity demonstrate the potential of this minimally invasive technique to provide good and safe treatment of these lesions, but more follow-up is needed to assess its true efficacy for the treatment of colloid cysts of the third ventricle. Open surgery remains, of course, a good alternative, whether through a transventricular or a transcallosal approach. There is also some place, in selected cases, for stereotactic puncture, and even also for shunting as the only procedure.

References

1. Abdou SM, Cohen AR: Endoscopic treatment of colloid cysts of the third ventricle. Technical note and review of the literature. *J Neurosurg* 89:1062-1068, 1998
2. Abernathy CD, Davis HD, Kelly PJ: Treatment of colloid cysts of the third ventricle by stereotaxic microsurgical laser craniotomy. *J Neurosurg* 70:525-529, 1989
3. Achard JM, Le Gars D, Veyssier P: Kyste colloïde du 3^e ventricule responsable de mort subite. *Presse Med* 20:3 1991
4. Akins PT, Roberts R, Coxe WS, et al: Familial colloid cyst of the third ventricle: case report and review of associated conditions. *Neurosurgery* 38:392-395, 1996
5. Anderson ML, Garcia JH: Immunocytochemical profile of third ventricle colloid cysts: histogenetic implications. *J Neuropathol Exp Neurol* 47: 373, 1988 (Abstract)
6. Antunes JL, Louis KM, Ganti SR: Colloid cysts of the third ventricle. *Neurosurgery* 7:450-455, 1980
7. Apuzzo MJ, Chi-ko-vani OK, Gott PS, et al: Transcallosal, interfornical approaches for lesions affecting the third ventricle: surgical considerations and consequences. *Neurosurgery* 10:547-554, 1982
8. Ariëns Kappers J. The development of the parapysis cerebri in man with comments on its relationship to the intercolumnar tubercle and its significance for the origin of cystic tumors of the third ventricle. *J Comp Neurol* 102:425-510, 1955
9. Aronica PA, Ahdab-Barmada M, Rozin L, et al: Sudden death in an adolescent boy due to a colloid cyst of the third ventricle. *Am J Forensic Med Pathol* 19:119-122, 1998
10. Asamoto S, Sugiyama H, Doi H, et al: A case of neuroaxis endodermal cyst. *No To Shinkei* 51:520-523, 1999
11. Auer LM, Holzer P, Ascher PW, et al: Endoscopic neurosurgery. *Acta Neurochir* 90:1-14, 1988
12. Batnitsky S, Sarwar M, Leeds NE, et al: Colloid cysts of the third ventricle. *Radiology* 112:327-341, 1974.
13. Bavetta S, El-Shunnar K, Hamlyn PJ: Neurenteric cyst of the anterior cranial fossa. *Br J Neurosurg* 10:225-227, 1996
14. Bejjani GK, Wright DC, Schessel D, et al: Endodermal cysts of the posterior fossa. Report of three cases and review of the literature. *J Neurosurg* 89:326-325, 1998
15. Bengtson BP, Hedeman LS, Bauserman SC: Symptomatic neuroepithelial (colloid) cysts of the third ventricle. A unique case report in non-twin brothers. *Cancer* 66:779-785, 1990
16. Bertalanffy H, Kretzschmar H, Giltsbach JM, et al: Large colloid cyst in lateral ventricle simulating brain tumour. Case report. *Acta Neurochir (Wien)* 104:151-155, 1990
17. Bognano JR, Edwards MK, Lee TA, et al: Cranial MR imaging in neurofibromatosis. *AJR* 151:381-388, 1988
18. Bosch DA, Rahn T, Backlund ED: Treatment of colloid cysts of the third ventricle by stereotactic aspiration. *Surg Neurol* 9:15-18, 1978
19. Budka H: Intracranial lipomatous hamartomas (intracranial "lipomas"): a study of 13 cases including combinations with medulloblastoma, colloid and epidermoid cysts, angiogenesis and other malformations. *Acta Neuropathol* 28:205-22, 1974
20. Buttner A, Winkler PA, Eisenmenger W, et al: Colloid cyst of the third ventricle with fatal outcome: a report of two cases and review of the literature. *Int J Legal Med* 110:260-266, 1997
21. Cabbell KL, Ross AD: Stereotactic microsurgical craniotomy for the treatment of third ventricular colloid cysts. *Neurosurgery* 38:301-307, 1996
22. Camacho A, Kelly PJ: Colloid cysts of the third ventricle. In: Rengachary SS, Wilkins RH (eds) *Principles of neurosurgery*, Mosby-Wolfe, 36.1-36.10, 1994
23. Campbell AD, Varma TRK: An extraventricular colloid cyst: case report. *Br J Neurosurg* 5:519-522, 1991
24. Cashion EL, Young JM: Intraventricular craniopharyngioma. Report of two cases. *J Neurosurg* 34:766-772, 1971
25. Chan RC, Thompson GB: Third ventricular colloid cysts presenting with acute neurological deterioration. *Surg Neurol* 19:358-362, 1983
26. Challa VR, Markesberry WR: Infratentorial neuroepithelial cyst (colloid cyst). Case report. *J Neurosurg* 49:457-459, 1978
27. Coca S, Martinez A, Vaquero J, et al: Immunohistochemical study of intracranial cysts. *Histol Histopathol* 8:651-654, 1993
28. Cohen AR, Shucart WA: Ventriculoscopic management of colloid cysts of the third ventricle. In: Manwaring KH, Crone KR (eds) *Neuroendoscopy*. Mary Ann Liebert, New York, pp 109-117, 1992
29. Coxe WS, Luse SA: Colloid cyst of the third ventricle. An electron microscopic study. *J Neuropathol Exp Neurol* 23:431-445, 1964
30. Creissard P, Godlewski J, Tadie M, et al: Faut-il aborder les kystes colloïdes du troisième ventricule? *Neurochirurgie* 27:225-228, 1981
31. Dandy WE: Case reports of colloid cysts in the third ventricle (group I). In: Benign tumors in the third ventricle of the brain: diagnosis and treatment. Williams and Wilkins, Baltimore, pp 4-37, 1933

32. Dauch WA, Hellwig D, Rossberg C, et al: Epithelial cyst of the central nervous system. A rare abnormality. *Neurochirurgia (Stuttg)* 34:111-115, 1991
33. Decq P, Le Guerin C, Brugieres P, et al: Endoscopic management of colloid cysts. *Neurosurgery* 42:1288-1294, 1998
34. Deinsberger W, Boker DK, Samii M: Flexible endoscopes in treatment of colloid cysts of the third ventricle. *Minim Invas Neurosurg* 37:12-16, 1994
35. Del Campio R, Cardinal E: Agenesis of the corpus callosum and colloid cyst of the third ventricle: magnetic resonance imaging of unusual association. *Can Assoc Radiol J* 41:375-379, 1990
36. Dias MS, Walker ML: The embryogenesis of complex dysraphic malformations: a disorder of gastrulation? *Pediatr Neurosurg* 18:229-253, 1992
37. Dorhman GJ, Bucy PC: Human choroid plexus: a light and electron microscopic study. *J Neurosurg* 33:506-516, 1970
38. Eiras Ajura J, Alberdi Vinas J: Traitement endoscopique des lésions intracrâniennes. A propos d'un cas. *Neurochirurgie* 37:278-283, 1991
39. El Khoury C, Brugieres P, Decq P, et al: Colloid cyst of the third ventricle: are MR imaging patterns predictive of difficulty with percutaneous treatment? *Am J Neuroradiol* 21: 489-492, 2000
40. Faris AA, Terrence CF: Limbic system symptomatology associated with colloid cyst of the third ventricle. *J Neurol* 236:60-61, 1989
41. Gaab MR, Schroeder HWS: Neuroendoscopic approach to intraventricular lesions. *J Neurosurg*, 88:496-505, 1998
42. Gaertner HG, Prager B, Hinkel GK: Colloid cyst of the third ventricle with XYY-Syndrome. *J Hirnforsch* 35:555-560, 1993
43. Garido E, Fahs GR: Cerebral venous and sagittal sinus thrombosis after transcallosal removal of a colloid cyst of the third ventricle: case report. *Neurosurgery* 26:540-542, 1990
44. Ghatak NR, Kasoff I, Alexander E: Further observation on the fine structure of a colloid cyst of the third ventricle. *Acta Neuropathol* 39:101-107, 1977
45. Go KG, Hew JM, Kamman RL, et al: Cystic lesions of the brain. A classification based on pathogenesis, with consideration of histological and radiological features. Review article. *Eur J Radiol* 17:69-84, 1993
46. Gokalp HZ, Yuceer N, Arasil E, et al: Colloid cyst of the third ventricle. Evaluation of 28 cases of colloid cysts of the third ventricle operated on by transcortical transventricular (25 cases) and transcallosal/transventricular (3 cases) approaches. *Acta Neurochir* 138:45-49, 1996
47. Gould SJ, Howard S, Papadaki L: The development of ependyma in the human fetal brain: an immunohistological and electron microscopic study. *Brain Res Dev Brain Res* 55:255-67, 1990
48. Graziani N, Dufour H, Figarella-Branger D, et al: Do the suprasellar neurenteric cyst, the Rathke cleft cyst and the colloid cyst constitute a same entity? *Acta Neurochir* 133:174-180, 1995
49. Grunert P, Hopft N, Perneczky A: Frame-based and frameless endoscopic procedures in the third ventricle. *Stereotact Funct Neurosurg* 68:80-89, 1997
50. Guillaume J, Sigwald J: Diagnostic neuro-chirurgical. PUF, Paris, p 457, 1947
51. Guiot G, Rougerie J, Fourestier M, et al: Une nouvelle technique endoscopique. Explorations endoscopiques intracrâniennes. *Presse Med* 72:1225-1231, 1963
52. Gutierrez-Lara F, Patino R, Hakim S: Treatment of tumors of the third ventricle: a new and simple technique. *Surg Neurol* 3:323-325, 1975
53. Hadfield MG, Ghatak NR, Wanger GP: Xanthogranulomatous colloid cyst of the third ventricle. *Acta Neuropathol* 66:343-346, 1985
54. Hall WA, Lundsford LD: Changing concepts in the treatment of colloid cysts: An 11-year experience in the CT era. *J Neurosurg* 66:186-191, 1987
55. Harris CP, Dias MS, Brockmeyer DL, et al: Neurenteric cysts of the posterior fossa: recognition, management, and embryogenesis. *Neurosurgery* 29:893-897, 1991
56. Harrison MJ, Morgello S, Post KD: Epithelial cystic lesions of the sellar and parasellar region: a continuum of ectodermal derivatives? *J Neurosurg* 80:1018-1025, 1994
57. Hattab N, Freger P, Tadie M, et al: Traitement des kystes colloïdes du 3^e ventricule par dérivation ventriculaire. *Neurochirurgie* 36:129-131, 1990
58. Hellwig D, Riegel T, Bertalanffy H: Neuroendoscopic techniques in treatment of intracranial lesions. *Min Invas Ther Allied Technol* 7/2:123-135, 1998
59. Hernesniemi J, Lievo S: Management outcome in third ventricular colloid cysts in a defined population: a series of 40 patients treated mainly by transcallosal microsurgery. *Surg Neurol* 45:2-14, 1996
60. Hirai O, Kondo A, Kusaka H: Endodermal epithelial cyst in the prepontine cistern extending into the fourth ventricle-case report. *Neurol Med Chir (Tokyo)* 31:283-286, 1991
61. Hirano A, Chatak NR: The fine structure of colloid cysts of the third ventricle. *J Neuropathol Exp Neurol* 33:333-341, 1974
62. Hirano A, Hirano M: Benign cystic lesions in the central nervous system. Light and electron microscopic observations of cyst walls. *Childs Nerv Syst* 4:325-333, 1988
63. Hirano A, Chatak NR, Wisoff HS, et al: Epithelial cysts of the spinal cord: light and electron microscopic studies. *Acta Neuropathol* 18:214-223, 1971
64. Hirano A, Matui T, Zimmermann HM: The fine structure of epithelial cysts of the central nervous system. *Neurosurgery* 3:639-646, 1975
65. Ho KL, Chason JL: Subarachnoid epithelial cyst of the cerebellum. Immunohistochemical and ultrastructural studies. *Acta Neuropathol* 78:220-224, 1989
66. Ho KL, Garcia JH: Colloid cysts of the third ventricle: ultrastructural features are compatible with endodermal derivation. *Acta Neuropathol* 83:605-612, 1992
67. Ho KL, Garcia JH: Ciliary claws: their existence in various epithelial cysts of the central nervous system. *Acta Neuropathol* 84:453-456, 1992
68. Ho KL, Garcia JH: Should colloid cysts of the third ventricle be called colloid cysts of the transverse cerebral fissure? *J Neuropathol Exp Neurol* 52:328, 1993
69. Ho KL, Tiel R: Intraspinal bronchogenic cyst: ultrastructural study of the lining epithelium. *Acta Neuropathol* 78:513-520, 1989
70. Hodges JR, Carpenter K: Anterograde amnesia with fornix damage following removal of III ventricle colloid cyst. *J Neurol Neurosurg Psychiatry* 54:633-638, 1991
71. Ibrahim AWM, Farg H, Naguib M, et al: Neuroepithelial (colloid) cyst of the third ventricle in identical twins. *J Neurosurg* 65:401-403, 1986
72. Ikeda H, Yoshimoto T, Suzuki J: Immunohistochemical study of Rathke's cleft cyst. *Acta Neuropathol* 77:33-38, 1988

73. Inoue T, Matsushima T, Fukui M, et al: Immunohistochemical study of intracranial cysts. *Neurosurgery* 23:576-581, 1988
74. Jan M, Zeze VB, Velut S: Colloid cyst of the fourth ventricle: diagnostic problems and pathogenic considerations. *Neurosurgery* 24:939-942, 1989
75. Jones AM: Psychiatric presentation in a third ventricular colloid cyst in a mentally handicapped woman. *Br J Psychiatry* 163:677-678, 1993
76. Kachhara R, Das K, Nair S, et al: Changing characteristics of a colloid cyst of the third ventricle. *Neuroradiology* 41:188-189, 1999
77. Kane PJ, Mendelow AD, Keoch AJ, et al: Cerebrospinal fluid rhinorrhoea associated with colloid cyst. Short report. *Br J Neurosurg* 5:317-320, 1991
78. Kelly R: Colloid cysts of the third ventricle: analysis of 29 cases. *Brain* 74:23-65, 1951
79. Kelly PJ: Resection of intraventricular tumors via a computer-assisted volumetric stereotactic approach. *Neurosurgery* 33:771-772, 1993
80. Kepes JJ: Colloid cysts of the third ventricle: are they really of parapheal or ependymal origin? *Acta Neurol Scand* 46:628-629, 1970
81. King WA, Ullman JS, Frazee JG, et al: Endoscopic resection of colloid cysts: surgical considerations using the rigid endoscope. *Neurosurgery* 44:1103-1111, 1999
82. Klein MR: Craniopharyngiome et tumeur du troisième ventricule: ablation des deux tumeurs. *Rev Neurol* 76:21, 1944
83. Kleinschmidt-DeMasters BK, Winston KR, Rubinstein D, et al: Ectopic pituitary adenoma of the third ventricle. Case report. *J Neurosurg* 79:139-142, 1990
84. Kondziolka D, Bilbao JM: Ontogenesis of colloid cysts. *J Neurosurg* 73:312, 1990
85. Kondziolka D, Lunsford LD: Stereotactic management of colloid cysts: factors predicting success. *J Neurosurg* 75:45-51, 1991
86. Kondziolka D, Lunsford LD: Aspiration of colloid cyst. *J Neurosurg* 79:965-966, 1993
87. Kondziolka D, Lunsford LD: Stereotactic techniques for colloid cysts: roles of aspiration, endoscopy and microsurgery. *Acta Neurochir (Suppl)* 61:76-78, 1994
88. Kondziolka D, Lunsford LD: Microsurgical resection of colloid cysts using stereotactic transventricular approach. *Surg Neurol* 46:485-492, 1996
89. Kunishio K, Yamamoto Y, Sunami N, et al: Craniopharyngioma in the third ventricle: necropsy findings and histogenesis. *J Neurol Neurosurg Psychiatry* 50:1053-1056, 1987
90. Küchelmeister K, Bergmann M: Colloid cysts of the third ventricle: an immunohistochemical study. *Histopathology* 21:35-42, 1992
91. Lach B, Scheithauer BW: Colloid cyst of the third ventricle: a comparative ultrastructural study of neuraxis cysts and choroid plexus epithelium. *Ultrastruct Pathol* 16:331-349, 1992
92. Lach B, Scheithauer BW, Gregor A, et al: Colloid cysts of the third ventricle. A comparative immunohistochemical study of neuraxis cysts and choroid plexus epithelium. *J Neurosurg* 78:101-111, 1993
93. Landolt-Weber UM: Ultrastructure of a third ventricle colloid cyst. *Acta Neuropathol* 26: 59-70, 1973
94. Lantos PL, Vandenberg SR, Kleihues P: Tumours of the nervous system. In: Graham DI, Lantos PL (eds) *Greenfield's neuropathology* 6th edn. Arnold, London, 1997
95. Leech RW, Freeman T, Johnson R: Colloid cysts of the third ventricle. A scanning and transmission electron microscopic study. *J Neurosurg* 57:108-113, 1982
96. Leventer DB, Merriam JC, Defendidni, et al: Enterogenous cyst of the orbital apex and superior orbital fissure. *Ophthalmology* 101:1614-1621, 1994
97. Lewis AI, Crone KR, Taha J, et al: Surgical resection of third ventricle colloid cysts. Preliminary results comparing transcallosal microsurgery with endoscopy. *J Neurosurg* 81: 174-178, 1994
98. Macauley RJB, Felix I, Jay V, et al: Histological and ultrastructural analysis of six colloid cysts in children. *Acta Neuropathol* 93:271-276, 1997
99. MacDonald RL, Humphreys RP, Rutka JT, et al: Colloid cysts in children. *Pediatr Neurosurg* 20: 169-177, 1994
100. Mackenzie IRA, Gilbert JJ: Cysts of the neuraxis of endodermal origin. *J Neurol Neurosurg Psychiatry* 54:572-575, 1991
101. Maeder PP, Holtas SI, Basibuyuk LN, et al: Colloid cysts of the third ventricle: correlation of MR and CT findings with histology and chemical analysis. *Ann J Neuroradiol* 11:575-581, 1990
102. Mamourian AC, Cromwell LD, Harbaugh RE: Colloid cyst of the third ventricle: sometimes more conspicuous on CT than MR. *Am J Neuroradiol* 19:875-878, 1998
103. Mathiesen T, Grane P, Lindgren L, et al: Third ventricle colloid cysts: a consecutive 12-year series. *J Neurosurg* 86:5-12, 1997
104. Mathiesen T, Grane P, Lindquist C, et al: High recurrence rate following aspiration of colloid cysts in the third ventricle. *J Neurosurg* 78:748-752, 1993
105. Matsushima T: Choroid plexus papillomas and human choroid plexus. A light and electron microscopic study. *J Neurosurg* 59:1054-1062, 1983
106. Matsushima T, Fukui M, Egami H: Epithelial cells in a so-called intraspinal neurenteric cyst: a light and electron microscopic study. *Surg Neurol* 24:656-660, 1985
107. Matsushima T, Fukui M, Kitamura K, et al: Mixed colloid cyst-xanthogranuloma of the third ventricle. A light and electron microscopic study. *Surg Neurol* 24:457-462, 1985
108. Matsushima T, Fukui M, Ohta M, et al: Ciliated and goblet cells in craniopharyngioma. Light and electron microscopic studies at surgery and autopsy. *Acta Neuropathol* 50:199-205, 1980
109. McLendon RE, Tien RD: Tumors and tumor-like lesions of maldevelopmental origin. In: Bigner DD, McLendon RE, Bruner JM (eds) *Russel and Rubinstein's pathology of tumors of the nervous system*, 6th edn. Arnold, London Sydney Auckland, pp 338-342, 1998
110. McLone DG, Dias MS: Normal and abnormal development of the nervous system. In: Cheek WR, Marlin AE, McLone, et al (eds) *Pediatric neurosurgery. Surgery of the developing nervous system*, 3rd edn. Saunders, Philadelphia, pp 3-39, 1994
111. McMackin D, Cockburn J, Anslow P, et al: Correlation of fornix damage with memory impairment in six cases of colloid cyst removal. *Acta Neurochir* 135:12-18, 1995
112. Merienne L, Leriche B, Roux FX, et al: Utilisation du laser Nd-Yag en endoscopie intracrânienne. Expérience préliminaire en stéréotaxie. *Neurochirurgie* 38:245-247, 1992
113. Mohadjer M, Teshmar E, Mundinger F: CT-stereotactic drainage of colloid cysts in the foramen of Monro and the third ventricle. *J Neurosurg* 67:220-223, 1987

114. Morita Y, Kinoshita K, Wakisaka S, et al: Fine surface structure of an intraspinal neurenteric cyst: a scanning and transmission electron microscopy study. *Neurosurgery* 27: 829-833, 1990
115. Morita Y, Kinoshita K, Wakisaka S, et al: Claws of cilia: further observation of ciliated epithelium in neurenteric cyst. *Virchows Arch A Pathol Anat Histopathol* 418:263-265, 1991
116. Morita A, Kelly PJ: Resection via a computer-assisted volumetric stereotactic approach. *Neurosurgery* 32:920-926, 1993
117. Muller A, Buttner A, Weis S: Rare occurrence of intracerebellar colloid cyst. Case report. *J Neurosurg* 91:128-131, 1999
118. Musolino A, Fosse S, Munari C, et al: Diagnosis and treatment of colloid cysts of the third ventricle by stereotactic drainage. Report of eleven cases. *Surg Neurol* 32:294-299, 1989
119. Nakasu S, Nakasu Y, Kyoshima K, et al: Pituitary adenoma with multiple ciliated cysts: transitional cell tumor? *Surg Neurol* 31:41-48, 1989
120. Nishio S, Fujiwara S, Morioka T, et al: Rathke's cleft cysts within a growth hormone producing pituitary adenoma. *Br J Neurosurg* 9:51-55, 1995
121. Nishio S, Mizuno J, Barrow DL, et al: Pituitary tumors composed of adenohypophysial adenoma and Rathke's cleft cyst elements: a clinicopathological study. *Neurosurgery* 21:371-377, 1987
122. Nader-Sepahi A, Hamlyn PJ: Familial colloid cysts of the third ventricle: case report. *Neurosurgery* 46:751-753, 2000
123. Okabe S, Kamata K, Kohno T, et al: Enterogenous cyst in the fourth ventricle. Case report. *Neurol Med Chir (Tokyo)* 35:40-44, 1995
124. Palacios E, Azar-Kia B, Shannon M, et al: Neuroepithelial (colloid) cysts. Pathogenesis and unusual features. *Am J Roentgenol* 126:56-62, 1976
125. Palma L, Celli P: Suprasellar epithelial cyst. Case report. *J Neurosurg* 58:763-765, 1983
126. Palma L, Di Lorenzo N: Spinal endodermal cysts without associated vertebral or other congenital abnormalities. Report of four cases and review of the literature. *Acta Neurochir* 33:283-300, 1976
127. Pasquier B, Couderc P, Pasquier, et al: Kyste colloïde du 3^e ventricule associé à un hémangiome de la fosse cérébrale postérieure. *Sem Hop* 53:2139-2140, 1977
128. Peragut JC, Riss JM, Farnarier P, et al: Kystes colloïdes du 3^e ventricule, scanner IRM et ponction stéréotaxique. A propos de 9 observations. *Neurochirurgie* 36:122-128, 1990
129. Probst C: Multiple frontobasal meningoencephaloceles in neurofibromatosis. *Neurofibromatosis* 2:233-237, 1989
130. Pollock BE, Huston J: Natural history of asymptomatic colloid cysts of the third ventricle. *J Neurosurg* 91:364-369, 1999
131. Pollock BE, Shreiner SA, Huston J: A theory on the natural history of colloid cysts of the third ventricle. *Neurosurgery* 46:1077-1083, 2000
132. Poirrier J, Catala M: Kystes épitheliaux intracrâniens et intrarachidiens. Un classement simplifié. *Rev Neurol (Paris)* 156:447-449, 2000
133. Powell MP, Torrens MJ, Thomson JLG, et al: Isodense colloid cysts of the third ventricle: a diagnostic and therapeutic problem resolved by ventriculoscopy. *Neurosurgery* 13:234-237, 1983
134. Powers JM, Dodds HM: Primary actinomycoma of the third ventricle. The colloid cyst. A histochemical and ultrastructural study. *Acta Neuropathol* 37:21-26, 1977
135. Rabb CH, Apuzzo MLJ: Transcallosal approach to the third ventricle. In: Schmidek HH, Sweet WH (eds) *Operative neurosurgical techniques, indications, methods and results*, 3rd edn. Saunders Philadelphia, pp 715-723, 1995
136. Rhon AL, Yamamoto I, Peace DA: Microsurgery of the third ventricle: Part 2. Operative approaches. *Neurosurgery* 8:357-373, 1981
137. Rivas JJ, Lobato RD: CT-assisted stereotactic aspiration of colloid cysts of the third ventricle. *J Neurosurg* 62:238-243, 1985
138. Rodziewicz GS, Smith MV, Hodges CJ: Endoscopic colloid cyst surgery. *Neurosurgery* 46:655-662, 2000
139. Ryder WJ, Kleinschmidt-Demaster BK, Keller TS: Sudden deterioration and death in patients with benign tumors of the third ventricle area. *J Neurosurg* 64:216-223, 1986
140. Sampath S, Yasha T, Shetty S, et al: Parasellar neurenteric cyst: unusual site and histology: case report. *Neurosurgery* 44:1335-1338, 1999
141. Scaravilli F, Lidov H, Spalton DJ, et al: Neuroenteric cyst of the optic nerve: case report with immunohistochemical study. *J Neurol Neurosurg Psychiatry* 55:1197-1199, 1992
142. Schröder R, Sanker P, Thun F, et al: Cysts of the third ventricle. *Zentralbl Neurochir* 51:42-48, 1990
143. Sener RN, Jenkins JR: Case report. CT of intrasellar colloid cyst. *J Comput Assist Tomogr* 15:671-672, 1991
144. Shemie S, Jay V, Rutka J, et al: Acute obstructive hydrocephalus and sudden death in children. *Ann Emerg Med* 29:524-528, 1997
145. Shibata T, Burger PC, Kleihues P: Origin of colloid cyst: immunoperoxidase study. *No To Shinkei* 39:953-958, 1987
146. Shimoji T, Shinohara A, Shimizu A, et al: Rathke cleft cysts. *Surg Neurol* 21:295-310, 1984
147. Shuangshoti S, Netsky MG: Neuroepithelial (colloid) cysts of the nervous system. Further observations on pathogenesis, location, incidence, and histochemistry. *Neurology* 16:887-903, 1966
148. Shuangshoti S, Phisitbur M, Kasantikul V, et al: Multiple neuroepithelial (colloid) cysts: association with other congenital abnormalities. *Neurol* 27:561-566, 1977
149. Shuangshoti S, Phonprasert C, Suwanwela N, et al: Combined neuroepithelial (colloid) cyst and xanthogranuloma (xanthoma) in the third ventricle. *Neurology* 25: 547-552, 1975
150. Shuangshoti S, Roberts MP, Netsky MG: Neuroepithelial (colloid) cysts. Pathogenesis and relation to choroid plexus and ependyma. *Arch Pathol* 80: 214-223, 1965
151. Stochdorf O: Zur Abkunft der Foramen-Monroi-Cysten. *Nervenarzt* 34:226-229, 1963
152. Stoodley MA, North JB, Reiley PL, et al: Short report. False aneurysm following intracranial surgery. *Br J Neurosurg* 8:599-602, 1994
153. Tatter SB, Ogilvy CS, Golden JA, et al: Third ventricular xanthogranulomas clinically and radiologically mimicking colloid cysts. *J Neurosurg* 81:605-609, 1994
154. Thapar K, Kovacs K: Neoplasms of the sellar region. In: Bigner DD, McLendon RE, Bruner JM (eds) *Russel and Rubinstein's pathology of tumors of the nervous system*, 6th edn. Arnold, London Sydney Auckland, pp 648-652, 1998

155. Tomita H, Tamaki N, Korosue K, et al: Xanthogranuloma with massive hematoma in the third ventricle: case report. *Neurosurgery* 39:591-594, 1996
156. Tsuchida T, Hruban RH, Carson BS, et al: Colloid cysts of the third ventricle: immunohistochemical evidence for non-neuroepithelial differentiation. *Hum Pathol* 23:811-816, 1992
157. Twiss JL, Horouptian DS: Pigmented intracerebral neuroepithelial cyst: report of a case. *Ultrastruct Pathol* 16:673-677, 1992
158. Uematsu Y, Komai N, Hirano A, et al: Cytokeratin immunohistochemical study of epithelial cysts in the central nervous system: with special reference to origins of colloid cyst of the third ventricle and Rathke's cleft cyst in the sella. *Noshuyo Byori* 10: 43-52, 1993
159. Uematsu Y, Rojas-Corona RR, Llena JF, et al: Epithelial cysts in the central nervous system, characteristic expression of cytokeratins in an immunohistochemical study. *Acta Neurochir (Wien)* 107:93-101, 1990
160. Upadhyaya AK, Sud PD: Psychiatric presentation of third ventricular colloid cyst. A case report. *Br J Psychiatry* 152: 567-569, 1988
161. Urso JA, Ross GJ, Parker RK, et al: Colloid cyst of the third ventricle: radiologic/pathogenic correlation. *J Comput Assist Tomogr*, 22:524-527, 1998
162. Vandertop WP: Familial colloid cyst of the third ventricle: case report and review of associated conditions. *Neurosurgery* 39:421, 1996
163. Vandertop WP, Gosselaar PH, Nesselroij B: Three sisters with colloid cyst of the third ventricle. *Lancet* 346:643-644, 1995
164. Villani R, Papagno C, Tomei G, et al: Transcallosal approach to tumors of the third ventricle. Surgical results and neuropsychological evaluation. *J Neurol Sci* 41:41-50, 1997
165. Vuia O: Congenital intracerebral epithelial cysts. *Neurochirurgia (Stuttg)* 19:219-226, 1976
166. Walls TJ, Purohit DP, Aji WS, et al: Multiple intracranial enterogenous cysts. *J Neurol Neurosurg Psychiatry* 49:438-441, 1986
167. Williams DJ, Tannenberg AEG: Unusual presentation of colloid cyst of the third ventricle. Case report. *Med Sci Law* 37: 254-256, 1997
168. Yagishita S, Itoh Y, Shiozawa T, et al: Ultrastructural observation on a colloid cyst of the third ventricle. A contribution to its pathogenesis. *Acta Neuropathol* 65: 41-45, 1984
169. Yamamoto K, Iwai Y, Nakajima H, et al: Multiple brain hemorrhages after removal of a giant colloid cyst of the third ventricle. *Neurol Med Chir (Tokyo)* 38:24-27, 1998
170. Young WB, Silberstein SD: Paroxysmal headache caused by colloid cyst of the third ventricle: case report and review of the literature. *Headache* 37:15-20, 1997
171. Yuceser N, Baskaya M, Gokalp HZ: Huge colloid cyst of the third ventricle associated with calcification in the cyst wall. *Neurosurg Rev* 19:131-133, 1996
172. Zamorano L, Chavantes C, Moure F: Endoscopic stereotactic interventions in the treatment of brain lesions. *Acta Neurochir (suppl)* 61:92-97, 1994
173. Zülch KJ: Brain tumors: their biology and pathology. Springer, Berlin Heidelberg New York, 1986

Hydrocephalus and Spinal Tumors

HELEN MAROULIS¹, WIRGINIA MAIXNER², ENRICO LEONE³ AND GIUSEPPE CINALLI⁴

Introduction

Spinal cord tumors are relatively rare in the pediatric population, comprising only 6%-10% of all central nervous system tumors in this group. Hydrocephalus and intracranial hypertension in the context of spinal cord tumors is a rare but well documented association. Since the first report of Nonne in 1900 [126], there have been more than 200 cases reported in the literature. The majority of these were published in the last 20 years, after the advent of CT and MRI. The interest that these rare cases generate is largely due to the intriguing pathophysiological mechanisms responsible for them.

Spinal cord tumors may be either benign or malignant, and the pathophysiological mechanisms for each of these subgroups may be different. Malignant lesions, which have a natural tendency to spread in the subarachnoid pathways [37, 83, 151], may alter cerebrospinal fluid (CSF) circulation by increasing CSF outflow resistance [24, 104, 151, 160, 163]. This is substantiated by the fact that the majority, if not all,

of the cases of malignant lesions associated with raised intracranial pressure show neoplastic meningeal infiltration, seen either neuroradiologically or at autopsy [7, 9, 15, 37, 48, 50, 58, 74, 80, 83, 86, 102, 104, 112, 120, 128, 130, 132, 135, 141, 146, 151, 165, 166, 175, 177, 193] (Fig. 1).

On the other hand, the causative relationship between benign lesions and hydrocephalus is much more controversial. Several pathophysiological explanations [9, 12, 57, 61, 151, 179] have been proposed, but without clear evidence of their validity. Following a review of the literature it is clear that patients can differ depending on the timing, the location of the spinal lesions, the histological diagnosis, and the existence of neoplastic meningeal infiltration. Although astrocytomas and ependymomas are the spinal tumors most frequently associated with hydrocephalus, almost any kind of spinal lesion, neoplastic or otherwise, can present with signs of raised intracranial pressure or result in the development of hydrocephalus following removal. Thus, in order to clarify the underlying mechanisms, we need to start with an accurate review of the literature.

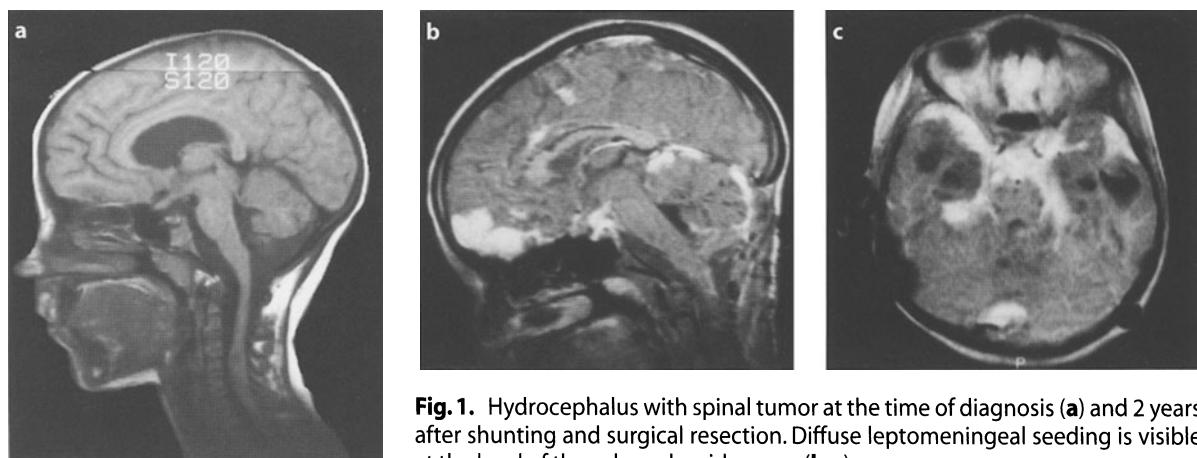


Fig. 1. Hydrocephalus with spinal tumor at the time of diagnosis (a) and 2 years after shunting and surgical resection. Diffuse leptomeningeal seeding is visible at the level of the subarachnoid spaces (b,c)

¹Department of Neurosurgery, Royal Children's Hospital, Melbourne, Australia; ²Departement of Neurosurgery, Royal Children's Hospital, Parkville, Australia; ³Department of Neuroradiology and ⁴Department of Pediatric Neurosurgery, Santobono-Pausilipon Children's Hospital, Naples, Italy

Literature Analysis

We have analyzed data from 269 cases reported in the literature. We divided these cases into three groups according to the location of the tumor: (1) intramedullary-140 cases; (2) intradural, extramedullary-107 cases (we included in this group 41 ependymomas of the conus medullaris and of the filum terminale that were described by the authors as extending into the subarachnoid space of the lumbar sac); (3) extradural-7 cases [110, 113, 133, 153, 156, 168]. In 15 cases data were insufficient for classification. For each case we evaluated the histology, the histological grading (when reported), the level of the lesion, its location with reference to the spinal cord, the timing and the interval between the diagnoses of the two pathologies, the evolution and treatment of hydrocephalus after spinal surgery, the outcome of the patients, the CSF protein content in lumbar, cisternal, and ventricular fluid, the existence of subarachnoid hemorrhage at the onset of the symptoms, and the occurrence of intracranial seeding. These data are summarized in Tables 1 and 2.

Table 1. Demographics

	Number	%
Sex		
Female	117	43
Male	116	43
Unknown	36	14
Age		
Range	birth - 75 years	
Mean	28.9 years	
Unknown	30	11
Level		
Cervical	61	22
Cervicothoracic	16	6
Thoracic	52	20
Thoracolumbar	51	19
Lumbar	67	25
Lumbosacral	5	2
Sacral	2	1
3+ regions	9	3
Unknown	6	2
Site		
Intradural intramedullary	140	52
Intradural extramedullary	107	40
Extradural	7	3
Unknown	15	5
Onset of hydrocephalus		
Before	64	24
Concurrent	103	38
After	52	19
Unknown	50	19
Delay to diagnosis of hydrocephalus ^a	Range 0.5–180 months Mean 24 months	
Intracranial metastases		
Positive	76	28
Unknown	38	14
Subarachnoid hemorrhage		
Positive	19	7
Unknown	36	13

^a Patient with delay of 34 years excluded

Table 2. Histology overall

Histology	%
Astrocytoma, low-grade	12
Astrocytoma, high-grade	16
Astrocytoma, grade unknown	8.5
Ependymoma, benign	1.8
Ependymoma, anaplastic	2.6
Ependymoma, grade unknown	16.4
Oligodendrogioma	6
Neurofibroma	13
Medulloblastoma / PNET	5
Meningioma	4.5
Hemangioblastoma	1.5
Ganglioglioma	1
Arteriovenous malformation	0.7
Cavernous angioma	0.4
Other tumor	4
Other lesion	1
Disc prolapse	
Granuloma	
Cyst	1
Unknown	5.6

PNET, peripheral neuroectodermal tumor

Group 1: Intramedullary Tumors

The details of these 140 cases are reported in Table 3. Sixty-five patients had subarachnoid intracranial spread as documented on neuroradiological or autopsy examination. All these were gliomas. In 34 cases (24%) hydrocephalus was diagnosed before the tumor

Table 3. Intradural intramedullary lesions

	%
Site of lesion	
Cervical	34
Thoracic	24
Lumbar	8
2 regions	30
3 regions	4
Diagnosis of hydrocephalus in relation to that of the tumor	
Hydrocephalus first (H>T)	24
Hydrocephalus at same time (H=T)	23
Hydrocephalus after (T>H)	29
Unknown	24
Intracranial metastases	
Present	46
Absent	39
Unknown	15
Management of hydrocephalus	
Resolved without shunt	38
Shunt prior to resection	28
Shunt after resection	16
Shunt at same time	0.7
Timing of shunt unknown	6.3
Unknown	5.6

was diagnosed; 18 of these patients had intracranial metastases. In 32 cases (22.8%) the diagnoses were made at the same time; 10 of these patients had intracranial metastases. In 40 cases (28.5%) the hydrocephalus appeared after tumor surgery; 25 of these patients had intracranial metastasis. In 34 cases the data were insufficient for a conclusion to be drawn.

Spontaneous resolution of hydrocephalus after tumor surgery was reported in 9 (14%) of the 66 cases where hydrocephalus was diagnosed before or at the same time as the tumor (none of these patients had intracranial metastases) and in only 4 of the 40 cases in which hydrocephalus appeared after tumor surgery.

Group 2: Extramedullary Lesions

The details of these 107 cases are reported in Table 4. In 30 cases hydrocephalus was diagnosed some time prior to the spinal tumor diagnosis. In most cases (64%) the hydrocephalus was diagnosed at the same time as the spinal tumor. In only 7 cases (6.7%) did hydrocephalus appear after tumor removal: 5 of these patients presented with intracranial metastases and in 1 patient intracranial seeding was probable.

In 18 patients the hydrocephalus was treated with a shunt prior to tumor surgery and in 1 case a shunt was placed during tumor surgery. In those who did not

Table 4. Intradural extramedullary lesions

	%
Site of lesion	
Cervical	7.5
Thoracic	12
Lumbar	50
Sacral	1.8
2 regions	24
3 regions	3.7
Unknown	1
Diagnosis of hydrocephalus in relation to that of the tumor	
Hydrocephalus first ($H > T$)	28
Hydrocephalus at same time ($H = T$)	62
Hydrocephalus after ($T > H$)	6
Unknown	4
Intracranial metastases	
Present	8
Absent	87
Unknown	5
Management of hydrocephalus	
Resolved without shunt	72
Shunt prior to resection	18
Shunt after resection	6.4
Shunt at same time	0.9
Timing of shunt unknown	0.9
Unknown	1.8

undergo shunt placement before tumor surgery, 84% had resolution of the hydrocephalus following removal of the tumor, 15% died for various reasons (in 3 the tumor was not operated upon; 3 died of infection, 3 of disease progression, and 2 of intractable intracranial hypertension in the pre-shunt era; in 2 cases the cause of death was unknown), and only 7% required shunt insertion after tumor surgery.

In 2 cases the data were insufficient.

Group 3: Extradural Lesions

The ages of the 7 patients in this group ranged from 2 to 47 years. From a histopathological point of view their tumors were: 2 sarcomas, 3 meningiomas, 1 disc hernia, and 1 neuroblastoma. In 3 cases hydrocephalus was diagnosed at the same time as the tumor; in 2 cases hydrocephalus was diagnosed before the tumor. These data were not reported for 2 cases. In 4 cases hydrocephalus resolved after tumor removal; 3 patients required shunt insertion (1 prior to tumor surgery, 2 cases not reported).

Comparison Between the Groups

Comparing the above three groups, three major differences are revealed between intramedullary tumors (group 1) and those in the extramedullary and extradural space (groups 2 and 3).

The first is the significantly higher frequency of intracranial leptomeningeal seeding in the group of intramedullary tumors (65/140) compared to the other two groups (11/114). The second is the more frequent resolution of hydrocephalus following tumor removal in those patients not shunted prior to tumor surgery in groups 2 and 3 (64/101) compared to group 1 (9/66). The third is the more frequent onset of hydrocephalus after tumor surgery in the first group (40/106) compared to groups 2 and 3 (7/108). Given the above observed differences it is conceivable that more than one pathophysiological mechanism is in operation.

Pathophysiology

Historical Theories

A purely mechanical explanation is based on the concept that the spinal subarachnoid space serves as an elastic reservoir to buffer the normal physiological variations of CSF pressure induced by rapid modifi-

cations of arterial pressure, venous pressure, and body position [103]. The anatomical and functional isolation of the spinal subarachnoid space from the intracranial compartment due to the presence of a spinal obstruction could prevent the normal compensation of CSF pressure fluctuations, thus causing papilledema and ventricular dilatation. Other authors [179, 196] suggested that in some patients the spinal pathways of CSF absorption around the spinal nerve sheaths could be more abundant than in the normal population, and their functional exclusion due to subarachnoid blockage induced by a spinal tumor could explain the impairment of CSF absorption and the development of intracranial hypertension.

Increased CSF Viscosity

An increase in CSF protein content is a very common finding in patients with spinal cord tumors. Several authors have related the ventricular enlargement to the increased CSF protein level and secondary increase in CSF viscosity and resistance to absorption [61, 71]. According to Poiseuille's law, the effect on the CSF outflow resistance of an increase in CSF viscosity is slight up to a viscosity of 1000 mg/100 ml. In the 269 cases summarized in Table 1, the lumbar CSF protein level was reported in 140 patients, in 133 of which it was elevated (range: 44 mg/100 ml to 29000 mg/100 ml; average: 1471 mg/100 ml, with 60 cases at levels greater than or equal to 1000 mg/100 ml).

It must be noted, however, that elevated CSF protein levels are not a surprising finding when sampled below the level of the obstructive lesion. Ideally, to support the theory that the increased CSF protein is responsible for the development of hydrocephalus, cisternal or ventricular CSF protein levels would also need to be elevated. The ventricular CSF protein level was reported in 42 cases, in 33 of which it was elevated (range: 45 mg/100 ml to 2200 mg/100 ml, average: 222 mg/100 ml), with only 2 cases above 1000 mg/100 ml. The cisternal CSF protein content was reported in only 32 cases, in 31 of which it was elevated (range: 40 mg/100 ml to 1020 mg/100 ml, average: 248 mg/100 ml), with two higher than 1000 mg/100 ml. Moreover, the animal experiments of Butler and al. [27] confirm that increased viscosity of the CSF due to higher protein content is unlikely to be responsible for a consistent increase in intracranial pressure and ventricular enlargement. Their findings suggest that a sustained elevation in CSF outflow resistance is more likely to be due to the abnormal presence of fibrinogen in the CSF, its conversion to fibrin, and the depositing of this substance within the subarachnoid space and villi.

Fibrinogen

Fibrinogen was documented in the CSF in three cases in the literature [12, 124, 131]. Its abnormal presence in the CSF could be the result of:

1. A chronic inflammatory reaction due to the presence of the spinal lesion – mechanism unknown (Fig. 2).
2. Loss of the blood-brain barrier, with direct passage of fibrinogen and serum proteins through the altered walls of the tumor vessels, as demonstrated by infusion tests in case 2 of Borgesen et al. [19] and by the study of CSF protein fractions in the case of Nishida et al. [124].
3. Acute or chronic subarachnoid bleeding from the tumor vessels [57].
4. Communication of the tumor cyst and the subarachnoid pathways (Fig. 3) [151].

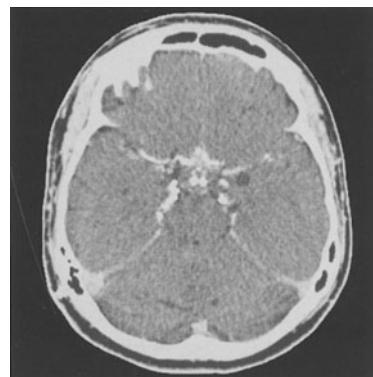


Fig. 2. Diffuse calcifications of the basal cisterns in a patient shunted for hydrocephalus and operated on for a cervicomedullary tumor



Fig. 3. Diffuse calcifications of the basal cisterns, leptomeningeal enhancement, and multiple foci of ischemia in a patient operated on for hydrocephalus and harboring a low-grade glioma

This theory is strongly supported by several findings:

1. The fact that the CSF sampled by lumbar tapping or cisternal tapping in some spinal tumor cases not only shows very high protein levels, but can also coagulate spontaneously in the test tube (Froin's syndrome), indicating the presence of very high levels of fibrinogen.
2. In some cases of spinal tumors, especially ependymomas, the onset of the hydrocephalus is the consequence of an acute episode of subarachnoid hemorrhage (Fincher's syndrome) or of repeated subarachnoid bleeding from the tumor (see "Clinical Presentation" below). In these cases the pathophysiology of hydrocephalus would be the same as in intracranial subarachnoid hemorrhage.
3. The experiments of Brinker et al. [21, 22] have demonstrated that the increase in the CSF outflow resistance and the subacute hydrocephalus observed after experimental subarachnoid hemorrhage could be treated by an intrathecal infusion of recombinant tissue plasminogen activator (rt-PA), which is a fibrinolytic substance.

The advantages of this theory are that it could be applied to a variety of etiologies and tumor sites, it could explain the resolution of intracranial hypertension after removal of the tumor (79 cases), and it could explain the presence of the papilledema and the intracranial hypertensive symptoms in spite of the absence of ventricular dilatation (8 cases). The chronic production or leakage of fibrinogen through tumor vessels into the CSF [12, 19, 124] and its conversion into fibrin would cause an increase in the CSF outflow resistance [21, 22], leading to communicating hydrocephalus. The stagnation of the CSF circulation in the subarachnoid spaces would allow the deposit and conversion of fibrinogen to fibrin at the level of the subarachnoid spaces of the convexity and of the basal cisterns, inducing basal arachnoiditis, fibrous adhesions, obliteration of the subarachnoid spaces, and further obstruction of the CSF circulation at this level [173]. This pathophysiological mechanism is very similar to that proposed for hydrocephalus following subarachnoid hemorrhage [21, 22, 174] and explains the frequent neuroradiological finding in the pre-CT era of no contamination of the basal cisterns nor of the subarachnoid spaces of the convexity following lumbar or cisternal injection of air or contrast medium.

Cyst of the Obex

Rifkinson-Mann et al. [151] described, in 12 cases of intramedullary spinal cord low-grade gliomas, oblit-

eration of the subarachnoid pathways at the level of the fourth ventricular outlets due to a cervicomедullary extension of a rostral tumor cyst. There are three disadvantages of this theory:

1. In most of the cases described in this paper (10/12) the hydrocephalus appeared some time after tumor surgery (the precise interval is not given), when the tumor cyst should be collapsed.
2. Extension of cystic or solid tumor up to the cervicomедullary junction is not necessarily associated with obliteration of the fourth ventricular outlets.
3. Hydrocephalus can be observed in intramedullary low-grade gliomas without tumor cysts extending up to the obex.

Their observations are probably related to the necessity to gain access to the cervicomедullary cyst at surgery with an occipital craniectomy and opening of the cisterna magna. In that event the resulting hydrocephalus could simply be due to post-operative adhesions at the level of the fourth ventricle outlets.

Neoplastic Arachnoiditis

The theory of neoplastic arachnoiditis was first clearly proposed in 1975 by Maurice-Williams and Lucey [104], although many authors had previously reported the association of spinal tumor, intracranial seeding, and hydrocephalus [29, 35, 35a, 40, 48, 50, 67, 101, 128, 135, 140, 158, 160, 162, 171, 180, 192]. They reported three intraspinal tumors (2 malignant schwannomas and 1 benign oligodendrogloma) associated with hydrocephalus that was attributed to basal cistern adhesions macroscopically evident at necropsy. Microscopic examination showed neoplastic elements in the two cases that were studied. The authors suggested that intracranial spread and proliferation of tumor cells through the subarachnoid pathways could be responsible for hydrocephalus in some cases and affirmed that "it may well be in fact that in many, perhaps in most of the reported cases such a neoplastic arachnoiditis was present." After analyzing the literature, it is unlikely that neoplastic seeding could explain the hydrocephalus when the tumor was extramedullary in location (group 2). In this group, in those patients not shunted before spinal surgery, the removal of the tumor definitely resolved the hydrocephalus in most of the cases (84%). Neoplastic seeding was histologically diagnosed only in the rare cases where the onset of hydrocephalus followed spinal surgery [104, 128, 140, 158].

On the contrary, Maurice-Williams and Lucey are probably correct when they affirm that the role of intracranial neoplastic seeding in the pathogenesis of the hydrocephalus has probably been underestimat-

ed in the literature in the cases of intramedullary tumors (group 1). In this group the occurrence of intracranial metastases was in fact significantly higher (54%), both in the low-grade (48%) and in the high-grade (66%) gliomas, than in the extramedullary group (8%). Hydrocephalus in this group resolved after simple surgical excision of the spinal lesion only in the few cases that did not have leptomeningeal seeding [13, 42, 43, 72, 120, 137, 150, 157, 171, 192]. The same strong association with intracranial metastases is observed when the hydrocephalus develops some months after tumor surgery (25/40 cases = 62%) [7, 15, 40, 48, 58, 74, 83, 104, 111, 120, 128, 130, 135, 149, 165, 166, 171, 175, 183, 193].

These data suggest that both groups of patients share the same pathogenic mechanism (fibrinogen > fibrin > fibrosis > basal arachnoiditis) at the onset of hydrocephalus, but that this condition remains reversible for extramedullary lesions, where removal of the tumor usually cures the hydrocephalus. In cases of intramedullary lesions of glial origin, however, the presence of obstructive hydrocephalus at or prior to presentation would cause stagnation of cells and ependymal damage, thus promoting implantation [163]. The neoplastic seeding favored by these factors and by the subarachnoid fibrosis would induce an irreversible and self-maintaining condition that would explain the rarity with which hydrocephalus is cured after tumor removal, the frequent late onset of hydrocephalus in the absence of local recurrence of the spinal lesion, and the higher mortality rate in this group of patients.

Clinical Presentation

In 47% of cases the hydrocephalus and the spinal tumor are diagnosed concurrently, with one of these two being clinically predominant. When neurological symptoms induced by the spinal lesion are the main clinical feature, the hydrocephalus is usually discovered because of the presence of papilledema. If the symptoms of intracranial hypertension are predominant, a spinal lesion is suspected because of a history of back pain, transient sphincter disturbance, or peripheral neurological signs. If the spinal lesion is clinically silent, its presence is usually suspected after analysis of the CSF. In some cases (29%) the hydrocephalus is diagnosed many months or years before the onset of clinical symptoms related to the spinal lesion. The interval between the two diagnoses is usually of the order of a few months (mean: 1 year), but cases are reported where the delay was of many years [151] (our cases 1 and 2).

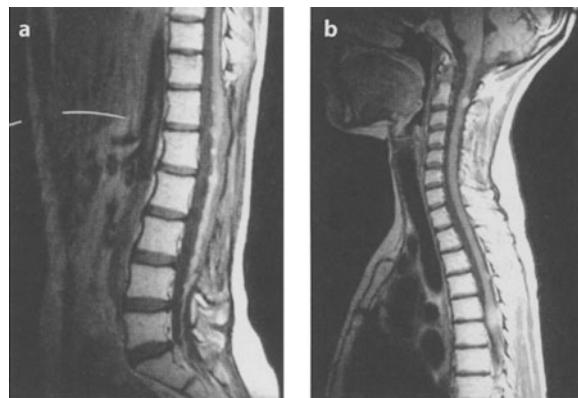


Fig. 4. Multiple nodules in the spinal subarachnoid spaces in a patient shunted for hydrocephalus and biopsied at the D5-6 level for a peripheral neuroectodermal tumor

The cases where hydrocephalus appeared some months or years after the removal of the spinal tumor (23%) deserve special attention. This clinical feature was more frequent in intramedullary tumors (75%). In the majority of these patients (62%) hydrocephalus was induced by leptomeningeal seeding of the spinal tumor, both in low-grade and high-grade lesions. The same high incidence of intracranial metastases is reported for extramedullary tumors (50%). Therefore, all patients presenting with late onset of hydrocephalus, regardless of the pathology of the primary spinal lesion, require close radiological follow-up to exclude meningeal infiltration (Fig. 4).

Subarachnoid Hemorrhage

André-Thomas et al. reported the first case of subarachnoid hemorrhage caused by a spinal tumor. Since this first report several cases have been described and many of them were associated with hydrocephalus [1, 4, 13, 17, 24, 32, 46, 57, 63, 69, 78, 93, 109, 117, 129, 134, 135, 145, 166, 169, 179, 192]. Clinically, several episodes (up to 25 have been described) of severe pain occur with sudden onset in the back, lower limbs, or perineal region with associated sphincteric disturbance and severe headache. Meningeal signs can usually be observed in the acute phase and lumbar puncture can show bloody or xanthochromic CSF. Spontaneous resolution of symptoms is usually observed in a few days. When hydrocephalus occurs, it is clearly related to the repeated episodes of subarachnoid hemorrhage and contamination of the CSF with fibrinogen and its transformation into fibrin at the level of the sub-

arachnoid spaces and pacchionian granulations. In all the cases described except one [28], hydrocephalus and papilledema resolved spontaneously after tumor removal without the insertion of a ventriculoperitoneal shunt.

Unusual Presentation: "Upward Spinal Coning"

In 1984 Jooma and Hayward [84] described four cases of patients affected by hydrocephalus caused by intracranial lesions (1 pineoblastoma and 3 posterior fossa tumors). In all cases the relief of hydrocephalus by ventriculoperitoneal shunting (2 cases) or by posterior fossa exploration (2 cases) was followed by the sudden onset of symptoms of spinal cord compression such as rapidly progressive paraparesis and urinary retention. The delay until onset ranged from 24 to 72 h. In all cases the neuroradiological examinations revealed spinal metastatic lesions from the primary intracranial tumor, which had to be surgically removed in one case. The authors attributed this phenomenon to the relief of CSF hypertension in the subarachnoid compartment above the tumor and to the sudden imbalance between this compartment and the one below the tumor. This would have induced an upward movement of the tumor, impacting it against the cord and triggering the sudden onset of the spinal symptoms. The authors concluded saying that "the syndrome of upward spinal coning is caused by impaction of a spinal secondary when the obstructive hydrocephalus associated with the primary intracranial tumor is relieved." It is conceivable that this mechanism could happen also when the hydrocephalus is not caused by an intracranial lesion, as in the four cases described by Jooma and Hayward, but rather by a primary spinal lesion.

Koshu et al. [90] described a case of quadripareisis occurring the second week following a ventriculoperitoneal shunt procedure in a 60-year-old hydrocephalic patient. MRI revealed an intradural extramedullary neurofibroma in the cervical region that was completely removed at surgery. In fact, this is not an unusual clinical presentation for spinal tumors associated with hydrocephalus. In our review of the literature we found several cases [17, 23, 28, 53, 86, 90, 92, 121, 150, 167, 191], where a shunting procedure for hydrocephalus induced within a short time (3 days to 1 month) the onset or the sudden aggravation of spinal symptoms, revealing an occult spinal tumor. The tumor was intramedullary in six cases and extramedullary in seven cases. In all cases but one [21] the lesion was

located in the thoracolumbar region. Spinal signs could be precipitated when the patient begins to walk, as in the case of Koshu et al. [90], since the siphon effect through the shunt in the upright position would induce a significant drop in the CSF pressure in the compartment above the tumor [60], creating a significant pressure differential between the two compartments.

In patients without hydrocephalus, there exists the possibility of rapid neurological deterioration after lumbar puncture [49, 75]. Hollis et al. [75] found a 14% risk of sudden neurological deterioration after lumbar puncture, whereas none of the patients explored by cisternal puncture deteriorated. In all cases the neurological deterioration was very rapid (from 30 min to 4 days). The authors explained this difference by the fact that a low-pressure CSF compartment could exist below a complete spinal subarachnoid block. This compartment would be isolated from the subarachnoid space located above the tumor. The withdrawal of CSF by lumbar puncture would increase the pressure differential above and below the tumor, inducing "spinal coning" [75] or rapid mobilization of the tumor with consequent impaction against the spinal cord [84]. In contrast, the withdrawal of CSF by cisternal puncture would reduce the pressure differential, inducing less dramatic hydrodynamic changes and explaining the lower morbidity of this procedure.

Radiology

Ventriculography and Pneumoencephalography

In most of the cases reported in the literature the contrast medium injected by lumbar or ventricular puncture passed without obstruction through the ventricular cavities and the basal cisterns to the subarachnoid space of the convexity. This hydrocephalus of the communicating type is the most frequent finding both in extramedullary [14, 19, 20, 26, 35, 40, 71, 91, 97, 107, 117, 124, 131, 148, 150, 172, 184, 190] and intramedullary lesions [32, 40, 43, 97, 116, 128, 141, 149, 150, 157, 167, 171, 183, 191]. Tentorial block with lack of opacification of the basal cisterns or lack of contamination of the subarachnoid spaces of the convexity can be observed [12, 24, 28, 35a, 44, 100, 104, 121, 137, 150, 170]. Obstructive hydrocephalus induced by aqueductal stenosis or obstruction of the outlets of the fourth ventricle has been described in only one case [68]. In

a few cases no ventricular dilatation was observed at the time of the existence of symptoms and signs of increased intracranial pressure [5, 28, 43, 117, 123, 134].

CT and MRI

The more frequent finding is ventricular dilatation with signs of transependymal absorption. In some cases the CT findings can be completely negative, with normal-sized ventricles without periventricular lucency [99, 110, 150]. When the hydrocephalus is induced by intracranial leptomeningeal seeding of an intramedullary glial tumor, diffuse calcifications or diffuse enhancement after contrast injection can be observed at the level of the basal cisterns and the subarachnoid spaces of the convexity. In these cases intraparenchymal areas of hypodensity can be observed, probably corresponding to small ischemic events related to cortical vessel thrombosis induced by tumor infiltration of the subarachnoid spaces.

MRI offers obvious advantages in the imaging of the spinal cord lesions and a higher resolution than CT scan in revealing the meningeal enhancement.

Histopathology

The histopathology of the spinal neoplasms most frequently associated with hydrocephalus is shown in Table 2. Low-grade lesions can modify their histological pattern, showing malignant transformation at the time of local recurrence or at the time of the diagnosis of intracranial leptomeningeal seeding [48, 74, 170, 193]. Autopsy examination of cases with intracranial seeding reveals diffuse thickening of the leptomeninges of the cranial base with white, firm tissue that can completely fill the subarachnoid spaces of the base and of the convexity, usually without infiltration of the brain parenchyma. Intraventricular lesions are less frequently observed. Histological examination of the intracranial leptomeningeal seeding usually showed malignant neoplastic elements, but in a few cases these lesions did not show any sign of malignant transformation [135]. CSF cytology shows tumor cells more frequently at the time of spinal tumor recurrence or when the intracranial dissemination becomes radiologically evident. By contrast, a very frequent and characteristic finding in the CSF is one of a chronic inflammatory reaction with lymphocytes, macrophages, and monocytes without

neoplastic elements. The fluid can coagulate immediately after withdrawal, indicating the presence of a very high fibrinogen content (Froin's syndrome). Nonneoplastic arachnoiditis has been described in a few cases treated in the pre-CT era where biopsy of the cisterna magna was performed [9, 38, 71, 97].

Surgical Management

Shunt Insertion

If the hydrocephalus is diagnosed at the same time as the spinal tumor, every effort should be made to avoid shunt insertion prior to tumor surgery, for two main reasons: the possibility of curing the hydrocephalus by the removal of the spinal tumor, especially in the case of extramedullary lesions, and the possibility of neurological deterioration induced by the shunt. In cases of intramedullary gliomas, cerebral MRI with contrast enhancement should be performed in order to rule out intracranial leptomeningeal seeding as the cause of hydrocephalus. In such a case, the hydrocephalus is less likely to resolve after tumor surgery and the insertion of a CSF shunt will be necessary, if possible during the operation for spinal tumor removal, or immediately following if the symptoms and signs of intracranial hypertension persist. Furthermore, if the hydrocephalus appears some weeks or months after spinal tumor surgery, it should be considered as and investigated as an early sign of neoplastic intracranial seeding, particularly if the spinal lesion was an intramedullary glial tumor.

The insertion of a CSF shunt to treat the hydrocephalus, before the diagnosis and definitive surgery of the spinal tumor or following incomplete removal or in the event of a local recurrence, could precipitate the process of intracranial leptomeningeal seeding by reversing the CSF flow, favoring upward flow in the spinal canal and retrograde flow within the ventricular system. This would promote the functional exclusion of the intracranial subarachnoid space by the physiological renewal of the CSF, causing its collapse and facilitating further adhesion and tumor cell implantation.

Surgical Trauma

Several authors [11, 15] have stressed the possible role of surgical trauma in the dissemination of neoplastic

cells along the CSF pathways. This etiological factor of tumor spread could be enhanced by the existence of a CSF shunt at the time of tumor surgery. Among the 50 cases in the literature where these data are reported, in 6 cases the diagnosis of intracranial metastases was done prior to tumor surgery and shunt placement [67, 86, 102, 109, 160]; in 5 cases, after shunt placement only [23, 141]; in 24 cases, after tumor surgery [8, 10, 15, 29, 48, 50, 74, 83, 104, 112, 128, 130, 135, 140, 158, 166, 175]; and in 15 cases, after both tumor surgery and shunt placement [15, 40, 59, 74, 80, 104, 120, 170, 191, 193]. According to these numbers, it seems that tumor surgery could be considered as an important factor in the pathogenesis of leptomeningeal intracranial seeding.

General Considerations

As may be seen from Table 1, the number of case reports described in the literature is much larger than was previously thought. The advent of the MRI has contributed to the increase in frequency of the diagnosis of spinal tumors associated with hydrocephalus [23, 59]. This association should always be considered in the differential diagnosis of hydrocephalus of unknown etiology, for three main reasons: the possibility of neurological deterioration when the patient is shunted prior to tumor removal, the possibility of resolving the hydrocephalus without shunting by simply removing the tumor, and the possible role of hydrocephalus as an early sign of intracranial metastasis in patients previously operated upon with intramedullary gliomas.

Due to the very slow evolution of the disease, a very close clinical and radiological follow-up are essential for many years. The presence of intracranial hypertension in a patient previously operated on for an intramedullary glial tumor should be considered and investigated as an early sign of neoplastic intracranial seeding.

References

- Abbott KH: Subarachnoid hemorrhage from an ependymoma arising in the filum terminale. Report of a case. Bull Los Angeles Neurol Soc 4:127-132, 1939
- Adson AW, Dodge HW, Kernohan JW: Communicating hydrocephalus from diffuse meningeal tumor. Report of two cases with increased intracranial pressure treated by use of polyethylene tube. AMA Arch Neurol Psychiat 68:329-338, 1952
- Albright L, Byrd RP: Ganglioglioma of the entire spinal cord. Child's Brain 6:274-280, 1980
- Amici R, Borghi GP: Emorragie subaracnoidee da tumori spinali intradurali del tratto lombare. Minerva Neurochir 3:192-198, 1959
- Ammermann BJ, Smith DR: Papilledema and spinal cord tumors. Surg Neurol 3:55-57, 1975
- André-Thomas, Ferrand, Schaeffer, De Martel: Syndrome d'hémorragie méningée réalisé par une tumeur de la queue de cheval. Paris Med 77:202-206, 1930
- Andreani A, Cantini R, Burchianti M, et al: Papilledema and spinal cord tumors. Ann Oft Clin Ocul 40:901-908, 1984
- Andrews AA, Enriques L, Renaudin J, et al: Spinal intramedullary glioblastoma with intracranial seeding: report of a case. Arch Neurol 35:244-245, 1978
- Arseni C, Maretis M: Tumors of the lower spinal cord associated with increased intracranial pressure and papilledema. J Neurosurg 27:105-110, 1967
- Asano N, Kitamura K, Seo Y, et al: Spinal cord glioblastoma multiforme with intracranial dissemination. Case report. Neurol Med Chir 30:489-494, 1990
- Balhuzien JC, Bots GTAM, Schaberg A, et al: Value of cerebrospinal fluid cytology for the diagnosis of malignancies in the central nervous system. J Neurosurg 48:747-753, 1978
- Bamford CR, Labadie EL: Reversal of dementia in normotensive hydrocephalus in childhood. J Neurosurg 45:104-107, 1976
- Barontini F, Casotto A: Su un caso di neoplasia midollare con papilla da stasi. Riv Neurobiol 8:143-151, 1962
- Beduschi A, Columella F, Papo I: Ependimoma della cauda con stasi papillare. Chirurgia (Milano) 10:310-315, 1955
- Bell WO, Packer RJ, Seigel KR, et al: Leptomeningeal spread of intramedullary spinal cord tumors: report of three cases. J Neurosurg 69:295-300, 1988
- Bergquist BJ: Intraspinal tumor with hydrocephalus. Neurosurgery 22:969-970, 1988
- Bessiere E, Pouyanne H, Verin P, et al: Stase papillaire hémorragique révélatrice d'un neurinome géant hémorragique du cône terminal. Neurochirurgie 15:224-228, 1969
- Bland LI, McDonald JV: Hydrocephalus following spinal cord schwannoma resection. Arch Neurol 49:882-885, 1992
- Borgesen SE, Sorensen SC, Olesen J, et al: Spinal tumors associated with increased intracranial pressure. Report of two cases and a discussion on the pathophysiology. Acta Neurol Scand 56:263-268, 1977
- Borghi GP, Corridori F: Papilla da stasi nelle lesioni spinali. Cervello 1:61-70, 1961
- Brinker T, Seifert V, Dietz H: Subacute hydrocephalus after experimental subarachnoid hemorrhage: its prevention by intrathecal fibrinolysis with recombinant tissue plasminogen activator. Neurosurgery 31:306-312, 1992
- Brinker T, Seifert V, Stolke D: Effect of intrathecal fibrinolysis on cerebrospinal fluid absorption after experimental subarachnoid hemorrhage. J Neurosurg 74:789-793, 1991
- Britton J, Marsh H, Kendall B, et al: MRI and hydrocephalus in childhood. Neuroradiology 30:310-314, 1988
- Buge A, Philippot J, Poisson M, et al: Hydrocephalie au cours d'un ependymome de la queue de cheval avec hémorragie méningée. Nouvelle Presse Medicale vol 3,17:1083-1086, 1974
- Buge A, Poisson M, Fohanno D, et al: L'hypertension intracrânienne des méningites carcinomatoseuses. Ann Med Intern 2(128):143-149, 1977

26. Burke WJ: A case of cauda equina tumor presenting with stupor and papilledema. *Proc Austr Assoc Neurol* 9:95-97, 1973
27. Butler AB, Mann JD, Maffeo CJ, et al: Mechanisms of cerebrospinal fluid absorption in normal and pathologically altered arachnoid villi. In: *Neurobiology of cerebrospinal fluid*. Plenum Press, New York, 1983
28. Camena D'Almeida MC: Contribution à l'étude des tumeurs intrarachidiennes dorso-lombaires avec oedème papillaire. A propos de trois cas. Thesis 95, Paris VI, 21/6/1974
29. Carlill H, Carling ER: Two cases of disease of the cervical spinal cord. *Lancet* 1:70-72, 1926
30. Catz A, Appel I, Reider-Grosswasser I, et al: Late onset papilledema following spinal injury. Case report. *Paraplegia* 31:131-135, 1993
31. Caviness J, Tucker M, Pia S, Tam D: Hydrocephalus as a possible early symptom in a child with a spinal cord tumor. *Pediatr Neurol* 18:169-171, 1998
32. Cecotto C, Mingrino S: Tumore del cono e della cauda con ipertensione endocranica. *Acta Chir Italica* 15:977-988, 1955
33. Celli P, Cervoni L, Morselli E, et al: Spinal ependymomas and papilledema: report of 4 cases and review of the literature. *J Neurosurg Sci* 37:97-102, 1993
34. Chandy M, Babu S: Management of intramedullary spinal cord tumors: Review of 68 patients. *Neurology India* 47(3) 1999
35. Chigasaki H, Pennybacker JB: A long follow-up study of 128 cases of intramedullary spinal cord tumours. *Neurol Med Chir* 10:25-66, 1968
- 35a. Cinalli G, Sainte-Rose C, Lellouch-Tubiana A, et al: Hydrocephalus associated with intramedullary low-grade gliomas. (Illustrative cases and review of the literature). *J Neurosurgery* 83:480-485, 1995
36. Civitello LA, Packer RJ, Rorke LB, et al: Leptomeningeal dissemination of low-grade gliomas in childhood. *Neurology* 38:562-566, 1988
37. Cohen AR, Wisoff JH, Allen JC, et al: Malignant astrocytomas of the spinal cord. *J Neurosurg* 70:50-54, 1989
38. Coxe WS: Tumors of the spinal canal in children. *Am Surg* 27:62-73, 1961
39. D'Andrea F, Constans JP, De Divitiis E: A propos de la carcinomatose lepto-méningée. *Neurochirurgie* 8:1-11, 1965
40. Dardenne G: Hypertension intracranienne et contaminations chimiques et cytologiques du liquide céphalo-rachidien. *Acta Neurochir* 17:46-70, 1967
41. Dario A, Dorizzi A, Marra A, et al: Lumbar neurinoma associated with hydrocephalus. Case report. *J Neurosurg Sci* 37:179-182, 1993
42. Davis TK: Double papilledema caused by blocking of cord at fourth cervical vertebra greatly relieved by operation. *Arch Neurol Psychiat (Chicago)* 9:255-256, 1923
43. Dechaume J, Mansuy L, Schott B, et al: Hypertension intracranienne avec oedème papillaire par tumeur de la queue de cheval. *Revue Neurol* 109:648-654, 1963
44. Diaz Bobillo I, Carrea R, Bordenave A, et al: Observaciones sobre las hidrocefalias: hipertension endocraneana asociada a tumores medulares caudales al primer segmento dorsal. *Archos Argent Pediatr* 43:245-258, 1955
45. Dietrich J, Fried H, Hommel HJ: Stauungspapille bei neurologisch symptomlosem Caudatumor. *Nervenarzt* 34:412-414, 1963
46. Djindjian M, Djindjian R, Houdart R, et al: Subarachnoid hemorrhage due to intraspinal tumors. *Surg Neurol* 9:223-229, 1978
47. Dott NM: A contribution to the surgery of hydrocephalus in childhood. 6th Internat Cong Pediat, Zurich. Summary of communications. Vol II p 194, 1950
48. Eade OE, Urich H: Metastasing gliomas in young subjects. *J Pathol* 103:245-256, 1971
49. Eaton LM, Craig WM: Tumor of the spinal cord: sudden paralysis following lumbar puncture. *Proc Staff Meet Mayo Clin* 15:170-172, 1940
50. Eden KC: Dissemination of a glioma of the spinal cord in the leptomeninges. *Brain* 61:298-310, 1938
51. Elsberg CA, Strauss I: Tumors of the spinal cord which project into the posterior cranial fossa. *Arch Neurol Psychiat* 21:261-269, 1929
52. Farmilo RW, Mc Auley DL, Osborne DRS: Papilloedema and spinal cord tumours. *NZ Med J* 80:100-104, 1974
53. Farnasier G, Roger J, Vigouroux R: Localisation médullaire d'un médroblastome avec syndrome d'hypertension intracranienne. *Rev Otoneuroophtalmol* 29:490-494, 1957
54. Farrell K, Hill A, Chuang S: Papilledema in Guillain-Barré syndrome. A case report. *Arch Neurol* 38:55-57, 1981
55. Fearnside MR, Adams CBT: Tumors of the cauda equina. *J Neurol Neurosurg Psychiatry* 41:24-31, 1978
56. Feldman E, Bromfield E, Navia B, et al: Hydrocephalic dementia and spinal cord tumor. Report of a case and review of the literature. *Arch Neurol* 43:714-718, 1986
57. Fincher EF: Spontaneous subarachnoid hemorrhage in intradural tumors of the lumbar sac. A clinical syndrome. *J Neurosurg* 8:576-584, 1951
58. Fortuna A, Celli P, Palma L: Oligodendrogliomas of the spinal cord. *Acta Neurochir* 52:305-329, 1980
59. Foschi N, Chiaroni L, Maricotti M, et al: Idrocefalo comunicante in portatori di processi espansivi midollari. A proposito di due casi. *Riv Neuroradiol* 3:345-350, 1990
60. Fox JL, McCullough DC, Green RC: Effect of cerebrospinal fluid shunts on intracranial pressure and on intracranial pressure hydrodynamics. 2. A new technique of pressure measurements: results and concepts. 3. A concept of hydrocephalus. *J Neurol Neurosurg Psychiatry* 36:302-312, 1973
61. Gardner WJ, Spitler DK, Whitten C: Increased intracranial pressure caused by increased protein content in the cerebrospinal fluid. *N Engl J Med* 250:932-936, 1954
62. Gelabert M, Bollar A, Paseiro MJ, et al: Hydrocephalus and intraspinal tumor in childhood. *Child's Nerv Syst* 6:110-112, 1990
63. Gibberd FB, Ngan H, Swann GF: Hydrocephalus, subarachnoid haemorrhage and ependymomas of the cauda equina. *Clin Radiol* 23:422-426, 1972
64. Girard P, Devic M, de Gevigney D: Neuro-papillite oedemateuse aiguë et discopathie cervicale. Récupération de la vision et disparition de l'oedème par élongation du cou. Le syndrome "névrite optique et acroparesthesie". *J Med Lyon* 183:161-168, 1950
65. Glasauer FE: Thoracic and lumbar intraspinal tumor associated with increased intracranial pressure. *J Neurol Neurosurg Psychiatry* 27:451-458, 1964
66. Goutelle A, Fischer G: Les épendymomes intracraniens et intrarachidiens. *Neurochirurgie* 23(suppl 1):168-213, 1977

67. Greenfield JG: Two cases of medulloepithelioma (Bailey and Cushing) with special reference to the relative malignancy of this type of tumor. *J Pathol Bacteriol* 38:11-16, 1938
68. Guidetti B, Fortuna A: Surgical treatment of intramedullary hemangioblastoma of the spinal cord. *J Neurosurg* 27:530-540, 1967
69. Halpern L, Feldman S, Peyer E: Subarachnoid hemorrhage with papilledema due to spinal neurofibroma. *AMA Arch Neurol Psychiatry* 79:138-141, 1958
70. Hardten DR, Wen DY, Wirtschafter JD, et al: Papilledema and intraspinal lumbar paraganglioma. *J Clin Neuro-ophthalmol* 12:158-162, 1992
71. Harris P: Chronic progressive communicating hydrocephalus due to protein transudates from brain and spinal tumours. *Dev Med Child Neurol* 4:270-278, 1962
72. Hatzidakis GI: To oidema ton optikon telon epi notiaion onkon (in Greek). *Nosokom Chron* 29:665-688, 1967
73. Heathfield KWG, Williams JRB: Carcinomatosis of the meninges: some clinical and pathological aspects. *Br Med J* 1:328-330, 1956
74. Hely M, Fryer J, Selby G: Intramedullary spinal cord glioma with intracranial seeding. *J Neurol Neurosurg Psychiatry* 48:302-309, 1985
75. Hollis PH, Malis LI, Zappulla RA: Neurological deterioration after lumbar puncture below complete spinal subarachnoid block. *J Neurosurg* 64:253-256, 1986
76. Huber A: Eye symptoms in brain tumors, 2nd edn. Mosby, St Louis, p 126, 1971.
77. Iacob M: Angiome du cône médullaire avec stase papillaire. *Neurochirurgie* 15:586-590, 1969
78. Iob I, Andrioli C, Rigobello L, et al: An unusual onset of a spinal cord tumour: subarachnoid bleeding and papilledema. *Neurochirurgia* 23:112-116, 1980
79. Ishikawa S, Kajikawa H, Tomihara K, et al: Intraspinal tumor associated with increased intracranial pressure and papilledema. *No Shinkei Geka* 2:409-413, 1974
80. Ito U, Tomita H, Yamazaki S, et al: CT findings of leptomeningeal and periventricular dissemination of tumors. Report of four cases. *Clin Neurol Neurosurg* 88:115-120, 1986
81. Jennings M, Slatkin N, D'Agelo M, et al: Neoplastic meningitis as the presentation of occult primitive neuroectodermal tumors. *J Child Neurol* 8:306-312, 1993
82. Jentzer A, Kessel K, Bonnant M: Tumeur de la queue de cheval avec stase papillaire. *Rev Neurol* 87:628-632, 1952
83. Johnson DL, Schwarz S: Intracranial metastases from malignant spinal cord astrocytoma. *J Neurosurg* 66:621-625, 1987
84. Jooma R, Hayward RD: Upward spinal coning: impaction of occult spinal tumours following relief of hydrocephalus. *J Neurol Neurosurg Psychiatry* 47:386-390, 1984
85. Joynt RJ: Mechanism of production of papilledema in the Guillain-Barré syndrome. *Neurology* 8:8-12, 1958
86. Kendrick FD, Bonnin JM, Garcia JH: Metastases of a spinal glioblastoma multiforme into an intracranial arachnoid cyst. *Neurosurgery* 20:780-783, 1987
87. Kesler A, Manor RS: Papilloedema and hydrocephalus in spinal cord ependymoma. *Br J Ophthalmol* 78:313-315, 1994
88. Kolomoitseva IP, Rumyantsev Yu V, Kachkoz IA: Congest optic nerve disk in tumors of the terminal portion of the spinal cord (in Russian). *Soviet Med* 32:104-108, 1969
89. Kopelson G, Linggood RM: Intramedullary spinal cord astrocytoma versus glioblastoma. *Cancer* 50:732-735, 1982
90. Koshu K, Tominaga T, Fujii Y, et al: Quadriparesis after a shunting procedure in a case of cervical spinal neurinoma associated with hydrocephalus: Case report. *Neurosurgery* 32:669-671, 1993
91. Koyama M, Hanakita J, Ishikawa J: Thoraco-lumbar spinal tumor associated with papilledema. *Neurol Surg (Tokyo)* 5:1171-1180, 1977
92. Kudo H, Tamaki N, Kim S, et al: Intra-spinal tumors associated with hydrocephalus. *Neurosurgery* 21:726-731, 1987
93. Kyriellis W: Die Augenveränderungen bei den entzündlichen Erkrankungen des Zentralnervensystems. In: Schieck F, Bruckner A (eds) *Kurzes Handbuch der Ophthalmologie*, vol 2. Springer, Berlin, pp 779-780, 1931
94. Labauge R, Gros C, Pages M, et al: Hypertension intracrânienne et épendymome de la terminaison de la moelle épinière. *Rev Neurol (Paris)* 140:212-216, 1984
95. Laterza A: La papilla da stasi nelle compressioni del cono e della cauda equina. *Riv ONO* 34:336-346, 1959
96. Lepoire J, Schmitt J, Barrucand D, et al: Ependymome de la queue de cheval avec stase papillaire. *Rev Otoneuro-ophthalmol* 38:265-272, 1966
97. Love JG, Wagener HP, Wolzman HW: Tumors of the spinal cord associated with choking of the optic disks. *AMA Arch Neurol Psychiatry* 66:171-177, 1951
98. Lusins J, Kotsilimbas D: Normal-pressure hydrocephalus associated with markedly elevated CSF protein. *N Y State J Med Oct-Nov*:1151-1152, 1983
99. Luxon LM, Harrison MJC: Subarachnoid hemorrhage and papilledema due to a cervical neurilemmoma. *J Neurosurg* 48:1015-1018, 1978
100. Luzecky M, Siegel BA, Coxe WS, et al: Papilledema and communicating hydrocephalus. *Arch Neurol* 30:487-489, 1974
101. Mallory FB: The results of the application of special histological methods to the study of tumors. *J Exp Med* 10:575-593, 1908
102. Maria BL, Cafferty LL, Singer HS, et al: Diffuse leptomeningeal seeding from a malignant spinal cord astrocytoma in a child with neurofibromatosis. *J Neurooncol* 4:159-163, 1986
103. Martins AN, Wiley JK, Myers PW: Dynamics of the cerebrospinal fluid and the spinal dura mater. *J Neurol Neurosurg Psychiatry* 35:468-473, 1972
104. Maurice-Williams RS, Lucey JJ: Raised intracranial pressure due to spinal tumors: 3 rare cases with a probable common mechanism. *Br J Surg* 62:92-95, 1975
105. McAlpine D: Papilloedema caused by a cervical cord tumor. *Lancet* 14:614-616, 1935
106. McCormick PC, Stein BM: Clinical evaluation of the spinal cord and nerve roots. *Neurosurg Clin North Am* 1:491-493, 1990
107. Menzel J: Stauungspapille bei spinalen Tumoren. *Nervenarzt* 43:571-573, 1972
108. Messer HD, Brinker RA: Hydrocephalus and dementia complicating spinal tumor. *J Neurosurg* 53:544-547, 1980
109. Michel D, Lemercier G, Beau G, et al: Gliomatose ménigée et ventriculaire diffuse secondaire à un oligodendrogliome intramedullaire. *Lyon Medical* 234,13:37-41, 1975

110. Michowitz SD, Rappaport HZ, Shaked I, et al: Thoracic disc herniation associated with papilledema. *J Neurosurg* 61:1132-1134, 1984
111. Miller G, Towfighi J, Page RB: Spinal cord ganglioglioma presenting as hydrocephalus. *J Neuro Oncol* 9:147-152, 1990
112. Miller TJ, Wang H: Case report: radiologic diagnosis of intracranial and intraspinal subarachnoid metastases from a malignant spinal cord astrocytoma. *Md Med J* 39:471-473, 1990
113. Mittal MM, Gupta NC, Sharma ML: Spinal epidural meningioma associated with increased intracranial pressure. *Neurology* 20:818-820, 1970
114. Mock A, Levi A, Drake JM: Spinal hemangioblastoma, syrinx, and hydrocephalus in a two-year-old child. *Neurosurgery* 27 (5):799-802, 1990
115. Morley JB, Reynolds EH: Papilloedema and the Landry-Guillain-Barré syndrome. *Brain* 89:205-222, 1966
116. Mortara R, Parker JC, Brooks WH: Glioblastoma multiforme of the spinal cord. *Surg Neurol* 2:115-119, 1974
117. Nassar SI, Correll JW: Subarachnoid hemorrhage due to spinal cord tumors. *Neurology* 18:87-94, 1968
118. Neau JP, Roualdes G, Bataille B, et al: Hypertension intracrânienne et hydrocéphalie par tumeur médullaire. A propos de trois observations. *Neurochirurgie* 33:216-219, 1987
119. Newman EW: Ocular signs of intracranial disease in children and juveniles. A report of forty two cases. *Am J Ophthalmol* 21:286-292, 1938
120. Newman RP, Schaefer EJ, Thomas CB, et al: Abetalipoproteinemia and metastatic spinal cord glioblastoma. *Arch Neurol* 41:554-556, 1984
121. Neyl-Dwyer G: Tentorial block of cerebrospinal fluid associated with a lumbar neurofibroma. Case report. *J Neurosurg* 38:767-770, 1973
122. Ng HK, Leung C, Boet R, Poon WS: Spinal cord astrocytoma with cranial meningeal metastases. *J Clin Neuroscience* 8:374-377 2001
123. Nicola GC, Nizzoli V: Increased intracranial pressure and papilledema associated with spinal tumors. *Neurochirurgia* 12:138-144, 1969
124. Nishida K, Ueda S, Matsumoto K, et al: Cauda equina neurinoma associated with normal pressure hydrocephalus: case report. *Neurol Med Chir (Tokyo)* 30:258-262, 1990
125. Nishio S, Korosue K, Tateishi J, et al: Ventricular and subarachnoid seeding of intracranial tumors of neuroectodermal origin. A study of 26 consecutive autopsy cases with reference to focal ependymal defect. *Clin Neuropath* 1:83, 1982
126. Nonne: Ueber einen Fall von intramedullaren ascendrem Sarcom sowie drei Fälle von Zerstörung des Halsmarks. *Arch Psychiat Nervenkrank* 83:393-430, 1900
127. Norstrom CW, Kernohan JW, Love JG: One hundred primary caudal tumors. *JAMA* 178:1071-1077, 1961
128. O'Connell JEA: The subarachnoid dissemination of spinal tumours. *J Neurol Neurosurg Psychiatry* 9:55-62, 1946
129. Odom GL: Vascular lesions of the spinal cord: malformations, spinal subarachnoid and extradural hemorrhage. *Clin Neurosurg* 8:196-236, 1962
130. Ogasawara H, Kiya K, Kurisu K, et al: Intracranial metastases from a spinal cord primitive neuroectodermal tumor. Case report. *Surg Neurol* 37:307-312, 1992
131. Ohta K, Gotoh F, Amano T, Obara K: Normal pressure hydrocephalus associated with cauda equina neurinoma. *Ann Neurol* 27:441-443, 1990
132. Oi S, Galichich J: Intracranial metastasis of malignant tumor. The classification of parenchymal type, leptomeningeal type and diffuse type and its clinical significance: clinical manifestations. *Neurol Surg* 6:29-37, 1978
133. Oi S, Raimondi AJ: Hydrocephalus associated with intraspinal neoplasms in childhood. *Am J Dis Child* 135:1122-1124, 1981
134. Paillas JE, Combalbert A, Bille J, et al: Hypertension intracrânienne et stase papillaire par tumeur de la queue de cheval. *Presse Med* 72:403-404, 1964
135. Perese DM, Slepian A, Nigogosyan G: Postoperative dissemination of astrocytoma of the spinal cord along the ventricles of the brain. A case report. *J Neurosurg* 16:114-119, 1959
136. Phan T, Krauss W, Fealey R, et al: Recurrent lumbar ependymomas presenting as headache and communicating hydrocephalus. *Mayo Clin Proc* 75:850-852, 2000
137. Phanthumchinda K, Locharernkul C, Hemachuda T, et al: Increased intracranial pressure associated with spinal cord astrocytoma: a case with CSF dynamic study. *J Med Assoc Thai* 72:400-403, 1989
138. Philippides D, Buchheit F, Thiebaut JB, et al: Oedème papillaire dans les tumeurs de la queue de cheval. A propos de deux nouveaux cas. *Otoneuroophtalmol* 44:451-458, 1972
139. Philippon J, Poisson M, Bleibel: Ependymome de la queue de cheval révélé par une hypertension intracrânienne sans dilatation ventriculaire. Une observation. *Nouv Presse Med* 9:303-304, 1980
140. Pignoli G, Bille J, Berard M, et al: Tumeurs géantes de la queue de cheval. *Neurochirurgie* 10:211-229, 1964
141. Pitt MA, Jones AW, Reeve RS, et al: Oligodendrogloma of the fourth ventricle with intracranial and spinal oligodendroglomatosis: a case report. *Br J Neurosurg* 6:371-374, 1992
142. Polmeteer FE, Kernohan JW: Meningeal gliomatosis. *Arch Neurol Psychiat* 57:593-616, 1947
143. Poussaint T, Yousuf N, Barnes P, Anthony D, et al: Cervicomедullary astrocytomas of childhood: clinical and imaging follow-up. *Pediatr Radiol* 29: 662-668, 1999
144. Prasad VSSV, Basha A, Prasad BCM, Raja Reddy D: Intraspinal tumor presenting as hydrocephalus in childhood. *Child's Nerv Syst* 10:156-157, 1994
145. Prieto A, Cantu RC: Spinal subarachnoid hemorrhage associated with neurofibroma of the cauda equina. Case report. *J Neurosurg* 27:63-69, 1967
146. Purhoit AK, Dinakar I, Sundaram C, et al: Anaplastic astrocytoma of the spinal cord presenting with features of raised intracranial pressure. *Child's Nerv Syst* 6:113-115, 1990
147. Ramos F, de Toffol B, Aesch B, Jan M: Hydrocephalus and cavernoma of the cauda equina. *Neurosurgery* 27:139-142, 1990
148. Rau H: Stauungspapille bei spinalen Tumoren. *Dtsch Med Wochenschr* 99:351-354, 1974
149. Raynor RB: Papilledema associated with tumors of the spinal cord. *Neurology* 19:700-704, 1969
150. Ridsdale L, Moseley I: Thoracolumbar intraspinal tumours presenting features of raised intracranial pressure. *J Neurol Neurosurg Psychiatry* 41:737-745, 1978
151. Rifkinson-Mann S, Wisoff JH, Epstein F: The association of hydrocephalus with intramedullary spinal cord tumors: a series of 25 patients. *Neurosurgery* 27:749-754, 1990

152. Riley K, Palmer C, Oser A, Paramore C: Spinal cord hamartoma: Case report. *Neurosurg* 44:1125-1127, 1999
153. Rohr H, Hoffmann W: Ruckenmarkstumoren mit Stauungspapille. *Nervenarzt* 30:391-396, 1959
154. Rossberg C, Litzenberger J: Intramedullares Glioblastoma multiforme mit ungewöhnlicher, intrakranieller Meningeosis neoplastica. *Nervenarzt* 59:401-404, 1988
155. Rosset SO: Przypadek guza dolnego odcinka kanalu kregowego z tarcza zastoinowa (in Polish). *Neur Neurochir Pol* 26:599-602, 1976
156. Roth S, Mathai KV, Chandy J: Multiple meningiomas of the spinal canal. *J Neurosurg* 26:639-640, 1967
157. Rovetta P: Idrocefalo ed edema papillare secondari a tumori midollari di basso livello. *Arch Neurochir (Firenze)* 3:317-325, 1956
158. Rubinstein LJ, Logan WJ: Extraneural metastases in ependymoma of the cauda equina. *J Neurol Neurosurg Psychiatry* 33:763-770, 1970
159. Rudnicki S, Lebkowski J: O tarczy zastoinowej w przypadkach guzow rdzenia (in Polish). *Neur Neurochir Psych Pol* 1/51:49-54, 1951
160. Russell DS: Observation on the Pathology Of Hydrocephalus. Medical research council. Special report series no 265. His Majesty's Stationery Office, London, pp 112-113, 1949
161. Russell DS, Rubinstein LJ: Pathology of the tumors of the nervous system. Edward Arnold, London, pp 205-206, 1959
162. Russell DS, Rubinstein LJ: Pathology of the tumors of the nervous system, 3rd edn. Edward Arnold, London, pp 252-255, 1971
163. Russell DS, Rubinstein LJ: Pathology of the tumors of the nervous system, 4th edn. Edward Arnold, London, pp 431, 1989
164. Saleh J, Afshar F: Spinal cord astrocytoma with intracranial spread: detection by magnetic resonance imaging. *Br J Neurosurg* 1:503-508, 1987
165. Saitoh M, Kuwamura K: Report of a case of intracranial metastases from malignant spinal cord astrocytoma (in Japanese). *Rinsho Hoshasen* 34:249-252, 1989
166. Sarabia M, Millan JM, Escudero L, et al: Intracranial seeding from an intramedullary malignant astrocytoma. *Surg Neurol* 26:573-576, 1986
167. Sato S, Inaba K, Suematsu K: Spinal cord tumor associated with papilledema. *No Shinkei Geka* 5:1375-1376, 1977
168. Schijman E, Zuccaro G, Monges JA: Spinal tumors and hydrocephalus. *Child's Brain* 8:401-405, 1981
169. Scotti G, Filizzolo F, Scialfa G, et al: Repeated subarachnoid hemorrhages from a cervical meningioma. *J Neurosurg* 66:779-781, 1987
170. Simonati A, Mazza C, Rizzato N: An unusual case of meningeal gliomatosis. *Acta Neuropathol Suppl VII*:97-100, 1981
171. Sloof JL, Kernohan JW, Mc Carty CS: Primary intramedullary tumors of the spinal cord and filum terminale. Saunders, Philadelphia, pp 255, 1964
172. Smith JAR, Northcroft GB: Lumbar ependymoma. *Br J Clin Pract* 28:220-222, 1974
173. Sullivan RL, Reeves AG: Normal cerebrospinal fluid protein, increased intracranial pressure, and the Guillain-Barré syndrome. *Ann Neurol* 1:108-109, 1977
174. Suzuki S, Ishii M, Ottomo M, et al: Changes in the subarachnoid space after experimental subarachnoid hemorrhage in the dog: scanning electron microscopic observation. *Acta Neurochir* 39:1-14, 1977
175. Takara E, Ide M, Yamamoto M, et al: A case of the intracranial and spinal dissemination of primary spinal glioma. *No Shinkei Geka* 13:301-305, 1985
176. Tanaka K, Waga S, Shimosaka S: Papilledema and spinal cord tumors. *Surg Neurol* 29:462-466, 1988
177. Tashiro K, Tachibana S, Tsuru M: Clinicopathological studies of spinal cord neoplasms with disseminating intracranial metastases possibly producing akinetic mutism (in Japanese). *No To Shinkei* 28:1311-1318, 1976
178. Taylor J, Collier J: The occurrence of optic neuritis in lesions of the spinal cord. Injury, tumor, myelitis. An account of twelve cases and one autopsy. *Brain* 25:532-553, 1901
179. Teng P, Wagner JH, Buxbaum MW: Giant ependymoma of the spinal cord associated with papilledema. *Arch Neurol* 2:657-662, 1960
180. Toso V: Diffusioni metastatiche alle leptomenigi. *Acta Neurol* 22:366-376, 1967
181. Toulemonde V, Labrune P, Sainte Rose C, et al: Hypertension intracrânienne intermittente révélatrice d'une tumeur de la moelle cervicale. *Arch Fr Pediatr* 46:667-669, 1989
182. Tourniaire D, Sankei R, Pagès M: Hydrocéphalie à pression normale et neurinome lombaire. *Rev Neurol (Paris)* 149:802-804, 1993
183. Ucar S, Florez G, Garcia J: Increased intracranial pressure associated with spinal cord tumors. *Neurochirurgia* 19:265-268, 1976
184. Ulbricht W: Ruckenmarkstumoren mit Stauungspapille. *Acta Neurochir* 15:138-149, 1966
185. Wang AM, Haykal HA: Thoracic spinal meningioma associated with hydrocephalic dementia. *AJNR Am J Neuroradiol* 8:383-384, 1987
186. Webb JH, Craig WMCK, Kernohan JW: Intrad spinal neoplasms in the cervical region. *J Neurosurg* 10:360-366, 1953
187. Weickmann F: Caudatumor und Stauungspapille, ein Beitrag zur Frage der Liquorzirkulation und Resorption. *Nervenarzt* 25:65-68, 1954
188. Weiman CG, Mc Dowell FH, Plum F: Papilledema in poliomyelitis. *AMA Arch Neurol Psychiatr* 66:722-727, 1951
189. Wiersma D: Clinical and anatomical experiences in two cases of spinal cord tumor. *Acta Psychiatr Neurol* 3:63-91, 1928
190. Winkelmann VH: Hydrozephalus und stauungspapille bei Kaudatumoren. *Zentralbl Neurochir* 36:85-92, 1975
191. Wober G, Jellinger K: Intramedullares Oligodendrogliom mit meningozerebraler Aussaat. *Acta Neurochir* 35:261-269, 1976
192. Wolzman HW, Kernohan JW, Adson AW, et al: Intramedullary tumors of spinal cord and gliomas of intradural portion of filum terminale. *AMA Arch Neurol Psychiatr* 65:378-395, 1951
193. Yamagami T, Kikuchi H, Higashi K, et al: Intracranial metastasis of a spinal cord astrocytoma. Case report. *Neurol Med Chir (Tokyo)* 30:69-73, 1990
194. Yarnitsky D, Honigman S, Hemli JA, et al: Normal pressure hydrocephalus associated with spinal cord tumor. *Acta Neurol Scand* 76:302-305, 1987
195. Zarski S: Przypadek guza ogona konskiego przebiagajacy z tarcza zastoinowa (in Polish). *Neur Neurochir Pol* 6/22:153-156, 1972
196. Zavala LM, Adler JL, Greene CS, et al: Hydrocephalus and intraspinal tumor. *Neurosurgery* 22:751-754, 1988
197. Zeitlin R: Über einen Fall von Extramedullarer Rückenmarksgeschwulst mit Stauungspapille. Dissertation, Hamburg, 1937

Postinfectious Hydrocephalus in Children

ALEXANDER V. CIUREA, TEODORA C. COMAN AND DAN MIRCEA

There are few conditions treated in neurosurgery that are as frustrating as hydrocephalus; likewise there are few neurosurgical interventions performed by neurosurgeons that are as unforgettable as cerebrospinal fluid (CSF) shunt insertion. In this chapter the authors try to define the modern concepts of management of postinfectious hydrocephalus (PIH) in children, to evaluate the options and the timing of surgery or medical treatment only, in a category of patients that undoubtedly is more fragile than adults. The surgeon must have a good knowledge of the etiological infectious factors which have the potential to produce hydrocephalus, the pathogenesis, and the prophylaxis and treatment of these infections.

PIH may be defined such as hydrocephalus of infectious etiology, with high or normal pressure of CSF [38]. In the literature, postmeningitic hydrocephalus has been classified as communicating due to the predominant obstruction of the basal cisterns. Our opinion is that all cases of PIH are obstructive, because every obstruction to any part of the CSF pathways results in increasing resistance to the CSF flow, with a consequent rise in intracranial pressure (ICP) and stress on the ventricular walls. Once the hydrocephalic process has been initiated, other hydrodynamic and cellular mechanisms play a part in maintaining or progressing the hydrocephalus. PIH must be considered a complex disease and each case must be treated individually, taking account of the predominance of each pathogenic factor.

Hydrocephalus Following Prenatal Infections

In utero infections can induce hydrocephalus when they involve the central nervous system. In addition to impairing CSF, these infections are often responsible for parenchymal damage that greatly influences

the infant's ultimate developmental prognosis. These are the consequences of fetal sepsis due to maternal infections transmitted via the placenta. The fetal infection may result in abortion or fetal contamination, also affecting the CNS. Infections localized to the brain may result in hydrocephalus and/or various types of congenital malformations. The most frequent infections transmitted across the placenta are the following.

Toxoplasmosis

The incidence of human congenital toxoplasmosis varies among countries. The incidence in Britain is 0.6 subclinical infections and 0.09 cases of severe illness per 1000 births; in the USA the figure is between 1 per 1000 and 1 per 8000 live births, while in France the incidence is 1 in 2000 [35]. The risk of acquired toxoplasmosis during pregnancy (1.2% of susceptible women) and of transmission of *Toxoplasma gondii* to the fetus (1% of neonates) was estimated from results of serial serological tests done in 15,132 pregnant women from 1977 to 1982 [47, 71]. Fetal infection (congenital toxoplasmosis) is most severe when the fetus is infected during the first trimester; transplacental passage is more common when maternal infection occurs in the latter half of pregnancy, but fetal injury is then usually much less severe [47]. Acute infection with *T. gondii* may be clinically manifest in 10%-20% of pregnant women. Transplacental transmission occurs in about 55% of untreated and 22% of treated pregnant infected women [92]. At birth 8% of newborns with congenital toxoplasmosis will have severe impairment of the CNS or eyes and 75% are asymptomatic [75, 137]. Transplacental infections of the fetus may result in abortion, normal delivery of a dead fetus (stillbirth), Sabin's tetrad (hydrocephalus, chorioretinitis, convulsions, intracranial calcifications), or silent forms in which the newborn develops chorioretinitis 6 months after birth. Congenital toxoplasmosis can result in acute,

subacute, or chronic disease and is characterized by widespread CNS inflammation and necrosis. Necrotic areas are most prevalent in periventricular and periaqueductal regions. Choroid plexus involvement is frequent in patients with AIDS [42].

Toxoplasmosis and Hydrocephalus

The parasites invade and destroy the ependymal lining of the lateral ventricles. The debris falls into the ventricular cavities, obstructing the ventricular foramina and the aqueduct of Sylvius [120]. The lesions develop during the second trimester of pregnancy. In acute cases, extensive necrosis of the cerebral hemispheres can be observed with associated significant cerebral tissue loss contributing to ventricular enlargement [75]. Other authors deny the role of aqueductal stenosis on the basis of experimental observations in mice which suggest that the development of post-toxoplasmosis hydrocephalus (PTH) is consequent upon severe leptomeningeal inflammation blocking the subarachnoid spaces. Narrowing of the aqueduct of Sylvius, when present, was considered the result of compression of the midbrain by the enlarging lateral ventricles [120]. In a series of ten children presenting with PTH, aqueductal stenosis was present, with high ventricular fluid pressure and distinct cerebral mantle reduction. Intracerebral calcifications were common [60]. Cases of congenital toxoplasmosis with hydranencephaly are also reported. The anatomic lesions are the consequence of ischemic necrosis and fetal hydrocephalus. The risk of such lesions is higher during the second trimester of pregnancy [98].

PTH is diagnosed at ages ranging from birth to 1 year [60]. The patient can present with seizures or various degrees of developmental delay and cerebral palsy [35] or with isolated signs of intracranial hypertension. Several ocular abnormalities (Fig. 1) have been



Fig. 1. CT scan showing microphthalmia in a patient affected by congenital toxoplasmosis

reported in the more severe forms (microphthalmia, strabismus, cataracts, glaucoma retinochoroiditis, optic atrophy) [75]. In the long term endocrinological troubles have been described [83]. The parasite can be isolated from the placenta, blood, body fluids. In patients with obstructive hydrocephalus, tachyzoites are more likely to be found in ventricular rather than lumbar specimens of CSF [23]. Histologically the tachyzoites of *T. gondii* can be observed in tissue sections or smears of body fluids. Serology remains irreplaceable, allowing diagnosis of congenital toxoplasmosis by determination of increased IgM antibody (in the serum of newborn infant). The fetus is able to produce IgM-specific antibody. The presence of IgM antibodies in serum obtained from the neonate is evidence of fetus infection in utero, since maternal IgM antibodies do not pass the placenta. IgM antibodies can also be demonstrated in the CSF.

Plain skull X-rays and CT in infants with congenital toxoplasmosis may show characteristic spotty intracerebral calcifications (Fig. 2). Radiological signs of PTH associated with one or more rounded isodense or hypodense lesions with ring or nodular enhancement on CT scan, or hyperintense lesions indistinguishable from surrounding edema, or isointense-to-hypointense lesions surrounded by hyperintense edema on MRI, suggest a toxoplasmic origin of hydrocephalus. Hydrocephalus, microcephaly, porencephaly, and subdural hygroma may be common findings [130]. Cases of unilateral ventriculomegaly due to toxoplasmosis have been described in the prenatal period [117]. In immunocompromised patients, masses in the third and fourth ventricles associated with obstructive PTH or multiple parenchymal lesions in the cortex, the juxtacortical white matter, and the basal ganglia have been described [19, 42].

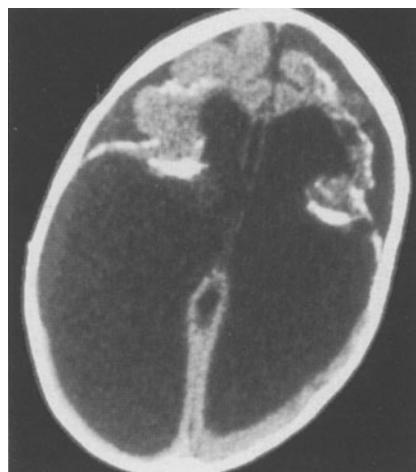


Fig. 2. Congenital toxoplasmosis: significant ventricular dilatation with parenchymal damage and diffuse intraparenchymal and periventricular calcifications

Treatment and Prognosis

Health education may decrease the incidence of toxoplasmosis during pregnancy by 60% [44]. Drugs indicated in congenital toxoplasmosis, even in the subclinical form, are pyrimethamine plus sulfadiazine or trisulfapyrimidines plus folinic acid, for 21 days. During the first year of life the child should receive three or four courses of pyrimethamine plus sulfadiazine separated by 30–45 days. No treatment is given after 12 months of age. In congenital toxoplasmosis with evidence of an inflammatory process, glucocorticoid treatment should be added. Neonatal hydrocephalus associated with extensive intracerebral calcification and severe parenchymal damage is an indirect sign of severe leptomeningeal involvement and should ideally be treated with ventriculoperitoneal CSF shunt (Fig. 2). In patients with postnatal onset and less severe parenchymal damage, aqueductal stenosis can be usually observed on MRI (Fig. 3), and endoscopic third ventriculostomy is indicated as a first option [29]. Pre-

natal diagnosis of PTH and brain anomalies is associated with poor neurological outcome [117], but in fact all patients presenting with PTH are at risk of poor prognosis at 5 years of age, even if they receive prompt surgical and medical treatment after birth [34]. Factors that contribute to the more severe disabilities included delayed diagnosis of toxoplasmosis and delayed initiation of therapy, prolonged concomitant neonatal hypoxia and hypoglycemia, profound visual impairment, and delayed diagnosis of PTH [80].

Cytomegalovirus Infections

Cytomegalovirus (CMV), a member of the herpesvirus group, is the most common infectious cause of nervous system damage in the fetus and newborn infant. It exerts its teratogenic effect during early pregnancy. Symptomatic disease results particularly in immunosuppressed patients [5]. In pregnant women CMV infections are usually silent, but exogenous acquisition of CMV results in transplacental passage of the virus in approximately 50% of cases [58]. After infection in utero, 10%–15% of infants will have obvious CMV inclusion disease at birth [12]. Findings include microcephaly, intracerebral calcifications, chorioretinitis, seizures, mental retardation, hepatosplenomegaly, jaundice, interstitial pneumonitis, and thrombocytopenia with petechiae or purpura [52].

Pathology

In experimental studies the main targets of viral attack were the meninges and ependyma, with limited parenchymal invasion from these sites. Characteristic features of CMV disease observed included cytomegaly, formation of nuclear and cytoplasmic inclusions, and polykaryocytosis. Hydrocephalus developed in a few of the animals and was studied in late phases of the disease [63]. On postmortem histological studies in patients with AIDS and CMV encephalitis, the “owl’s eye” intracellular inclusions of CMV are pathognomonic [102]. CMV can be also responsible for progressive CNS damage after birth, accounting for some unexplained brain malformations and for a portion of the neurodegenerative disorders occurring in babies who appear normal at birth [21]. Cases of progressive CMV encephalitis have been described [77].



Fig. 3. **a** Postnatal hydrocephalus in a patient affected by congenital toxoplasmosis; aqueductal stenosis is evident in the lower third of the aqueduct. The hydrocephalus was treated by endoscopic third ventriculostomy (**b**)

CMV and Hydrocephalus

The percentage of hydrocephalus cases that are a consequence of CMV infection (CMVH) is highly

variable according to the different series in the literature. Infection occurring in preterm infants is frequently lethal. Perlman and Argyle, in a study on 15 premature infants with lethal congenital CMV infection, found that the most frequent clinical findings in live-born infants (9 cases) were microcephaly (77%) and seizures (55%); CMVH was observed only in 2 cases [97]. Some authors report CMVH as a frequent complication [2], in other series CMVH was uncommon finding, but in all cases patients presented mental retardation and hepatomegaly [118]. Authors relate the presence of major cerebral migrational defects with the spectrum of lissencephaly-pachygryria associated with congenital CMV infection [52].

Pregnant women with and without serological evidence of active CMV infection must be followed until delivery to detect the incidence and types of overt congenital CMV infection in neonates. Infection may be diagnosed by the detection of CMV-IgM, using enzyme-linked immunosorbent assay [2]. Neuroradiological findings described in CMVH are intracranial calcifications (one-third of cases), cortical atrophy, ventricular enlargement, subdural effusions, porencephaly, and polycystic encephalomalacia [11]. If the CMVH is not symptomatic and there are no radiological signs of activity, the child must be observed by serial follow-up imaging. Serial CT head scans may display CMVH progressing to extensive loss of brain substance and CMVH or normal scan going on to polycystic encephalomalacia [21]. Neuroradiological features include broad, flat gyri, shallow sulci, incomplete opercularization, ventriculomegaly, periventricular calcifications; white-matter hypodensity on CT scans, or increased signal intensity on long-TR MRI scans were also related in congenital cytomegalovirus infection [52]. Alonso et al. reported a child who exhibited extensive inflammatory lesions in the periventricular area and at the level of the quadrigeminal plate with the formation of a pseudotumor at this level. The latter produced aqueduct obstruction resulting in CMVH [4]. In patients with CMV encephalitis and AIDS, CT scan is not very sensitive for the detection of parenchymal involvement compared to autopsy findings, but cortical atrophy and mild ventricular dilatation *ex vacuo* is usually seen in all patients [102]. In infants, ultrasonography is very useful to observe the changes of the brain parenchyma such as cystic degeneration and periventricular calcification [79].

Treatment is directed toward the CMV infection and treatment of CMVH. Pharmacological treatment is based on ganciclovir [9-(1,3-dihydroxy-2-propoxymethyl) guanine] which acts on the viral DNA polymerase and eradicates infections from the blood and secretions within 72 h of initiation of

therapy [58]. In recent years, DNA vaccination strategies have been developed for many pathogens including CMV [126]. Surgery is suitable for patients with symptomatic and progressive hydrocephalus on serial CT/MRI. Ventriculoperitoneal shunt placement is indicated because of the constant involvement of parenchyma and leptomeninges, which contraindicates third ventriculostomy.

The prognosis in congenital CMV inclusion disease is poor. Reports of the neurological sequelae of CMV have emphasized varying degrees of psychomotor retardation, cerebral palsy and epilepsy due to polymicrogyria, periventricular calcification, microcephaly, or rarely, hydrocephalus (CMVH). The prognosis of CMVH correlates with the brain parenchymal destruction produced by CMV disease. Progression of CMVH may be stopped by surgery, but the neurological sequelae remain stable, hampering the normal neuropsychological development of the child. Patients appear to manifest extremely severe effects of CMV on neurological growth, maturation, and development [52].

Hydrocephalus Following Neonatal Infections

Bacterial Infections

Various form of hydrocephalus may develop months to years after recovery from acute bacterial meningitis [39, 49]. The incidence of neonatal meningitis is 40 to 50 per 100 000 live births, with about two-thirds of the cases occurring in hospitals [51, 92, 100, 135]. The etiology of meningitis in neonates has changed substantially over the past several years. At the end of the 1980s, group B β -hemolytic streptococci (GBS) overtook *E. coli* as the leading cause of neonatal bacterial meningitis. This was accompanied by a fall in the mortality rate, but with a sustained high incidence of complications and sequelae [27, 65]. At present, approximately 75% of cases of meningitis that occur during the first 14 days of life are caused by gram-negative bacteria (Enterobacteriaceae in 60%). In contrast, about 66% of the cases in infants over 14 days old are caused by gram-positive bacteria (GBS in 20%-45%) [92]. A recent study on very low-birth-weight neonates, identifies as the most common causes of meningitis coagulase-negative staphylococci in 43% of episodes, other gram-positive bacteria in 19%, gram-negative bacteria in 17%, and *Candida* species in 20% of episodes [39].

Hydrocephalus

The incidence of PIH after bacterial meningitis in neonates has not been established. Renier et al. in a study of 30 neonates of brain abscesses, mostly caused by *Proteus* species infections, relate that the ventricles were enlarged on the first CT scan in 13 cases, and a shunt for hydrocephalus was necessary in 14 infants [106]. On the basis of the follow-up analysis, the authors concluded that the absence of initial seizures, sterile CSF, normal ventricles on CT scans, and early aspiration of the abscess seem to be factors portending a better prognosis in terms of epilepsy and mental sequelae [106]. In a series of 61 children aged 0-12 months affected by CSF-confirmed meningitis, a 46% rate of cerebral complications was found: hydrocephalus in 20 cases (71.4%), ventriculitis in 5 cases (17.9%), abscess and ventriculitis in 2 cases (7.1%), and cerebral atrophy in 1 case (3.6%) [49].

Undiagnosed brain abscess may lead to ventricular rupture with ventriculitis (Figs. 4, 5) [13, 17, 22]. Hydrocephalus usually occurs within 2-3 weeks following diagnosis and treatment of the abscess, and can easily take on a complicated form, with loculation of the CSF spaces and formation of multiple intraventricular septations [91]. This mainly occurs in neonates [105], most commonly following gram-negative bacterial meningitis [103]. The pathogenic hypothesis is an inflammatory vasculitis at the subependymal level [9], with the subsequent infarct giving rise to the cysts. The osmotic pressure within the cavities, rather than intraventricular fluid, would account for the enlargement of the cysts [15]. The ventricular septa are formed by glial protrusion into the ventricles [103]. The management is difficult, requiring multiple shunt revisions or multiple shunt implants [61]. The morbidity and mortality remain high [82]. The intellectual prognosis in these cases is poor.

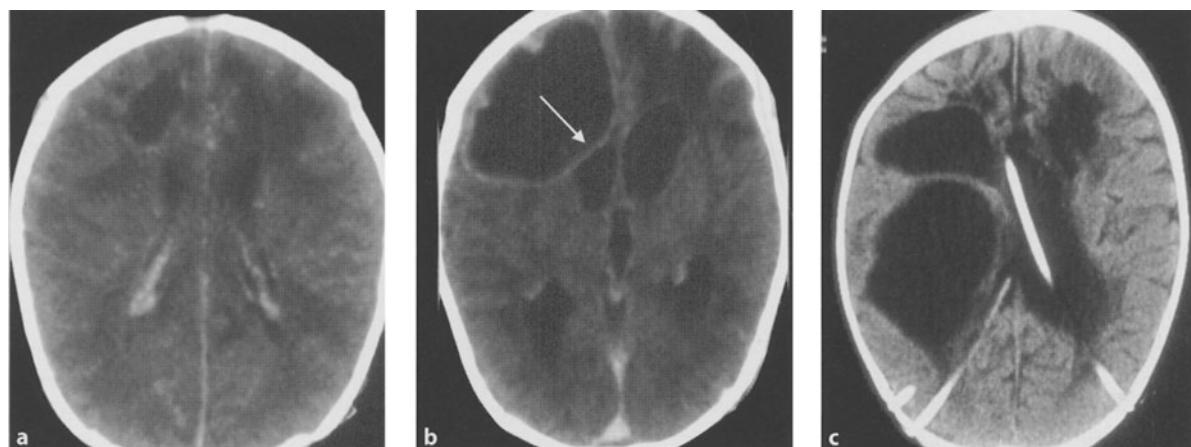


Fig. 4. Progressive development (a, b) of a frontal abscess during *E. coli* meningitis, leading to rupture of the abscess into the ventricle and ventriculitis (arrow shows the thin layer of ependyma), with consequent multiloculated hydrocephalus (c)



Fig. 5. Ventriculitis following gram-negative bacterial meningitis: there is strong contrast enhancement of the ependymal layer and beginning of ventricular loculation with asymmetric dilatation

Treatment

The treatment of PIH in the newborn must be directed both toward infections and to proper hydrocephalus. Antibiotic therapy is specifically indicated by antibiogram. The focal collection should be surgically treated as soon as possible using a minimally invasive approach (puncture with instillation of antibiotics into the brain abscess). In the presence of active infection, an external drainage is indicated until the CSF samples become sterile [1, 86]. If the PIH occurs after resolution of the infection, this is more frequently of the communicating type with tetraventricular di-

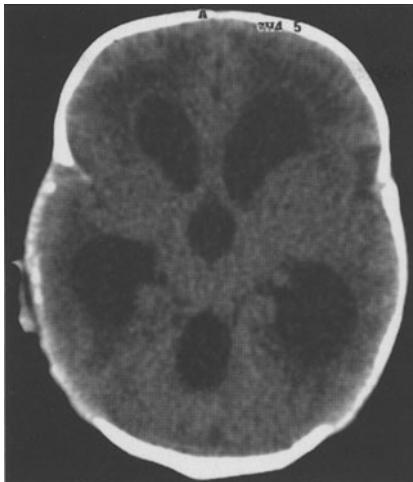


Fig. 6. Tetraventricular dilatation following neonatal bacterial meningitis

latation (Fig. 6) and a ventriculoperitoneal shunt should be implanted. In multicompartamental PIH more shunt devices may be necessary (see Chapter 20).

Mycotic Infections

Fungal meningitis tends to be a subacute or chronic process; however, it can be just as lethal as bacterial meningitis if untreated. There are many similarities between the pathogenic fungi. Most are aerosolized and inhaled, and initiate a primary pulmonary infection which is usually self-limited. Hematogenous dissemination may follow the initial infection, with subsequent involvement of the CNS. Rarely, trauma or local extension provides the route to CNS infection. The host is frequently, although not always, immunosuppressed. The hyphae of molds generally cause focal disease with hemorrhagic necrosis secondary to vascular thrombosis. The yeasts tend to cause a more diffuse process with the base of the brain being primarily affected, so that hydrocephalus is seen as a frequent complication of chronic disease [128]. Diagnosis may be difficult, as the CSF may be normal, with negative smears and sterile cultures, although more often there is at least one abnormality indicating disease. Serology (if available, depending on the fungus) may point towards the proper diagnosis, as may a careful travel history [128]. Contrast-enhanced cranial CT reveals multiple, homogeneously ring-like enhanced lesions with peripheral edema. Candidosis in newborns was reported to produce small calcified granulomas and an area of encephalomalacia [55].

Treatment

Follow-up CT examination shows regression of the lesions [55]. AmBisome represents an effective, safe, and convenient antifungal agent in the treatment of systemic fungal infections in very low-birth-weight infants [59]. Significant clinical recovery after amphotericin B treatment was reported in varied studies. When fungal meningitis is present, a course of amphotericin B should be initiated and the CSF sterilized prior to placement of the permanent extracranial shunt. Where acute hydrocephalus occurs, temporary ventricular drainage should be employed. In some cases of fungal meningitis, the symptoms of hydrocephalus can resolve with antifungal therapy alone, obviating the need for CSF drainage [76]. Intraventricular loculation has been described following fungal meningitis, effectively treated by endoscopic fenestration alone [95].

Hydrocephalus Following Infections in the Postneonatal Period

Bacterial Infections: Meningitis

About 60%-75% of postneonatal bacterial meningitis in children is caused by *Haemophilus influenzae* type B. The incidence is highest at 7-11 months of age and declines slowly after 12 months, so that *Haemophilus*-related meningitis is seen about as frequently as meningococcal and pneumococcal meningitis in 2-year-old children [92]. There is a temporal relationship of the onset of vulnerability to disease with the waning of maternally acquired humoral antibody that is bactericidal for *H. influenzae*. The cumulative probability of meningitis caused by *H. influenzae* during the first 5 years of life is approximately 150 to 200 per 100,000 [92]. The presence of hydrocephalus in the context of bacterial meningitis is recognized as a factor [48] increasing the possibilities of adverse neurodevelopmental sequelae or death [74].

Gram-negative bacterial infections of the CNS are generally associated with high morbidity and mortality rates. In patients with ventriculitis induced by gram-negative CSF infection, a reduction in CSF formation has been reported, suggesting that gram-negative ventriculitis is able to alter the normal functioning of the choroid plexus [25] by decreasing the number of microvilli and flattening the epithelial surface [25]. CT scan abnormalities can be observed in more than 50% of cases [36], mainly in patients

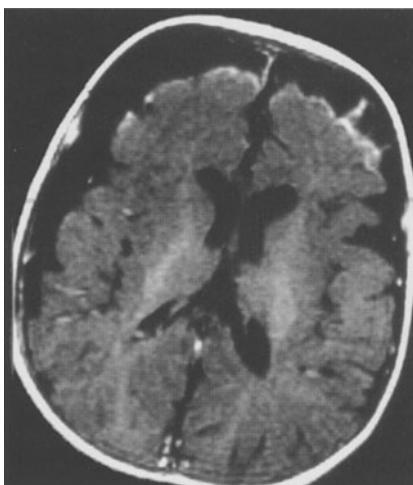


Fig. 7. Pericerebral collection with contrast enhancement of the meningeal layers of the convexity following *Haemophilus* meningitis

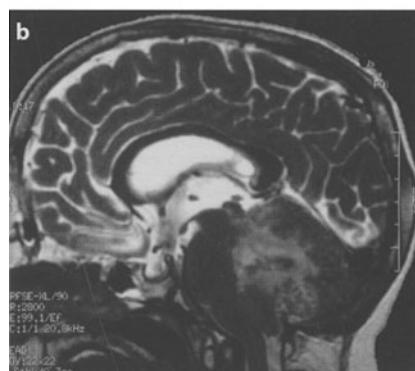
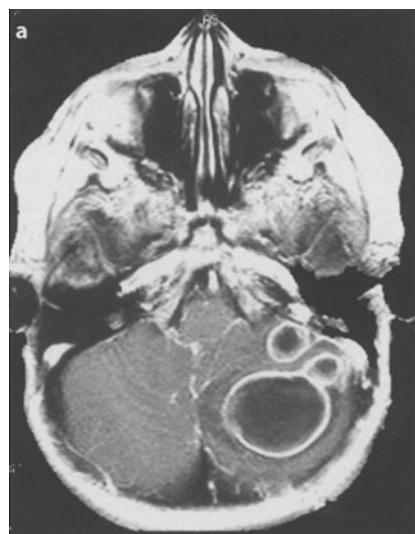


Fig. 8. Cerebellar abscess (a) and hydrocephalus following left middle ear infection, treated by abscess puncture and third ventriculostomy (b)

who present with complex seizure disorders. The commonest abnormal findings are subdural collection (33%), followed by hydrocephalus (7%) (Fig. 7). Subdural collection is observed mainly in patients with *H. influenzae* bacterial meningitis (90%) (Fig. 7), while hydrocephalus is mainly seen in tuberculous meningitis [36].

Treatment

Prevention, especially administration of *H. influenzae* type B vaccine at an early age, is probably the most effective way to reduce the significant mortality and morbidity associated with bacterial meningitis in children [99]. Antibiotic therapy should be started as an emergency treatment, and dexamethasone has become an important adjunct to antimicrobial therapy for meningitis due to *H. influenzae* type B. Shunt placement is indicated if spontaneous recovery does not occur. In most cases of bacterial meningitis, ventriculostomy should be used until the CSF is sterile before permanent shunt placement.

Cerebral Focal Collections

A cerebral abscess may induce hydrocephalus by mechanical compression of the CSF pathways, especially if it is located in the posterior fossa (Fig. 8). This kind of hydrocephalus is usually obstructive in nature, unless meningitis is associated, and can be treated con-

servatively by abscess puncture, antibiotics, and antiedema treatment. If ventricular dilatation persists following treatment of the abscess, external ventricular drainage can be implanted until the CSF become sterile or until the parenchymal edema has completely resolved. Third ventriculostomy can be the ideal solution, allowing definitive resolution of the hydrocephalus without the implantation of foreign material and avoiding the risk of extending the infection to the CSF incurred by the presence of an external drainage.

Rupture of abscess in the ventricle leads to ventriculitis, with dramatic clinical and pathological consequences. Adequate antibiotic therapy instituted as soon as possible in the presence of brain infections may be curative.

Subdural empyema can rarely be complicated by hydrocephalus if it develops close to a large dural sinus and induces thrombosis.

Viral Infections

Encephalitis, an inflammation of the brain parenchyma, presents as diffuse and/or focal neuropsychological dysfunction. From both the epidemiological and the pathological perspective, encephalitis is distinct from meningitis, although clinically the two often co-exist. *Cerebritis* is the stage preceding abscess formation and implies a highly destructive bacterial infection of brain tissue, whereas *acute encephalitis* is most commonly a viral infection with parenchymal damage varying from mild to profound.

The virus replicates outside the CNS and gains entry by hematogenous dissemination or by dispersion along neural and olfactory pathways. Once across the blood-brain barrier, viruses penetrate the neural cells, resulting in disruption in cell functionality with perivascular congestion, hemorrhage, and inflammatory response which diffusely affect gray matter disproportionately to white matter. Different subpopulations of cells are specific targets of herpes zoster (dorsal root ganglion cells), the poliomyelitis virus (anterior horn motor neurons), papovaviruses (oligodendroglia), rabies virus (pyramidal neurons of the hippocampus and Purkinje cells), herpes simplex (inferior frontal and temporal lobes) and CMV (ependymal cells and microglia), probably because there are different membrane receptors [40]. Several viruses (mumps, CMV, lymphocytic choriomeningitis, influenza A, and parainfluenza 2) selectively infect ependymal cells and are an important cause of acquired aqueductal stenosis without inflammation [56, 123]. Damaged ependyma may not be able to perform its function in the regulation of transport of fluid, ions, and small molecules between cerebral parenchyma and ventricular fluid and thus may contribute to hydrocephalus. Damage to the fetal ependyma may result in secondary focal dysplasias of the developing brain [112].

Histology

The pathological findings in virus-induced aqueductal stenosis are usually similar to those in the “simple stenosis” (without gliosis) described by Russell [110]; the ependymal infection may be clinically inapparent. Thus, some authors [108] hypothesize a pathogenetic role of viral infection (in particular mumps infection) in inducing the “unknown etiology” forms of aqueductal stenosis. Viruses may cause granular ependymitis and ependymal cell loss resulting in desquamation of the ependyma and subsequent aqueduct occlusion [54]. Wolinski [142] suggested an alternative pathogenetic mechanism: viral absorption on the outer surface of the ependymal cell plas-

malemma and viral penetration into the cell cause fusion of the cilia of adjacent cells, and thus ependymal cells are cross-linked by viral particle bridges. Cell fusion is favored by the high concentration of particles that occur in the aqueduct, which continues to be bathed by CSF into which virions are released.

Several experimental studies, especially with mumps virus, confirm the role of viral infection in the genesis of hydrocephalus, the pathological mechanisms, and the relationship with the age factor. The ependymal cilia disappear and only the microvilli remain; supraependymal cells are observed on the surface of the lateral ventricles [122]. Transmission electron microscopy revealed intracytoplasmic viral-like inclusions in the infected ependymal cells. The authors suggest that functional and morphological disturbances in infected ependymal cells may cause early ventricular dilatation before aqueductal stenosis occurs [122]. The ependymal involvement, which is potentially capable of producing aqueductal stenosis and hydrocephalus, was also described in other experimental studies in hamsters with attenuated and natural strains of mumps virus [64]. Age-related hydrocephalus was studied in various experiments, suggesting that tight junctions in the early postnatal period are more immature and fragile than in the adult, and the brain susceptibility in mumps virus-induced hydrocephalus, is intimately related to the maturity of the brain barriers [131].

Aqueductal stenosis is rare or occurs in the later phase of viral brain infection. Ogata et al. report a case of an acquired form of hydrocephalus due to aqueductal stenosis developing as a sequela of a fulminant phase of mumps ventriculitis [89], but this feature was also reported in mumps meningoencephalitis with acute hydrocephalus [134].

Experimental Models of Virus-Induced Hydrocephalus

Parvovirus infection occurring late in the first or early in the second trimester of pregnancy induces malformations in kittens, such as bilateral or unilateral hydrocephalus or hydranencephaly, cerebellar agenesis, or severe hypoplasia [119]. The Theiler's murine encephalomyelitis virus variant induces in infected mice macrocephaly and meningitis with apoptosis but without parenchymal involvement in the acute phase of infection. During the chronic phase, communicating hydrocephalus develops without demyelination and without viral persistence [129]. In contrast to viruses that invade gray matter directly, the immune-mediated or allergic processes determined by the measles virus, Epstein-Barr virus, and CMV result in multifocal demyelination of perivenous white matter.

Influenza virus encephalitis induces ependymal damage; aqueduct forking; hydrocephalus; neuronal heterotopias; and agenesis of the cerebellum, pontine, and inferior olfactory neurons. Agenesis of the optic and olfactory systems and corpus callosum may occur with persistence of influenza virus antigens in the brain [32]. Parainfluenza 3 virus may be associated with severe fetal infection in the first half of pregnancy. Serological studies for this virus should be considered in cases of fetal hydrocephalus [115].

Respiratory syncytial virus (RSV) induces hydrocephalus in 35% of animals. Histologically, eosinophilic inclusion bodies are visible within the cytoplasm of ependymal and meningeal cells, but a patent aqueduct is constantly found [67, 68]. Experimental Pneumovirus infections reveal general infection of the ependyma and very limited infection of the leptomeninges and the choroid plexus. Hydrocephalus occurs in 80% of inoculated mice. Lagace-Simard et al. (1980) describes the sequence of pathological events leading to hydrocephalus and supports recent studies indicating that stenosis of the aqueduct is a secondary phenomenon not causally related to the pathogenesis of hydrocephalus [67]. In conclusion, varied experimental models of hydrocephalus have shown that the type of obstruction producing hydrocephalus and the clinical course depends on the virus class and the host's age. Morbidity and mortality also depend on host factors and the virulence of the infecting organism. Poor outcomes are expected in infants younger than 1 year.

Diagnosis

CSF polymerase chain reaction (PCR) for DNA herpes simplex virus is 100% specific and 75%-98% sensitive within the first 25-45 h. Types 1 and 2 cross-react, but no cross-reactivity with other herpes viruses occurs. CT scans with or without contrast may show signs of elevated ICP, obstructive hydrocephalus or mass effect. MRI is more likely to show abnormalities earlier in the disease course than CT scans. In herpes simplex encephalitis (HSE), MRI shows foci of increased T2 signal in the medial temporal lobes and inferior frontal gray matter. CSF analysis is essential. The lumbar puncture must be performed after CT/MRI in order to exclude elevated ICP which can produce brain herniation. Biopsy of the brain is the standard test, having 100% specificity.

Treatment

With the exception of HSE and varicella zoster encephalitis, the viral encephalitides are not treatable. In the Emergency Care Department, for acutely ill pa-



Fig. 9. Hydrocephalus occurring 9 years following mumps meningoencephalitis, treated by third ventriculostomy. Obstruction is evident in the lower third of the aqueduct; flow artifact is present through the third ventriculostomy

tients, the goal is to start therapy as soon as possible after collecting laboratory samples and blood cultures, with acyclovir [81] (dose 0.15 mg/kg i.v. every 6 h in neonates) with or without antibiotics and with or without steroids. For hydrocephalus and elevated ICP, the first step is drug therapy based on the use of diuretics, dexamethasone (0, 15 mg/kg i.v. q6h) for cerebral edema management, and hyperventilation. In cases of acute hydrocephalus, an external drainage may be instituted as an emergency maneuver. In later phases a shunt insertion is possible. Third ventriculostomy by the endoscopic route may be useful in aqueductal stenosis due to ependymal hypertrophy (Fig. 9). Brain biopsy can be considered at any time of the treatment.

Post-tuberculous Hydrocephalus

In places where tuberculosis is endemic, intracranial tuberculomas can comprise as many as 10% of all space-occupying lesions, including neoplastic and infectious processes. In children younger than 5 years of age, this figure may reach 21.5% [78]. Hydrocephalus after infections of the CNS by lymphohematogenous dissemination of tubercle bacilli may be of the obstructive type, caused by mass effect of an intracranial tuberculoma or by brainstem involvement in basal meningitis, but is more frequently of the communicating type, after tuberculous meningitis affecting the basal cisterns. Children who develop disseminated tuberculosis at the time of primary infection are at greater risk of developing meningitis than adults [72]. Raised ICP resulting from obstructive hydrocephalus is the most treatable complication of tuberculous meningitis, occurring in more than 80% of children who present with the advanced stages (stages II and III) of the disease [113]. Clinical diagnosis of raised ICP is even more difficult in tuberculous

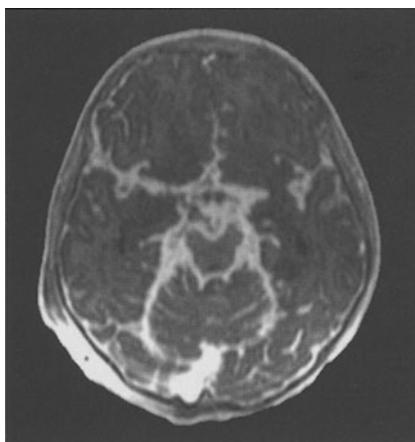


Fig. 10. Diffuse meningeal enhancement of the subarachnoid spaces in a patient affected by tuberculous meningitis and hydrocephalus

meningitis than in other types of infantile hydrocephalus because signs of impending cerebral herniation such as decerebration and papillary abnormalities may also result from direct involvement of the brainstem by the basal tuberculosis infection [113]. The clinical pattern of this meningitis is that of indolent meningitis, with headache, stiff neck, vomiting, and cranial nerve deficits. The symptoms are believed to be the result of a hypersensitivity reaction to tuberculoprotein released into the CSF [72]. Infections involving vascular channels cause an obliterative arteritis which can result in cerebral infarction. From the pathogenic point of view, the genesis of the hydrocephalus is based on collections of meningeal exudates at the base of the brain, entrapping the major vessels of the circle of Willis and the cranial nerves (Fig. 10). Hydrocephalus results when the exudate obstructs the foramina that provide egress of the CSF from the fourth ventricle. Death may result from herniation of the brainstem. When cerebral tuberculomas appear, cerebral meningitis may or may be not present [72].

Diagnosis

Cranial CT scan findings have become the basis for the diagnosis and treatment of tuberculous hydrocephalus. Jinkins classified CT findings in cerebral tuberculosis in [57] as isolated meningeal involvement (type I), isolated parenchymal forms (type II), or compound parenchymal/meningeal lesions (type III). MRI findings can be meningeal enhancement (90.9%), hydrocephalus (63.6%), infarction (45.5%), tuberculomas (27.2%), cranial nerve involvement (27.2%), and severe cortical atrophy (9.1%) [132]. Pathological fea-

tures are different in HIV-positive patients, reflecting severely reduced and atypical inflammatory response and extensive vasculopathy. These manifest as absent or minimal meningeal enhancement and absence of communicating hydrocephalus on CT scan [62, 84]. CSF laboratory study in tuberculous meningitis reveals abundance of leukocytes, with predominance of the mononuclear type, increased protein, and reduction of the concentration of glucose to less than 40% of the contemporaneous blood glucose. Tuber bacilli in the CSF are rare and CSF may normalize early in the course of the disease. Use of enzyme-linked immunosorbent assay to detect IgG antibody to purified tuberculoprotein in the CSF may provide a more rapid diagnostic test [72]. ICP monitoring offers information about the pressure pattern in tuberculosis hydrocephalus and about the presence of B waves. Sahar found ventricular pressure to be very high immediately after the induction of CSF obstruction, but declining as the acute obstructive process progressed into the chronic hydrocephalus stage [111]. Experimentally, B waves were associated with impending loss of cerebral autoregulation. The authors provoked B waves synchronously with oscillations of the pial vasculature diameter and cerebral blood volume by increasing ICP, and found that maximum oscillations occur near the limit of cerebral autoregulation a short time before total vasoparalysis, and concluded that disappearance of B waves indicated complete loss of cerebral autoregulation [10].

Schoeman et al. in a large study in children treated noncommunicating hydrocephalus by ventriculoperitoneal shunting and communicating hydrocephalus by daily administration of acetazolamide and furosemide. The response of ICP to treatment in the communicating group was assessed by means of repeated CSF pressure monitoring and CT scanning. No relationship was found between the baseline CSF pressure and the degree of hydrocephalus as demonstrated by CT scanning on admission; 75% of the patients with communicating hydrocephalus that survived the 1st month of treatment complied with the CT criteria for compensated hydrocephalus. All these patients had a baseline CSF pressure below 15 mmHg and absence of high-amplitude B waves on the pressure recording done at the end of the 1st month. In this study repeated lumbar CSF pressure monitoring proved to be an effective instrument to assess the response of communicating tuberculous hydrocephalus to medical treatment and also accurately predicted the timing of compensation of the hydrocephalus [114]. Patients with normal or slightly dilated ventricles and very high values of CSF pressure show good response to medical therapies and ventriculoperitoneal shunt may be indicated only as emergency procedure if the hydrocephalus is noncommunicating.

Correlation between ICP values and B waves reveals that a very high baseline CSF pressure and pulse pressure with absence of B waves probably reflects the more severe end of the spectrum of raised ICP in tuberculous meningitis, indicating the loss of cerebral autoregulation [114].

Treatment

Shoeman et al. proved that repeated lumbar CSF pressure monitoring in children affected by tuberculous meningitis is an effective instrument to assess the response of communicating tuberculosis hydrocephalus to medical treatment and also accurately predicts the timing of compensation of the hydrocephalus [114]. Hydrocephalus is often an early finding and may be helpful in establishing the diagnosis of CNS tuberculosis. Treatment of CNS tuberculosis should be for 12 months. Children with tuberculous meningitis should be followed up monthly [136]. If cultures remain positive for extended periods, or signs or symptoms respond slowly, treatment should be extended to 18 months. Patients with HIV also may need longer courses of therapy [24].

Patients with mass effect from their lesions are treated with an open craniotomy with partial excisional decompression and biopsy. Deep-seated lesions are sampled stereotactically, targeting both the contrast-enhancing rim and the center.

Conservative medical therapy is reserved for inaccessible or risky regions such as the brainstem. In such cases, medical therapy with careful imaging follow-up is the treatment of choice. Treatment with antituberculous medication before surgery does not mean that a negative culture will be obtained. Moreover, a tuberculoma may respond to therapy despite a negative culture [18]. Some authors have considered that antituberculous drugs should be used immediately if there is a clinical suspicion of tuberculous meningitis [16]. Despite the availability of these drugs, the morbidity remains high and mortality is up to 50% [30, 87, 90].

In patients with moderate disease, corticosteroids appear to improve neurological sequelae and survival. Dexamethasone 6-12 mg per day and prednisone 60-80 mg per day tapered over 4-8 weeks may be used. Symptoms of CNS inflammation may recur if the corticosteroid taper is implemented too soon or too fast [24]. Steroids and diuretics such as furosemide and acetazolamide are sometimes used to treat hydrocephalus [24]. Ventriculoperitoneal or ventriculoatrial shunting may be required to relieve signs and symptoms of hydrocephalus. Surgical treatment should be considered and performed early if the level of consciousness is altered, ICP is increased,

and/or hydrocephalus or a growing exudative mass is observed [30]. Lamprecht et al. in a study on 217 children with tuberculous meningitis and hydrocephalus (29.9% operated) used a protocol on the basis of which ventriculoperitoneal shunting was performed in the acute stage if the hydrocephalus was noncommunicating (58.5%) or following failed medical therapy if the hydrocephalus was communicating (41.5%) [70]. The shunted patients in this study had a high complication rate of 32.3%, with shunt infection and shunt obstruction each occurring in 13.5% of cases. Tuberculous meningitis complicated by hydrocephalus remains a devastating condition and ventriculoperitoneal shunt in these patients has a high complication rate. Identifying those patients who may be managed without shunting will save costs and reduce complications; however, early ventriculoperitoneal shunt is still indicated in patients with non-communicating hydrocephalus [70].

Particular attention must be accorded to CNS tuberculosis in patients affected by AIDS. *Mycobacterium avium-intracellulare* and, rarely, other atypical mycobacteria occur frequently in HIV-1-infected patients, often in extrapulmonary sites [104]. In one study, *M. avium-intracellulare* was the most common bacteremia observed in these patients [138]. HIV-1 infection increases the risk of meningitis with *M. tuberculosis* but does not appear to alter the clinical manifestations or response to therapy [14]. In patients with *M. avium-intracellulare* infection, single or multiple mass lesions were more than twice as common as meningitis. The CSF may on occasion be normal or acellular, further emphasizing the value of brain biopsy in establishing the diagnosis in some patients [69].

Hydrocephalus Following Cryptococcal Meningitis

Cryptococcus infection is the most common fungal infection of the CNS. More than 50% of the cases of cryptococcal infection are superimposed on an immunosuppressive or other general debilitating condition. Cerebral cryptoccosis usually presents as meningitis or meningoencephalitis, although cerebral granuloma has also been reported. Hydrocephalus is the most common neurosurgical complication of cerebral cryptoccosis. Cryptococcal disease usually develops only when CD4 helper lymphocyte counts fall below 100 cells/mm³. At this stage macrophage function is also impaired. The mean annual incidence during 1994-1997 was 6.6 cases per million people per year in Australia, and 2.2 cases per million people per year in New Zealand. C.

neoformans var. *neoformans* caused 85% of 312 episodes (98% of episodes in immunocompromised hosts) and *C. neoformans* var. *gattii* caused 15% (44% in immunocompetent hosts) [28]. The AIDS-specific incidence declined significantly over the 3 years. Mortality from cryptococcosis remains substantial.

Cryptococcal meningoencephalitis presents acutely or subacutely, can have a fulminant picture, and is consistent with progressive meningoencephalitis. Children are more likely than adults to have seizures (38% vs 11%) and normal CSF protein (67% vs. 10%) [50]. The most important differences between tuberculous and cryptococcal meningitis are: headache not accompanied by fever at the onset, failing eyesight, striking elevation of initial CSF pressure, moderate or serious degree of optic papilledema. Normal CSF protein content occurs more usually in cryptococcal than in tuberculous meningitis [144]. On the other hand, striking elevation of CSF protein content ($>2\text{ g/l}$) usually occurs in tuberculous meningitis [144]. Leptomeningeal inflammatory lesions with the characteristic capsules of *Cryptococcus* are common in the subarachnoid space. Lesions may also persist after treatment or in the absence of CSF positivity. These result in chronic meningitis or hydrocephalus by obstruction of the basal cisterns.

The diagnosis of cryptococcal meningitis is based on lumbar puncture with measurement of the opening pressure, standard laboratory assessment including cell count, protein, and glucose, fungal culture, and identification of cryptococcal polysaccharide antigen (serum cryptococcal antigen is of great diagnostic value in individuals infected with HIV).

On neuroradiological investigations the majority of patients have normal cranial CT findings when diagnosed, but repeated CT scanning shows progressive enlargement of the subarachnoid space and ventricular system [113]. MRI shows dilated Virchow-Robin (perivascular) spaces (Fig. 11a) with hyperintensity on T2-weighted images and leptomeningeal enhancement [6]. The lateral cerebral ventricles may be dilated [33,124], sometimes with cystic changes and loculations [133], and choroid plexuses may show enlargement and contrast enhancement [96, 101]. Cryptococcomas with progressive evolution, located preferentially in the basal ganglia and in the cerebral white matter, present low signal on T1-weighted images, without contrast enhancement [85] (Fig. 11b). Cerebral edema or hydrocephalus on CT scan has a poorer prognosis [127].

Patients with a history of cryptococcal meningitis may show intracranial lesions on CT and MRI that persist for more than 5 years after successful cure with antifungal drugs [53]. Persistence of lesions on neuroimaging should not be misinterpreted as evidence of active cryptococcosis [53]. Intraparenchymal lesions include enhancing masses and gelatinous pseudocysts. Gelatinous pseudocysts, also termed “soap bubble” or “unreactive type” meningoencephalitis, are collections of highly encapsulated organisms on biopsy with a limited immune response [31, 109]. Gelatinous pseudocysts are isodense or hypodense on CT scanning and do not enhance with contrast injection [101, 109]. On MRI these lesions appear as dilated perivascular spaces. Though sometimes called “cryptococcoma”, these lesions are histo-

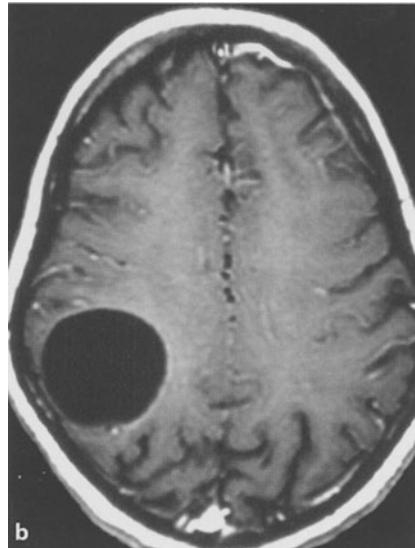
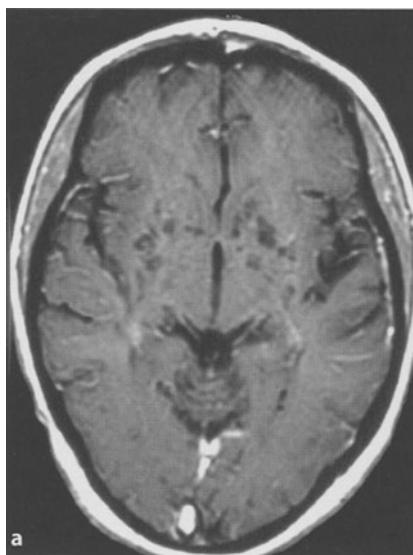


Fig. 11a, b. Nineteen-year-old girl affected by HIV infection and cryptococcal meningoencephalitis, with severe papilledema and high CSF pressure at lumbar puncture (opening pressure 40 mmHg) without hydrocephalus. MRI shows dilated perivascular Virchow-Robin spaces (a) and large parietal cryptococoma (b)

logically and radiologically more similar to dilated perivascular spaces. Differentiation of dilated perivascular spaces from pseudocysts is often based on size: lesions >3 mm visible by neuroimaging are called gelatinous pseudocysts [109]. These lesions are most commonly seen in the basal ganglia. Cerebral cryptococcosis are not unusual and occurred in 7.8% of our cases of cryptococcal meningitis [8]. Although CSF shunting proved to be of great importance in patients with demonstrable hydrocephalus, total surgical extirpation of the granuloma when demonstrated would appear to be essential [8]. Autopsy and biopsy examination of these lesions reveals them to be hard or firm on gross examination and with a granulomatous inflammatory response [45, 116]. Larger, usually more acute lesions may have a central mass containing only cryptococci [73].

Treatment

Combined drugs such as amphotericin B and 5-fluorocytosine are frequently used for the treatment. If no relapse has occurred 3 years after completion of treatment, patients are considered as cured. Smears may remain positive for years after completion of treatment, and retreatment is indicated only if cultures are positive [127].

Cryptococcus and Hydrocephalus

Raised ICP often complicates the course of cryptococcal meningitis. The pathogenesis of the severely raised CSF pressure commonly associated with this condition is largely unexplained [113]. Hydrocephalus is associated with increased morbidity and mortality in cryptococcal meningitis if left untreated. Both ventriculoperitoneal and ventriculoatrial shunting have been used in persons with cryptococcosis complicated by hydrocephalus, but the indications, complications, success, and timing of these interventions are not well known [94]. Shunting results in noticeable improvements in dementia, gait [94], papilledema, and paraparesis [125]. *Cryptococcus neoformans* invades the optic pathways both directly and by optochiasmatic arachnoiditis, resulting in visual failure [125]. Shunt placement in patients with acute infection does not disseminate cryptococcal infection into the peritoneum or bloodstream; these procedures are a safe and effective therapy for hydrocephalus in patients with cryptococcal meningitis and need not be delayed until patients are mycologically cured [94]. A low protein concentration in the CSF is a favorable indicator for surgery [125]. The active stage of cryptococcal meningitis does not contraindicate shunting,

and premedication with antifungal drugs is unnecessary [125]. Nevertheless, external ventricular drainage in the acute phase results in a lower complication rate than ventriculoperitoneal shunt [26].

Management of elevated ICP (>20 cm CSF during lumbar puncture) in patients with HIV-associated cryptococcal meningitis is different. In patients with elevated opening pressures who had focal neurological deficits or mental status changes refractory to serial lumbar puncture, management consists of immediate placement of lumbar drains for continuous drainage of CSF to maintain normal ICP (10 cm CSF). Patients with persistent elevations of spinal neuraxis pressure following lumbar drainage are candidates for the placement of lumbar peritoneal shunts. The most important predictor of early mortality is mental status at presentation; patients who present with altered mental status have up to 25% mortality [43].

Hydrocephalus in Coccidioidomycosis

Coccidioidomycosis was once confined to the southwestern United States and northern Mexico. It has become a wider concern because of the concentration of military bases in these areas, the increasing mobility of populations, and the rising population of immunocompromised persons. Outside endemic areas, the diagnosis is rarely considered [107].

Coccidioidomycosis is a highly variable disease. It is usually acquired by inhalation of *Coccidioides immitis* in certain areas of the Western hemisphere [93]. Initial respiratory tract infection can lead to self-limited pneumonia, pulmonary complications, and extrapulmonary disease, but the early infection requires no therapy except in immunosuppressed patients and other selected patients [66]. The majority of extrapulmonary disease occurs in the skin, bones and joints, or meninges and is an indication for treatment with antifungal agents and sometimes adjunctive surgery [66]. *Coccidioidal meningitis* following open head injury was reported in the literature as an unusual complication of the latter [88]. Primary traumatic cutaneous inoculation of *Coccidioides immitis* into a previously uninfected person, associated with lymphadenopathy, was also reported [141]. A recent study reported a case of recurrent coccidioidal meningitis in which a fungal biofilm on the tip of ventriculoperitoneal shunt tubing was probably responsible for a 4-year persistence of *Coccidioides immitis* despite the patient's taking an adequate dosage of fluconazole. Fungal biofilms should be considered as a cause of treatment failure and fungal persistence, especially when artificial prostheses or indwelling catheters are present [37]. Another case was

reported in which the patient developed hydrocephalus necessitating placement of a ventriculoperitoneal shunt, and in which coccidioidal meningitis was diagnosed incidentally 3 years later during an evaluation for shunt malfunction [3]. Studies performed in endemic areas suggest an association between facial cutaneous coccidioidomycosis and meningitis [7]. Cutaneous dissemination involving the face is associated with meningitis to a greater degree than that limited to the body [7].

The diagnosis is usually not difficult and can be accomplished by histopathological, cultural, and serological methods. A high ($>1:2$) titer of complement-fixing antibody in the CSF may be relevant [107]. Antibodies against a 33-kDa antigen from *Coccidioides immitis* were detected by enzyme-linked immunosorbent assay in patients' CSF [46]. Anti-33-kDa antibodies were detected at dilutions greater than 1:80 in only 1.4% of patients without coccidioidal meningitis and in 71.8% of those with meningitis [46]. The authors concluded that measurement of anti-33-kDa antibodies is a sensitive indicator of coccidioidal meningitis and of its clinical course [46].

Meningitis is a particularly serious consequence of dissemination [7, 66, 107] because patients develop occult basilar meningitis progressing to communicating hydrocephalus and death [107, 121]. Coccidioidomycosis should be considered in the differential diagnosis of occult basilar meningitis. Vasculitis complicating coccidioidal meningitis is becoming increasingly recognized, but predisposing clinical features have not been elucidated [139]. Different degrees of vasculitis have been described in the acute and chronic phases [139]. The diagnosis of vasculitis/encephalitis due to *Coccidioides immitis* infection must be based on clinical judgment, since serum antibody titers, CSF findings, and initial radiological studies are not always helpful [140].

In the early stage MRI shows ventricular dilatation, signal abnormalities, and evidence of white matter or cortical infarction. The patterns of enhancement can be focal or diffuse in the basal cisterns, sylvian fissures, or pericallosal region [41]. In the late stage, focal enhancement, ventricular dilatation, deep infarcts, intense enhancement of the cervical subarachnoid space, and interhemispheric cisterns can be observed [41, 143]. Abnormal MR enhancement decreases during treatment, although patients develop cortical and/or brainstem atrophy [143]. Communicating hydrocephalus is a common complication of untreated coccidioidal meningitis; it may develop during appropriate treatment (oral fluconazole 200-400 mg/day, continued indefinitely) and is one of the factors associated with a bad prognosis [20]. The coccidioidosis etiology must be considered in all cases of communicating hydrocephalus produced by the basilar menin-

gitis. Nonrecognition of hydrocephalus may lead to progressive disease and death. Patients with hydrocephalus and evidence of increased ICP require a shunt [107].

References

1. Abubacker M, Bosma JJD, Mallucci CL, et al: Spontaneous resolution of acute obstructive hydrocephalus in the neonate. *Child's Nerv Syst* 17:182-184, 2001
2. al-Ali HY, Yasseen SA, Raof TY: Follow-up of pregnant women with active cytomegalovirus infection. *East Mediterr Health J* 5:949-954, 1999
3. Almoujahed MO, Johnson LB, Gehring R, et al: Coccidioidal meningitis: incidental diagnosis 3 years after ventriculo-peritoneal shunt placement for hydrocephalus. *Scand J Infect Dis* 34:142-143, 2002
4. Alonso A, Alvarez A, Seara MJ, et al: Unusual manifestations of postnatally acquired cytomegalovirus infection: findings on CT and MR. *Pediatr Radiol* 26:772-774, 1996
5. Andreoni KA, Wang X, Huang SM, et al: Human CMV-IGIV (CytoGam) neutralizes human cytomegalovirus (HCMV) infectivity and prevents intracellular signal transduction after HCMV exposure. *Transpl Infect Dis* 3(Suppl 2):25-30, 2001
6. Andreula CF, Burdi N, Carella A: CNS cryptococcosis in AIDS: spectrum of MR findings. *J Comput Assist Tomogr* 17:438-441, 1993
7. Arsura EL, Kilgore WB, Caldwell JW, et al: Association between facial cutaneous coccidioidomycosis and meningitis. *West J Med* 169:13-16, 1998
8. Arumugasamy N: Intracerebral cryptococcosis. *Ann Acad Med Singapore* 14:16-21, 1985
9. Asano T, Shigeno T, Johshita H, et al: A novel concept on the pathogenetic mechanism underlying ischemic brain edema. *Acta Neurochir (Wien)*, 41(Suppl):85-94, 1987
10. Auer LM, Sayama I: Intracranial pressure oscillations (B-waves) caused by oscillations in cerebral blood volume. *Acta Neurochir (Wien)* 68:93-100, 1983
11. Bale JF Jr, Bray PF, Bell WE: Neuroradiographic abnormalities in congenital cytomegalovirus infection. *Pediatr Neurol* 1:42-47, 1985
12. Bale JF Jr, Reiley TT, Bray PF, et al: Cytomegalovirus and dual infection in infants. *Arch Neurol* 37:236-238, 1980
13. Bell WE, McGuiness GA: Suppurative central nervous system infections in the neonate. *Semin Perinatol* 6:1-24, 1982
14. Berenguer J, Moreno N, Laguna F, et al: Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med* 326:668-672, 1992
15. Bering EA, Sato O: Changes in formation and absorption of cerebrospinal fluid within the cerebral ventricles. *J Neurosurg* 20:1050-1063, 1963
16. Beøkonakli E, Cayali S, Turgut M, et al: Primary giant granulomatous basal meningitis: an unusual presentation of tuberculosis. *Child's Nerv Syst* 14:79-81, 1998
17. Black PM, Levine BW, Picard EH, et al: Asymmetrical hydrocephalus following ventriculitis from rupture of a thalamic abscess. *Surg Neurol* 19:524-527, 1983
18. Bouchama A, Al-Kawi MZ, Kanaan I, et al: Brain biopsy in tuberculoma: the risks and benefits. *Neurosurgery* 28: 405-409, 1991

19. Bourgouin PM, Melancon D, Carpenter S, et al: Hydrocephalus and prominence of the choroid plexus: an unusual computed tomographic presentation of cerebral toxoplasmosis in AIDS. *Can Assoc Radiol J* 43:55-59, 1992
20. Bouza E, Dreyer JS, Hewitt WL, et al: Coccidioidal meningitis. An analysis of thirty-one cases and review of the literature. *Medicine (Baltimore)* 60:139-172, 1981
21. Bray PF, Bale JE, Anderson RE, et al: Progressive neurological disease associated with chronic cytomegalovirus infection. *Ann Neurol* 9:499-502, 1981
22. Britt RH: Brain abscess. In: Wilkins RH, Rengachary SS (eds) *Neurosurgery*. McGraw-Hill, New York, pp 1928-1956, 1985
23. Brogi E, Cibas ES: Cytologic detection of *Toxoplasma gondii* tachyzoites in cerebrospinal fluid. *Am J Clin Pathol* 114:951-955, 2000
24. Byrd T, Zinszer P: Tuberculosis meningitis. *Curr Treat Options Neurol* 3:427-432, 2001
25. Cardia E, Molina D, Abbate F, et al: Morphological modifications of the choroid plexus in a rodent model of acute ventriculitis induced by gram-negative liquor sepsis. Possible implications in the pathophysiology of hypersecretory hydrocephalus. *Child's Nerv Syst* 11:511-516, 1995
26. Chan KH, Mann KS, Yue CP: Neurosurgical aspects of cerebral cryptococcosis. *Neurosurgery* 25:44-48, 1989
27. Chang Chien HY, Chiu NC, Li WC, et al: Characteristics of neonatal bacterial meningitis in a teaching hospital in Taiwan from 1984-1997. *J Microbiol Immunol Infect* 33:100-104, 2000
28. Chen SC: Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother* 49(Suppl A): 57-61, 2002
29. Cinalli G, Sainte-Rose C, Chumas P, et al: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90:448-454, 1999
30. Clark C, Metcalf JC, Muhlbauer MS, et al: Mycobacterium tuberculosis meningitis: a report of twelve cases and a literature review. *Neurosurgery* 18:604-610, 1986
31. Coenjaerts FE, Walenkamp AM, Mwinzi PN, et al: Potent inhibition of neutrophil migration by cryptococcal mannoprotein-4-induced desensitization. *J Immunol* 167:3988-3995, 2001
32. Conover PT, Roessmann U: Malformational complex in an infant with intrauterine influenza viral infection. *Arch Pathol Lab Med* 114:535-538, 1990
33. Cornell SH, Jacoby CG: The varied computed tomographic appearance of intracranial cryptococcosis. *Radiology* 143:703-707, 1982
34. Cotté F, Carpentier MA, Descamps P, et al: Congenital toxoplasmosis with hydrocephalus diagnosed in utero: outcome of treatment. *Arch Pediatr* 4:247-250, 1997
35. Couvreur J, Desmonts G: Toxoplasmosis. In: Vinken PJ, Bruyn GW (eds) *Handbook of clinical neurology*, vol 35. North Holland, Amsterdam, pp 115-141, 1978
36. Daoud AS, Omari H, al-Sheyyab M, et al: Indications and benefits of computed tomography in childhood bacterial meningitis. *J Trop Pediatr* 44:167-169, 1998
37. Davis LE, Cook G, Costerton JW: Biofilm on ventriculo-peritoneal shunt tubing as a cause of treatment failure in coccidioidal meningitis. *Emerg Infect Dis* 8:376-379, 2002
38. Detwiler PW, Porter RW, Rekate HL: Hydrocephalus-clinical features and management. In: Choux M, Di Rocco C, Hockley AD, Walker LM (eds) *Pediatric neurosurgery*. Churchill Livingstone, London Edinburgh New York, pp 253-272, 1999
39. Doctor BA, Newman N, Minich NM, et al: Clinical outcomes of neonatal meningitis in very-low birth-weight infant. *Clin Pediatr (Phila)* 40:473-480, 2001
40. Doherty RL, Jordan MC: Viral meningoencephalitis. In: Hoeprich PD, Jordan MC (eds) *Infectious diseases*, 4th edn. Lippincott, Philadelphia, pp 1098-1108, 1989
41. Erly WK, Bellon RJ, Seeger JF, et al: MR imaging of acute coccidioidal meningitis. *AJR Am J Neuroradiol* 20:509-514, 1999
42. Falangola MF, Petito CK: Choroid plexus infection in cerebral toxoplasmosis in AIDS patients. *Neurology* 43:2035-2040, 1993
43. Fessler RD, Sobel J, Guyot L, et al: Management of elevated intracranial pressure in patients with cryptococcal meningitis. *J Acquir Immune Defic Syndr Hum Retrovirol* 17:137-142, 1998
44. Foulon W, Naessens A, Ho-Yen D: Prevention of congenital toxoplasmosis. *J Perinat Med* 28:337-45, 2000
45. Fujita NK, Reynard M, Sapico FL, et al: Cryptococcal intracerebral mass lesions: the role of computed tomography and nonsurgical management. *Ann Intern Med* 94:382-388, 1981
46. Galgiani JN, Peng T, Lewis ML, et al: Cerebrospinal fluid antibodies detected by ELISA against a 33-kDa antigen from spherules of *Coccidioides immitis* in patients with coccidioidal meningitis. The National Institute of Allergy and Infectious Diseases Mycoses Study Group. *J Infect Dis* 173:499-502, 1996
47. Gagne SS: Toxoplasmosis. *Prim Care Update Ob Gyns* 8:122-126, 2001
48. Gomes I, Melo A, Lucena R, et al: Prognosis of bacterial meningitis in children. *Arq Neuropsiquiatr* 54:407-411, 1996
49. Gonsu-Fotsin J, Kago I, Dzogang MT, et al: Cerebral complications of purulent meningitis in children assessed by transfontanellar ultrasonography in Yaounde (Cameroon). *Ann Radiol (Paris)* 33:195-199, 1990
50. Gumbo T, Kadzirange G, Mielke J, et al: Cryptococcus neoformans meningoencephalitis in African children with acquired immunodeficiency syndrome. *Pediatr Infect Dis J* 21:54-56, 2002
51. Harvey D, Holt DE, Bedford H: Bacterial meningitis in the newborn: a prospective study of mortality and morbidity. *Semin Perinatol* 23: 218-225, 1999
52. Hayward JC, Titelbaum DS, Clancy RR, et al: Lissencephaly-pachygryria associated with congenital cytomegalovirus infection. *Child Neurol* 6:109-114, 1991
53. Hospenthal DR, Bennett JE: Persistence of cryptococcosis on neuroimaging. *Clin Infect Dis* 31:1303-1306, 2000
54. Hower J, Clar HE, Ducthing M: Mumps as a cause of hydrocephalus. *Pediatrics* 50: 346-347, 1972
55. Incesu L, Akan H, Arslan A: Neonatal cerebral candidiasis: CT findings and clinical correlation. *J Belge Radiol* 77:278-279, 1994
56. Jellinger G: Anatomopathology of nontumoral aqueductal stenosis. *J Neurosurg Sci* 30: 1-16, 1986
57. Jenkins JR: Computed tomography of intracranial tuberculosis. *Neuroradiology* 33:126-135, 1991
58. Jordan C, Hoeprich PD, Jordan MC: *Infectious diseases*, 4th edn. Lippincott, Philadelphia, pp 805-811, 1989

59. Juster-Reicher A, Leibovitz E, Linder N, et al: Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. *Infection* 28:223-226, 2000
60. Kaiser G: Hydrocephalus following toxoplasmosis. *Z Kinderchir* 40(Suppl 1):10-11, 1985
61. Kalsbeck JE, DeSousa AL, Kleiman MB, et al: Compartmentalization of the cerebral ventricles as a sequela of neonatal meningitis. *J Neurosurg* 52:547-552, 1980
62. Katrak SM, Shembalkar PK, Bijwe SR, et al: The clinical, radiological and pathological profile of tuberculous meningitis in patients with and without human immunodeficiency virus infection. *J Neurol Sci* 181(1-2):118-126, 2000
63. Kilham L, Margolis G: Encephalitis in suckling rats induced with rat cytomegalovirus. *Lab Invest* 33:200-206, 1975
64. Kilham L, Margolis G: Induction of congenital hydrocephalus in hamsters with attenuated and natural strains of mumps virus. *J Infect Dis* 132:462-466, 1975
65. Klinger G, Chin CN, Beyene J, et al: Predicting the outcome of neonatal bacterial meningitis. *Pediatrics* 106: 477-482, 2000
66. Knoper SR, Galgiani JN: Systemic fungal infections: diagnosis and treatment. I. Coccidioidomycosis. *Infect Dis Clin North Am* 2:861-875, 1988
67. Lagace-Simard J, Descoteaux JP, Lussier G: Experimental pneumovirus infections: 1. Hydrocephalus of mice due to infection with pneumonia virus of mice (PVM). *Am J Pathol* 101:31-40, 1980
68. Lagace-Simard J, Descoteaux JP, Lussier G: Experimental pneumovirus infections. 2. Hydrocephalus of hamsters and mice due to infection with human respiratory syncytial virus (RS). *Am J Pathol* 107:36-40, 1982
69. Laguna F, Adrados M, Ortega A, et al: Tuberculous meningitis with acellular cerebrospinal fluid in acquired immune deficiency syndrome patients. *AIDS* 6:1165-1167, 1992
70. Lamprecht H, Schoeman J, Donald P: Ventriculoperitoneal shunting in childhood tuberculous meningitis. *Br J Neurosurg* 15:119-125, 2001
71. Lapierre J, Tourte-Schaefer C, Heyer F, et al: Congenital toxoplasmosis. Remarks apropos of serologic surveillance in 15,000 pregnant women. *Sem Hop* 59:2741-2745, 1983
72. Lawrence RM: Extrapulmonary tuberculosis In: Hoeprich PD, Jordan MC (eds) *Infectious diseases*, 4th edn. Lippincott, Philadelphia, pp 435-440, 1989
73. Lee SC, Dickson DW, Casadevall A: Pathology of cryptococcal meningoencephalitis: analysis of 27 patients with pathogenic implications. *Hum Pathol* 27:839-847, 1996
74. Lee WS, Puthucheary SD, Omar A: *Salmonella* meningitis and its complications in infants. *J Paediatr Child Health* 35(4):379-382, 1999
75. Luft BJ, Remington JS: Toxoplasmosis. In: Hoeprich PD, Jordan MC (eds) *Infectious diseases*, 4th edn. Lippincott, Philadelphia, pp 1199-1214, 1989
76. Mangham D, Gerdin DN, Peterson LR, et al: Fungal meningitis manifesting as hydrocephalus. *Arch Intern Med* 143:728-731, 1983
77. Manz HJ, Schuelein M, McCullough DC, et al: New phenotypic variant of adrenoleukodystrophy. Pathologic, ultrastructural, and biochemical study in two brothers. *J Neurol Sci* 45:245-260, 1980
78. Mathai KV, Chandy J: Tuberculous infections of the nervous system. *Clin Neurosurg* 14:145-177, 1967
79. Matsumoto N, Yano S, Miyao M, et al: Two-dimensional ultrasonography of the brain: its diagnostic usefulness in herpes simplex encephalitis and cytomegalic inclusion disease. *Brain Dev* 5:327-33, 1983
80. McAuley J, Boyer KM, Patel D, et al: Early and longitudinal evaluations of treated infants and children and untreated historical patients with congenital toxoplasmosis: the Chicago Collaborative Treatment Trial. *Clin Infect Dis* 18:38-72, 1994
81. McGrath N, Anderson NE, Croxson MC, et al: Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry* 63:321-326, 1997
82. McLoone DG, Naidich TP, Cunningham T: Posterior fossa cysts: management and outcome. *Concepts Pediatr Neurosurg* 7:134-141, 1987
83. Meenken C, Assies J, van Nieuwenhuizen O, et al: Long term ocular and neurological involvement in severe congenital toxoplasmosis. *Br J Ophthalmol* 79:581-584, 1995
84. Misra UK, Kalita J, Das BK: Single photon emission computed tomography in tuberculous meningitis. *Postgrad Med J* 76:642-645, 2000
85. Miszkiel KA, Hall-Craggs MA, Miller RF: The spectrum of MRI findings in CNS cryptococcosis in AIDS. *Clin Radiol* 51:842-850, 1996
86. Mizuno Y, Takada H, Urakami K, et al: Neurotrophin-3 levels in cerebrospinal fluid from children with bacterial meningitis, viral meningitis, or encephalitis. *J Child Neurol* 15:19-21, 2000
87. Molavi A, LeFrock JL: Tuberculous meningitis. *Med Clin North Am* 69:315-331, 1985
88. Morwood DT, Nicther LS, Wong V: An unusual complication of an open-head injury: coccidioidal meningitis. *Ann Plast Surg* 23:437-441, 1989
89. Ogata H, Oka K, Mitsudome A: Hydrocephalus due to acute aqueductal stenosis following mumps infection: report of a case and review of the literature. *Brain Dev* 14:417-419, 1992
90. Ogawa SK, Smith MA, Brennessel DJ, et al: Tuberculous meningitis in an urban medical center. *Medicine* 66:317-325, 1987
91. Okubo T, Shirane R, Mashiyama S: *Proteus mirabilis* brain abscess in a neonate. *No Shinkei Geka* 12(3 Suppl):395-400, 1984
92. Oversturf GD: Bacterial Meningitis, In: Hoeprich PD, Jordan MC(eds) *Infectious diseases*, 4th edn. Lippincott, Philadelphia, pp 1114-1132, 1989
93. Pappagianis D: Coccidioidomycosis. *Semin Dermatol* 12:301-309, 1993
94. Park MK, Hosenthal DR, Bennett JE: Treatment of hydrocephalus secondary to cryptococcal meningitis by use of shunting. *Clin Infect Dis* 28:629-633, 1999
95. Parrent AG: Endoscopically guided fenestration of the choroidal fissure for treatment of trapped temporal horn. *J Neurosurg* 93:891-894, 2000
96. Perlman JM, Argyle C: Lethal cytomegalovirus infection in preterm infants: clinical, radiological, and neuropathological findings. *Ann Neurol* 31:64-68, 1992
97. Plantaz D, Joannard A, Pasquier B, et al: Hydranencephaly and congenital toxoplasmosis. Apropos of 4 cases. *Pediatrie* 42:161-165, 1987

99. Pohl CA: Practical approach to bacterial meningitis in childhood. *Am Fam Physician* 15:47:1595-1603, 1993
100. Pong A, Bradley JS: Bacterial meningitis and the newborn infant. *Infect Dis Clin North Am* 13:711-733, 1999
101. Popovich MJ, Arthur RH, Helmer E: CT of intracranial cryptococcosis. *AJNR Am J Neuroradiol* 11:139-142, 1990
102. Post MJ, Hensley GT, Moskowitz LB, et al: Cytomegalic inclusion virus encephalitis in patients with AIDS: CT, clinical, and pathologic correlation. *AJR Am J Roentgenol* 146:1229-1234, 1986
103. Prats JM, Lopez-Heredia J, Gener B, et al: Multilocular hydrocephalus: ultrasound studies of origin and development. *Pediatr Neurol* 24:149-151, 2001
104. Pumarola-Sune T, Navia BA, Cardon-Cardo C, et al: Human immunodeficiency virus type 1 antigen in the brains of patients with acquired immune deficiency syndrome-dementia complex. *Ann Neurol* 21:490-496, 1987
105. Punt J: Principles of CSF diversion and alternative treatments. In: Schurr PH, Polkey CE (eds) *Hydrocephalus*. Oxford Medical Publications, Oxford, pp 139-160, 1993
106. Renier D, Flandin C, Hirsch E, et al: Brain abscesses in neonates. A study of 30 cases. *J Neurosurg* 69:877-882, 1988
107. Romeo JH, Rice LB, McQuarrie IG: Hydrocephalus in coccidioidal meningitis: case report and review of the literature. *Neurosurgery* 47:773-777, 2000
108. Rotilio A, Salar G, Dollo C, et al: Aqueductal stenosis following mumps infection. Case report. *Ital J Neurol Sci* 6: 237-239, 1985
109. Ruiz A, Post MJD, Bundschu CC: Dentate nuclei involvement in AIDS patients with CNS cryptococcosis: imaging findings with pathologic correlation. *J Comput Assist Tomogr* 21:175-182, 1997
110. Russell DS: Observations on the pathology of hydrocephalus. Medical Res Council, special report series No. 265. His Majesty's Stationery Office, London, 1949
111. Sahar A: Experimental progressive hydrocephalus in the young animal. *Child's Brain* 5: 14-23, 1979
112. Sarnat HB: Ependymal reactions to injury. A review. *J Neuropathol Exp Neurol* 54:1-15, 1995
113. Schoeman JF, Honey EM, Loock DB: Raised ICP in a child with cryptococcal meningitis: CT evidence of a distal CSF block. *Child's Nerv Syst* 12:568-571, 1996
114. Schoeman JF, Laubscher JA, Donald PR: Serial lumbar CSF pressure measurements and cranial computed tomographic findings in childhood tuberculous meningitis. *Child's Nerv Syst* 16:203-209, 2000
115. Seidman DS, Nass D, Mendelson E, et al: Prenatal ultrasonographic diagnosis of fetal hydrocephalus due to infection with parainfluenza virus type 3. *Ultrasound Obstet Gynecol* 7:52-54, 1996
116. Selby RC, Lopes NM: Torulomas (cryptococcal granulomata) of the central nervous system. *J Neurosurg* 38:40-46, 1973
117. Senat MV, Bernard JP, Schwarzler P, et al: Prenatal diagnosis and follow-up of 14 cases of unilateral ventriculomegaly. *Ultrasound Obstet Gynecol* 14:327-332, 1999
118. Sharma R, Bahl L, Goyal A, et al: Congenital cytomegalovirus infection in Shimla Hills, Himachal Pradesh, India. *J Commun Dis* 27:23-26, 1995
119. Sharp NJ, Davis BJ, Guy JS, et al: Hydranencephaly and cerebellar hypoplasia in two kittens attributed to intrauterine parvovirus infection. *J Comp Pathol* 121:39-53, 1999
120. Stahl W, Kaneda Y: Pathogenesis of murine toxoplasmic hydrocephalus. *Parasitology* 114 (Pt 3):219-229, 1997
121. Stevens DA, Shatsky SA: Intrathecal amphotericin in the management of coccidioidal meningitis. *Semin Respir Infect* 16:263-269, 2001
122. Takano T, Mekata Y, Yamano T, et al: Early ependymal changes in experimental hydrocephalus after mumps virus inoculation in hamsters. *Acta Neuropathol (Berl)* 85:521-525, 1993
123. Takano T, Takikita S, Shimada M: Experimental mumps virus-induced hydrocephalus: viral neurotropism and neuronal maturity. *Neuroreport* 10:2215-2221, 1999
124. Tan CT, Kuan BB: Cryptococcus meningitis, clinical: CT scan considerations. *Neuroradiology* 29:43-46, 1987
125. Tang LM: Ventriculoperitoneal shunt in cryptococcal meningitis with hydrocephalus. *Surg Neurol* 33:314-319, 1990
126. Temperton NJ: DNA vaccines against cytomegalovirus: current progress. *Int J Antimicrob Agents* 19:169-172, 2002
127. Tjia TL, Yeow YK, Tan CB: Cryptococcal meningitis. *J Neurol Neurosurg Psychiatry* 48:853-858, 1985
128. Treseler CB, Sugar AM: Fungal meningitis. *Infect Dis Clin North Am* 4:789-808, 1990
129. Tsunoda I, McCright IJ, Kuang LQ, et al: Hydrocephalus in mice infected with a Theiler's murine encephalomyelitis virus variant. *J Neuropathol Exp Neurol* 56:1302-1313, 1997
130. Ulbrzych-Jablonska A, Kalenik J: Role of toxoplasmosis in the development of central nervous system lesions in children [in German]. *Zentralbl Neurochir* 41:31-36, 1980
131. Uno M, Takano T, Yamano T, et al: Age-dependent susceptibility in mumps-associated hydrocephalus: neuropathologic features and brain barriers. *Acta Neuropathol (Berl)* 94:207-215, 1997
132. Uysal G, Kose G, Guven A, et al: Magnetic resonance imaging in diagnosis of childhood central nervous system tuberculosis. *Infection* 29:148-153, 2001
133. Vender JR, Miller DM, Roth T, et al: Intraventricular cryptococcal cysts. *AJNR Am J Neuroradiol* 17:110-113, 1996
134. Viola L, Chiaretti A, Castorina M, et al: Acute hydrocephalus as a consequence of mumps meningoencephalitis. *Pediatr Emerg Care* 14:212-214, 1998
135. Volpe JJ: Bacterial and fungal intracranial infections. In: Volpe JJ (ed) *Neurology of the newborn*, 4th edn. Saunders, Philadelphia, pp 774-810, 2001
136. Waacker NJ: Tuberculous meningitis in children. *Curr Treat Options Neurol* 4:249-257, 2002
137. Weber F: The cerebral lesions in congenital toxoplasmosis. Study of 9 personal cases and 61 cases in the literature. *Helv Paediatr Acta Suppl* 48:1-51, 1983
138. Whimbey E, Gold JWM, Polksky B, et al: Bacteremia and fungemia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 10:511-514, 1986
139. Williams PL: Vasculitic complications associated with coccidioidal meningitis. *Semin Respir Infect* 16:270-279, 2001
140. Williams PL, Johnson R, Pappagianis D, et al: Vasculitic and encephalitic complications associated with *Coccidioides immitis* infection of the central nervous system in humans: report of 10 cases and review. *Clin Infect Dis* 14:673-68, 1992

141. Winn WA: Primary cutaneous coccidioidomycosis. Reevaluation of its potentiality based on study of three new cases. *Arch Dermatol* 92:221-228, 1965
142. Wolinsky JS: Mumps virus-induced hydrocephalus in hamsters. Ultrastructure of the chronic infection. *Lab Invest* 37:229-36, 1977
143. Wrobel CJ, Meyer S, Johnson RH, et al: MR findings in acute and chronic coccidioidomycosis meningitis. *AJNR Am J Neuroradiol* 13:1241-1245, 1992
144. Xie D, Cao H, Yu H: Differential diagnosis in patients with tuberculous meningitis and cryptococcal meningitis [in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi* 22:731-733, 1999

Multiloculated Hydrocephalus

PIETRO SPENNATO¹, GIUSEPPE CINALLI², GIUSEPPE CARANNANTE³, CLAUDIO RUGGIERO² AND MARIA LAURA DEL BASSO DE CARO⁴

Introduction

The presence of compartmentalization inside the ventricular system makes the management of hydrocephalus very challenging. Despite the existence of several therapeutic options, which include multiple shunt insertion, stereotactic aspiration, membrane puncture with a multiperforated catheter, and microsurgical or endoscopic fenestration, multiloculated hydrocephalus still remains associated with poor outcome [10, 29, 30, 69].

Multiloculated hydrocephalus was difficult to recognize in the pre-CT area. The poor specificity of the symptoms, which resemble those of shunt malfunction, often led neurosurgeons to perform multiple shunt revisions without repeating the invasive diagnostic studies then available. Moreover, ventriculography, requiring to document the presence of noncommunicating cavities, required multiple ventricular puncture. Salmon [66] in 1970 suggested that the condition was under-recognized rather than rare, and that “it should be considered when the patient’s head continues to enlarge despite a functioning shunt”.

Nowadays the real incidence of multiloculated hydrocephalus is still unknown, but (although few series are reported in the literature), given the increasing survival of children who suffer neonatal meningitis or intraventricular hemorrhage (the two major etiological factors), it is not likely to be negligible. The estimated incidence of hydrocephalus in infants who survive neonatal meningitis is greater than 30% [40]. All these children are at risk of developing ventricular compartmentalization. Reinprecht et al. [62], reviewing the long-term follow-up of infants affected by posthemorrhagic

hydrocephalus, calculated that compartmentalization occurred in 7% of cases. Cipri and Gambardella [13] calculated that multiloculated hydrocephalus occurred in 20% of hydrocephalic patients under 3 years of age admitted to their department. Thus, multiloculated hydrocephalus represents a significant proportion of hydrocephalus in the continuing care of pediatric cases, accounting for 13% of the patients with hydrocephalus treated endoscopically in the series of Lewis et al. [38] and 21% in our series.

Definition and Classification

The term “multiloculated hydrocephalus” refers to the presence of an isolated CSF compartment or compartments within the ventricular system that may progressively enlarge despite a functioning shunt system. The presence of intraventricular septations or obstructions between the site of CSF production and the tip of the ventricular catheter may obstruct the CSF flow, leading to accumulation of fluid in the compartment.

The anatomic and radiographic appearance of multiloculated hydrocephalus varies on the basis of the site of the obstruction or obstructions and the subsequent accumulation of fluid, and can be classified as follows: (1) multiple intraventricular septations; (2) isolated lateral ventricle/unilateral hydrocephalus; (3) entrapped temporal horn; (4) isolated fourth ventricle; and (5) expanding cavum septi pellucidi/cavum vergae (Fig. 1a-g). The peculiarities of each form of multiloculated hydrocephalus will be discussed in the various sections below.

¹ Department of Neurosurgery, Second University of Naples; ² Department of Pediatric Neurosurgery and ³ Department of Pediatric Neuroradiology, Santobono-Pausilipon Children’s Hospital, Naples; ⁴ Department of Biomorphological and Functional Sciences, Section of Pathology, Federico II University of Naples, Italy

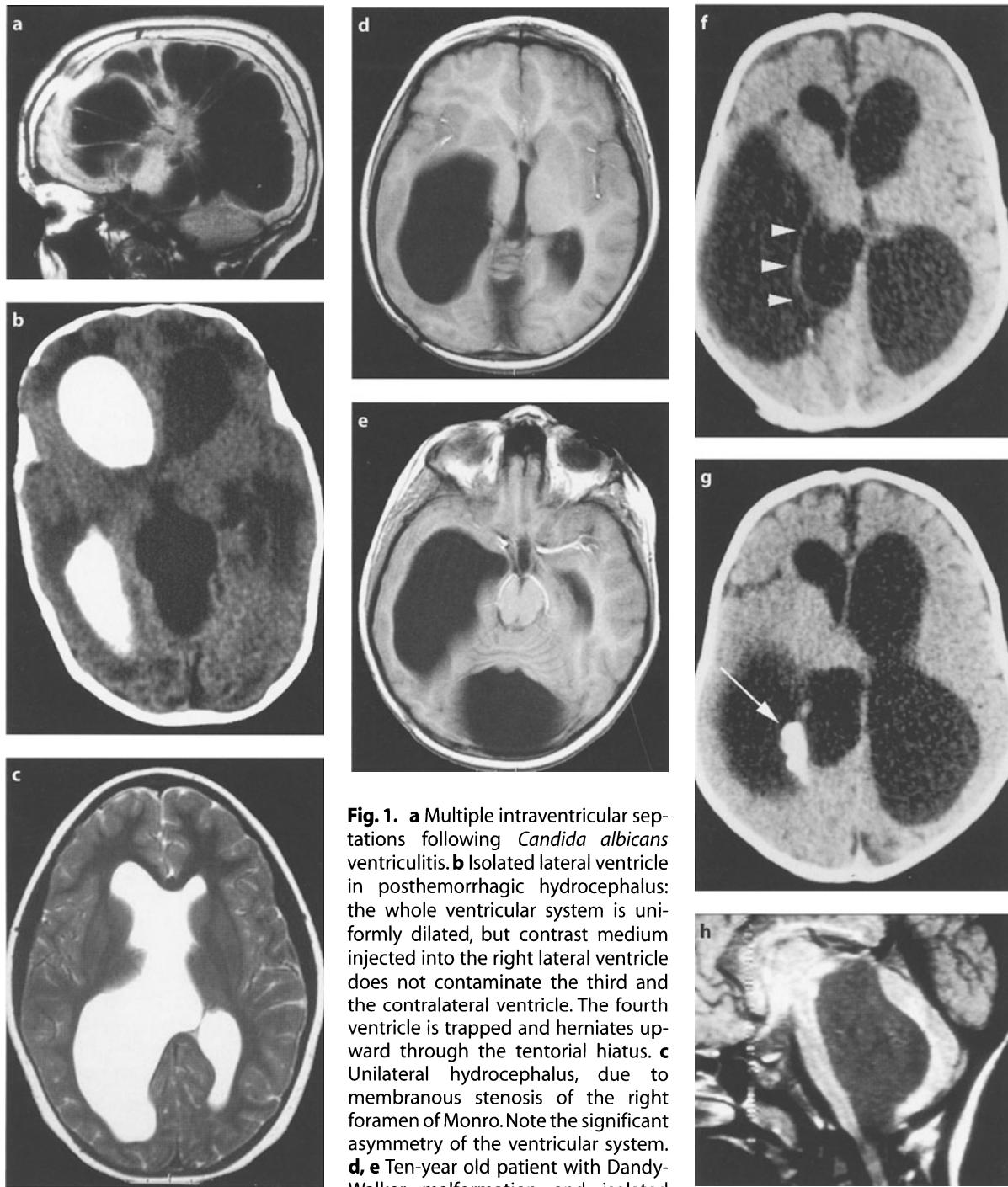


Fig. 1. **a** Multiple intraventricular separations following *Candida albicans* ventriculitis. **b** Isolated lateral ventricle in posthemorrhagic hydrocephalus: the whole ventricular system is uniformly dilated, but contrast medium injected into the right lateral ventricle does not contaminate the third and the contralateral ventricle. The fourth ventricle is trapped and herniates upward through the tentorial hiatus. **c** Unilateral hydrocephalus, due to membranous stenosis of the right foramen of Monro. Note the significant asymmetry of the ventricular system. **d, e** Ten-year old patient with Dandy-Walker malformation and isolated temporal horn following repeated

shunt infections. **f, g** Premature baby with neonatal asphyxia and intraventricular hemorrhage. The right temporo-occipital horn is extremely dilated, separated by the remaining ventricular system by a thick septum (arrowheads in **f**) originating from the choroid plexus hematoma with dense calcifications (arrow in **g**). **h** Isolated fourth ventricle

Etiology and Pathogenesis

Multiloculated hydrocephalus is traditionally attributed mostly to insults occurring during the neonatal

period, such as intraventricular hemorrhage and neonatal meningitis. However, other conditions may also play important roles as etiological factors: shunt-related infection [29, 49], overdrainage [52, 53], direct ependymal trauma during catheter insertion [22],

head injury [1], and intracranial surgery [41]. The common link between these conditions is the resultant ventriculitis [49]. Ventricular septations develop after an average of 2–4 months following ventriculitis [1, 29, 30]. Compartmentalization is a progressive disease with new septa appearing until the ventricular pattern gradually becomes unrecognizable and the cerebral mantle encloses a single, large, multiloculated cavity [1]. The progressive dilatation of the loculated cavities may be secondary to CSF production inside the isolated compartment or to CSF entrapment by a valve mechanism; further formation of inflammatory exudates [10] (in the case of postmeningitic hydrocephalus) or an osmotic gradient caused by lysis of clotted blood (in the case of posthemorrhagic hydrocephalus) may contribute to the enlargement. Actually some loculated cysts may remain unchanged in size without shunting: this is because the lining membrane may be permeable [30] or the CSF production may be reduced in consequence of the effect of ventriculitis on the choroid plexus [9, 29].

Schellinger et al. [67] have observed spontaneous disappearance or partial resolution of isolated cavities. They believe that ventricular enlargement may cause stretching and rupture of the septa, creating spontaneous fenestration.

Ventriculitis

Neonatal meningitis, first recognized as an etiological factor of multiloculated hydrocephalus by Salmon [66] in 1970 and subsequently reviewed by Kalsbeck et al. [30], is associated with ventriculitis in 75%–92% of cases [7, 66]. The pathogenesis of ventriculitis appears to be related to the lowered host resistance of the neonate and the virulence of the organism, which in most cases is a gram-negative bacterial agent (see Chap. 15, p. 206) [1, 29, 30]. The occurrence of direct hematogenous spread to the choroid plexus has also been hypothesized [7]. Hydrocephalus develops in more than 30% of patients who survive [40]: obstructions at the aqueduct of Sylvius, at the outlet foramina of the fourth ventricle, or in the subarachnoid spaces are common findings [69]. Moreover, the inflammation of the ependyma may encourage the proliferation of the subependymal glia, upon which exudates and debris may organize and form fibroglial webs. The destruction of the ependyma allows glia to project into the lumen, bridging and obstructing crucial areas (atria of the lateral ventricles, interventricular foramina, aqueduct, foramina of Luschka and Magendie) and serving as a nidus for the formation of intraventricular septations [10, 29, 69]. The septations alter the ventricular anatomy and CSF flow pattern.

Ventriculitis, a condition associated with high mortality and morbidity, may become even more difficult to eradicate with the appearance of compartmentalization, because of the impaired diffusion of leukocytes and antibiotics in the ventricular system. The role in the development of septa played by intraventricular antibiotic therapy administered before the compartmentalization, and the role of elevated fluid protein concentration, are still under debate, but they do not seem to be significant [1, 29, 30, 69]. Several factors such as premature birth, perinatal complications, and congenital CNS malformations are associated with multiloculated hydrocephalus, probably because they predispose to bacterial meningitis [1].

Intraventricular Hemorrhage

In recent years multiloculated hydrocephalus has been more frequently associated with neonatal intraventricular hemorrhage. This etiology was first recognized by Eller and Pasternak [22] in 1985. They described a case of acute unilateral ventricular dilatation caused by pieces of clot or other debris that directly obstructed the foramen of Monro, and a case of delayed isolated lateral ventricle caused by chronic inflammation of the ependyma and subsequent formation of ependymal flaps and membranes, with the same mechanism as described for postmeningitic multiloculated hydrocephalus (Fig. 1e, f). Posthemorrhagic hydrocephalus in the premature population is typically associated with a high incidence of loculation, especially of isolated fourth ventricle.

Shunt Infection

Shunt infection with the resultant ventriculitis can result in ventricular septations and closure of the foramen of Monro, of the aqueduct, and of the outlet foramina of the fourth ventricle, but this complication of shunt infection is fortunately rare [20]. Jamjoon et al. [29] found that most of their patients who developed multiloculated hydrocephalus after shunt infection had other predisposing factors (intraventricular hemorrhage or neonatal meningitis as the initial cause of the hydrocephalus). On this basis they doubted that shunt infection could be the sole etiological factor, but they emphasized its role as a contributing factor in the origin or progression of the loculations. These data agree with those of Nida and Haines [49]: they suggested that the pathological process could become quicker after shunt infection, often requiring more aggressive treatment. At all events, shunt infection is a common finding in pa-

tients with multiloculated hydrocephalus, and the presence of loculations prevents the diffusion of intrathecally administered antibiotics, creating bacterial reservoirs inside the isolated compartments. Thus the management of the initial ventriculitis and of CSF infection is very problematic [44]. Multiloculated hydrocephalus should be regarded as a condition that predisposes to persistent and recurrent shunt infection [30].

Repeated Shunt Surgery

Shunt placement may also be related to compartmentalization via other mechanisms than shunt infection. Direct ependymal trauma during catheter insertion may potentially contribute to loculation [22, 30, 34]. Kuiper and Vandertop [34] reported bilateral obliteration of the foramina of Monro as a consequence of direct irritation and mechanical erosion during shunt insertions and revisions. Salmon [66] first observed that the mass effect of a loculated CSF collection and midline shift were encouraged by drainage of CSF through a functioning shunt. Several authors [29, 52] have since investigated the role played by overdrainage. Oi et al. [52–55] observed that the isolation of the compartment after shunt placement was closely related to the slit-like ventricle. Obstruction at the foramen of Monro (see Chap. 23, p. 336) or at the aqueduct may occur in a previously communicating ventricular system after reduction of the size of all ventricles subsequent to shunt insertion and overdrainage: isolation gradually develops, leading to re-enlargement of the isolated compartment. Eller and Pasternak [22] also suggested that overdrainage of CSF might result in unilateral ventricular collapse or in obstruction of the aqueduct. Children with Chiari II malformation and myelomeningocele, because of anomalies of the ventricular system and of foramina of Monro which are distorted and narrowed [12], are predisposed, if overdrainage occurs, to develop torsion and occlusion of the foramen of Monro ipsilateral to the shunt, resulting in isolation of the contralateral and third ventricles [6]. Ventricular compartmentalization may interfere with the drainage of the dilated ventricular system, resulting in mechanical shunt malfunction [30, 49] and multiple shunt revisions. Shunt failure is caused by collapse of shunted compartment around the catheter tip and subsequent occlusion of the shunt openings by proliferated fibrillary astrocytes [38, 67]. Moreover, embedded ventricular catheter that cannot be removed without the risk of intraventricular hemorrhage may serve as a nidus for infection and contribute to cyst formation [38].

Tumor Surgery

Multiloculated hydrocephalus has been reported to occur as a consequence of tumor removal in children and adults [41]. Marquadt et al. [41] observed that hydrocephalus developing after resection of supratentorial malignant gliomas was associated with ventricular entry during surgery. Protein precipitation and deposition over the cerebral hemispheres may cause communicating hydrocephalus due to malabsorption of CSF through arachnoid granulations; intraventricular precipitation and deposition may act as a chemical irritant leading to denudation and glial proliferation with formation of thin veils or septa and isolation of compartments.

Congenital

Intraventricular septations rarely occur at birth. Congenital septa may be caused by developmental error [64, 67], often associated with other CNS or systemic anomalies, or may be the consequence of an intrauterine inflammatory process, such as congenital toxoplasmosis or cytomegalovirus infection [67]. Bauman et al. [4] have described obstruction of a foramen of Monro in a case of intrauterine mumps ependymitis.

Periventricular Leukomalacia

Intraventricular septa may originate outside the ventricles in the periventricular territories that later become ventricularized (pseudosepta) [67]. They have been found in neonates with cystic periventricular leukomalacia and cystic encephalopathies [67]. These cystic lesions may enlarge, become confluent, and form uni- or multicompartmental cavities separated from the lateral ventricles only by ependymal or gliotic tissue (Fig. 2). After disruption and fragmentation of the dividing ependyma, extraventricular septa are converted into intraventricular septa. Like true septa, they may alter ventricular anatomy and the CSF pathway. Only serial observations during their development may be useful in differentiating pseudosepta from true septa [67]. However, because of their association with intraventricular hemorrhage and cerebral infarction – a common complication of the vasculitis caused by neonatal meningitis – true septa and pseudosepta may coexist.

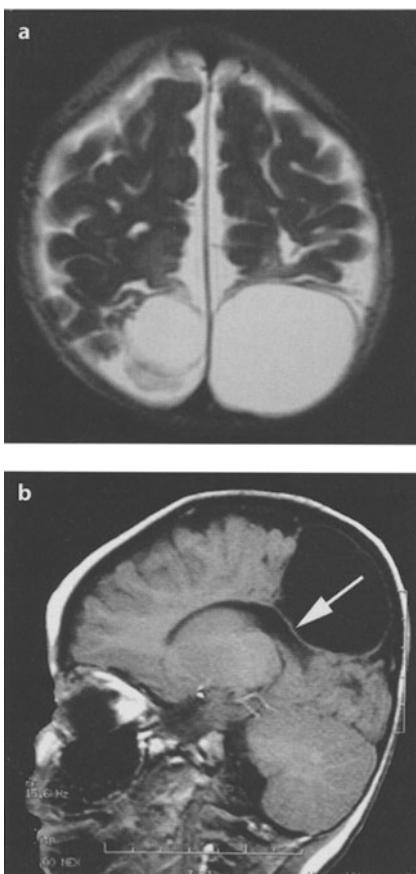


Fig. 2 a, b. Two-year old baby born prematurely with neonatal asphyxia. Large bilateral cavities in the parietal regions (a) apparently separated from the ventricular cavity (b) only by the ependymal layer (arrow)

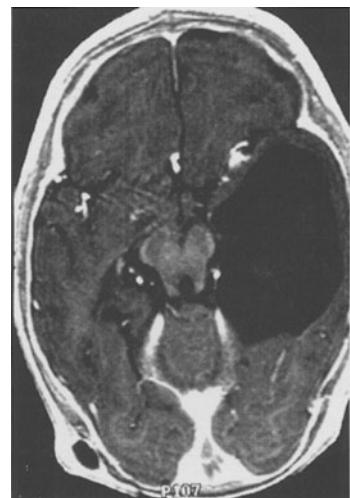


Fig. 3. Eighteen-month-old boy with postmeningitic hydrocephalus with a right ventriculoperitoneal shunt implanted in the first month of life. Loculation of the left temporo-occipital horn

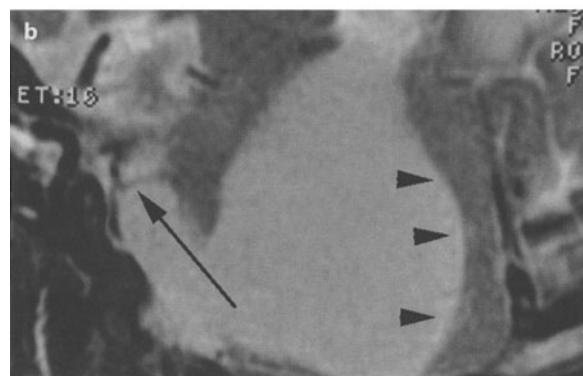
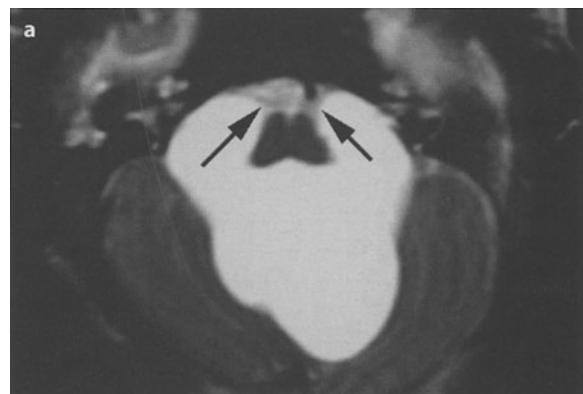


Fig. 4 a, b. Posthemorrhagic hydrocephalus, tetraventricular dilatation with trapped fourth ventricle. **a** Axial view at the level of the two foramina of Luschka, which are extremely dilated with diverticular enlargement; septations (arrows) divide the fourth ventricle from the subarachnoid spaces of the peribulbar cistern. **b** Sagittal paramedian view; note the diverticular enlargement of the Luschka foramen (arrow) and the severe deformation of the vermis (arrowheads)

Pathology

The septations are often located in characteristic positions inside the ventricular system and tend to lead to symmetrical compartmentalization [30]. A block within the body of the lateral ventricle, just posterior to the foramen of Monro (the most common form as reported by Kalsbeek et al. [30]) divides the lateral ventricle into two compartments: a frontal horn that communicates with the opposite ventricle (unless additional obstructions) and a blind posterior compartment consisting of the atrium and occipital and temporal horns (Fig. 1d, e). Adhesions in the region of the trigone prevent the temporal horn from communicating with the rest of the ventricle, leading to entrapped temporal horn [43] (Fig. 3). A veil in the aqueduct may isolate the fourth ventricle [23], while the occlusion of the foramen of Monro isolates the lateral ventricle. Septations also frequently occur in the posterior fossa (Fig. 4) [1].

The protein concentration in different cavities may vary greatly; in the pre-CT era this finding was considered diagnostic of compartmentalization [1, 30, 64, 66]. The appearance of septa is variable: they may be complete, spanning the ventricular walls, or incomplete, floating in the lumen; they may be transparent, thin, and avascular, or thick and highly vascularized; they may be complex, occupying the entire ventricle, resembling cobwebs, or focal with only solitary membranes.

The pathological findings of multiloculated hydrocephalus were characterized by Schultz and Leeds [69]. Microscopically the membranes are composed of fibroglial elements and round and polymorphonuclear cells. Findings of chronic ventriculitis are usually present, with subependymal gliosis, small areas of denuded ependyma, and glial tufts extending through the denuded ependyma into the ventricular lumen. The dura mater is often attached to the cerebral cortex by synechial adhesions because of leptomeningeal inflammation [1].

Clinical Features

The clinical features of multiloculated hydrocephalus are not specific and are often difficult to recognize, because they usually arise in infants or children already neurologically compromised by neonatal meningitis, intraventricular hemorrhage, or hydrocephalus.

Salmon [66] in 1970 described the typical patient: an infant, likely to have been born prematurely, that develops meningitis or intraventricular hemorrhage and subsequent hydrocephalus, initially symmetrical. Despite the insertion of a ventriculoatrial or ventriculoperitoneal shunt, which seems on palpation to be functioning, the head continues to grow and several revisions are done. The patient may develop nonspecific signs of increased intracranial pressure and new neurological deficits.

Nowadays the diagnosis of multiloculated hydrocephalus is most often made during the routine ultrasonographic or CT scan follow-up in children with postmeningitic or posthemorrhagic hydrocephalus [67], or by diagnostic procedures performed because of mechanical shunt failure or shunt infection, especially in the immediate follow-up CT scan after shunt revision, which may show the collapse of the ventricular system and expansion of the isolated compartments.

Actually, in infancy symptoms attributable to enlargement of ventricular compartments reflect increased intracranial pressure and resemble those of

generalized hydrocephalus [34], and thus those of shunt failure in shunted patients. The presenting symptoms are usually insidious, although some cases of sudden death secondary to cardiorespiratory arrest (massive shift of the midline or entrapment of the fourth ventricle) have been reported [28, 66]. Irritability, full fontanel, head enlargement, psychomotor retardation, seizures, increased muscle tone, papilledema, headaches, vomiting, and decreased consciousness are the most frequent symptoms in infancy [1, 28, 38, 59, 66]. In older children the symptomatology is more directly related to the mass effect of the isolated compartment: hemiparesis [57, 66] in the case of isolated lateral ventricle; hemiparesis, homonymous hemianopsia, and memory disturbances in the case of entrapped temporal horn [66, 78]; ataxia, lethargy, diplopia, nystagmus, mental confusion, dysarthria, and multiple cranial nerve palsies in the case of entrapped fourth ventricle [23]. Many cases are asymptomatic and are discovered as incidental findings on CT scan [17, 28]. Many children are already severely affected as the result of ventriculitis and hydrocephalus, so that recognizing new and subtle neurological symptoms may be very difficult. Thus it may be difficult to attribute symptoms such as psychomotor retardation, seizures, or developmental delay to the presence of isolated compartment. However, James [28] suggested that isolated compartment should be considered "symptomatic" if the infant or child is not progressing to the expected developmental milestones.

Neuroradiology

In the pre-CT era the diagnosis of multiloculated hydrocephalus was based on ventriculographic evidence of the accumulation of dye in some dilated cavities and not in others. This technique requires multiple bilateral punctures (between the sutures and through burr holes) or the presence of a functioning ventricular catheter or catheters for instillation of diagnostic agents. Nowadays ventriculography can be done with CT scanning. Contrast CT ventriculography is considered the best preoperative imaging study [38], because it defines the margins of the compartments and the anatomic relationship between the cavities and normal CSF pathways, and verifies noncommunication with the ventricular system (Fig. 5).

Multiloculated hydrocephalus is difficult to diagnose by noncontrast CT scan early in the disease process [1, 29, 38, 49]: the cavities have a density iden-

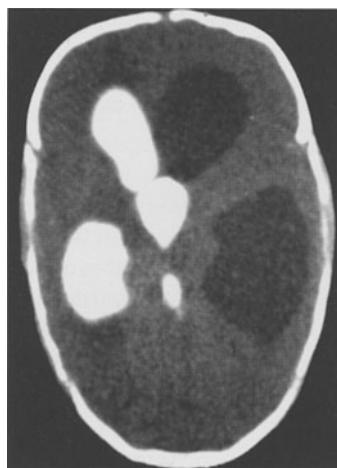


Fig. 5. Two-month-old baby girl, born at 37 weeks' gestational age, affected by posthemorrhagic hydrocephalus. Right intraventricular injection of contrast medium. There is good enhancement of the third ventricle and aqueduct, and complete exclusion of the left lateral ventricle

tical to that of CSF and their walls too are usually iso-dense [8]. As the disease progresses, the presence of ventricular septations or asymmetrical dilatation of a part of the ventricular system may become evident. Serial scans are reliable in demonstrating the enlargement of isolated compartments. In advanced phases the architecture of the ventricular system becomes distorted.

MRI is more sensitive than CT scan in detecting septations [15, 29, 38, 49], and even if it cannot confirm absence of communication with the rest of the ventricular system, MRI may obviate the need for contrast ventriculography in many cases [38] (Fig. 6). The recently more widespread high-resolution MRI technique, in particular constructive interference steady-state (CISS) MRI, has been proven superior to conventional MRI in the diagnosis and preoperative evaluation of multiloculated hydrocephalus [2]. This image acquisition technique is a software reconstructive program that, performing a three-dimensional mathematical Fourier transformation, leads to enhanced CSF-brain contrast [35] and better spatial resolution. Accurate anatomic information regarding the cause of hydrocephalus and the presence of septa or thin membranes within the ventricles and cisterns is essential for the selection of surgical procedures and improves the surgeon's spatial orientation, especially during endoscopic surgery, in which orientation may become very difficult after a large cavity has been entered (see Chap. 28). Thus, contrast ventriculography should be reserved only for selected cases.

CISS imaging can be useful in the postoperative evaluation of surgical procedures: due to the excellent

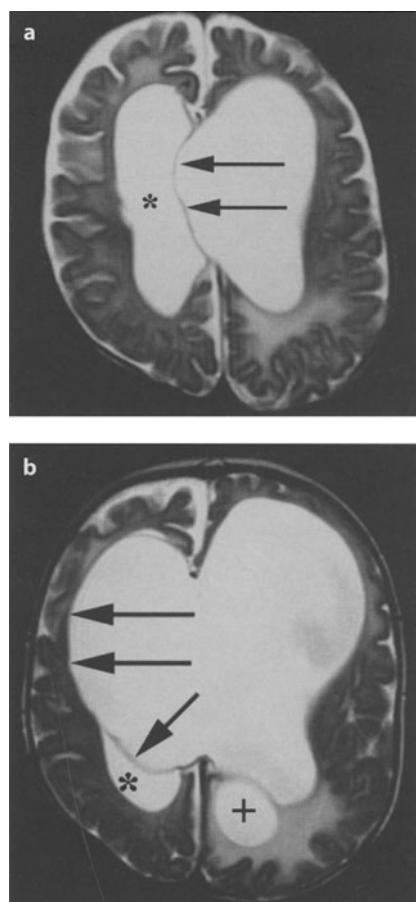


Fig. 6 a, b. Posthemorrhagic hydrocephalus treated by right ventriculoperitoneal shunt. **a** Two weeks after the implantation of the shunt. The septum pellucidum has mildly deviated (arrows) toward the right lateral ventricle (*). **b** Two months later, there is impressive deviation of the septum pellucidum towards the right lateral ventricle (*), which is almost completely occupied by the septal diverticulum. Loculation of the left occipital horn (+) is evident

cisternographic effect it can provide clear structural demonstration of the fenestration site that usually cannot be visualized by conventional MRI. Flow voids have not been observed after fenestration of intracranial cysts or intraventricular septations [2], probably because the pressure gradient in these cases is too small to produce high velocities and/or turbulence [2]. Lewis et al. [38] have suggested that restoration of normal ventricular architecture and air in the cyst on CT scan indicate that the cyst has been successfully fenestrated.

In infancy, ultrasonography is useful in detecting ventricular septations [67]. They appear as solid membranes or as firmly interwoven structures. Schellinger et al. [67] have demonstrated the superiority of ultrasonography over CT scan in the diagnosis of intraventricular septations.

Treatment

The goal of treatment is the control of hydrocephalus and signs and symptoms of increased intracranial pressure; often, significant neurological deficits are related to the primary CNS insult and cannot be reversed by treatment of the hydrocephalus.

Several operative approaches have been described: multiple shunt placement, multiperforated ventricular catheter, stereotactic aspiration, craniotomy, and transcallosal fenestration of intraventricular septations and endoscopic fenestration. Whatever technique is preferred, the first step in multiloculated hydrocephalus must always be the detection of possible CSF or shunt infection. All the scars and the catheter track must be carefully evaluated, if necessary after reduced shaving, in order to detect cutaneous signs of inflammation or shunt infection. Blood samples must be taken in order to evaluate the laboratory indexes of infection, abdominal ultrasonography should be performed to detect intraperitoneal loculations, and clinical history should be rigorously reconstructed to uncover any possible evidence of infection (e.g., fever, irritability, increasing seizures). If CT or MRI proves the existence of evolving loculations, CSF should be sampled from all the possible access sites (lumbar tapping and all the existing reservoirs), since in loculated hydrocephalus CSF cell count and biochemistry can vary in different cavities. CT scans should be carefully scrutinized for catheters lost in the ventricles. If one of the CSF samples gives evidence of CSF infection, the infected shunt system should be removed and replaced with an external ventricular drainage. If careful review of the serial CT scans suggests that the infected system is no longer useful, an attempt can be made simply to remove the infected shunt and to monitor the evolution of the infected cavity. If all CSF samples are infected – as is most frequently the case – all foreign shunt material should be removed, one or more external drainages implanted in the various cavities, and appropriate antibiotic treatment administered based on CSF cultures and antibiograms. After resolution of the CSF infection, the most appropriate surgical technique should be selected.

Multiple Shunt Placement

The traditional method by which to treat multiloculated hydrocephalus is multiple shunt placement in the expanding isolated compartments [1, 22, 29, 30]. This operative approach, though the most widely used, is burdened by a high rate of mechanical shunt failure and infection and subsequently high mortality

and morbidity. Nida and Haines [49] and Lewis et al. [38] have calculated medians of 2.75 and 3.04 shunt revisions respectively per year in their series. The collapse of the shunted compartment and the embedding of the catheter tip may explain the high reported rate of shunt dysfunction [29, 49]. The septa can be so thick that they can be difficult to perforate without endoscopic or radiographic guidance (Fig. 7). Historically, patients treated with this approach typically become very difficult to manage because of the significant complexity of the shunt system (Figs. 8, 9), leading to catastrophic consequences if CSF infection occurs, which often necessitates removal of all the implanted material.

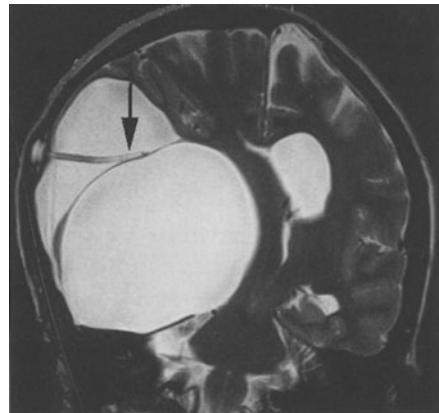


Fig. 7. The proximal catheter (arrow) failed to perforate the septum of a trapped temporal horn

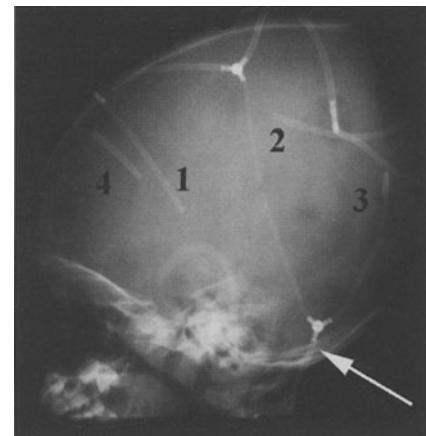


Fig. 8. Loculated hydrocephalus in a patient operated on for a large occipital encephalocele. Three proximal catheters (1, 2, and 3) are connected with Y connectors before the single distal catheter (arrow). One proximal catheter is lost in the ventricle (4)



Fig. 9. Loculated hydrocephalus following neonatal gram-negative meningitis and ventriculitis. Four different shunts have been used, and different valves can be recognized (differential pressure valve, *arrow*; and flow-regulating valve, *arrowhead*)

Kalsbeck et al. [30] suggested that puncture of membranes during insertion of a multiperforated ventricular catheter might obviate the need for multiple shunting. Unfortunately this approach is often inadequate [38, 49].

With the aim of simplifying the pre-existing shunt system and reducing operative mortality and morbidity, various treatment strategies have been investigated.

Stereotactic Aspiration

Stereotactic aspiration has been performed to decompress the encysted cavity, to relieve mass effect, and to restore the CSF pathway [38, 42]. Actually, because stereotactic aspiration alone fails to create a large fenestration with the ventricles and to devascularize the septal walls, the risk of recurrence is high [38, 42]. Moreover, difficulties may be encountered in the case of compartments with thick, mobile walls that are resistant to stereotactic puncture [33, 64]. Stereotactic aspiration may be associated with stereotactic insertion of a ventricular catheter into the cyst, configuring a cyst-peritoneal or an internal shunt (between the isolated compartment and the rest of the ventricles). However, these shunts are also prone to occlusion by collapse of the cyst [38].

Craniotomy

Craniotomy and transcallosal fenestration was first performed by Rhiton and Gomez [64] in

1972 with the aim of converting multiloculated hydrocephalus into uniloculated hydrocephalus, allowing the drainage of CSF through a single shunt system. This approach was reviewed by Nida and Haines [49]. They managed six cases of multiloculated hydrocephalus by shunting and craniotomy with lysis of intraventricular septations. A standard transcallosal microsurgical approach to the lateral ventricle was performed and the septations were individually identified and excised. Adequate hemostasis can be easily achieved through this approach. Following open surgery the shunt revision rate was reduced from 2.74 to 0.25 per patient per year. Initially open surgery was reserved for patients in whom other methods had failed, but on the basis of their good results Nida and Haines [49] performed transcallosal fenestration followed by shunt placement as the initial procedure upon first-time presentation. However, transcallosal surgery is quite an invasive option and carries potential risks: venous infarction from sacrificing bridging veins, and damage to the pericallosal artery, fornices, and subcortical nuclei. Subdural collections are frequent and troublesome after cortical incision because the cortical mantle is usually thinned by the hydrocephalus [30].

Endoscopy

Endoscopic fenestration is a useful approach to avoid the morbidity, the mortality, and the long recovery period associated with open surgery. As recommended by Lewis et al. [38], it should be considered as the initial treatment for multioculated hydrocephalus, craniotomy being kept for more complex cases. Lewis et al. [38] in their series had the same good result as with craniotomy (reduction of shunt revision rate from 3.04 to 0.25 per patient per year after surgery) with the advantage of less invasiveness and greater operative simplicity than microsurgery. In a recent paper, Nowoslawska et al. [50] compared two groups of patients affected by multiloculated hydrocephalus, one treated using endoscopic procedures and the other treated by conventional multiple shunt implantations, and found not only that endoscopy reduced the shunt revision rate as a result of simplification or elimination of the shunt system, but also that children treated by endoscopic technique were in much better clinical condition than the other group. Moreover, there were fewer complications, especially CNS infection, among the endoscopically treated children.

Thus, the presence of symptomatic compartmentalizations, enlargement of an isolated compartment on serial CT scans, shunt failure, and shunt infection in patients with multiloculated hydrocephalus should be considered indications for endoscopic surgery to simplify the pre-existing shunt system and remove infected hardware.

Endoscopic fenestration and placement of a ventriculoperitoneal shunt was first attempted by Kleinhaus [32] in 1982. A major problem was to adequately and safely fenestrate the rather thickened septations. In 1986 Powers [60], using a steerable endoscope and argon laser, performed multiple perforations circumferentially in the septal wall and removed the central part either by biopsy forceps or advancing the endoscope; Heilman and Cohen [26] used a “saline torch”, a radiofrequency dissecting needle. Lewis [38] used a steerable fiberoscope and a potassium titanyl phosphate (KTP) 600- μm laser fiber to open the septa and biopsy forceps or scissors to widen the fenestrations. Finally, Rhoten [63] used biopsy forceps and Fogarty balloon dilatation. Whatever technique is used, all these authors recommend performing a large window in the septal walls, at least 1 cm in diameter, and devascularizing the septa to prevent their regrowth. However, in the event of recurrence, or if for anatomical and technical reasons it is impossible to achieve lysis and excision of all septations, multiple procedures should be considered: they have given encouraging results [38]. Controlling bleeding during endoscopic fenestration is usually not problematic: the diameter of the vessels within the septal walls is usually less than 1 mm and bleeding is easily controllable by laser, monopolar coagulation, or bipolar cautery [38].

The choice of endoscopic approach is dictated by the location of the septal walls, the entry site of the ventricular catheter, and the potential need for a new shunt. In fact, endoscopy is also useful to remove an embedded ventricular catheter [38], to insert a new shunt under direct vision, and to perform a third ventriculostomy when needed. In cases in which the patient has not already undergone shunting, a standard coronal burr hole is usually the most indicated approach. If the septations are located more posteriorly within the ventricular system, a more anterior frontal burr hole, near the hair line, may provide access to the occipital horns. An occipital approach, with the patient’s head turned 90°, should be used for loculations located within the temporal horns. A combination of occipital and coronal approach may be useful when a ventricular catheter has been previously placed through an oc-

cipital burr hole [38]. When loculations are present on both sides of the ventricular system the burr hole is beveled laterally, allowing fenestration of the septum pellucidum in order to reach the contralateral ventricle (Fig. 10). The aim of endoscopic fenestration is to restore communication between isolated intraventricular compartments so as to allow a single proximal catheter to drain all the intracranial CSF cavities. Thus, the tip of ventricular catheter, if already implanted, should be visualized through the endoscope at the end of the procedure. After completion of the fenestration, to confirm free communication inside the ventricular system, real-time ultrasonography may be performed while saline is injected into the ventricles [38].

In some cases the endoscopic procedure may be difficult because of the distorted anatomy and the lack of orienting landmarks for the surgeons. Rhoten et al. [63] have used a neuronavigation system to guide the tip of endoscope in complex endoscopic procedures. This “computer-assisted neuroendoscopy” in patients with multiloculated hydrocephalus may be useful in the preoperative planning of burr hole placement and to define the ideal trajectory to the target, so that every cyst may be entered in one pass of the endoscope, thus limiting the number of endoscopic movements in the penetrated white matter and cortex. During surgery the system helps in identifying specific septa and in identifying the best site for fenestration such that no cyst remains unfenestrated. However, intraoperative changes such as brain shift and cyst drainage of the cysts can invalidate the preoperative planning. “Real-time neuronavigation” may be obtained by the device for ultrasound guidance of neuroendoscopic procedures described by Strowitzki et al. [74] or with the assistance of intraoperative magnetic resonance, as described by Balmer et al. [3].

The success rate of neuroendoscopy (conversion of multilocular to unilocular hydrocephalus, allowing simplification of the shunt system to a single ventricular catheter) varied between 61.8% and 100% in the published series [38, 50, 52, 63, 76]. The best results have been achieved in children suffering from monoventricular hydrocephalus [24, 47].

The rate of complications after operative treatment was low in the series of Lewis et al. [38], with CSF leak in 3% of cases and CNS infection in 3%. It was higher in the series of Valenzuela and Trellez [76], with ventriculitis in 12%, CSF leak in 5%, and hemorrhage in 4%; and also in the series of Nowoslawka et al. [50], who encountered infection in 9% of cases and CSF leak in 6%.

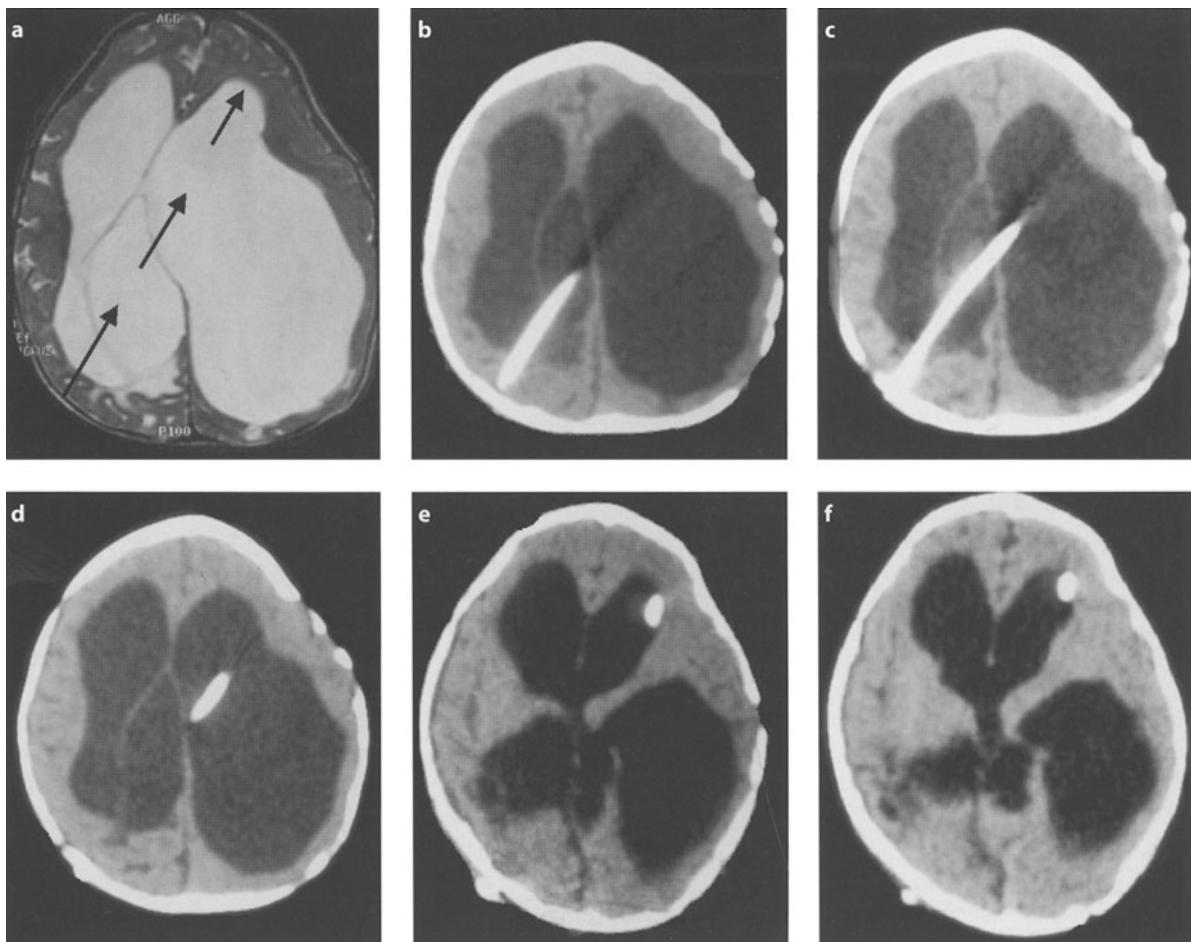


Fig. 10 a-f. One-year-old boy, no available history on the prenatal and neonatal period. **a** Four loculated compartments are visible on the MRI; the ideal trajectory for perforation of all the septations in a straight line is carefully chosen on the scan (arrows). **b-f** Postoperative CT: all the septa have been perforated under endoscopic control and a ventricular catheter has been inserted under endoscopic guidance across the fenestrations after multiple holes have been made along it. The tip is inserted into the most distal cavity in the left frontal horn (**f**). The ventricular catheter is then connected to a peritoneal shunt system

Prognosis and Outcome

Despite the progress in surgical technique the prognosis of these children remains poor; this is partly related to their initial disease and partly to multiloculated hydrocephalus. In the larger reported series [1,30,69] of the last thirty years or so, mortality rates have ranged between 50% and 70%. Nowadays mortality has decreased [29, 38, 49, 50], but many children have cognitive deficits which range from profound psychomotor retardation to mild learning disability; most are seriously affected [49]. The causes of death are usually related to infection or to prematurity [50].

Anatomical Forms of Compartmentalization

Entrapped Temporal Horn

The trapped temporal horn is a subtype of multiloculated hydrocephalus in which the choroid-plexus-containing temporal horn is excluded from the rest of the ventricle by adhesions in the region of the trigone [43]. The temporal horn progressively enlarges as the result of CSF production in the choroid plexus. This form of “focal obstructive hydrocephalus” was first

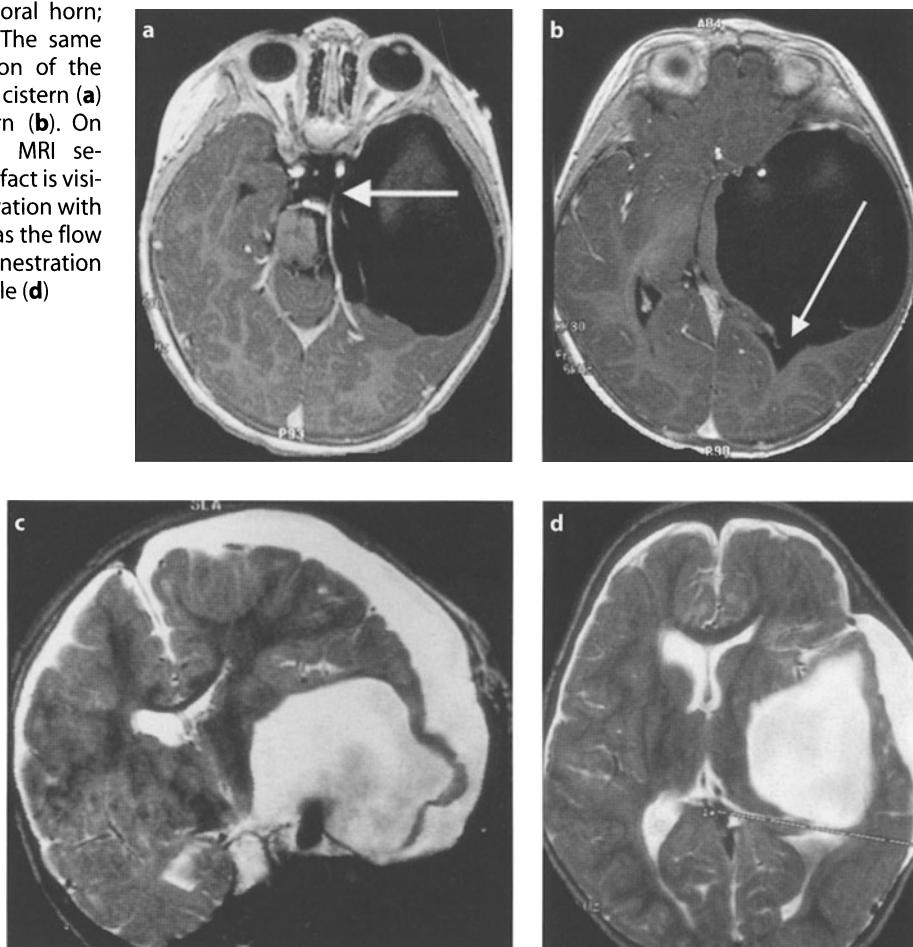
described by Cairns et al. [11], who reported a case of localized hydrocephalus “following penetrating wounds of the ventricle”. Since then entrapment of the temporal horn has been reported to occur in the presence of meningitis, intraventricular hemorrhage, tumor, neurosarcoïdosis, choroid plexitis, and as a complication of surgery in the trigone region [59].

The clinical features are usually more specific than those of other forms of multiloculated hydrocephalus: Watanabe and Katayama [78] described a characteristic triad of hemiparesis, homonymous hemianopsia, and memory disturbance. The hemiparesis is attributable to compression of the internal capsule, the memory disturbance (usually short-term memory problems) to distortion of the hippocampus, and the visual field defect (homonymous hemianopsia or superior quadrantanopsia) to distortion or edema of Meyer’s loop.

Therapeutic options include cystoperitoneal shunt [43, 78], craniotomy and microsurgical fenestration, and endoscopic fenestration. Endoscopic fenestration should be considered the procedure of choice as the initial treatment [38, 59]. Fenestration into the ventri-

cle may be performed through an occipital approach, if the occipital horn is enlarged enough, or through a temporal approach. Parrent [59] has proposed fenestration of the choroid fissure to allow drainage of the temporal horn into the basal cisterns. The endoscope is inserted into the dilated temporal horn, where identification of the choroid plexus permits recognition of the choroid fissure, which is located anterior and inferior to the choroid plexus and should be perforated in its more anterior aspect. Entry into the basal cistern is confirmed by visualization of the cerebral peduncle and the P1 segment of the posterior cerebral artery [59]. This technique has the advantage of permitting communication with the basal cisterns, allowing greater CSF flow through the stoma because of the high compliance of the spinal subarachnoid spaces (Fig. 11); moreover, with proper preoperative planning, additional fenestration into the lateral ventricle at the level of the trigone can be performed, closing an ideal loop for CSF circulation. It should be kept well in mind that opening a temporal horn in the basal cistern is not an easy task if performed under

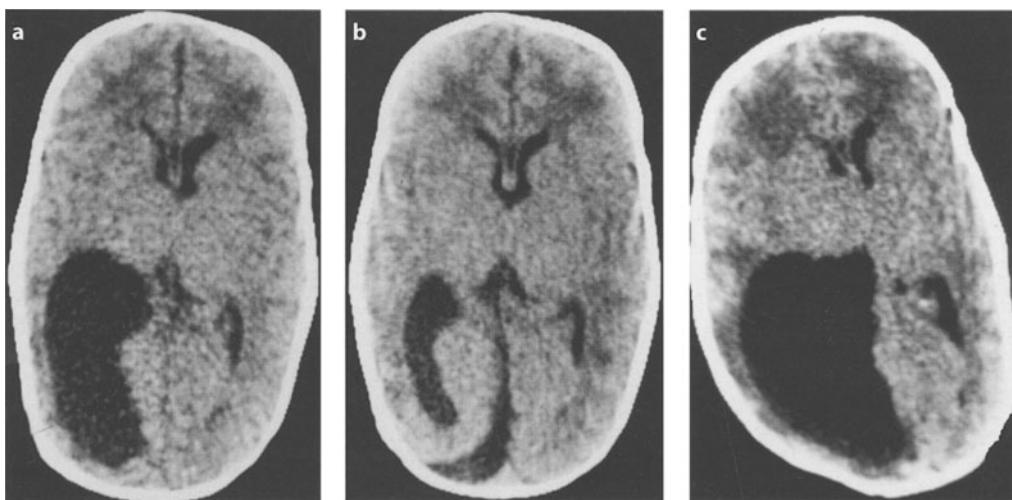
Fig. 11 a-d. Trapped temporal horn; preoperative T1 axial MRI. The same approach allows fenestration of the trapped horn into the basal cistern (a) and into the occipital horn (b). On postoperative T2-weighted MRI sequences, significant flow artifact is visible at the level of the fenestration with the basal cisterns (c), whereas the flow artifact at the level of the fenestration with the ventricle is negligible (d)



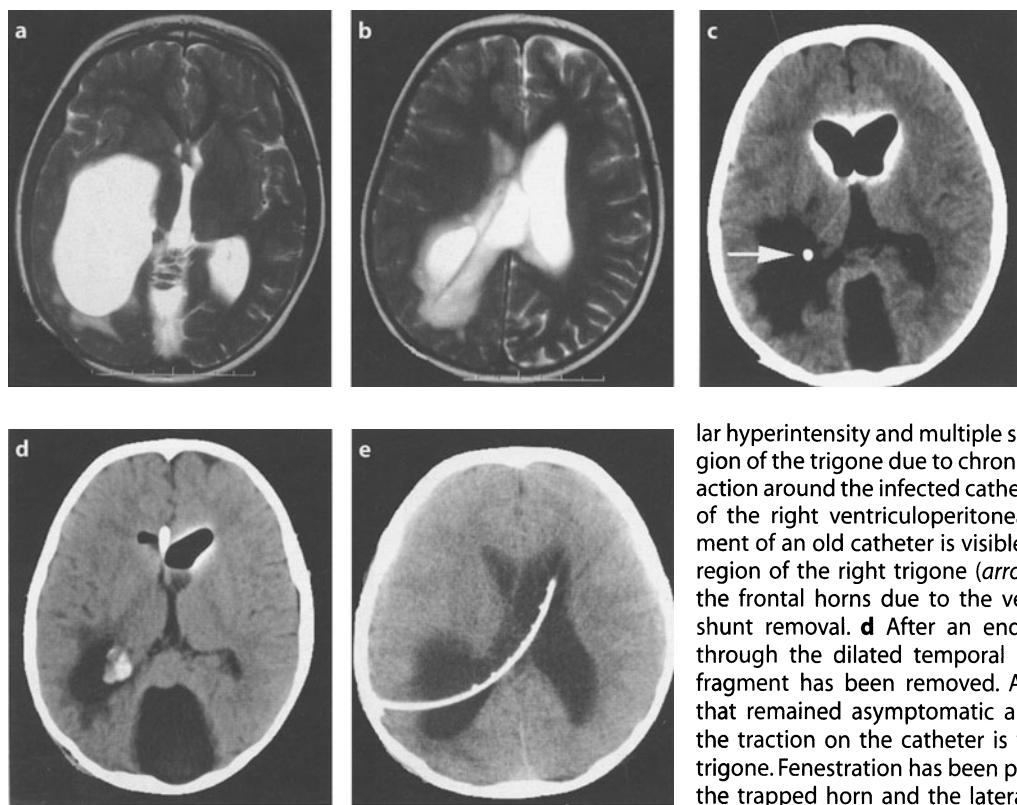
endoscopic control because of the importance and caliber of the vessels located in this region. A micro-surgical approach should be preferred by any surgeon without adequate training in endoscopic procedures.

The occipital approach means working in the region of the trigone, where adhesions and scar tissue can

modify the anatomy and make the procedure difficult. This approach allows fenestration within the body of the lateral ventricle, but the size of the opening can be insufficient because of the presence of the choroid plexus, and can lead to early reclosure of the fenestration with recurrence of the loculation (Figs. 12, 13).



poro-occipital horn into the right lateral ventricle: significant decrease in the volume of the loculated compartment is evident; no stent was left in place. **c** One month following fenestration, loculation has recurred



tration for removal 10 days later. **e** Two months after **d**, trapping of the temporal horn recurred (see Fig. 1d-e), the patient was reoperated on, and a stent was implanted under endoscopic control and left in place connected to a subcutaneous reservoir. The hydrocephalus was finally cured by posterior fossa fenestration (see Chap. 18, Fig. 13)

Fig. 12 a-c. Premature baby (33 weeks' gestational age) with neonatal hemorrhage in the right choroid plexus. **a** Note the isolated temporo-occipital horn and the normal size of the remaining ventricular system. **b** Ten days following endoscopic fenestration of the trapped temporo-occipital horn into the right lateral ventricle: significant decrease in the volume of the loculated compartment is evident; no stent was left in place. **c** One month following fenestration, loculation has recurred

Fig. 13 a-e. Ten-year-old patient affected by Dandy-Walker malformation and entrapped temporal horn due to multiple intractable shunt infections caused by a fragment of lost catheter. **a** Entrapped temporal horn. **b** Periventricular hyperintensity and multiple septations in the region of the trigone due to chronic inflammatory reaction around the infected catheter. **c** After removal of the right ventriculoperitoneal shunt, the fragment of an old catheter is visible embedded in the region of the right trigone (arrow). Air is visible in the frontal horns due to the ventriculoperitoneal shunt removal. **d** After an endoscopic approach through the dilated temporal horn, the catheter fragment has been removed. A small hematoma that remained asymptomatic and was caused by the traction on the catheter is visible in the right trigone. Fenestration has been performed between the trapped horn and the lateral ventricle and an external drainage has been left through the fenestration for removal 10 days later. **e** Two months after **d**, trapping of the temporal horn recurred (see Fig. 1d-e), the patient was reoperated on, and a stent was implanted under endoscopic control and left in place connected to a subcutaneous reservoir. The hydrocephalus was finally cured by posterior fossa fenestration (see Chap. 18, Fig. 13)

lar hyperintensity and multiple septations in the region of the trigone due to chronic inflammatory reaction around the infected catheter. **c** After removal of the right ventriculoperitoneal shunt, the fragment of an old catheter is visible embedded in the region of the right trigone (arrow). Air is visible in the frontal horns due to the ventriculoperitoneal shunt removal. **d** After an endoscopic approach through the dilated temporal horn, the catheter fragment has been removed. A small hematoma that remained asymptomatic and was caused by the traction on the catheter is visible in the right trigone. Fenestration has been performed between the trapped horn and the lateral ventricle and an external drainage has been left through the fenestration for removal 10 days later. **e** Two months after **d**, trapping of the temporal horn recurred (see Fig. 1d-e), the patient was reoperated on, and a stent was implanted under endoscopic control and left in place connected to a subcutaneous reservoir. The hydrocephalus was finally cured by posterior fossa fenestration (see Chap. 18, Fig. 13)

Obstruction of the Foramen of Monro

Obstruction of the foramen of Monro results in unilateral dilatation of the ipsilateral ventricle. This uncommon entity, defined by Oi and Matsumoto [57] as “progressive unilateral hydrocephalus”, may be attributed to various causes: obstruction by tumor (usually thalamic glioma), abscess, vascular anomaly, intrauterine infection, and developmental errors resulting in congenital atresia; but primary forms can be observed with membranes occluding the foramen. Moreover, the obstruction of the foramen may develop after treatment of a previously communicating hydrocephalus. This condition, known as “isolated lateral ventricle”, like other forms of multiloculated hydrocephalus, is a consequence of ventriculitis. Postshunt occlusion of the interventricular foramen secondary to overdrainage and slit-like unilateral ventricle [57] is also a well-documented phenomenon, with or without ventriculitis [57, 81] (Fig. 14). Myelodysplastic children, because of anatomic anomalies of the ventricular system, are particularly predisposed to torsion and obstruction of the foramen of Monro if overdrainage occurs [6]. Thalamic gliomas and third ventricular tumors are also well-recognized etiological factors for loculation of the lateral ventricle following shunting of the contralateral cavity (Fig. 15), because of the narrowing and distortion of the foramen of Monro induced by the neoplasm. Preventive implantation of a biventriculoperitoneal shunt (Fig. 16) or of a catheter across an endoscopically performed septostomy should be considered if the clinical conditions do not allow tumor removal first.

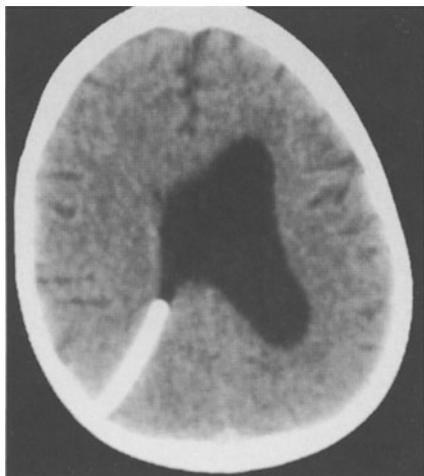


Fig. 14. Patient affected by type I neurofibromatosis, cervicomедullary astrocytoma, and hydrocephalus. Loculation of the left lateral ventricle has occurred after implantation of a right ventriculoperitoneal shunt

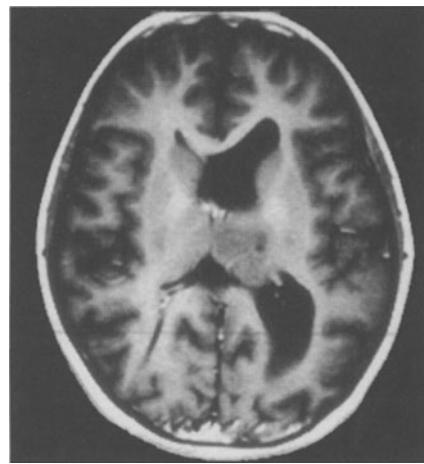


Fig. 15. Ten-year-old girl affected by hydrocephalus and asymmetric bifthalamic glioma. The implantation of a right ventriculoperitoneal shunt induced distortion and stenosis of the left foramen of Monro with trapping of the left lateral ventricle

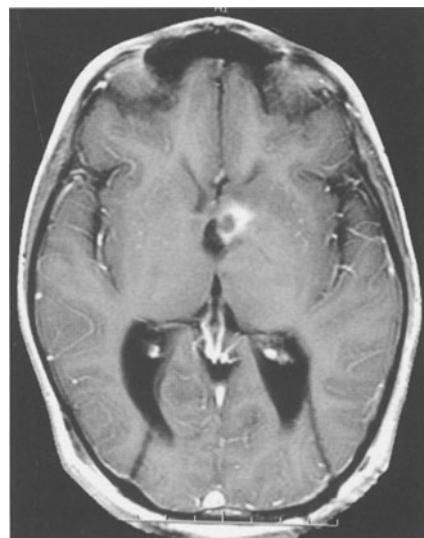


Fig. 16. Eleven-year-old girl affected by tumor of the third ventricle with hydrocephalus. A biventriculoperitoneal shunt has been implanted as an emergency procedure for severe hydrocephalus before tumor removal

Oi and Matsumoto [57] have observed unilateral hydrocephalus without obstruction of the foramen of Monro. If intracranial compliance is asymmetrically distributed (e.g., as the result of cerebral infarction, an encephalitic lesion, or a cranial vault defect), an alteration of CSF pathway such as aqueductal stenosis or cisternal block may result in unilateral ventricular enlargement. This condition should be kept in mind because the treatment should be finalized in such a manner as to restore CSF pathway.

Nonneoplastic occlusion of the foramen of Monro usually acquires the appearance of a membranous occlusion. Clinically progressive dilatation of only one lateral ventricle is often associated with unilateral long tract signs or focal brain symptoms, such as hemiparesis and aphasia. Treatment options include additional shunting procedures, endoscopic fenestration of the septum pellucidum, and Monro foraminoplasty [47, 52, 57, 81]. Fenestration of the obstructed foramen of Monro (foraminoplasty) is as effective as fenestration of the septum pellucidum, or foraminoplasty with septostomy [81], and should be considered the initial treatment (Figs. 17, 18). Endoscopy may fail to locate the obstructed foramen, obscured by the covering membrane. The thalamostriate vein, located on the posterolateral aspect of the foramen, and the choroid plexus are the most important landmarks. The use of an optical navigation system may be helpful. As an alternative, fenestration of the septum pellucidum may be performed. For bilateral membranous obstructions, bilateral foraminoplasty may be performed through a bilateral approach.

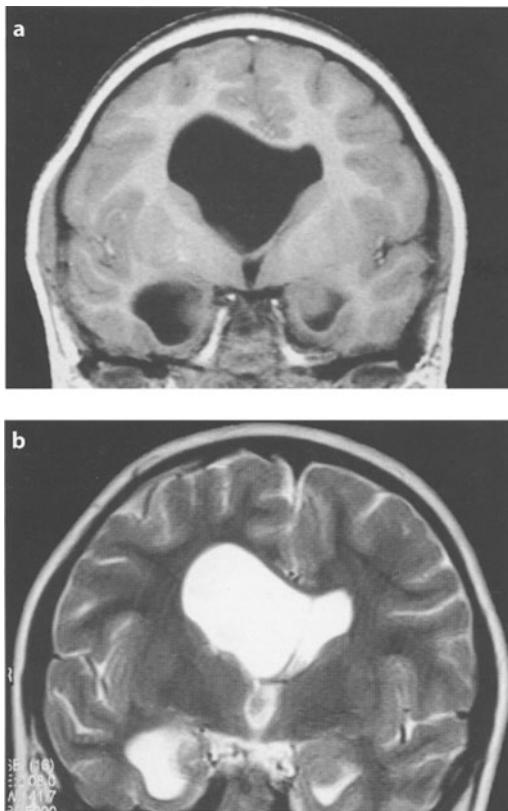


Fig. 17 a, b. Thirteen-year-old girl, born at term, no relevant medical history. Unilateral hydrocephalus due to membranous stenosis of the right foramen of Monro. **a** Preoperative MRI. **b** After endoscopic fenestration of the membrane occluding the foramen of Monro, flow artifact is visible within the third ventricle

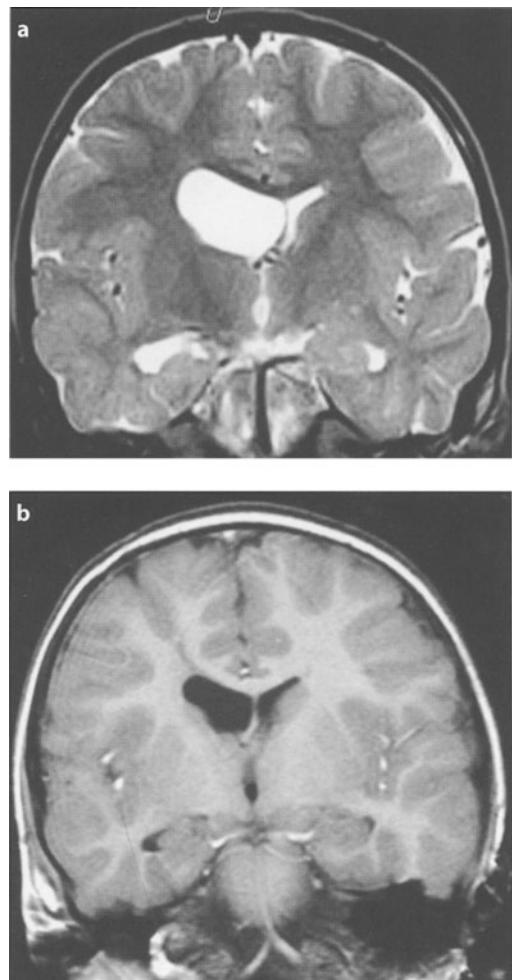


Fig. 18 a, b. Three-year-old boy, born prematurely, suffered intraventricular hemorrhage at birth but no shunt was implanted. **a** Unilateral ventricular dilatation with significant bulging of the septum pellucidum. The patient presented with a left hemiparesis and mild delay in psychomotor development. **b** Following endoscopic foraminoplasty, the right ventricle has decreased in size and the patient has improved significantly

Isolated Fourth Ventricle

The isolated or trapped fourth ventricle is an anatomopathological entity characterized by marked dilatation of the fourth ventricle, secondary to accumulation of CSF, which, secreted by the posterior fossa choroid plexus, cannot flow freely through the subarachnoid space or the aqueduct [71]. This form of fourth ventricle enlargement must be differentiated from enlargement of the fourth ventricle accompanied by lateral ventricular dilatation, in which the fourth ventricle is larger than usual on CT scan. This

kind of hydrocephalus, with a “disproportionately large fourth ventricle” [14, 27, 52, 71], is usually secondary to obstruction of the foramina of Luschka and Magendie with a patent aqueduct of Sylvius, and thus single shunting of the lateral ventricle or endoscopic third ventriculostomy may control the hydrocephalic state.

Forms

According to the site of obstruction, the isolated fourth ventricle may be categorized into two forms that may differ in regard to treatment. In the first type, originally described by Foltz and De Feo [23] under the name of “double compartment hydrocephalus”, the fourth ventricle is prevented by aqueductal obstruction (usually an arachnoid veil) from communicating with the third ventricle, while still communicating with the cisterna magna and spinal subarachnoid space, but CSF absorption is impaired over the cerebral hemispheres, leading to accumulation of CSF. In the second, more common form, the obstruction to CSF flow occurs rostrally at the aqueduct and caudally at the foramina of Luschka and Magendie.

Etiology

Isolated fourth ventricle seems never to be a primary condition: it usually occurs after shunting of the lateral ventricles for communicating hydrocephalus, aqueductal stenosis, or obstruction of the foramina of Luschka and Magendie [23, 25, 71] as the result of additional areas of CSF obstruction secondary to scarring of the ependyma and subarachnoid space after intraventricular hemorrhage, meningitis, shunt infection, mechanical irritation by ventricular catheter, or intracranial surgery [23, 25, 28, 71]. However, occlusion of the aqueduct in cases of shunted communicating hydrocephalus is often a complication of shunt management due to overdrainage, which may cause a pressure difference between the supratentorial and infratentorial compartments, resulting in upward displacement of the midline cerebellar structures into the tentorial incisura and distortion and “functional obstruction” of the aqueduct [28, 54, 61]. Raimondi et al. [61] and Oi and Matsumoto [56] observed that this condition could be reversed and the aqueduct reopened by decreasing the pressure in the infratentorial compartment, or by obtaining enlargement of the slit-like lateral cerebral ventricles.

Thus, some rare forms of isolated fourth ventricle may be considered reversible (with correction of

overdrainage), while other forms are not reversible due to inflammatory changes following meningitis, hemorrhage, and operative procedures [54, 56].

Clinical Signs

Although isolated fourth ventricle may be an incidental finding and in most cases is asymptomatic and does not require treatment, some patients exhibit signs and symptoms of increased intracranial pressure or, more often, of an expanding posterior fossa lesion. The clinical presentation is variable and may run from an acute posterior fossa syndrome with cranial nerve deficits and cerebellar tonsil herniation, to a slowly progressive syndrome that may go undetected for years [14, 71]. According to Foltz and De Feo [23], ataxia, lethargy, and diplopia in combination are the most characteristic signs indicating fourth ventricle enlargement in patients who have already undergone shunting for hydrocephalus. In infants the most common findings are irritability, increased head size, and full fontanel; in childhood, most common are headache, emesis, lethargy, cardiorespiratory arrest, nystagmus, dysarthria, and mental confusion [23, 28, 54, 71]. The clinical picture is rarely clear-cut, often resembling that of shunt malfunction [23]. In some case the pre-existing neurological signs such as hemi- or tetraparesis or seizures may be accentuated without the appearance of posterior fossa signs [71].

Onset of symptoms usually occurs years after the initial shunt placement [54, 71]. Moreover, this syndrome develops in children who received the initial shunt in the neonatal period or early infancy. However, the isolation of the fourth ventricle may occur not only in infancy, but also into childhood and adulthood [28]. Incidentally discovered cases, which according to many authors [28, 45] do not require treatment, should be carefully followed to rule out progressive signs: in the series of Eder et al. [21], two of four asymptomatic children developed cerebellar signs 6 and 12 months after the initial diagnosis.

Radiology

CT and MRI diagnosis of isolated fourth ventricle is usually accurate, in many cases making contrast CT ventriculography unnecessary [14, 28, 71]. The most striking finding is the presence of a very large fourth ventricle, accompanied by very small or “slit-like” lateral and third ventricles [28]. The fourth ventricle appears rounded or ballooned, the brain stem is displaced ventrally, and posterior fossa subarachnoid spaces and cisterna magna are reduced in size or obliterated. The upper pole of the fourth ventricle can her-

niate upward through the tentorial hiatus, thinning the tectal plate and bulging into the third ventricle (Fig. 19). In myelomeningocele patients who present cerebellar tonsils herniated into the spinal canal and thickened and dysplastic tectal plates the fourth ventricle herniates more posteriorly, through the anterior medullary velum (Fig. 20). If there is significant supratentorial dilatation, the upward bulging can lead to thinning out of the medial wall of the ventricular trigone, with important implications for the surgical strategy (Fig. 21). This aspect is very different from the

sharper and less rounded image of the fourth ventricle that accompanies atrophy of the cerebellum, seen as a consequence of cerebellar hemorrhage and infarcts in premature infants [28]. Other cystic lesions, such as cystic astrocytoma and arachnoid and parasitic cysts, usually present no problems in differential diagnosis [71]. For differential diagnosis with the Dandy-Walker complex, see Chap. 18. In selected cases intraventricular pressure monitoring may be useful to analyze the pressure gradient or pressure dynamics and isotope cisternography to study the CSF pathway [23, 54].



Fig. 19. Five-year-old girl, suffered repeated meningitis due to a misdiagnosed neuroenteric cyst. Supratentorial hydrocephalus was shunted 3 months ago. The upper pole of the fourth ventricle dilates the aqueduct and herniates into the third ventricle, thinning the tectal plate. The lower pole displaces the cerebellar tonsils upward and posteriorly

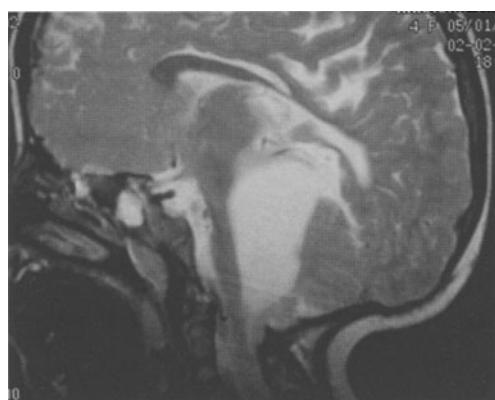


Fig. 20. Four-year-old child with myelomeningocele, shunted at birth. The dilation of the fourth ventricle is more posterior than in the case shown in Fig. 19, with thinning out of the anterior medullary velum. The tonsils remain herniated into the cervical canal

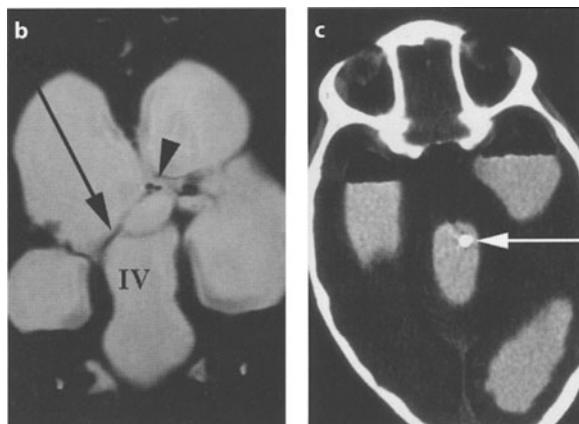
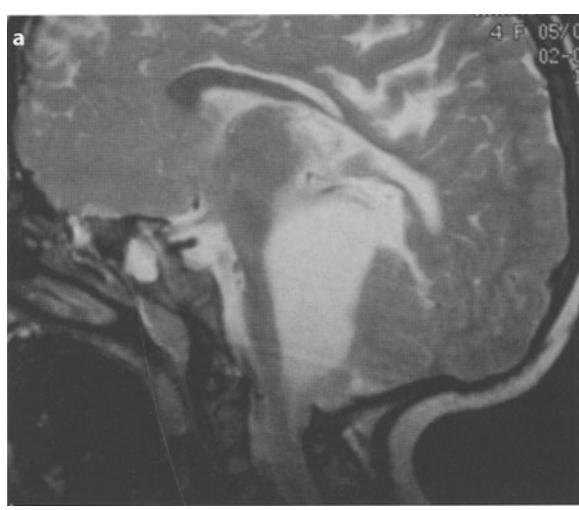


Fig. 21 a-c. One-year-old baby girl, born prematurely at 32 weeks' gestational age, admitted with malfunction of an infected shunt. Sagittal T2-weighted MRI (a) shows a trapped fourth ventricle; coronal T2-weighted MRI (b) shows that an approach through the lateral ventricle is anatomically possible (arrow), with low risk of injury to the two internal cerebral veins that are displaced (arrowhead). c Postoperative CT scan with intraventricular contrast injection shows the catheter of the external drainage implanted into the fourth ventricle (arrow) and good contrast enhancement of the whole ventricular system

Treatment

Treatment options for isolated fourth ventricle include: fourth ventricle-peritoneal shunting [25, 28, 51, 71], direct microsurgical approach, veil excision, and aqueduct canalization [23] or outlet fenestration of the fourth ventricle [17, 77]. Oi and Matsumoto [54], in cases of functional aqueductal stenosis due to overdrainage, recommend controlling the over-functioning shunt from the lateral ventricle first. This may be done by upgrading the shunt pressure or equalizing the pressure gradient between the supra- and infratentorial compartments, decompressing the fourth ventricle by fluid aspiration via an Ommaya reservoir. However, because the distinction between “reversible” and “irreversible” aqueductal obstruction often requires operative or invasive diagnostic procedures, most authors [28, 45, 51] consider shunting of the fourth ventricle as the less invasive and more effective approach.

Shunting of the Fourth Ventricle

The operative technique of inserting a fourth ventricle-peritoneal shunt starts with placement of an infratentorial burr hole 2 cm paramedian over the right or left hemisphere (depending on the site of the existing lateral ventricular catheter) with the patient in a prone or lateral decubitus position. The catheter, the length of which is predetermined on CT or MRI, is inserted so that the tip reaches the center of the ventricle. The shunt tubing is then connected by a Y connector to the valve of the pre-existing ventriculoperitoneal shunt, to reduce the risk of pressure gradient and the risk of single shunt dysfunction.

This approach, although effective in allowing full recovery in many cases [54], exposes the patients (as discussed in Chap. 18) to complications directly related to fourth ventricular catheter insertion, such as new cranial nerve deficits and embedding of the catheter tip in the floor of the fourth ventricle. Moreover, fourth ventricle shunting carries a high rate of shunt dysfunction and dislocation [18] (Fig. 22). To improve the safety and effectiveness of shunting, Lee et al. [37] recommend cannulating the posterior fossa cyst under direct ultrasonic guidance through a lateral suboccipital craniotomy. Eder et al. [21] also recommend ultrasound or endoscopic guidance to avoid possible direct trauma to the brain stem and to ensure exact placement. Montes et al. [48] have developed a stereotactic technique to insert the shunt in the fourth ventricle through a right parietal burr hole and a transtentorial hiatus approach. A catheter trajectory parallel rather than perpendicular to the

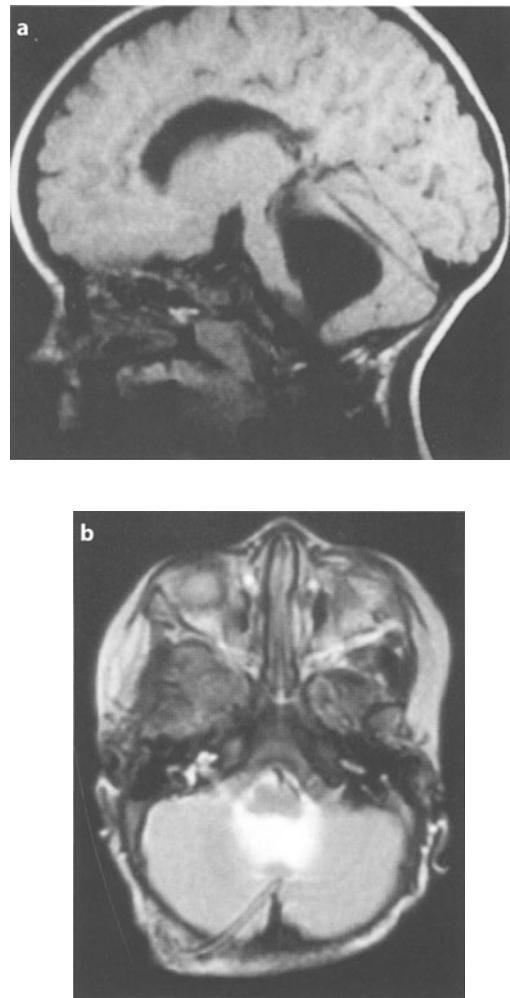


Fig. 22 a, b. Examples of fourth ventricle catheter misplacement. In **a** the entry point is too close to the midline and to the transverse sinus and the trajectory is too high. In **b** the catheter is too short

floor of the fourth ventricle may be achieved through this approach, minimizing the risk of injury to the brain stem.

Overdrainage of the fourth ventricle shunt should also be avoided because the decreasing size of the cavity may cause shunt dysfunction and also secondary penetration of the catheter tip into the floor of the fourth ventricle: using catheters that are as short as possible and flow-regulating or medium-high pressure valves might be helpful in this regard. However, the most important rule to observe is always to connect the fourth ventricular catheter with a Y connector to the pre-existing ventriculoperitoneal shunt. The Y connector should be placed upstream from the valve, so that both compartments (supra- and infratentorial) of the ven-

tricular system will have the same pressure level, dictated by the same valve. The implantation of a completely new fourth ventricle-peritoneal shunt in the presence of a functioning supratentorial lateral ventriculoperitoneal shunt could result in the creation of a pressure gradient between the infra and supratentorial compartment, with possible onset of terrible, disabling headaches triggered by the move from reclining to upright standing. The clinical pictures can become dramatic, with the onset of opisthotonus-like postures that are at odds with the emergency CT or MRI scans usually performed in these cases, which show nothing to explain the gravity of the symptoms. Transforming the double shunt into a Y shunt usually allows immediate resolution of the symptoms.

Open Surgery

Open surgery, though widely performed in the last thirty years or so [23, 27, 61], should nowadays be reserved for selected cases. A suboccipital craniotomy with fenestration of the fourth ventricle outlets with or without internal shunting (between the fourth ventricle and cisterna magna) has been recently recommended by Villavicencio et al. [77] in cases of multiple shunt revision and infection in order to simplify the shunt system (see Chap. 18). This approach, also used successfully by Dollo et al. [17], is useful when an obstruction is present at the level of the outlet foramina, without impairment of absorption over the cerebral hemispheres. In 1980 Foltz and De Feo [23] performed direct microsurgical excision of the veil occluding the aqueduct (aqueductoplasty) in six cases of isolated fourth ventricle, in order to re-establish communication between the fourth ventricle and the supratentorial ventricular system, in which a single shunt could control hydrocephalus.

Endoscopy

Conceptually and practically, endoscopic aqueductoplasty is the ideal treatment by far. However, although endoscopic aqueductoplasty may be an interesting approach in cases of isolated fourth ventricle to eliminate the need for a complicated shunt system, Oi et al. [52] performed two endoscopic aqueductoplasties from the rostral and the caudal approach respectively, with poor results. More encouragingly, Teo et al. [75] reported good results in eight patients treated endoscopically out of a series of 16 patients affected by trapped fourth ventricle. In their experience, the endoscopic approach led to

a lower shunt revision rate during the postoperative follow up than was seen in the patients treated with fourth ventricle shunts, although the complication rate was quite high and was equal for both treatments (25%). Three options are available to the surgeon, depending upon the anatomy of the distorted ventricular system: lateral ventricle-fourth ventriculostomy, third ventricle-fourth ventriculostomy, and fourth ventricle-third ventriculostomy.

Lateral ventricle-fourth ventriculostomy is possible in some very long-standing cases where the supratentorial system is dilated and the trapped fourth ventricle, herniating through the tentorial hiatus, compresses the inferomedial wall of the ventricular trigone, reducing it to a translucent membrane. A parietal burr hole allows good visualization and control of this membrane. The side should be chosen taking into consideration the position of the internal cerebral veins (see Fig. 21b), which are usually displaced to one side, allowing safe perforation of the membrane with monopolar or bipolar coagulation followed by enlargement of the perforations and removal of cyst wall fragments (Fig. 23). As a rule a stent should be left in place across the perforation, because reduction of the volume of the fourth ventricle leads to shrinking of the membrane and progressive obliteration of the fenestration that has been performed. If an external drainage is left in place through the fenestration after the endoscopic procedure because of coexistent shunt infection, then injection of metrizamide is useful to confirm good communication between all the ventricular cavities (see Fig. 21c).

Third ventricle-fourth ventriculostomy is by far the most frequently used technique for cannulation of the aqueduct in a trapped fourth ventricle. A prerequisite for this technique is sufficient dilatation of at least one lateral ventricle with an open foramen of Monro and of the third ventricle (Fig. 24a-d) and the existence of a short-segment aqueductal stenosis. If the ventricles are slit, they can be dilated by upgrading the valve opening pressure in the case of externally adjustable valves, or by externalizing the distal catheter and slowly elevating the level of the CSF drainage bag. The burr hole placement is much further anterior than for a third ventriculostomy and should be placed at the level of the airway, at least 4 cm anterior to the coronal suture, in order to obtain a good trajectory for the stent (Fig. 25). Two stents can be used: a 5-cm preshaped right-angle catheter is a good solution because its curve will avoid downward displacements and precise calculation of the catheter length is not necessary. However, the right-angle curve can make manipulation difficult during endoscopic surgery. We personally prefer a normal straight ventricular catheter that we

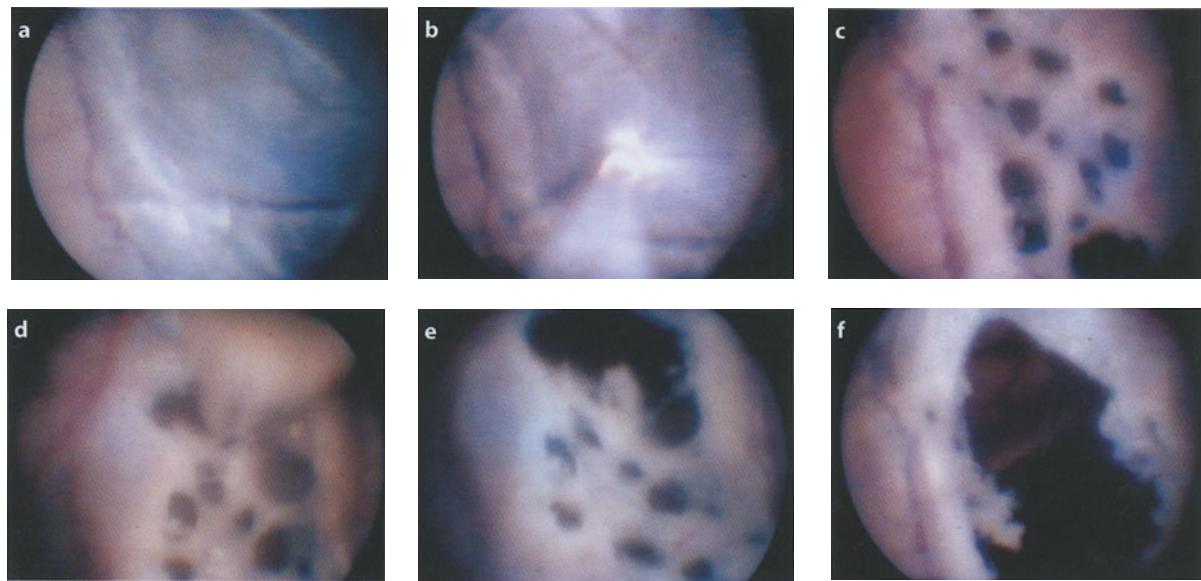


Fig. 23 a-f. Endoscopic view of lateral ventricle-fourth ventriculostomy. **a** There is a clear difference between the normal yellowish ependyma on the left and the translucent ependyma that covers the upper pole of the trapped fourth ventricle on the right. **b** The ependyma is coagulated and perforated to create a communication between the lateral and the fourth ventricle. **c** Several perforations are performed over the whole surface. **d** The tissue between the holes is removed with a forceps. **e** Intermediate view. **f** Final view: the cavity of the fourth ventricle is well seen through a large fenestration

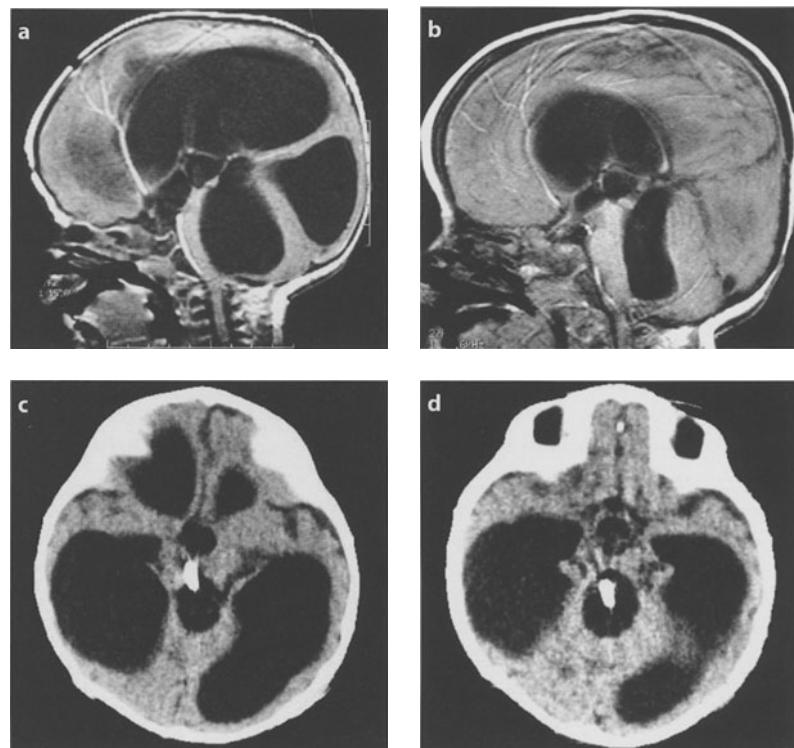


Fig. 24 a-d. Three-month-old baby girl, posthemorrhagic tetraventricular hydrocephalus with trapped fourth ventricle. **a** Preoperative and **b** Postoperative sagittal T1-weighted MRI. Endoscopic aqueductoplasty has been performed and a ventricular catheter has been inserted through a right coronal burr hole and connected to a peritoneal shunt system. **c, d** View of the catheter across the aqueduct

cut before inserting it into the ventricle. The length must be calculated on the basis of the sagittal MRI, knowing that the catheter will fall into the fourth ventricle and its distal tip will remain in the deepest part

of the fourth ventricle, which in the operating position is in the very lowest part of the vermis; the catheter must be long enough to allow the proximal tip to remain within the third ventricular cavity, but not too

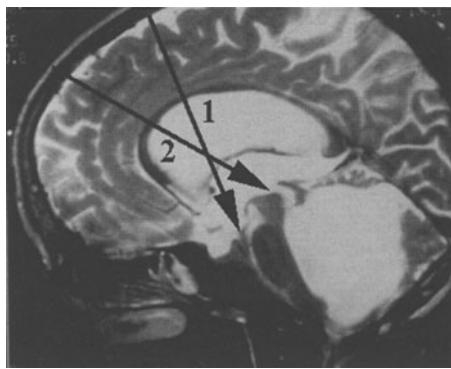


Fig. 25. Surgical trajectories for third ventriculostomy (arrow 1) and for endoscopic aqueductoplasty (arrow 2)



Fig. 26. Distance to calculate to cut the ventricular catheter at the correct length before insertion in order to avoid migration into the fourth ventricle

long, because after a decrease in the volume of the fourth ventricular the catheter could then be pushed upward into the roof of the third ventricle (Fig. 26). Failure to measure the length of the stent accurately could result in losing it into the fourth ventricle (if too short), with possible problems if shunt infection occurs, or possible damage to the mesencephalon in any attempt to remove it during surgery.

After entering the third ventricle the aqueduct is perfectly visualized if the burr hole has been correctly placed. The membrane occluding its inlet is easily broken by simply probing the aqueduct with a smooth Fogarty balloon (Fig. 27a). Inspection of the inlet usually permits good visualization of the fourth ventricular cavity (Fig. 27b); dilatation with the Fogarty balloon is rarely necessary and should be avoided if possible in order to minimize the risks of oculomotor dysfunction. The endoscope is then withdrawn into the lateral ventricle and the straight catheter is inserted through a second burr hole, visualized in the frontal horn (Fig. 27c), and under visual control inserted into the sylvian aqueduct (Fig. 27d).

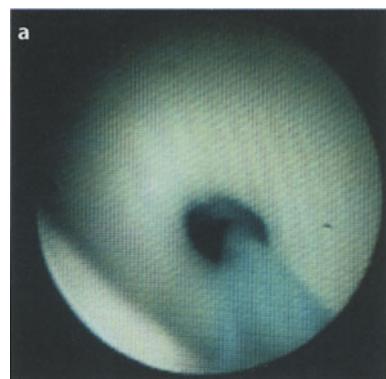


Fig. 27 a-d. Endoscopic aqueductoplasty and aqueductal stent implant as seen through a steerable fiberscope. For explanation see text

Fourth ventricle–third ventriculostomy consists in cannulating the sylvian aqueduct from below, entering the dilated fourth ventricle with the endoscope in the case of a small or slit-like supratentorial ventricular system. This situation (slit-like lateral and third ventricle with abnormally large fourth ventricle) is by far the most frequent in everyday clinical practice, and this procedure looks like the most logical and appealing. In fact, it is rarely performed because of the higher risk of severe consequences if hemorrhagic complications occur, and because the rarity of the condition makes this approach less natural even for experienced neuroendoscopists. The patient is placed in the prone position and the burr hole is drilled 2–3 cm from the midline. Neuronavigation is extremely helpful in placing the burr hole on the ideal trajectory in the axis of the aqueduct to be cannulated, in order to minimize the risk of entering the periaqueductal gray matter. It is very helpful also in identifying with certainty the inlet of the aqueduct, which can be difficult to recognize in the unusual and distorted anatomy of the trapped fourth ventricle. With the rapid spread of neuroendoscopy associated with neuronavigation, this technique has the potential to become the most widely used surgical procedure for trapped fourth ventricle. Its only theoretical limitation is the danger of cannulation of a very narrow aqueductal stenosis along the whole length of the aqueduct. In this case the periaqueductal gray matter could be entered by the catheter, with damage to the oculomotor nuclei and midbrain structures [68]. Precise preoperative MRI criteria will be necessary in order to make this procedure the rule of treatment.

Expanding Cavum Septi Pellucidi and Cavum Vergae

The cavum septi pellucidi (CSP) and cavum vergae (CV) were formerly called the fifth and sixth ventricles of the brain, but this nomenclature has been abandoned because of the absence of an ependymal lining and a choroid plexus inside the cava [72]. They are fluid-filled midline cavities interposed between the third ventricle and the corpus callosum, common findings in brains of premature infants and of other neonates at birth. Usually their involution occurs early in the course of life. Persistence of the CSP has been reported in 0.14%–18.9% of adults, while the CV is more rare (from 0 to 1.3%) [65, 72].

The persistence of one or both cavities may in many cases be considered a normal variant that does not cause any symptoms. Exceptionally, the CSP and CV may enlarge, becoming symptomatic. In addition, the CSP and CV may be associated with other dysgenetic lesions of the brain [73].

The septum pellucidum is usually composed of a single midline membrane with an ependymal lining on each surface [39]. More rarely it consists of two separate leaves that delineate a potential space. These leaves may be separated by a space of variable size: the cavum septi pellucidi. The cavum is bounded anteriorly by the genu of the corpus callosum, superiorly by the body of the corpus callosum, posteriorly by the columnae fornici, and inferiorly by the rostrum of the corpus callosum. The cavum vergae, first described in 1851 by the Italian anatomist Verga, is a cystic formation located in the prolongation of the septum pellucidum between the columnae fornici. The boundaries of the cavum vergae are anteriorly the columnae fornici, superiorly and posteriorly the splenium of the corpus callosum, and inferiorly the hippocampal commissure. The CV usually communicates with the CSP, forming a dumbbell-shaped cavum, due to the convergence of the columnae fornici, the anterior part being the CSP and the posterior the CV. The closure of the septal cavities in a caudorostral direction explains why a CV is rarely observed in the absence of a CSP, but a CSP is often observed in the absence of a CV. Histologically the walls of the cava are composed of glial fibers with fibrillary astrocytes and arachnoid cells without ciliae [19, 65], usually in immediate contact with cystic fluid.

The cava may be communicating or noncommunicating with the ventricular system through perforations in their walls [19, 36, 65]. The communicating type is the most common [19, 65] and is considered to cause no clinical manifestations. In contrast, the less frequent noncommunicating type, originally asymptomatic, may enlarge, compressing the neighboring neural structures and obliterating the foramina of Monro and/or the aqueduct. The CSP may also communicate with the subarachnoid space of the interhemispheric fissure, through a hole behind the rostrum [65].

The conditions that lead to enlargement of the CSP/CV and the origin of the fluid inside the cava are unclear. The cyst fluid resembles CSF [36, 65, 72]. Lanson et al. [36] suggested that cysts that present early in life may have a cellular lining in their walls able to secrete fluid from birth; in contrast, cysts that do not expand until later in life probably acquired the ability to secrete fluid through delayed differentiation of ependymal precursors or migration of ventricular ependymal cells through a congenital or acquired cystoventricular communication. However, a recent morphological and immunohistochemical study suggests that the lining cells are incapable of fluid secretion. Ronsin et al. [65] have proposed a flow of fluid (possibly with a valve mechanism) through an opening in the interhemispheric fissure. This opening may be the result of either a persistent congenital perfora-

tion or an acquired tear due to increased ventricular pressure. Oteruelo [58] suggested a different mechanism and claimed that fluid travels passively from the ventricle into the cavum by pressure gradient in the absence of any communication. Reabsorption of the fluid is performed by septal capillaries and veins. Thus, impaired reabsorptive mechanisms may result in progressive enlargement of CSP/CV. Sencer et al. [72] have reported a case in which the presence of venous hypertension due to sinus thrombosis had caused progressive enlargement of a CSP and CV, which resolved after normalization of venous return. In addition, as suggested by Lancon et al. [36], the enlarging CSP/CV may further compress the origin of the internal cerebral veins, aggravating the elevated intraventricular pressure and resulting in venous infarction. Wester et al. [79] noting in their series that the ventricular enlargement was present before the cava started to grow, and that draining the cava into the lateral ventricles caused the cystic cava to collapse but the ventricular enlargement to remain unchanged, suggested that the expansive growth of a CSP/CV might be the result rather than the cause of hydrocephalus: a slightly elevated intracranial pressure might be a driving force behind the filling of the cyst and a valve mechanism would responsible for trapping the fluid inside the cyst.

The velum interpositum and the hippocampal commissure offer less resistance to the enlarging cyst than the thick corpus callosum, enabling the cyst to displace the fornix and the anterior commissure caudally and encroach on the septal and periseptal nuclei of the hypothalamus. The thinning walls of the cava may rupture into the third or lateral ventricles, leading to resolution of the clinical symptoms [36]. The rupture may occur spontaneously as a consequence of excessive pressure within the cyst, as a result of head trauma. If fibrosis occurs at the site of rupture, the cyst may begin to expand again [36].

Clinical manifestations usually are related to intermittent obstruction of the foramen of Monro that results in raised intracranial pressure. However, the resulting hydrocephalus is usually much less dramatic than that produced by other midline cystic lesion, such as a colloid cyst. No cases of sudden death have been reported in the literature [79]. This difference may be explained by the fact that, with progressive dilatation of the lateral ventricles and upward stretching of the corpus callosum, the cyst walls, which compress the foramina from above, are lifted away from the lateral ventricular outlets and the obstruction is relieved [36], whereas colloid cysts are situated like plugs in the foramina and may be adherent to their walls [79].

Headache, emesis, papilledema, and syncope are the most frequent symptoms. Behavioral and auto-

nomic symptoms such as mental status signs, emotional lability, bizarre behavior, memory loss, developmental delay, hyperactivity, declining school performance, disturbance of sleep pattern, incontinence, hyperthermia, anorexia, and weight loss have been described in association with a CSP/CV with or without hydrocephalus [36, 46, 65, 72, 79]. They may be considered the consequence of direct compression of hypothalamic structures. Neuro-ophthalmological signs and symptoms, including abducens palsy, nystagmus, and visual field defects, are the result of hydrocephalus and direct compression on visual pathways [36].

Neuroradiological demonstration of CSP/CV is simple, but neuroradiological diagnosis of expanding CSP/CV may be difficult. A spherical appearance with biconvex bulging of the walls may indicate increased pressure inside the cava. Serial scans are useful in detecting the expansion. The indication for surgery is based on the presence of neurological symptoms with or without hydrocephalus [36, 46]. However, in a case of CSP/CV associated with obstruction of CSF flow distal to the third ventricle, it may be difficult to establish whether the CSP/CV is an expanding symptomatic lesion or is an incidental finding in a hydrocephalic patient: there are no certain radiographic criteria for identifying a symptomatic CSP/CV. MRI clearly demonstrates the benign histological nature of the lesion and provides information regarding the patency of the ventricular system. Enhancement of the cyst walls would suggest a neoplastic or inflammatory process. Abnormalities of the size or signal characteristic of the basal ganglia or diencephalon or the presence of hypothalamic signs and symptoms should be considered indications for MR venography [36].

The treatment of symptomatic CSP/CV is disputed. Therapeutic options reviewed by Lancon et al. [36] include: no treatment in the case of spontaneous rupture and relief of symptoms; craniotomy and fenestration of the cyst into the lateral ventricle, as initially proposed by Dandy [16] in 1931; cystoperitoneal shunting [46]; stereotactic placement of an internal shunt between the cyst and the ventricle [5, 19, 36, 79]; and endoscopic fenestration into the ventricle. Endoscopic fenestration should be considered the first-line treatment [70] because it avoids open surgery, which is burdened by a 30% rate of recurrence [36], and obviates long-term commitment to a shunt; it also allows direct visual inspection of the interventricular foramina for evidence of fibrosis. In some cases after the treatment of the cyst, when the cyst walls have collapsed, the hydrocephalus may persist [36, 79]. Nevertheless, according to Lancon et al. [36] fenestration of the cava should be performed prior to ventricular shunting, because it removes the local pressure on neighboring structures and theoretically prevents the

development of a transmural pressure differential between the cyst and ventricle that could further distort the fornix or deep cerebral veins. In contrast to this, Wisoff [80], considering that the expanding cava might be the result and not the cause of the hydrocephalus, suggests that appropriate management should be treatment of the hydrocephalus either by shunting or by third ventriculostomy, and subsequently, if the cava remain enlarged, endoscopic fenestration of the cava walls. If, in a patient with a shunt already in place, cavum expansion occurs as a possible result of loculation or a valve-like mechanism, then endoscopic fenestration into the already shunted cavity usually resolves the problem without the need to implant further material (Fig. 28).

In the majority of patients symptomatic improvements rapidly occur following treatment. Failure of

symptoms to improve may be the consequence of deep venous infarction [36] or distal impairment of CSF circulation, that should be managed appropriately [79].

Conclusion

The treatment and prognosis of multiloculated hydrocephalus, in all its anatomical presentations, has been dramatically changed in the last ten years by the advent and development of neuroendoscopy. There is the feeling, in the present state of knowledge, that neuroendoscopy has not yet fulfilled all its potential in this field. All efforts should be made to allow further progress and the wider use of neuroendoscopy to treat this frequent and otherwise dramatic condition.

References

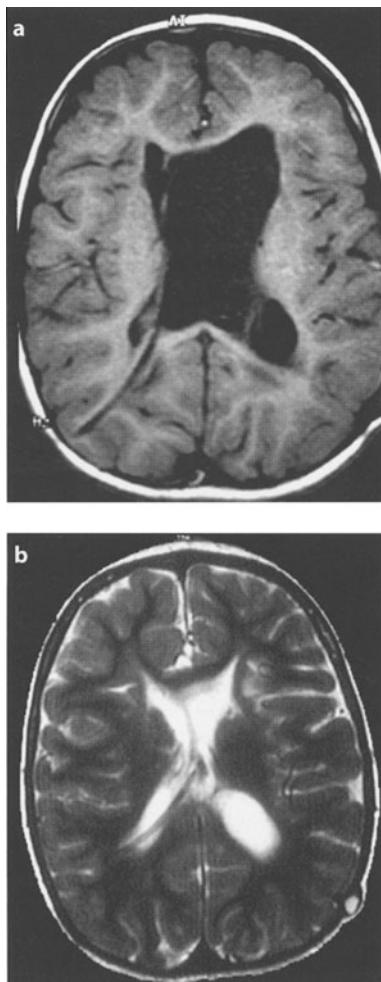


Fig. 28 a, b. Expanding cavum septi pellucidi in a patient affected by postmeningitic hydrocephalus treated with right ventriculoperitoneal shunt. Before (a) and after (b) endoscopic treatment

1. Albanese V, Tomasello F, Sampaolo S: Multiloculated hydrocephalus in infants. *Neurosurgery* 8: 641-646, 1981
2. Aleman J, Jokura H, Higano S: Value of constructive interference in steady-state, three dimensional, Fourier transformation magnetic resonance imaging for the neuroendoscopic treatment of hydrocephalus and intracranial cysts. *Neurosurgery* 48: 1291-1296, 2001
3. Balmer B, Bernays RL, Kollias SS: Interventional MRI-guided neuroendoscopy: a new therapeutic option for children. *J Pediatr Surg* 37: 668-672, 2002
4. Bauman B, Dannon L, Weitz R: Unilateral hydrocephalus due to the obstruction of the foramen of Monro: another complication of intrauterine mumps infection? *Eur J Pediatr* 139: 158-159, 1982
5. Behrens P, Ostertag CB: Stereotactic management of congenital midline cysts. *Acta Neurochir (Wien)* 123: 141-146, 1993
6. Berger MS, Sundsten J, Lemire RJ: Pathophysiology of isolated lateral ventriculomegaly in shunted myelodysplastic children. *Pediatr Neurosurg* 16: 301-304, 1990
7. Berman PH, Bamker BQ: Neonatal meningitis. A clinical and pathological study. *Pediatrics* 38: 6-24, 1966
8. Blom R, Witt N, Johnson ES: Demonstration of a symptomatic intraventricular cyst using direct intraventricular metrizamide instillation. *AJNR Am J Neuroradiol* 7: 1093-1095, 1986
9. Breeze RE, McComb JG, Hyman S: CSF production in acute ventriculitis. *J Neurosurg* 70: 619-622, 1989
10. Brown LW, Zimmerman RA, Bilaniuk LT: Polycystic brain disease complicating neonatal meningitis: documentation of evolution by computed tomography. *J Pediatr* 94: 757-759, 1979
11. Cairns H, Daniel P, Johnson RT, et al: Localized hydrocephalus following penetrating wounds of the ventricle. *Br J Surg War Surg Suppl* 1: 187-197, 1941
12. Cameron AH: The Arnold-Chiari and other neuro-anatomical malformations associated with spina bifida. *J Pathol Bact* 73: 195-206, 1957

13. Cipri S, Gambardella G: Neuroendoscopic approach to complex hydrocephalus. Personal experience and preliminary report. *J Neurosurg Sci* 45: 92-96, 2001
14. Collada M, Kott J, Kline DG: Documentation of fourth ventricle entrapment by metrizamide ventriculography with CT scanning. *J Neurosurg* 55: 838-840, 1981
15. Czervionke LF, Daniels DL, Meyer GA, et al: Neuroepithelial cysts of the lateral ventricles: MR appearance. *AJNR Am J Neuroradiol* 8: 609-613, 1987
16. Dandy WE: Congenital cerebral cysts of the cavum septi pellucidi (fifth ventricle) and cavum Vergae (sixth ventricle). Diagnosis and treatment. *Arch Neurol Psychiatry* 25: 44-66, 1931
17. Dollo C, Kanner A, Siomin V: Outlet fenestration for isolated fourth ventricle with and without an internal shunt. *Child's Nerv Syst* 17: 483-486, 2001
18. Domingo Z, Peter J: Midline developmental abnormalities of the posterior fossa: correlation of classification with outcome. *Pediatr Neurosurg* 24: 111-118, 1996
19. Donauer E, Moringlane JR, Ostertag CB: Cavum vergae cyst as a cause of hydrocephalus, "almost forgotten"? Successful stereotactic treatment. *Acta Neurochir (Wien)* 83:12-19, 1986
20. Drake JM, Kulkarni AV: Cerebrospinal fluid shunt infections. *Neurosurg Q* 3: 283-294, 1993
21. Eder HG, Leber KA, Gruber W: Complications after shunting isolated fourth ventricle. *Child's Nerv Syst* 13: 13-16, 1997
22. Eller TW, Pasternak JF: Isolated ventricles following intraventricular hemorrhage. *J Neurosurg* 62: 357-362, 1985
23. Foltz EL, De Feo DR: Double compartment hydrocephalus - a new clinical entity. *Neurosurgery* 7: 551-559, 1980
24. Gangemi M, Maiuri F, Donati PA, et al: Endoscopic surgery for monoventricular hydrocephalus. *Surg Neurol* 52: 246-251, 1999
25. Hawkins JC III, Hoffman HJ, Humphreys RP: Isolated fourth ventricle as a complication of ventricular shunting. *J Neurosurg* 49: 910-913, 1978
26. Heilman CB, Cohen AR: Endoscopic ventricular fenestration using "saline torch". *J Neurosurg* 74: 224-229, 1991
27. Hubbard JL, Houser OW, Laws ER: Trapped fourth ventricle in an adult: radiographic findings and surgical treatment. *Surg Neurol* 28: 301-306, 1987
28. James HE: Spectrum of syndrome of the isolated fourth ventricle in posthemorrhagic hydrocephalus of the premature infant. *Pediatr Neurosurg* 16: 305-308, 1990-91
29. Jamjoom AB, Mohammed AA, Al-Boukai A, et al: Multiloculated hydrocephalus related cerebrospinal fluid shunt infection. *Acta Neurochir (Wien)* 138: 714-719, 1996
30. Kalsbeck JE, DeSousa AL, Kleiman MB, et al: Compartmentalization of the cerebral ventricles as a sequela of neonatal meningitis. *J Neurosurg* 52: 547-552, 1980
31. Kehler U, Gliemroth J, Arnold H: Asymmetric hydrocephalus: safe endoscopic perforation of septum pellucidum: technical note. *Minim Invasive Neurosurg* 40: 101-102, 1997
32. Kleinhaus S, Germann TR, Sheran M et al: A role for endoscopy in the placement of ventriculoperitoneal shunt. *Surg Neurol* 18: 179-180, 1982
33. Kondziolka D, Lunsford LD: Stereotactic management of colloid cysts: factors predicting the success. *J Neurosurg* 75: 45-51, 1991
34. Kuiper EJ, Vandertop WP: Trapped third ventricle. *Acta Neurochir (Wien)* 143: 1169-1172, 2001
35. Laitt RD, Mallucci CL, Jaspan T, et al: Constructive interference in steady-state 3D Fourier-transform MRI in the management of hydrocephalus and third ventriculostomy. *Neuroradiology* 41: 117-123, 1999
36. Lancon JA, Haines DE, Raila FA, et al: Expanding cyst of the septum pellucidum. *J Neurosurg* 85:1127-1134, 1996
37. Lee M, Leahu D, Weiner HL, et al: Complications of fourth-ventricle shunts. *Pediatr Neurosurg* 22: 309-314, 1995
38. Lewis AI, Keiper GL, Crone KR: Endoscopic treatment of multiloculated hydrocephalus. *J Neurosurg* 82: 780-785, 1995
39. Liss L, Mervis L: The ependymal lining of the cavum septi pellucidi: a histological and histochemical study. *J Neuropathol Exp Neurol* 23: 355-367, 1964
40. Lorber J, Pickering D: Incidence and treatment of postmeningitic hydrocephalus in newborn. *Arch Dis Child* 41: 44-50, 1966
41. Marquadt G, Setzer M, Lang J, et al: Delayed hydrocephalus after resection of supratentorial malignant gliomas. *Acta Neurochir (Wien)* 144: 227-231, 2002
42. Mathisen T, Grane P, Lindquist C, et al: High recurrence rate following aspiration of colloid cysts in the third ventricle. *J Neurosurg* 78: 748-752, 1993
43. Maurice-Williams RS, Choksey M: Entrapment of the temporal horn: a form of focal obstructive hydrocephalus. *J Neurol Neurosurg Psychiatr* 49: 238-242, 1986
44. McCracken GH, Mize SG: A controlled study of intrathecal antibiotic therapy in gram negative enteric meningitis in infancy. *J Pediatr* 89: 66-71, 1976
45. Milhorat TH: Comment. In: Foltz EL, De Feo DR: Double compartment hydrocephalus - a new clinical entity. *Neurosurgery* 7: 551-559, 1980
46. Miyamori T, Miyamori K, Hasegawa T: Expanded cavum septi pellucidi and cavum Vergae associated with behavioral symptoms relieved by a stereotactic procedure: case report. *Surg Neurol* 44: 471-475, 1995
47. Mohanty A, Das BS, Sastry Kolluri VR, et al: Neuro-endoscopic fenestration of occluded foramen of Monro causing unilateral hydrocephalus. *Pediatr Neurosurg* 25: 248-251, 1996
48. Montes JL, Clarke DB, Farmer JP: Stereotactic transtentorial hiatus ventriculoperitoneal shunting for the sequestered fourth ventricle. *J Neurosurg* 80: 759-761, 1994
49. Nida TY, Haines SJ: Multiloculated hydrocephalus: craniotomy and fenestration of intraventricular septations. *J Neurosurg* 78: 70-76, 1993
50. Nowoslawska E, Polis L, Kaniewska D, et al: Effectiveness of neuroendoscopic procedures in the treatment of complex compartmentalized hydrocephalus in children. *Child's Nerv Syst*, 2003 in press
51. O'Brian MS: Comment. In: Foltz EL, De Feo DR: Double compartment hydrocephalus - a new clinical entity. *Neurosurgery* 7: 551-559, 1980
52. Oi S, Hidaka M, Hinda Y, et al: Neuroendoscopic surgery for specific forms of hydrocephalus. *Child's Nerv Syst* 15: 56-68, 1999
53. Oi S, Kudo H, Yamada H: Hydromyelic hydrocephalus. Correlation of hydromyelia with various stages of hydrocephalus in post shunt isolated compartments. *J Neurosurg* 74: 371-379, 1991
54. Oi S, Matsumoto S: Isolated fourth ventricle. *J Pediatr Neurosci* 2: 125-133, 1986
55. Oi S, Matsumoto S: Slit ventricles as a cause of isolated ventricles after shunting. *Child's Nerv Syst* 1: 189-193, 1985

56. Oi S, Matsumoto S: Pathophysiology of aqueductal obstruction in isolated fourth ventricle after shunting. *Child's Nerv Syst* 2: 282-286, 1986
57. Oi S, Matsumoto S: Pathophysiology of nonneoplastic obstruction of the foramen of Monro and progressive unilateral hydrocephalus. *Neurosurgery* 17: 891-896, 1985
58. Oteruelo FT: On the cavum septi pellucidi and cavum Vergae. *Anat Anz* 162: 271-278, 1986
59. Parrent AG: Endoscopically guided fenestration of the choroidal fissure for treatment of trapped temporal horn. *J Neurosurg* 93: 891-894, 2000
60. Powers SK: Fenestration of intraventricular cysts using a flexible steerable endoscope and argon laser. *Neurosurgery* 18: 637-641, 1986
61. Raimondi AJ, Samuelson G, Yarzagharay L, et al: Atresia of the foramen of Luschka and Magendie: the Dandy-Walker cyst. *J Neurosurg* 31: 202-216, 1969
62. Reinprecht A, Dietrich W, Berger A: Posthemorrhagic hydrocephalus in preterm infants: long term follow up and shunt related complications. *Child's Nerv Syst* 17: 663-669, 2001
63. Rhoten RLP, Luciano MG, Barnett GH: Computer-assisted endoscopy for neurosurgical procedures: technical notes. *Neurosurgery* 40: 632-638, 1997
64. Rhoton AL Jr, Gomez MR: Conversion of multilocular hydrocephalus to unilocular. *J Neurosurg* 36: 348-350, 1972
65. Ronsin E, Grosskopf, Perre J: Morphology and immunohistochemistry of a symptomatic septum pellucidum cavum Vergae cyst in man. *Acta Neurochir (Wien)* 139: 366-372, 1997
66. Salmon JH: Isolated unilateral hydrocephalus following ventriculoatrial shunt. *J Neurosurg* 32: 219-226, 1970
67. Schellinger D, Grant EG, Manz HJ: Ventricular septa in the neonatal age group: diagnosis and considerations of etiology. *AJR Am J Neuroradiol* 7: 1065-1071, 1986
68. Schroeder HWS, Gaab MR: Endoscopic aqueductoplasty: technique and results. *Neurosurgery* 45: 501-518, 1999
69. Schultz P, Leeds NE: Intraventricular septations complicating neonatal meningitis. *J Neurosurg* 38: 620-626, 1973
70. Schut L. Comment. In: Wester K, Kråkenes J, Moen G: Expanding cava septi pellucidi and cava Vergae in children: report of three cases. *Neurosurgery* 37: 134-137, 1995
71. Scotti G, Musgrave MA, Fitz CR, et al: The isolated fourth ventricle in children: CT and clinical review of 16 cases. *AJR Am J Radiol* 135: 1233-1238, 1980
72. Sencer A, Sencer S, Turantan I: Cerebrospinal fluid dynamics of the cava septi pellucidi and Vergae. *J Neurosurg* 94: 127-129, 2001
73. Shaw CM, Ellsworth CA Jr: Cava septi pellucidi et Vergae: their normal and pathological states. *Brain* 92: 213-224, 1969
74. Strowitzki M, Kiefer M, Steudel WI: A new method of ultrasonic guidance of neuro-endoscopic procedures. Technical note. *J Neurosurg* 96: 628-632, 2002
75. Teo C, Burson T, Misra S: Endoscopic treatment of the trapped fourth ventricle. *Neurosurgery* 44: 1257-1262, 1999
76. Valenzuela S, Trellez A: Pediatric neuroendoscopy in Chile. Analysis of the first 100 cases. *Child's Nerv Syst* 15: 457-460, 1999
77. Villavicencio AT, Wellos JC, George TM: Avoiding complicated shunt systems by open fenestration of symptomatic fourth ventricular cysts associated with hydrocephalus. *Pediatr Neurosurg* 29: 314-319, 1998
78. Watanabe T, Katayama Y: Evaluation by magnetic resonance of the entrapped temporal horn syndrome. *J Neurol Neurosurg Psychiatr* 66: 113-117, 1999
79. Wester K, Kråkenes J, Moen G: Expanding cava septi pellucidi and cava Vergae in children: report of three cases. *Neurosurgery* 37: 134-137, 1995
80. Wisoff JH. Comment. In: Wester K, Kråkenes J, Moen G: Expanding cava septi pellucidi and cava Vergae in children: report of three cases. *Neurosurgery* 37: 134-137, 1995
81. Wong TT, Lee LS: Membranous occlusion of the foramen of Monro following ventriculoperitoneal shunt insertion: a role for endoscopic foraminoplasty. *Child's Nerv Syst* 16: 213-217, 2000

Hydrocephalus in Neurocysticercosis and Other Parasitic and Infectious Diseases

SÉRGIO CAVALHEIRO¹, SAMUEL T. ZYMBERG¹ AND MÁRCIA C. DA SILVA^{1,2}

The cestode species are the most common parasites that affect the central nervous system (CNS). Five different cestode infections of the nervous system are: cysticercosis, from the larva of *Taenia solium* – the most common of them, with more than 50 000 people infected worldwide; hydatidosis (hydatid cyst disease), from the larva of *Echinococcus granulosus*; alveolar cyst disease from the larva of *Echinococcus multilocularis*; coenurosis, a rarer type, from the larva of *Taenia multiceps*; and, exceptionally, sparganosis from the larva of *Spirometra mansonioides*. Only the most important ones and those related to hydrocephalus will be discussed here – cysticercosis and hydatidosis. Three other infections are common and may lead to hydrocephalus. They are fungal, viral, and infections by *Mycobacterium tuberculosis*. Other bacterial ventriculitis will not be discussed in this chapter.

Neurocysticercosis

Epidemiology

Cysticercosis infects about 50 million people around the world, 50 000 of whom die each year. It is found, alongside pork tapeworm infestation, in countries with poor hygiene habits. It is rare in most of Europe; in Asia reports are sparse. It occurs frequently in India, the northern coast of Africa, especially Egypt, and among the aborigines of southern Africa. Cysticercosis is rare in the United States of America, but is the leading cause of hydrocephalus and seizures among Hispanic Americans living in Los Angeles and California [4, 59]. Latin America is the area with the highest incidence of cysticercosis – it is referred from Mexico to Argentina and Chile. From all autopsies in Mexico in

1979, 1.9% showed infection by *T. solium*. Colli et al. reported that 2.7% of hospital admissions for neurological diseases in the city of São Paulo in 1986 were due to neurocysticercosis [17]. Admissions in the pediatric age group due to neurocysticercosis comprised 2%-10% of all cases. The habit of repeatedly introducing their fingers into their mouths and easy contact with the soil expose children to a higher risk of massive cestode infections. Statistically, older people are less affected [12, 39].

Cysticercosis affects mostly people with lower living standards. Though a few studies have shown a higher incidence among males, there seems to be no sex preponderance, and as to age, the peak incidence is between 25 and 35 years [52].

Incidence of Hydrocephalus in Neurocysticercosis

In general terms, hydrocephalus is responsible for 15%-30% of clinical manifestations of neurocysticercosis [42]. Neurocysticercosis can be classified into two forms: benign and malignant [25]. In the benign form, the parasites are usually parenchymatous, on the meninges outside the cisterns, or, in a small number of cases, ventricular. Patients are asymptomatic or present with headaches or seizures. Prognosis is good and response to treatment is quick. In the malignant form of the disease, the parasites are located in the subarachnoid space, inside the cisterns or inside the ventricles. Blood vessels are affected. Hydrocephalus is the most common clinical presentation and may be the result of basal arachnoiditis or of the presence of intraventricular cysticerci. Patients may present with myriad symptoms or develop symptoms of increased intracranial pressure. Prognosis is poor and therapeutic response not good. Wei et al. [70] analyzed 1400 cases of cerebral cysticercosis and detected ven-

¹Department of Neurosurgery, Escola Paulista de Medicina, Federal University of São Paulo, São Paulo; ²Department of Neurosurgery, Hospital Infantil São Camilo, Belo Horizonte, Brazil

triculomegaly in 204 patients (14.5%). Seventy patients had global dilatation of the ventricles and 67 (32.8%) isolated dilatation of the fourth ventricle. In 1984, Apuzzo et al. [4] demonstrated in a series of 45 cases of intraventricular cysticercosis that the fourth ventricle is most commonly affected (24 patients). In 12 cases, the cysticerci were located in the third ventricle, and in 5, inside the lateral ventricles. This series, however, did not show any case of isolated blockage of the temporal horn of the lateral ventricle. Conversely, in our series the presence of cysts completely blocking the temporal horn is somewhat common (Fig. 1). The cysticerci may move from one ventricular cavity to another, a fact that has been verified during ventriculography [4, 15].

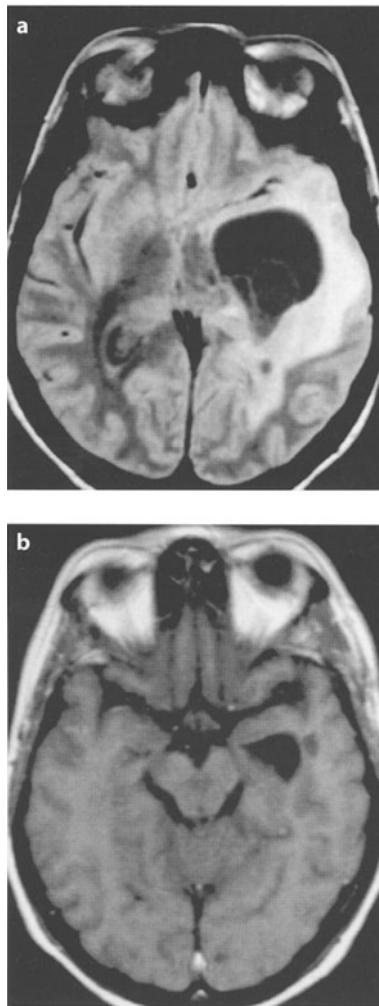


Fig. 1. **a** Axial FLAIR MRI demonstrating blockage of the temporal horn by cysts. **b** Axial T1-weighted MRI after endoscopic cyst removal

Transmission and Life Cycle of the Parasite

Humans are the only definitive hosts of *T. solium*, harboring the mature tapeworms in the lumen of the small intestine. Usually, there are only minimal clinical symptoms or even no symptoms at all. The mature *T. solium* is composed of a head or scolex that contains four suckers and a double crown of hooks, a narrow neck, and a body that is sometimes many meters long and is composed of hermaphroditic proglottids. A few proglottids are released daily from the distal extremity of the tapeworm and eliminated with the host's feces. The host thus delivers proglottids with large numbers of fertile eggs to the exterior, where they contaminate the soil. These eggs are resistant to being dried out and may remain in the soil or water for months. In some cases, the eggs are released inside the intestinal lumen, and these are the eggs released with the host's feces. Around 50% of these eggs are mature and fertile. The usual intermediate host, the pig, becomes infected by ingesting water or food contaminated by human feces. The parasites then take shelter in organs with a high oxygenation and movement level, such as the brain, chewing muscles, tongue, and heart (Fig. 2). By consuming uncooked pork containing the larva (intermediate form), humans acquire tapeworms – the mature form of the parasite (Fig. 2).

Human cysticercosis may result from two mechanisms: autoinfestation and heteroinfestation. In the former, the proglottids may release the fertile eggs inside the host's intestines, leading to internal self-infestation. This is considered one of the ways man can become infected by *T. solium*. In order to liberate the larvae, the eggs need to be exposed to the stomach acid. Thus, vomiting or antiperistaltic movements of the intestines push proglottids with fertile eggs toward the stomach. These proglottids may, in turn, fragment and release their eggs to the effects of the stomach acids, and suffer, back into the duodenum, intestinal digestion and disintegration of the embryophore and release of the oncosphere. In the small intestine, the larva attaches itself to the intestinal wall using its hooks, and insinuates itself between the epithelial cells of the villi, with the help of cytolytic substances secreted by special glands. It reaches the connective tissue corium and, once the lumen of the capillaries is reached, invades the tissues through the blood vessels. Other facts corroborate this infestation mode, such as the presence in one individual of both cysticerci and the mature tapeworm. A history of tapeworm infection is found in 7%-22% of patients with cysticercosis [59]. External self-infestation occurs when the individuals are

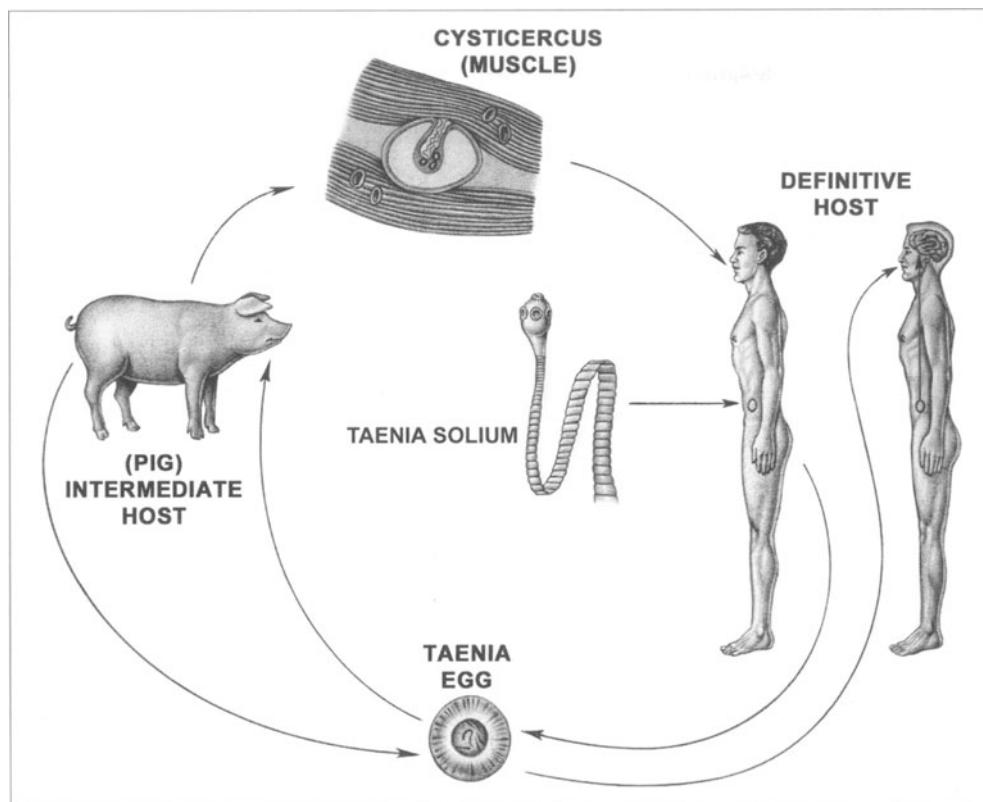


Fig. 2. Life cycle of the parasite

contaminated by their own feces, ingesting eggs or proglottids of their own tapeworm [2].

The mechanisms involved in heteroinfestation include ingestion of water, vegetables, or fruit contaminated by *T. solium* eggs, either through poor hygiene habits or by soil fertilized with human feces. Usually, consumption of contaminated pork leads to tape-worm infection.

The mature proglottids of the *T. solium* are eliminated from the intestine with the feces into the environment, degenerate, and release the eggs (embryophores), which harbor the embryo (hexacanth). Once ingested, the egg undergoes the effects of the gastric acids and passes to the intestines where, 24-72 h afterwards, its shell fragments, releasing the oncosphere. The oncosphere, in turn, penetrates the intestinal wall with the help of its hooks, reaches the mesenteric veins and then the blood stream. The stomach is thus the first barrier against this infestation, as only eggs whose shells have resisted the gastric acidity will release their oncosphere in the intestinal alkaline medium. Once liberated in the blood stream, the embryos will be retained in places where the diameter of the vessels is too small or the circulation slow (muscle, retina and brain).

The larval form of *T. solium*, *Cysticercus cellulosae*, develops from the embryo. It possesses a head and a neck, invaginated inside a vesicle. The head is similar to that of the adult form and the neck is very small; both are wrapped around themselves. The vesicle is clear, semitransparent, of variable shape, and measures about 10-15 mm; its interior is filled with crystalline fluid. When the cysticercus is located within the cerebral ventricles or in the subarachnoid space around the brainstem, the head and neck may disappear and secondary vesicles may form from its walls, mostly interconnected, taking the aspect of an irregular grape cluster (2-15 cm). This cluster is called *Cysticercus racemosus* [13, 14].

Pathological Findings in Neurocysticercosis

From one to hundreds of embryos may reach the CNS, where they may survive for 1-30 years in the form of *Cysticercus cellulosae*, or as *Cysticercus racemosus* (its intermediate form) or even as both forms coexisting together. Once settled, the cysticerci, while alive, cause almost no response from the surrounding tissues. The inflammatory response is related to the number of parasites and their state of degeneration, which, in turn,

depends essentially on the release of antigens [26]. In many cases, the immune response develops slowly, allowing the parasites to survive for many years inside the host in a state of relative immunological tolerance. In some cases the parasites are rapidly destroyed due to an intense inflammatory reaction. This reaction can elicit concomitant injury to the brain tissue around the cysticerci. Between these two extremes, there is a myriad of immune response levels. Women have been found to present a more intense tissue inflammatory reaction than men [53]. The human leukocyte antigen (HLA) participates in the pathogenesis of cysticercosis. Some cysticerci have HLA molecules adhering to their membranes. The parasites covered with HLA molecules give rise to an inflammatory reaction more intense than that of cysticerci without those molecules adhering to the surface, probably because HLA molecules are modified by the parasite or because the parasite itself produces an HLA-like molecule [20]. Patients with cysticercosis present an elevated HLA-A-28 antigen, while the antigen HLA-DQw2 is decreased, with a relative risk of developing the disease 3.5 times higher in the presence of the antigen HLA-A-28 [21]. These findings suggest that the susceptibility or resistance of an individual to develop cysticercosis may be related in part to genetic characteristics.

The cysticerci are round vesicles of variable size, filled with liquid, constituted by an external layer known as vesicular membrane and an internal portion called scolex [24]. The scolex presents a structure that is similar to the adult parasite that can be absent in parasites located in the subarachnoid space, especially the basal cisterns, where they group in numerous adherent membranous vesicles, grouped in clusters. Classically, cysticerci with scolex are called *Cysticercus cellulosae* and those without scolex, *Cysticercus racemosus*. Parenchymal cysticerci measure about 1 cm diameter, being located preferentially at the level of the basal ganglia and cerebral cortex due to their increased vascularity.

Once implanted in the CNS, the hexacanth begins its development onto the embryonic form, the cysticercus [24]. In its first stage of development, called the vesicular stage, the membrane is thin and transparent, the fluid is clear, and an invaginated scolex is the norm. The cysticerci can remain in this phase or start a degenerative process as a result of the host's immune response, which may lead to their destruction in three stages. The first stage of this process, when the vesicular fluid becomes cloudy and the scolex shows signs of hyalin degeneration, is called the colloidal stage. Later on, the walls of the cyst become thick and the scolex is transformed into a granular mineralized structure. Lastly, the whole parasite becomes an inert calcified nodule (Fig. 3).

The intensity of the tissue changes around the cysticerci depends on which stage the parasites are in

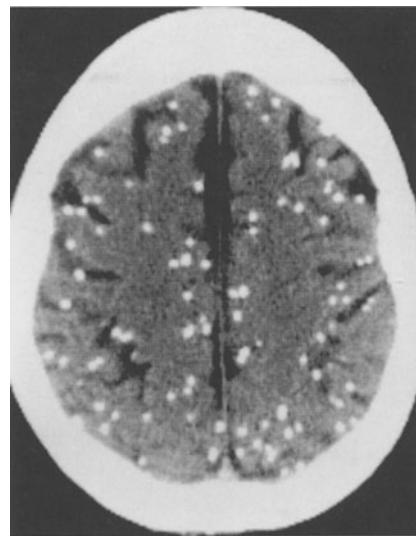


Fig. 3. Unenhanced CT scan demonstrating calcifications as a result of cysticercus degeneration

and on their location in the CNS [24]. In the vesicular stage they induce a perilesional inflammatory reaction, composed mainly of lymphocytes, plasma cells, and eosinophils. In the colloidal stage, a dense collagen membrane is formed around the vesicular membrane and the perilesional inflammatory infiltrate may also endanger the parasite. The surrounding brain tissue presents reactive gliosis, which explains one of the most common clinical manifestations of neurocysticercosis, epilepsy [20, 22, 52, 53].

The degeneration is of the hyalin type and is characterized by calcification of the parasite structure. Glial proliferation develops around the inflammatory reaction, and there may be damage to neighboring neurons and vessels giving rise to ischemic damage to the parenchyma. Rarely, the tissue reaction can diffuse to the brain and meninges. The meningeal cysticerci also give rise to the diffuse formation of a dense exudate in the subarachnoid space composed of collagen fibers, multinucleated giant cells, eosinophils, and hyalinized parasitic membranes, with thickening of the basal meninges. This chronic inflammation is responsible for the development of hydrocephalus in more than half of the cases.

When the cysticercus is located within the ventricular system, it also gives rise to intense perilesional inflammatory reaction (Fig. 4), if it is adherent to the ventricular wall. In these cases, the ependymal cell layer is altered, forming subependymal giant cells that tend to group and protrude into the interior of the ventricular cavities, leading to obstruction to the free flow of cerebrospinal fluid (CSF) at the level of the foramen of Monro or the aqueduct of Sylvius.

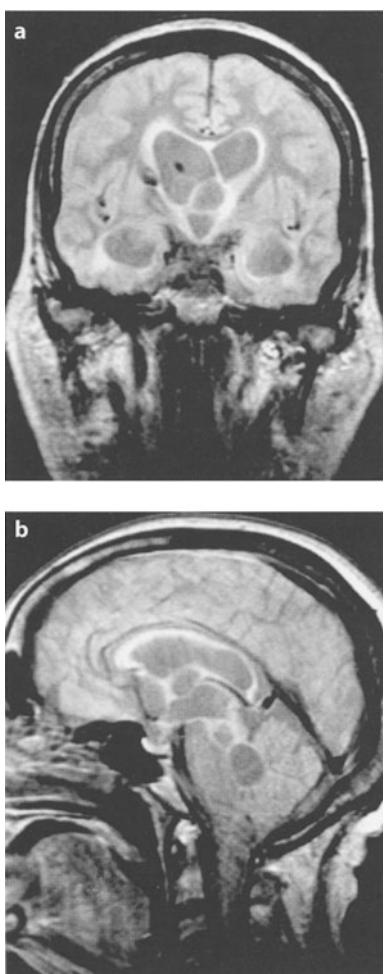


Fig. 4. **a** Coronal and **b** sagittal FLAIR MRI showing intraventricular cysts and ependymal inflammatory reaction

This process is called granular ependymitis and leads to obstructive hydrocephalus. Hydrocephalus may be asymmetrical if only one foramen of Monro is obstructed. However, the development of granular ependymitis due to a cysticercus may not fix it, allowing it still to move around. This can lead to transient obstruction by the cysticercus.

Intramedullary forms of the disease have been described, mainly at the mid-thoracic level, whereas spinal subarachnoid localizations are more common at the cervical level [7,15].

Clinical Manifestations and Diagnosis

With regard to its pathophysiology, neurocysticercosis may present as a high- or low-intensity disease that may be located in the ventricles, parenchyma,

meninges, or mixed location. It may manifest as an acute, subacute, or chronic disease, in remission or exacerbation; it may have a simple or complicated clinical evolution, be asymptomatic, symptomatic, or fatal. It may subside with or without treatment; its symptoms may disappear for long periods of time or persist until death. The onset of the symptoms may be insidious or abrupt, and the clinical course is variable and unpredictable. The prognosis is always severe [2].

The clinical presentation may have an insidious beginning and lead to death within a few minutes or in over 30 years' time. The polymorphous nature of the symptoms is characteristic of the disease and is due to a series of factors such as the number, location, form, size, and stage of development of the parasite, the nature of the parasite's action in the host's organism, and the host's individual immunological response [63-66]. In 1988, Zee et al. [84] reported that out of 46 patients with intraventricular cysts, 6 died of hydrocephalus a short time after admission.

Diagnosis may be reached by appropriate clinical observation that includes epidemiological aspects, clinical and neurological examination, along with detailed study of the CSF and imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI).

Cutaneous cysticercosis may be associated with neurocysticercosis in 65% of the cases. It usually suggests a benign neurocysticercosis. The most common clinical symptoms of the disease are: epilepsy, intracranial hypertension, psychiatric changes, meningitis, and meningoencephalitis. Occasionally, headache is the only complaint. Although the association of these symptoms is common, isolated epilepsy seems to be the predominant form of presentation. Partial seizures are the most frequent; intractable seizures are rare. Intracranial hypertension is usually severe and tends to occur in association with other symptoms, especially epilepsy. Its treatment is difficult, although once the acute phase has passed, these children frequently present a good recovery. Sequelae may ensue in some cases. Behavioral disturbances such as aggressiveness, agitation, and irritability may also be seen. One should bear in mind the possibility of these children developing a clinical picture of neurological and psychological regression that, when associated with epilepsy, resembles a degenerative disease of the CNS.

The analysis of the disease is the most important aspect of its treatment. Neurocysticercosis can be divided into two major forms: active and inactive. In the active forms of the disease one may have clinical manifestations such as (1) arachnoiditis, (2) hydrocephalus due to meningeal inflammation, (3) parenchymal cysts, (4) cerebral infarction due to vasculitis, (5) mass effect due to large cysts, (6) intraventricular cysts, and

(7) spinal cysts. The inactive forms present as (1) parenchymal calcifications and (2) hydrocephalus due to meningeal fibrosis.

Cerebral cysticercosis may be entirely asymptomatic, being demonstrated only at autopsy. In the symptomatic cases the neurological examination is normal in 25% of the total [22]. The initial symptoms that prompt the patient to seek medical help are seizures, meningeal signs, visual disturbances, headaches, and vomiting. Epilepsy may be an isolated symptom for a long time, being called idiopathic epilepsy still to the present day. Neurocysticercosis may lead to an intracranial hypertension syndrome, with headache, vomiting, dizziness, and papilledema. Altered mental status may be a manifestation of the disease, and pure psychotic forms are found in 15% of the cases. Cysticerci on the motor or sensory cortical areas can cause seizures, usually generalized. Chronic focal epilepsy is related to residual calcifications and areas of gliosis that represent the inactive form of the disease.

Meningitis due to neurocysticercosis may show acute or chronic headaches, neck pain, and occasionally fever. In some cases, the typical presentation of increased intracranial pressure can be seen. In other cases, meningitis may progress slowly and with only mild symptoms, leading to communicating hydrocephalus due to basilar arachnoiditis. The pathogenesis of neurocysticercosis is that of a chronic inflammatory process with an irregular period of activation that occurs when cysticerci die and disintegrate, causing antigen release [54, 56].

Intraventricular cysticercosis occurs in 11%-17% of the patients, being a potentially lethal form of the disease [85]. The oncospheres probably reach the ventricles through the choroid plexus. They may develop and float freely in the CSF or adhere to the ependyma by a granulomatous reaction. Occlusion of the aqueduct or the foramina of Luschka and Magendie may result in acute obstructive hydrocephalus, sometimes associated with sudden death. Nausea, vomiting, dizziness, headache, diplopia, syncope, and altered state of consciousness are common manifestations of intraventricular cysts.

CSF analysis is one of the most important examinations in the diagnosis of neurocysticercosis, even though the results may be normal in approximately 20%-25% of the cases despite the presence of viable cysticerci. In these cases, an indirect approach to diagnosis is a trial drug therapy. In roughly 75% of the cases, the immunodiagnosis is positive or, at least, there are changes in one or more of the CSF parameters. On the other hand, if the patient's condition permits, close clinical observation with CSF examination, CT, and/or MRI may lead to an unequivocal diagnosis. The definitive diagnosis of neurocysticercosis is based on immunodiagnosis in the CSF and/or on lesions sugges-

tive of this parasitic disease on CT or MRI. The changes in CSF that characterize the syndrome are lymphocytic pleocytosis, increased eosinophilic content, elevated total protein levels, hypoglycorrachia, and positive immunological reactions in the CSF. Two or more positive tests increase the certainty of the diagnosis. The complement fixation test, one of the first tests utilized for the diagnosis of this disease, is positive in 83% of the cases of active meningeal cysticercosis if there are inflammatory changes of CSF. Conversely, the test sensitivity is only 22% if CSF examination is normal. Another immunoassay used nowadays is the ELISA (enzyme-linked immunosorbent assay), which has a specificity of 95% and a sensitivity of 87% in cases of active meningeal neurocysticercosis.

Images made by CT scanning vary according to the phase of maturation of the parasite and its location. Viability of the cysticercus usually is determined by contrast enhancement. Neurocysticercosis may show on CT as single, multiple, or racemose vesicles, generally localized in the brain parenchyma. The cysts have well-defined contours, no perilesional edema, and little or no enhancement after contrast administration; colloidal-phase cysts show perilesional edema, have less defined contours, and may present annular contrast enhancement separating the cyst from surrounding cerebral edema. This tomographic picture was defined as the acute encephalitic phase. Granulomas indicate a degenerating parasite; they may be single or multiple, ordinarily nodular and located on the parenchyma. Calcifications are the most common tomographic findings. They present as minuscule hyperdense lesions not surrounded by edema, that do not change after administration of intravenous contrast; they may be single or multiple, of various sizes, always round, and appear at least 36 months after the start of the degeneration. The presence of diffuse or localized edema without vesicles in the treated patient may indicate the beginning of the evolutive phase, due to an inflammatory reaction, hydrocephalus, increased ventricular size, sometimes in the absence of vesicles, calcifications or granulomas. This is the characteristic pattern of cysticercotic encephalitis, a particularly severe form of neurocysticercosis in which the immune system responds actively and intensely against a massive invasion of the brain parenchyma by cysticerci.

CT findings of subarachnoid neurocysticercosis include hydrocephalus, abnormal enhancement of the basal meninges, and cerebral infarction. Ventricular cysticerci may be isodense in relation to CSF, making their visualization difficult on CT scan. Ventriculography allows precise identification of these cysts [16].

The MRI characteristics depend on the stage of the disease. Vesicular cysts are seen as round lesions with

well-defined contours and a signal intensity similar to CSF in both T₁- and T₂-weighed images. The scolex is seen as a hyperdense point inside the cystic lesion. The details of the cyst wall and perilesional edema, in addition to the presence of intraventricular cysts, are better visualized. All MRI sequences can identify the vesicles. The degenerating vesicles are recognized by the presence of edema, which appears bright on T₂ sequences and is enhanced by contrast material. Granulomas and residual calcifications appear as a signal void. These forms of neurocysticercosis demonstrate one of the most important diagnostic limitations of MRI. MRI easily diagnoses meningeal cysticerci, as they present a signal different from the CSF.

In childhood, the diagnosis through imaging demonstrates two factors that are different from the disease in adults. The first is the number of lesions: only a small group presents with an intact parasite, the vesicle; also, most images are from the acute phase of the disease. Secondly, increased intracranial pressure in infancy is due to cerebral edema from the inflammatory reaction and not to hydrocephalus secondary to ventricular obstruction, the latter being common in adult patients.

Treatment

It is known that neurocysticercosis may be treated surgically or medically. Surgery for removal of cysticerci, employed in only a small and specific number of cases (racemose cisternal cysticerci, ventricular cysticerci), is practically never used in children as these forms of the disease do not ordinarily occur in this age group. Carbamazepine is suggested for the control of epilepsy because of the increased frequency of partial seizures. Del Brutto and Sotelo [20-22] demonstrated that 83% of the patients became drug-free if anticonvulsants were used in conjunction with cysticercocidal drug therapy. Conversely, only 26% of the patients were drug-free when only anticonvulsants were utilized. Increased intracranial pressure is treated especially dexamethasone, with good results. If increased intracranial pressure is severe, due to encephalitis, treatment is prolonged for one month or more. Dexamethasone should be slowly tapered off at the end of the treatment. For those few patients who present severe intracranial hypertension that is unresponsive to dexamethasone, mannitol or a lumboperitoneal shunt might be used as a last resort.

Etiological treatment involves drugs that penetrate the CNS and destroy the parasite. Currently two drugs are utilized: praziquantel (PZQ) and albendazole (ABZ). Their use is restricted to patients who exhibit intact forms of the parasite, i.e., vesicles. The simultaneous administration of corticosteroids and cysticercocidal drugs to patients with intra-

parenchymal lesions is also controversial [20, 21]. ABZ has been the preferred initial cysticercocidal drug, as it is cheaper, has fewer side effects, and is used for a shorter period of time. If the lesions persist, PZQ may be used after 3 months, or the ABZ treatment may be repeated [7, 16]. PZQ is an isoquinoline with strong antiparasitic activity that leads to the disappearance of 60%-70% of intraparenchymal cysts after 15 days of treatment at a dosage of 50 mg/kg per day. ABZ is a benzimidazole with antihelmintic properties, currently the drug of choice for the treatment of neurocysticercosis. It destroys 75%-90% of intraparenchymal cysts when administered for 8 days at a dosage of 15 mg/kg per day. Furthermore, it also acts on the meningeal and intraventricular forms of the disease, due to its good penetration into the subarachnoid space [21]. Despite the use of PZQ and ABZ, a large number of patients will require surgical treatment to treat hydrocephalus or remove isolated cysts (Fig. 5). Patients

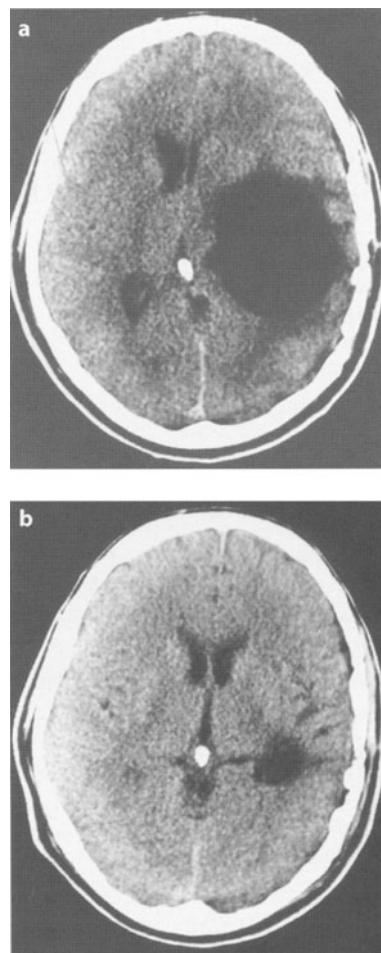


Fig. 5 a, b. Axial CT scans. **a** Blockage of temporal horn by ependymitis. **b** Postoperative follow-up after endoscopy

presenting with compression of cranial nerves, brain tissue, or spinal cord are also amenable to surgery.

Three mechanisms may produce increased intracranial pressure: diffuse brain edema, hydrocephalus, or mass effect (pseudotumoral form).

Diffuse Brain Edema

This form is found in 2.8% of the cases that present increased intracranial pressure. It is seen in cases of extensive infestation, cysts, inflammatory reaction, and diffuse brain expansion. Treatment is mostly non-surgical, but in intractable cases lumboperitoneal shunts are indicated. In extreme cases, decompressive craniotomies may be performed in a heroic attempt to save lives.

Pseudotumoral Form

Giant cysts may be located in the brain parenchyma or in the cisterns and are easily identified by imaging studies. If located within the parenchyma, complete removal of the cysts is readily accomplished. However, if the cysticerci lie in the cisterns and their degeneration process has already started, complete removal may be difficult or even impossible.

Hydrocephalus

Hydrocephalus can be identified in 15%-30% of the cases with neurological symptoms [42, 51]. In the majority of cases it derives from chronic basal arachnoiditis or meningeal fibrosis. A small percentage of cases may be due to intraventricular cysts. It is believed that the larvae invade the ventricular system through the choroid plexus. Hydrocephalus corresponds to 90.5% of the cases of intracranial hypertension treated with surgery. Involvement of the ventricular system is ordinarily associated with higher mortality and morbidity rates than is the intraparenchymal form of the disease [4, 7, 42, 60]. There is still no consensus in the literature as to the best kind of treatment. On the whole, there are three types of treatment: drug therapy, which has little or no efficacy in this form of the disease; ventricular shunts; and surgical removal of cysts (Fig. 6).

Hydrocephalus may be produced by mechanical obstruction of the CSF pathways by cysts (Fig. 7), inflammatory reaction caused by cyst degeneration, or an association of both factors. Migration of the cysts within the ventricles may lead to the intermittent

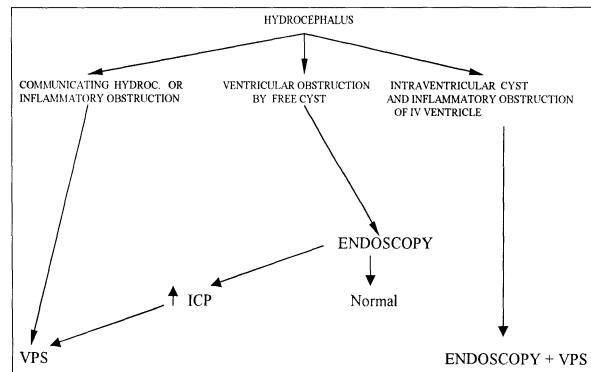


Fig. 6. Treatment algorithm for patients with hydrocephalus

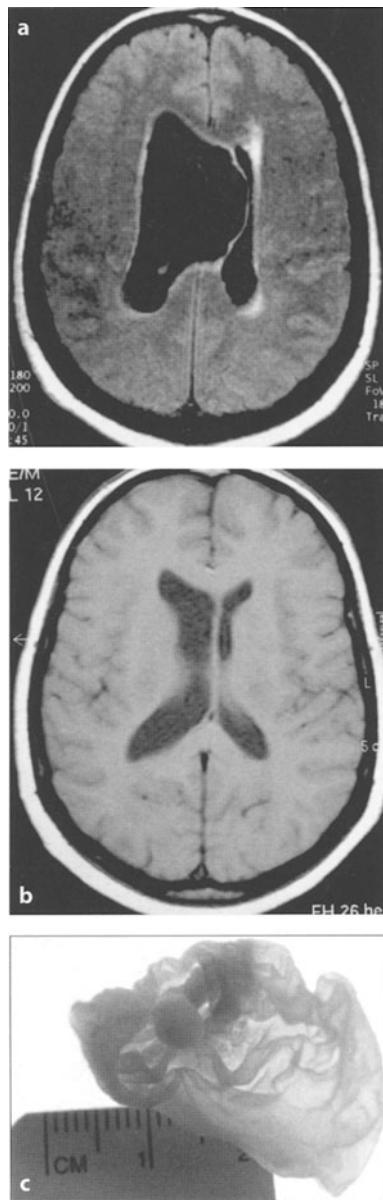


Fig. 7. **a** FLAIR MRI revealing a giant intraventricular cysticercus. **b** Postoperative T1-weighted MRI. **c** Cysticercus cellulosae endoscopically extracted

headaches that characterize Bruns syndrome. Many authors recommend ventricular shunts as the first or definitive form of treatment [7, 14, 15].

Ventriculoperitoneal shunts are the treatment of choice for those patients who present with inflammatory obstruction of the ventricular system and hydrocephalus. As a rule, the patients exhibit a good recovery. However, mechanical and inflammatory complications are prevalent among these patients, with a high incidence of ventriculitis, meningitis, and obstruction of the catheter by the cyst. Colli et al. [16] report an 82% (46 cases) shunt revision rate in a study of 56 patients with neurocysticercosis treated by ventricular shunts. In those cases in which ependymitis caused ventricular loculation, an endoscopic procedure followed by a ventricular shunt showed good results. Free intraventricular cysts, even those located inside the third and fourth ventricles and basal cisterns, are easily removed by endoscopic procedures. Neurocysticercosis is a chronic inflammatory disease in which there may be communicating and noncommunicating hydrocephalus (Fig. 6).

Cisternal forms with cranial nerve compression (Fig. 8) and spinal forms with spine compression have been described.

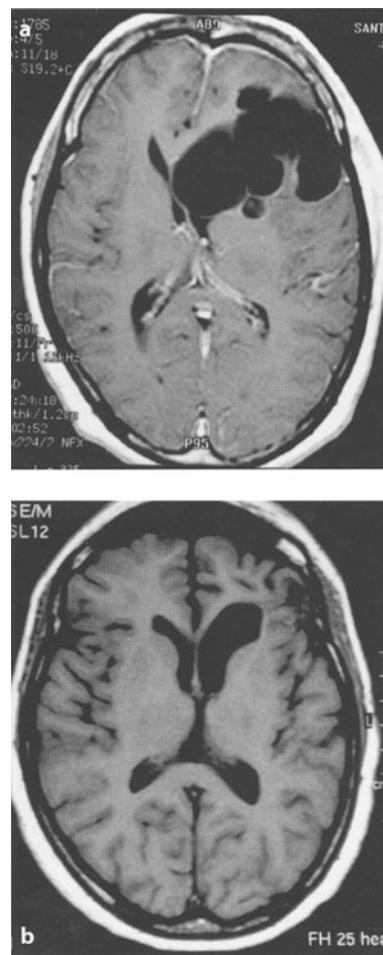


Fig. 8. Axial enhanced T1-weighted MRI. Clusters of cysticerci arising from the sylvian fissure. Note the normal ventricular size. **b** Axial unenhanced T1-weighted MRI, postoperative follow-up after endoscopy

Pitfalls in Surgical Treatment

Viable intraventricular cysts may shift position frequently, moving from the lateral ventricles to the third and fourth ventricles. A recent imaging study, preferably one obtained during the immediate pre-operative period, should allow detection of any cyst migration and thus help with the surgical strategy, hopefully preventing cysts from being overlooked during surgery.

Endoscopic Treatment

It is estimated that 2.4 million people throughout the world have cysts from neurocysticercosis in the ventricular cavities [42,70]. The cysts' lack of vascularization and mobility allow easy handling and easy removal in the absence of ependymitis. Large cysts with scolex in their interior need to be completely removed. Even if the cyst ruptures during the procedure, there is no associated ventriculitis. In the event of ependymitis with multiple intraventricular localizations, endoscopy may allow communication between various cavities and placement of a single ventricular shunt system. Endoscopic third ventriculostomy is typically performed when there is a noninflammatory CSF blockage at the level of the aqueduct or fourth ventricle (Fig. 6). Once an inflammatory process at the level of the basal cisterns has occurred, its usefulness is limited. In cases presenting the parenchymal tumoral form of the disease, endoscopy is useful in the removal of cysts and verification of other cysts not detected by imaging studies. In the severe racemose form, in which numerous cysts located within the interpeduncular cistern may present mass effect and symptoms such as altered consciousness, visual and vegetative changes, endoscopic opening of the tuber cinereum can allow removal of these cysts and improvement of the symptoms.

Surgical approach to the lateral or third ventricles through a transcallosal or transcortical-transventricular approach is recommended for the treatment of intraventricular cysts [4]. The advantages of neuroendoscopy are numerous in comparison to craniotomy. Neal in 1995 [40] reported the removal of a cyst of the posterior portion of the third ventricle, using a combination of rigid and flexible endoscope. Irrigation using positive pressure may be another tool to help mobilize and aspirate the cysts. In our experience, out of 310 patients who underwent endoscopic procedures, in 20 cases (7.4%) it was for treatment of hydrocephalus asso-

ciated with the disease. Bergsneider et al. [9], while studying ten patients with hydrocephalus due to neurocysticercosis, concluded that endoscopic procedures should be considered as the first treatment option. Only three of their patients required a shunt afterwards.

Outcome of Hydrocephalus Due to Neurocysticercosis

Given that hydrocephalus in neurocysticercosis can be attributed to various mechanisms, it may be said that the outcome will depend on its etiology. Intraventricular cysts can be treated using endoscopic techniques or a direct approach, as for cysts of the fourth ventricle (Fig. 9) or of the periaqueductal region (Fig. 10). Communicating hydrocephalus resulting from inflammatory blockage of the basal cisterns and treated by ventricular shunts (Fig. 6) may present a higher incidence of complications [13]. Recurrent inflammatory reactions with CSF pleocytosis and increased protein levels due to the rupture of small intraventricular cysts is probably one of the causes of these complications [13]. It is known that drug therapy for neurocysticercosis is



Fig. 10. Sagittal T1-weighted MRI. Mesencephalic hydatid cyst. (Courtesy of Dr. Zaher Boudawaca)

far from ideal and for the intraventricular forms of the disease is not efficacious at all [63]. In a series that studied large groups of patients, forms of neurocysticercosis considered hypertensive comprised 20%-36% of the cases [48, 59, 66] and usually resulted in the worst outcome. Stepien [59] reported on 43 patients who presented hydrocephalus. There was improvement in only 12 cases (28%); 29 patients died (67%). In a study from the city of Ribeirão Preto (Brazil) of 500 patients in a period of 23 years [66], 68 (13.6%) underwent some form

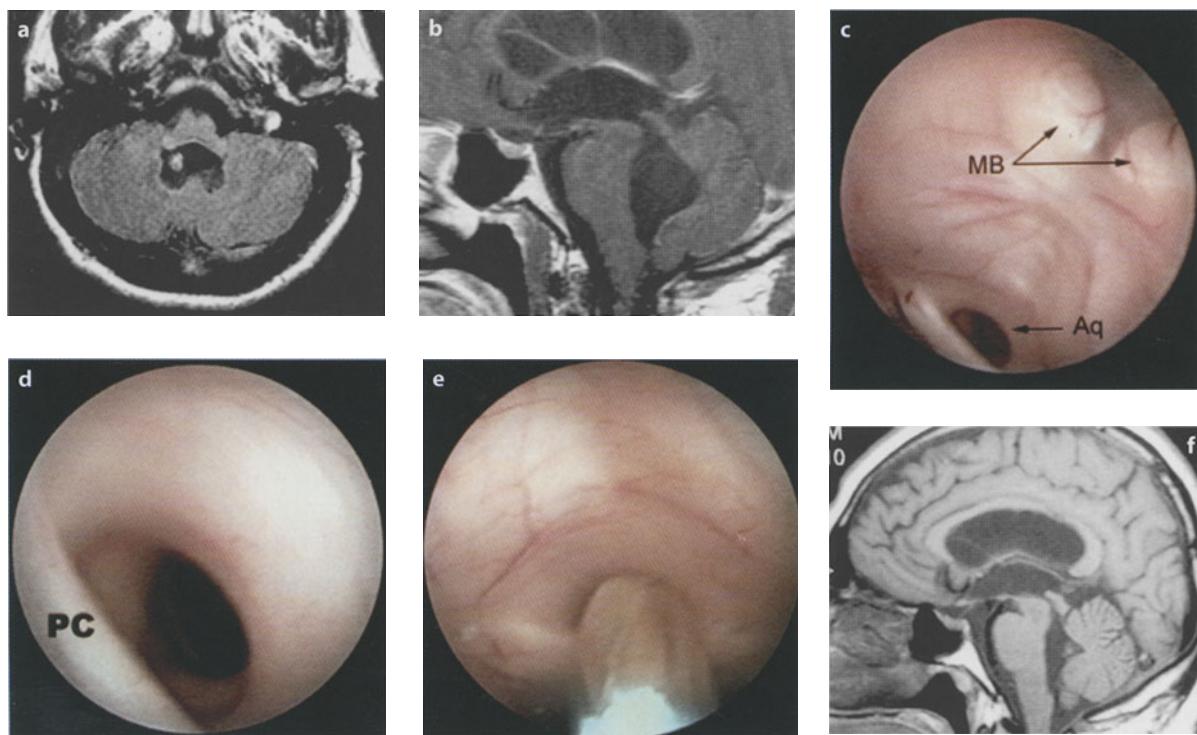


Fig. 9. **a, b** Axial and sagittal T1-weighted MRI. Fourth ventricular cysticercus and scolex. **c, d** Endoscopic views of the floor of the third ventricle. MB, mammillary bodies; Aq, cerebral aqueduct; PC, posterior commissure. Note the cyst appearing inside the fourth ventricle. **e** Endoscopic view of the cysticercus being extracted. **f** Sagittal T1-weighted MRI, 3-month follow-up

of CSF shunt diversion or surgical removal of cysts. Out of 74 patients classified as having a pure hypertensive form of the disease, 21 (28.4%) died. Canelas [14] noted that of 63 patients who underwent a surgical procedure, 28(44.4%) died. Takayanagui [64] pointed out that, of his series of 56 patients that presented with signs of increased intracranial pressure, 12 (21.4%) died and 12 developed incapacitating neurological sequelae. Studies concerning the intellectual development of these patients are extremely difficult, as pointed out by Scharf [48], for each patient has a different individual outcome depending on the lesions, the number of parasites, the duration of the infestation, and the immunological response of the host.

Prophylaxis

Control of neurocysticercosis demands attention to hygiene habits and environmental sanitation. Widespread medical treatment aimed at eradicating human tapeworm infection would be an alternative control technique. The economic cost of treating a case of tapeworm intestinal infection is 150 times smaller than the cost of the same medication used to treat neurocysticercosis [47]. At the present time there are two kinds of strategies recommended by the World Health Organization: the first, for short term results, is based on widespread treatment of tapeworm infection and foci of transmission; the other, aimed at long-term results, focuses on the development of breeding and inspection techniques for pork, adequate sanitary measures, and actions to detect and treat humans infected by tapeworms [47].

Other Parasitic Diseases Responsible for Hydrocephalus

Histoplasmosis

Histoplasma capsulatum is a dimorphic fungus that exists as a mycelial form at ambient temperature and as a yeast form in mammals. Its distribution is universal, being endemic in certain regions of the United States and Latin America [75]. The fungus exists in the soil of endemic areas, especially in dusty places where the soil contains bat or bird feces, such as for instance a hen house [30]. The initial infection is due to spore inhalation. In endemic areas, almost the entire population is in-

fected and subject to multiple cases of re-infection [72, 76].

Disseminated chronic histoplasmosis is a rare event, its incidence estimated at 1 per 100 000 to 1 per 150 000 infected individuals per year [30]. Symptomatic CNS involvement is believed to occur in 10%-25% of the cases of disseminated histoplasmosis [18, 45, 49, 74].

Shapiro classified the lesions of histoplasmosis of the CNS as follows: (1) miliary granuloma; (2) histoplasmoma; (3) meningitis/ventriculitis, the most frequent CNS presentation, affecting preferentially the skull base meninges; (4) spinal compression [30, 50].

The diagnosis of histoplasmosis is becoming more and more common due to an increase in the number of immunocompromised patients due to AIDS or immunosuppression. Ventriculitis can progress to hydrocephalus, requiring a CSF shunt. In most cases, many shunt revisions are necessary. In other cases, a parenchymal lesion is detected and a biopsy suggested. *Histoplasma capsulatum* should be considered in the differential diagnosis even in cases of communicating idiopathic hydrocephalus (no associated meningitis or ventriculitis). A common factor among all cases, irrespective of the clinical presentation, is the insidious clinical course, characterized by numerous admissions to the hospital, a number of times because of a shunt revision, with no etiological diagnosis.

The authors have treated eight cases of histoplasmosis, one being in a 12-year-old patient who had already undergone 28 shunt revisions and an erroneous tuberculosis treatment. Another patient had had 16 shunt revisions. After treatment the shunt complications disappeared. One patient underwent an endoscopic third ventriculostomy that obliterated 3 months later.

Another common characteristic shared by these cases are the CSF findings. They are characterized by a modest increase in cell number, usually below ten cells, mostly due to lymphocytic/monocytic infiltrate, and modest hypoglycorrachia or normal glucose levels; protein content is always related to the phase of the disease. During recurrence episodes, levels are more elevated and protein/cell dissociation is more evident. Intraventricular protein levels are usually above 1 g and may continue to rise even if external ventricular drainage is instituted.

The rate of positive results obtained in CSF cultures varies from 25%-to 65%. The best results can be obtained with bone marrow cultures, which have a positivity index of about 75%. Blood cultures are positive in 50%-70% of the cases [46]. The mean time for the results of the cultures is 4 weeks. Serological test results for histoplasmosis are very difficult to interpret. Antibody detection tests in the CSF have a positivity of about 80% and antibody detection in the blood a positivity rate of 92%. However, the rate of false-positive

results must also be considered. Cross-reaction rates can reach 50%, especially with tuberculosis and other fungal infections (mainly aspergillosis, blastomycosis, coccidioidomycosis) [73]. In 1986, Wheat et al. [77] proposed studying the histoplasma polysaccharide antigen (HPA) in blood, urine, and CSF. The best positivity rates (91%) are obtained in the urine of patients with disseminated disease. When the disease is restricted to the CNS, positivity falls to 19%. The classical treatment consists of intravenous amphotericin B for 3 weeks and fluconazole for 6 months during the maintenance phase of the treatment. Once treatment is initiated, there is a rapid fall in CSF protein levels, reducing shunt obstruction incidents.

References

- Abbassioun K, Amirjamshidi A, Moinipoor MT: Hydatic cyst of the pons. *Surg Neurol* 26:297-300, 1986
- Acha PN, Szyfres B: Zoonosis enfermedades transmisibles comunes de hombre y a los animales. OMS 503:763-774, 1986
- Agapajev S, Alves-Moreira D, Barriviera B: Neurocysticercosis: treatment with albendazole and destrocloropherini-nami. *Trans R Soc Trop Med Hyg* 83:377-83, 1989
- Apuzzo MJ, Dobukin WR, Zee C, et al: Surgical considerations in treatment of intraventricular cysticercosis. An analysis of 45 cases. *J Neurosurg* 60:400-407, 1984
- Aristotle: Historie des Animaux, vol III, book VIII, para XXI. Paris, Société d'Editions Les Belles Lettres, pp 48-49, 1969
- Bamberger DM: Successful treatment of multiple cerebral histoplasmosomas with itraconazol. *Clin Infect Dis* 28:915-916, 1999
- Bandres JC, White AC, Samo T, et al: Extraparenchymal neurocysticercosis: report of five cases and review of management. *Clin Infect Dis* 15:799-81, 1992
- Bérard H, Astoul PH, Frenay C, et al: Histoplasma disseminée à *Histoplasma capsulatum* avec atteinte cérébrale survenue 13 ans après la primo-infection. *Ver Mal Resp* 16:829-831, 1999.
- Bergsneider M, Holly LT, Lee JH, et al: Endoscopic management of cysticercal cysts within the lateral and third ventricles. *Neurosurg Focus* 6(4):article 7, 1999
- Boppana S, Pass RF, Britt WS: Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J* 11:93-99, 1992
- Boudawara MZ, Jemel H, Ghorbel M, et al: Les kystes hydatiques du tronc cérébral. A propos de deux cas. *Neurochirurgie* 4:321-324, 1999.
- Bruck I, Antoniuk SA, Wittig E, Accorsi A: Neurocisticercose na infância: diagnóstico clínico e laboratorial. *Arg Neuropsiquiatr* 49:43-46, 1991
- Canelas HM: Neurocisticercose: incidência, diagnóstico e formas clínicas. *Arg Neuropsiquiatr* 20:1-16, 1962
- Canelas HM: Cisticercose do sistema nervoso central. *Rev Hosp Clin Fac Med S Paulo* 47:75-89, 1963
- Colli BC, Assirati JA, Machado HR, et al: Cysticercosis of the central nervous system II. Spinal cysticercosis. *Arg Neuropsiquiatr* 52:187-199, 1994
- Colli BO, Martelli N, Assirati JA, et al: Cysticercosis of the central nervous system I. *Arg Neuropsiquiatr* 52:166-186, 1994
- Colli BO, Martelli N, Assirati JA, et al: Results of surgical treatment of neurocysticercosis in 69 cases. *J Neurosurg* 65:309-315, 1986
- Cooper RA, Golstein E: Histoplasmosis of the central nervous system. Report of two cases and review of the literature. *Am J Med* 35:45-47, 1963
- Davis LE: Fungal infections of the central nervous system. *Neurol Clin* 4:761-781, 1999
- Del Brutto OH: Cisticercosis and cerebrovascular disease: a review. *J Neurol Neurosurg Psychiatry* 55:252-254, 1992
- Del Brutto OH, Sotelo J: Albendazole therapy for subarachnoid and ventricular cisticercosis: case report. *J Neurosurg* 72:816-817, 1990
- Del Brutto OH, Sotelo J: Neurocysticercosis: an update. *Rev Infect Dis* 10:1075-1087, 1988
- Enarson DA, Keys TF, Onofrio BM: Central nervous system histoplasmosis with hydrocephalus. *Am J Med* 64:895-896, 1978
- Escobar A: The pathology of neurocysticercosis. In: Palacios E, Rodrigues-Carbal J, Taveras (eds) *Cysticercosis of the central nervous system*. Charles C. Thomas, Springfield, pp 27-54, 1983
- Estanol B, Kleriga E, Loyer M, et al: Mechanisms of hydrocephalus in cerebral cysticercosis: implications for therapy. *Neurosurgery* 13:119-123, 1983
- Filsser A, Woodhouse H, Larralde L: Human cysticercosis; antigens, antibodies and nonresponders. *Clin Exp Immunol* 39:27-31, 1980
- Frenkel JK: Toxoplasmosis: mechanisms of infection, laboratory diagnosis and management. *Curr Top Pathol* 54:27-75, 1971
- Frenkel JK, Friedlander S: Toxoplasmosis. Pathology of neonatal disease. Pathogenesis, diagnosis and treatment. Public Health Service Publication no 141. US Government Printing Office, Washington, DC, 108 pp, 1952
- Go JL, Kim PE, Ahmadi J, et al: Fungal infections of the central nervous system. *Neuroimaging Clin North Am* 10:409-425, 2000
- Goodwin RA, Shapiro JL, Thurman GH, et al: Disseminated histoplasmosis: clinical and pathological correlations. *Medicine* 59:1-33, 1980
- Gottlieb T, Marriott D: Disseminated histoplasmosis in an AIDS patient. *Aust N Z Med* 20:621-622, 1990
- Hanshaw JB, Dudgeon JA (eds): *Viral diseases of the fetus and newborn*. Saunders, Philadelphia, 1978
- Karalakulasingam R, Arora KK, Adams G, et al: Meningoencephalitis caused by *Histoplasma capsulatum*. *Arch Intern Med* 136:217-220, 1976.
- Khamlich A, Belefkihi N, Guarzazi A, et al: Le kyste hydatique de la fosse cérébrale postérieure (Revue de la littérature à propos de 5 cas). *Maroc Med* 4:223-233, 1982
- Knapp S, Turnherr M, Dekan G, et al: A case of HIV-associated cerebral histoplasmosis successfully treated with fluconazole. *Eur J Clin Microbiol Infect Dis* 88:658-661, 1999
- Lambert RS, George RB: Evaluation of enzyme immunoassay as a rapid screening test for histoplasmosis and blastomycosis. *Am Rev Respir Dis* 136:316-319, 1987
- Le Bourgeois PA: Isolated central nervous system histoplasmosis. *Southern Med J* 72:1624-1625, 1979
- Lombardo L, Mateos JH, Estanol B: La cisticercosis cerebral en México. *Gac Med Mex* 118:1-8, 1982
- Mitchell WG, Crawford TO: Intraparenchymal cerebral cysticercosis in children: diagnosis and treatment. *Pediatrics* 82:76-82, 1988

40. Neal JH: An endoscopic approach to cysticercosis cysts of the posterior third ventricle. *Neurosurgery* 36:1040-1043, 1995
41. O'Doherty DS: Invasion of central nervous system by cysticercosis cellulosa. *Georgetown Med Bull* 15:128-136, 1961
42. Obrador S: Cysticercosis cerebri. *Acta Neurochir* 10:320-364, 1962
43. Pratt-Thomas HR, Cannon WM: Systemic infantile toxoplasmosis. *Am J Pathol* 22:779-795, 1946
44. Rawlinson WD, Packham DR, Gardner FJ, MacLeod C: Histoplasmosis in the acquired immunodeficiency syndrome (AIDS). *Aust N Z J Med* 19:707-709, 1989
45. Salaki JS, Louria DB, Chmel H: Fungal and yeast infections of the central nervous system. *Medicine* 63:108-132, 1984
46. Sathapatayavongs B, Batteiger BE, Wheat J, et al: Clinical and laboratory features of disseminated histoplasmosis during two outbreaks. *Medicine* 62:263-70, 1983
47. Schantz PM: Echinococcosis (hydatidosis). In: Warren KS, Mahmoud AAF (eds) *Tropical and geographical medicine*. McGraw Hill, New York, pp 487-497, 1984
48. Scharf D: Neurocysticercosis. Two hundred thirty-eight cases from a California hospital. *Arch Neurol* 45:777-780, 1988
49. Schulz DM: Histoplasmosis of the central nervous system. *JAMA* 151:549-551, 1953
50. Shapiro JL, Lux JJ, Sprofkin BE: Histoplasmosis of the central nervous system. *Am J Pathol* 31:319-334, 1955
51. Sotelo J, Marin C: Hydrocephalus secondary to cysticercotic arachnoiditis. A long term follow-up review of 92 cases. *J Neurosurg* 66:686-689, 1987
52. Sotelo J, Escobedo F, Rodrigues J, et al: Therapy of parenchymal brain cysticercosis with praziquantel. *N Engl J Med* 310:1001-1007, 1984
53. Sotelo J, Guerrero V, Rubio F: Neurocysticercosis: a new classification based on active and inactive forms. A study of 753 cases. *Arch Intern Med* 145:442-445, 1985
54. Spina-França A: Aspectos biológicos da neurocisticercose: alterações do líquido cefalorraquidiano. *Arq Neuropsiquiatr São Paulo* 20:17-30, 1962
55. Spina-França A, Livramento JA, Machado LR: Cysticercosis of the central nervous system and cerebral fluid: immunodiagnosis of 1573 patients in 63 years (1929-1992). *Arq Neuropsiquiatr* 51:16-20, 1993
56. Spina-França A: Neurocisticercose e imunologia. *J Bras Med* 45:7-8, 1983
57. Spina-França A: Incidência de neurocisticercose no serviço de neurologia do Hosp. Das Clínicas da FMUSP. *Rev Paul Med* 43:160-161, 1953
58. Stagno S, Reynolds DW, Huang ES: Congenital cytomegalovirus infection: occurrence in an immune population. *N Engl J Med* 296:1254-1258, 1977
59. Stepién L: Cerebral cysticercosis in Poland: clinical symptoms and operative results in 132 cases. *J Neurosurg* 19:505-513, 1962
60. Stern WE: Neurosurgical considerations of cysticercosis of the central nervous system. *J Neurosurg* 55:382-385, 1981
61. Sullivan AA, Benson SM, Ewart AH, et al: Cerebral histoplasmosis in an Australian patient with systemic lupus erythematosus. *Med J Aust* 169:201-202, 1998
62. Tabbal SD, Harik SI: Cerebral histoplasmosis. *N Engl J Med* 339:1176, 1999
63. Takayanagi OM: Neurocisticercose II. Avaliação da terapêutica com praziquantel. *Arq Neuropsiquiatr São Paulo*, 48:11-15, 1990.
64. Takayanagi OM, Castro e Silva AA, Santiago RC, et al: Notificação compulsória da cisticercose em Ribeirão Preto-SP. *Arch Neuropsiquiatr* 54:557-564, 1996
65. Takayanagi OM, Jardim E: Therapy for neurocysticercosis: comparison between albendazole and praziquantel. *Arch Neurol* 49:290-294, 1994
66. Takayanagi OM, Jardim E: Aspectos clínicos da neurocisticercose - análise de 500 casos. *Arq Neuropsiquiatr São Paulo* 41:50-63, 1983
67. Tiraboshi I, Parera IC, Pikielny R, et al: Chronic *Histoplasma capsulatum* infection of the central nervous system successfully treated with fluconazole. *Eur Neurol* 32:70-73, 1992
68. Tynes BS, Crutcher JC, Utz JP: Histoplasma meningitis. *Ann Intern Med* 59:615-618, 1963
69. Walpole HT, Gregory DW: Cerebral histoplasmosis. *Southern Med J* 80:1575-1577, 1987
70. Wei G, Li C, Meng J, Ding M: Cysticercosis of the central nervous system. A clinical study of 1400 cases. *Chinese Med J* 101:493-500, 1988
71. Weller TH: The cytomegaloviruses: ubiquitous agents with protean clinical manifestations. *N Engl J Med* 285:203-214, 1971
72. Wheat J, French MLV, Batteiger B, Kohler R: Cerebrospinal fluid histoplasma antibodies in central nervous system histoplasmosis. *Arch Intern Med* 145:1237-1240, 1985
73. Wheat J, French MLV, Kamel S, Tewari RP: Evaluation of cross-reaction in *Histoplasma capsulatum* serologic tests. *J Clin Microbiol* 23:493-499, 1986
74. Wheat J: Histoplasmosis - experience during outbreaks in Indianapolis and review of the literature. *Medicine* 76:339-354, 1997
75. Wheat LJ, Batteiger BE, Sathapatayavongs B: *Histoplasma capsulatum* infections of the central nervous system - a clinical review. *Medicine* 69:244-260, 1990
76. Wheat LJ, Kohler RB, Tewari RP, et al: Significance of *Histoplasma* antigen in the cerebrospinal fluid of patients with meningitis. *Arch Intern Med* 149:302-304, 1989
77. Wheat LJ, Kohler RB, Tewari RP: Diagnosis of disseminated histoplasmosis by detection of *Histoplasma capsulatum* antigen in serum and urine specimens. *N Engl J Med* 314:83-88, 1989
78. White HH, Fritzlen TJ: Cerebral granuloma caused by *Histoplasma capsulatum*. *J Neurosurg* 19:260-264, 1962
79. Wilson CB, Remington JS: What can be done to prevent congenital toxoplasmosis? *Am J Obstet Gynecol* 138:357-363, 1980
80. Wolf A, Cowen D: Perinatal infections of the nervous central system. *J Neuropathol Exp Neurol* 18:191-243, 1959
81. Wolf A, Cowen D, Paige BH: Toxoplasmic encephalomyelitis. VI. Clinical diagnosis of infantile or congenital toxoplasmosis. Survival beyond infancy. *Arch Neurol Psychiatr* 48:689-739, 1942
82. Wong SY, Remington JS: Toxoplasmosis in the setting of AIDS. In: Broder S, Merigan TC, Bolognesi D (eds). *Textbook of AIDS medicine*. Williams & Wilkins, Baltimore, pp 223-258, 1994
83. Young RF, Gade G, Grinnell V: Surgical treatment for fungal infections in the central nervous system. *J Neurosurg* 63:371-381, 1985
84. Zee C, Segall HD, Boswell W: MR imaging of neurocysticercosis. *J Comput Assist Tomogr* 12:927-934, 1988
85. Zee CS, Segal HD, Miller C, et al: Unusual neuroradiological features of intracranial cysticercosis. *Radiology* 137:397-407, 1980

Hydrocephalus and the Dandy-Walker Malformation

GIUSEPPE CINALLI¹, PIETRO SPENNATO², MARIA LAURA DEL BASSO DE CARO³ AND MARIA CONSIGLIO BUONOCORE⁴

“Gallia est omnis divisa in partes tres ...”
C. Julius Caesar, De Bello Gallico

“All Gaul is divided into three parts ...”
C. Julius Caesar, The Gallic War

Definition and Classification

The vermis is clockwise divided into nine lobules (lingula, lobulus centralis, culmen, declive, folium, tuber, pyramis, uvula, nodulus) in normal anatomy (Fig. 1). Two deep main fissures (the primary fissure

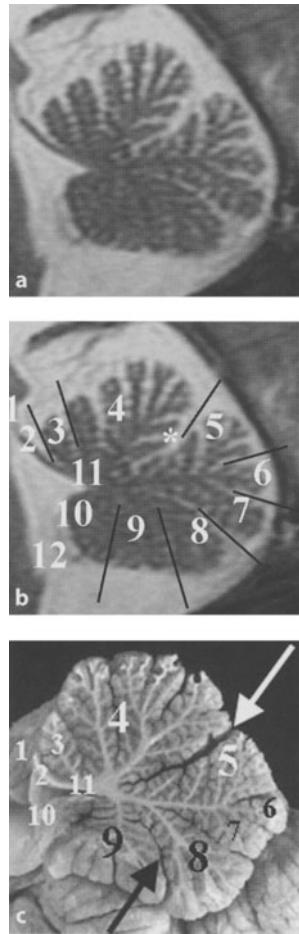


Fig. 1a-c. Normal radiology and anatomy. **a** Sagittal T2 MRI of normal vermis. **b** Subdivision into lobules. The asterisk (*) is in the upper main fissure (fissura prima, primary fissure). The lower main fissure (fissura secunda, secondary fissure), between the pyramis and the uvula, is usually less visible on MRI. **c** Anatomical view on a sagittal midline cut: note the primary fissure (white arrow) and the secondary fissure (black arrow). 1, Superior medullary velum; 2, lingula; 3, lobulus centralis; 4, culmen; 5, declive; 6, folium; 7, tuber; 8, pyramis; 9, uvula; 10, nodulus; 11, fastigium; 12, Magendie foramen

between the culmen and the declive, and the secondary fissure between the pyramis and uvula) divide them into three main lobes: an upper lobe composed of the lingula, lobulus centralis, and culmen, a middle lobe composed of the declive, folium, tuber, and pyramis, and a lower lobe composed of the uvula and nodulus [65].

The term “Dandy-Walker syndrome” or “Dandy-Walker malformation” was coined by Benda [9] to indicate the association of hydrocephalus, posterior fossa cyst, and hypoplasia of the cerebellar vermis. Although the first report of this entity has been attributed to Sutton, the descriptions by Dandy and Blackfan [23] in 1914 and by Taggart and Walker [83] in 1942 were more complete, so that Dandy and Blackfan’s triad can be still used as partial diagnostic criteria [43]: (1) cystic dilatation of the fourth ventricle, (2) partial or complete absence of the cerebellar vermis, and (3) hydrocephalus.

Brown [14] enlarged the diagnostic criteria to include three other clinical and pathological features: elevation of the transverse sinus, enlargement of the posterior fossa, and lack of patency of the foramina of Luschka and Magendie. Nowadays the presence of all six of the criteria proposed by Brown is not required for a diagnosis of the Dandy-Walker malformation [81]. In particular, often the outlet foramina of the fourth ventricle are patent. Moreover, the degree of hydrocephalus, the degree of vermician hypoplasia, and the size of the posterior fossa cyst vary considerably from case to case, with no correlation with each other or with the patency of the foramina [81].

The remarkable variability of the pathological features of Dandy-Walker malformation has posed some problems in distinguishing this entity from other types of posterior fossa cyst, such as persistent Blake’s pouch, retrocerebellar cyst, mega cister-

¹ Department of Pediatric Neurosurgery, Santobono-Pausilipon Children’s Hospital, Naples; ² Department of Neurosurgery, Second University of Naples; ³ Department of Pathologic Anatomy and Department of Biomorphological and Functional Sciences, Section of Pathology, Federico II University of Naples; ⁴ Department of Pediatric Neuroradiology, Santobono-Pausilipon Children’s Hospital, Naples, Italy

Table 1. Classification of posterior fossa cysts according to Barkovich et al.[7]

Dandy-Walker complex	Midline CSF collection with clear communication with fourth ventricle.
Type A	Absence of the vermis on axial images.
Dandy-Walker malformation	
Dandy-Walker variant	
Type B	Partial absence of the vermis on axial images.
Mega cisterna magna	
Persistent Blake's pouch	
Posterior fossa cyst	Midline CSF collection with no communication with the fourth ventricle. Mass effect on brainstem or cerebellum may be present. Cerebellar hemispheres are well formed.
Prominent cisterna magna	Midline CSF collection due to atrophy of vermis and cerebellar hemispheres.

na magna, and arachnoid cyst. Harwood-Nash and Fitz [44], Raybaud [75], and finally Barkovich et al. [7] have revised the classification of posterior fossa cystic collections. The most widely accepted radiological classification was proposed by Barkovich et al. [7] in 1988 (Table 1). They categorized the posterior fossa cystic collections into three main groups on the basis of clinical data and MRI findings.

Dandy-Walker Complex

“Dandy-Walker complex” is the term employed by Barkovich et al. [7] to refer to a group of malformations in which the posterior fossa CSF collections show clear communication with the fourth ventricle. On the basis of the presence or absence of the cerebellar vermis on MR (or CT) axial images at the level of the fourth ventricle, a Dandy-Walker type A or type B malformation can be recognized.

Type A, in which the vermis is not visible because of hypoplasia and/or rotation (see below), includes (1) the classic form of Dandy-Walker malformation (DWM), which meets Dandy and Blackfan's criteria, and (2) “Dandy-Walker variant”, a term used by Harwood-Nash and Fitz [44] and afterwards by Raybaud [75] to describe an “abortive” form of the malformation, where the fourth ventricle is better formed, less dilated, and usually communicates with the perimedullary arachnoid space; the vermis is less dysgenetic; and the posterior fossa is not markedly enlarged [2]. Actually there is no clear differentiation between DWM and Dandy-Walker variant (Fig. 2).

In type B, a portion of the cerebellar vermis is interposed between the fourth ventricle and the enlarged cisterna magna. This malformation was traditionally regarded as “mega cisterna magna”: a clear communication with the fourth ventricle via the vallecula distinguishes this form from the “extra-axial” arachnoid posterior fossa cysts. Tortori-Donati et al.

[86] further classify this group into “mega cisterna magna” and “persistent Blake's pouch” [15], but most authors [7, 24] consider these terms to be synonymous. According to Tortori-Donati et al. [86], only in the case of persistent Blake's pouch, probably produced by evagination of the rudimentary tela choroidea (Blake's pouch), is there insufficient communication with the perimedullary arachnoid space, producing severe obstruction to CSF circulation. By contrast, the mega cisterna magna, possibly secondary to delayed formation of the foramen of Magendie, communicates freely with the subarachnoid space and does not produce hydrocephalus, although the posterior fossa may be wider than normal, the torcular displaced cranially, and the inner table of the occipital bone scalloped. In fact, this classification based only on the presence or absence of hydrocephalus is too simplistic for a pathology that presents a wide variety of anatomical forms (Fig. 3). Moreover, hydrocephalus can also be observed in cases of mega cisterna magna. In type B the developing cerebellum is less involved than in type A, but all intermediate forms can be observed.

The malformations included in the Dandy-Walker complex of Barkovich et al. could represent steps on a continuum of developmental anomalies. Evidence of similar pathogenetic origin is also based on observation of their occurrence in monozygotic twins, in which a sib can be affected by Dandy-Walker variant, the brother by mega cisterna magna, and so on [76]. Nevertheless, we think that including all these forms under the same Dandy-Walker label has in fact added confusion instead of facilitating everyday clinical work, because groups A and B have different clinical prognoses and treatment strategies.

We believe that the patients in group A are quite homogeneous, corresponding to very precise radiological and clinical criteria, and their condition should not be confused with the other cystic or pseudocystic collections of the posterior fossa. These

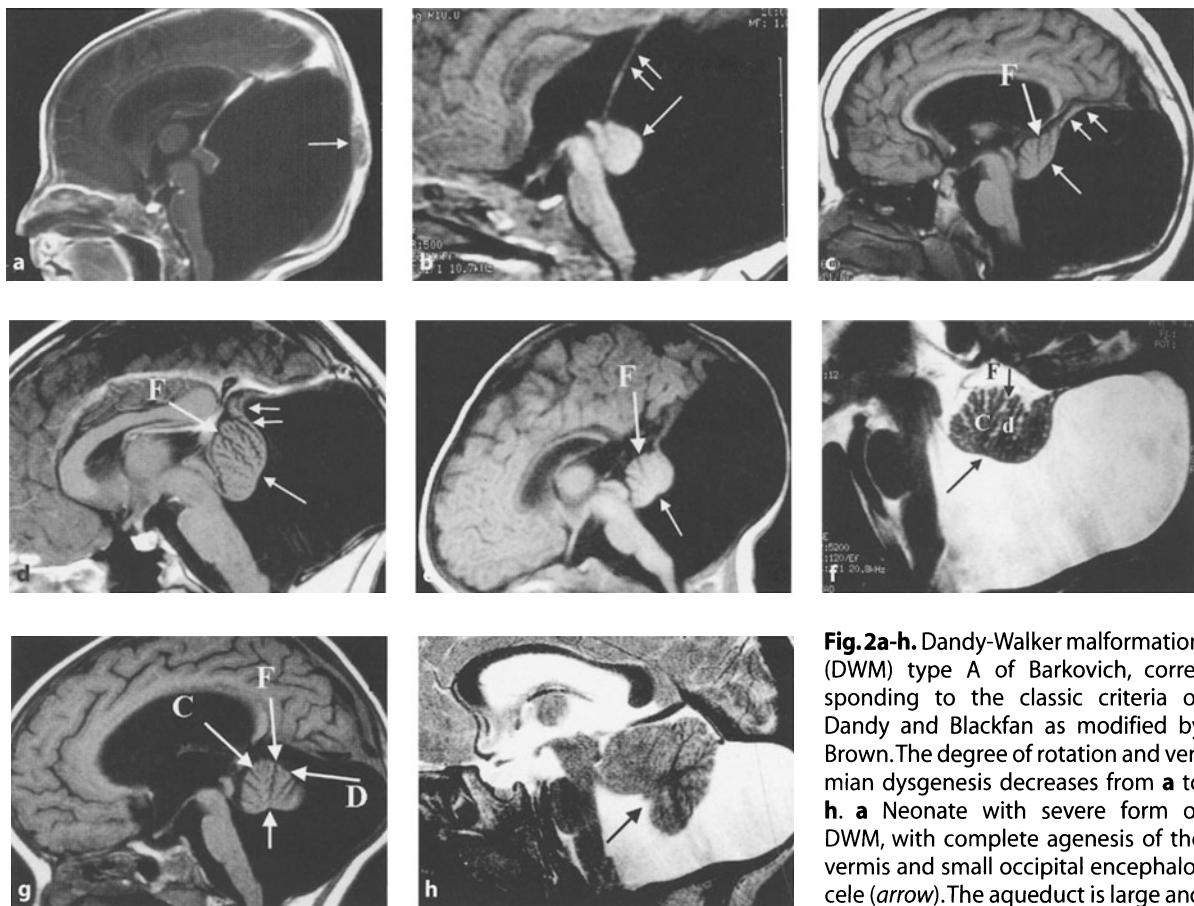


Fig. 2a-h. Dandy-Walker malformation (DWM) type A of Barkovich, corresponding to the classic criteria of Dandy and Blackfan as modified by Brown. The degree of rotation and vermian dysgenesis decreases from **a** to **h**. **a** Neonate with severe form of DWM, with complete agenesis of the vermis and small occipital encephalocele (arrow). The aqueduct is large and patent. **b** Less severe form than in **a**: note the small remnant of the vermis (arrow), which does not present the typical pattern of foliation with no visible lobules. The upper part of the cyst rotates around the remnant of the vermis and is separated by the third ventricle only by a thin membrane (double arrow). **c** The upper part of the vermis, although hypoplastic, is better represented than in **b**, with the clear architectural pattern of cerebellar foliation (long arrow). Five lobules are visible and one main fissure, the primary fissure (*F* arrow). The lower part of the vermis is extremely hypoplastic and hardly recognizable on the upper part of the cyst membrane (double short arrows). **d** The upper third of the vermis is almost normal, although extremely rotated upward and anteriorly. The region corresponding to the fastigium is flattened (long arrow), the remnants of the lower third of the vermis are more visible than in **c** (short arrows). Six lobules are visible and one main fissure, the primary fissure (*F* arrow) between the culmen and declive. **e** The vermis, although more hypoplastic, is less rotated than in **d** and presents at least six lobules. The angle of the fastigium is evident although very wide (arrow). The primary fissure between culmen and declive is well identified (*F* arrow). **f** Good architecture of the upper half of the vermis, with flattening of the lower half. At least six lobules are visible. The fastigium is present although very flattened (arrow), significant rotation of the vermis is present, the primary fissure is evident (*F* arrow) between the culmen (*C*) and the declive (*d*). **g** The upper vermis is normal with a well visible culmen (*C* arrow) and primary fissure (*F* arrow). The declive has a normal appearance (*D* arrow), but the vermis below is still hypoplastic, the fastigium is visible (arrow) but flattened, and significant rotation is still evident. **h** Vermis is normal with nine lobules, rotation is still present but less marked than in **a-g**, the fastigial angle is well represented (arrow), and the posterior fossa is smaller than in **a-g**.

note the small remnant of the vermis (arrow), which does not present the typical pattern of foliation with no visible lobules. The upper part of the cyst rotates around the remnant of the vermis and is separated by the third ventricle only by a thin membrane (double arrow). **c** The upper part of the vermis, although hypoplastic, is better represented than in **b**, with the clear architectural pattern of cerebellar foliation (long arrow). Five lobules are visible and one main fissure, the primary fissure (*F* arrow). The lower part of the vermis is extremely hypoplastic and hardly recognizable on the upper part of the cyst membrane (double short arrows). **d** The upper third of the vermis is almost normal, although extremely rotated upward and anteriorly. The region corresponding to the fastigium is flattened (long arrow), the remnants of the lower third of the vermis are more visible than in **c** (short arrows). Six lobules are visible and one main fissure, the primary fissure (*F* arrow) between the culmen and declive. **e** The vermis, although more hypoplastic, is less rotated than in **d** and presents at least six lobules. The angle of the fastigium is evident although very wide (arrow). The primary fissure between culmen and declive is well identified (*F* arrow). **f** Good architecture of the upper half of the vermis, with flattening of the lower half. At least six lobules are visible. The fastigium is present although very flattened (arrow), significant rotation of the vermis is present, the primary fissure is evident (*F* arrow) between the culmen (*C*) and the declive (*d*). **g** The upper vermis is normal with a well visible culmen (*C* arrow) and primary fissure (*F* arrow). The declive has a normal appearance (*D* arrow), but the vermis below is still hypoplastic, the fastigium is visible (arrow) but flattened, and significant rotation is still evident. **h** Vermis is normal with nine lobules, rotation is still present but less marked than in **a-g**, the fastigial angle is well represented (arrow), and the posterior fossa is smaller than in **a-g**.

criteria (in almost complete agreement with the ones recently proposed by Klein et al. [50]) are:

1. Large median posterior fossa cyst widely communicating with the fourth ventricle.
2. Absence of the lower portion of the vermis to varying degrees (lower three-fourths, lower half, lower one-fourth).
3. Hypoplasia, anterior rotation, and upward displacement of the remnant of the vermis.

4. Absence or flattening of the angle of the fastigium.
5. Large bossing posterior fossa with elevation of the torcular.
6. Anterolateral displacement of normal or hypoplastic cerebellar hemispheres (Fig. 2).

Hydrocephalus is not always observed (it is present in 80% of cases) and should not be considered specific part of the syndrome. Other central nervous system malformations can be observed, such as oc-

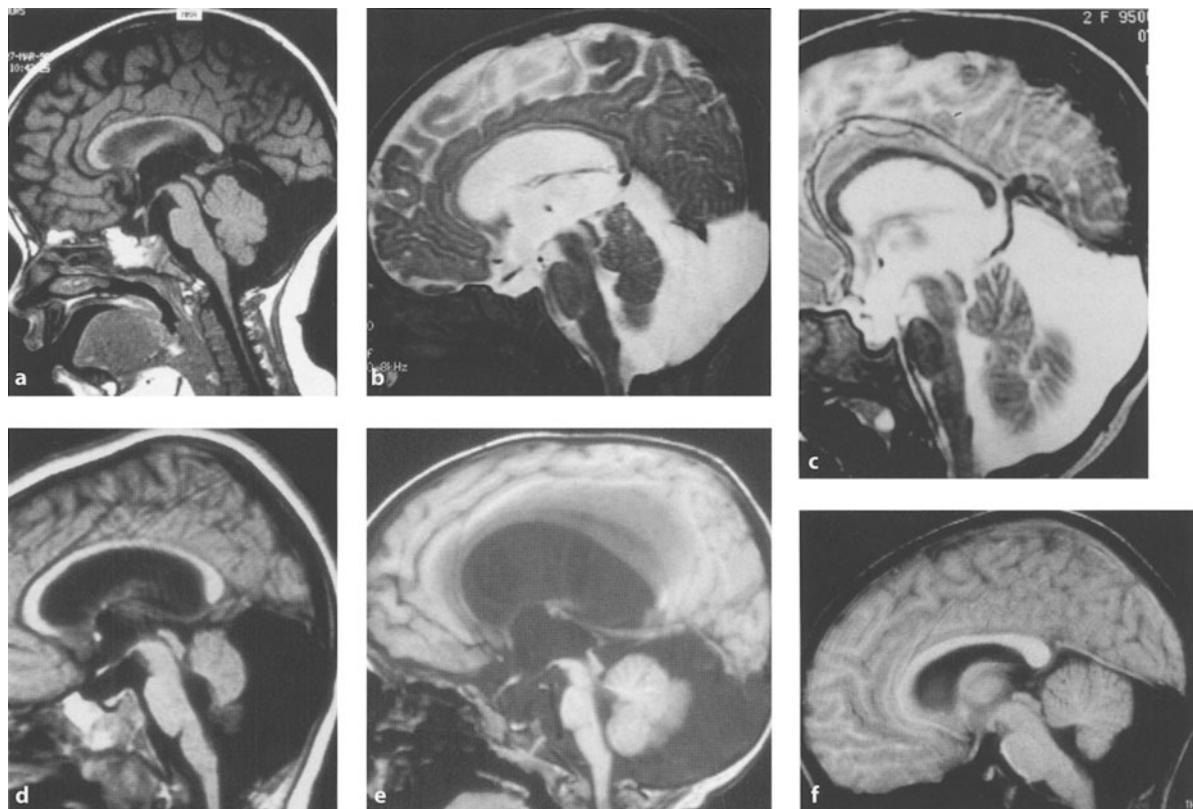


Fig. 3a-f. Dandy-Walker malformation type B of Barkovich, corresponding to the classic criteria of mega cisterna magna. **a-c** These three patients have quite similar radiological features, with mild flattening of the vermis in the anteroposterior axis, normal (**a**) or slightly enlarged (**b, c**) fourth ventricle, normal fastigium angle. **d-f** The features of these patients differ significantly from those in **a, b** and **c**: the vermis is very hypoplastic in **d** but normal in **e** and **f**. It is never flattened on its anteroposterior axis

cipital encephaloceles (Fig. 4), corpus callosum agenesis (Fig. 5), schizencephaly, and glial heterotopias [7]. Recently, Klein and Boddaert, in an attempt to redefine the radiological criteria of DWM, have proposed a relation between the degree of malformation of the vermis and the intellectual outcome, offering a major contribution to the classification and understanding of the malformation [12, 50]. Klein and Boddaert propose that a more complete lobulation of the vermis, with radiological visibility of the three lobes and of the two main fissures, speaks for a less severe malformation with better intellectual prognosis.

Different degrees of vermian amputation and rotation of the vermis remnant can be observed, but nevertheless all these patients will fit within all these criteria. For these reasons, in this chapter, unless otherwise specified, we use the term “Dandy-Walker malformation” (DWM) to refer only to the malformations that correspond to the criteria listed above and that fit into group A of the Barkovich classification.



Fig. 4. Dandy-Walker malformation associated with large occipital meningocele communicating with the posterior fossa cyst

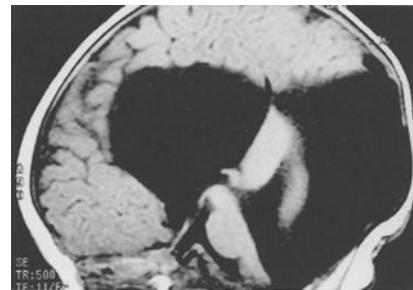


Fig. 5. Dandy-Walker malformation associated with agenesis of the corpus callosum

Posterior Fossa Arachnoid Cysts

Posterior fossa arachnoid cysts are CSF collections in the posterior fossa that do not communicate directly with the fourth ventricle. They may be associated with compression but not with atrophy or agenesis of the vermis (Fig. 6). Clinical features, prognosis, and management are different from those of the Dandy-Walker complex [3], because the pathophysiology of hydrocephalus is different, being related to the compression exerted by the cyst on the cerebellum, with mechanical obstruction of the aqueduct or the fourth ventricular outlets.

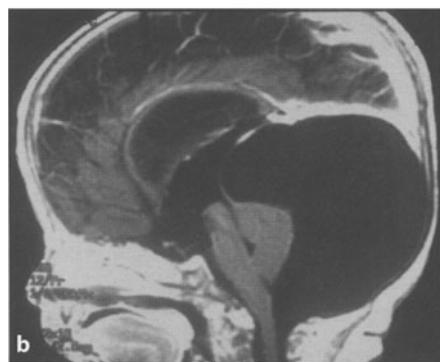
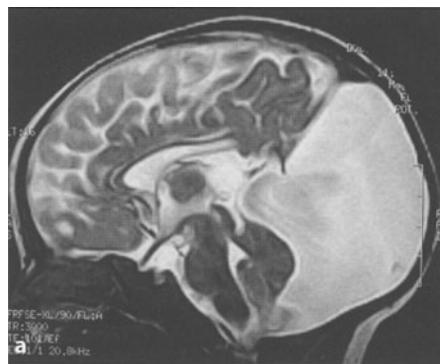


Fig. 6a, b. Arachnoid cysts of the posterior fossa. Note the normal position and orientation of the vermis, which is extremely compressed

Prominent Cisterna Magna

This condition is recognized on the basis of the presence of atrophic vermis and cerebellar hemispheres due to degenerative diseases of the central nervous system and consequent enlargement of the cisterna magna and fourth ventricle, without enlargement of the posterior fossa.

Pathological Findings

Fourth Ventricle and "Cyst" Wall

The neuropathological picture of DWM is dominated by cystic dilatation of the fourth ventricle, aplasia of the vermis, heterotopia of the cerebellar cortex, and enlargement of the posterior fossa, with a high position of the tentorium and transverse sinuses [81]. In the case of "classic" DWM a huge encysted fourth ventricle occupies almost the entire posterior fossa, displacing the brainstem forward and flattening the pons against the clivus [74]. A thin translucent membrane, situated between the two, widely separated, cerebellar hemispheres, forms the roof of the enlarged fourth ventricle; usually, this membrane is quite distinct from the dura mater (Fig. 7), which lies behind, but in some cases it is not possible to identify a cisterna magna [74]. The lower pole of the cystic ventricle can be so displaced downward that the membrane may herniate through the foramen magnum into the spinal canal [19, 41]; superiorly the membrane reaches the tentorium. The membrane consists of two distinct layers [22]: an inner layer of glial tissue covered by ependyma that blends into the ependymal lining of the floor of the fourth ventricle; and an outer pia-arachnoidal layer. Anteriorly and laterally, the wall of the ventricle are formed by white matter belonging to the cerebellar hemispheres and to the remnants of the vermis. The cystic distension of the lateral recess may cause stretching of the ninth and tenth cranial nerves and flattening of the floccu-

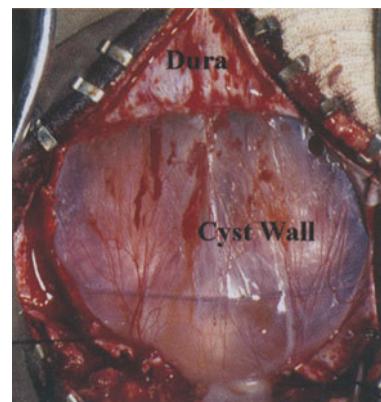


Fig. 7. Surgical view of Dandy-Walker malformation. The patient is in a sitting position. The dura has been opened in a Y fashion and tilted upward. The thick, translucent membrane is the Dandy-Walker "cyst" wall. Cerebrospinal fluid is visible in the lower half of the cystic cavity. (Photograph courtesy of Professor Jean-François Hirsch)

lus. The choroid plexus of the fourth ventricle lies high on the medial walls of the cerebellar hemispheres and along the inner surface of the posterior and inferior portion of the membrane.

Cerebellum

Cerebellar involvement varies widely. The inferior vermis is the most affected, often represented only by a membranous gliotic structure, which in some cases may permit escape of CSF; the remaining superior vermis is often displaced superiorly and rotated anteriorly. It may herniate through the incisura into the quadrigeminal cistern, causing compression of the aqueduct [36, 74]. The cerebellar hemispheres are displaced laterally and dorsally (Fig. 8). The fact that initially small cerebellar hemispheres frequently develop dramatically after shunting indicates that small initial size is attributable to compression rather than hypoplasia.

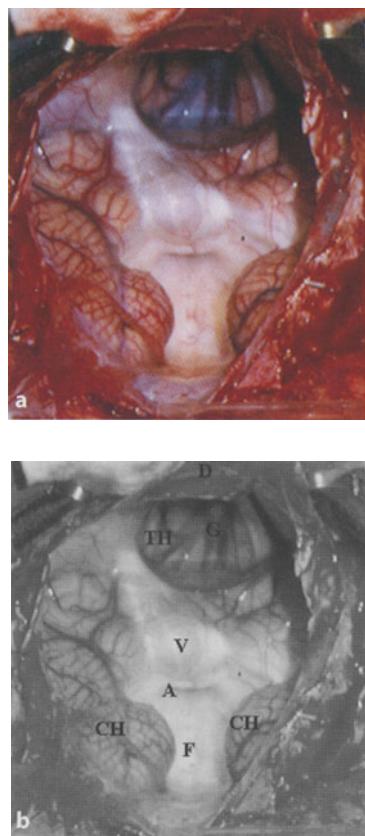


Fig. 8. a Surgical view after complete removal of the cyst wall. **b** Explanatory version of a. *F*, Floor of the fourth ventricle; *CH*, cerebellar hemispheres; *A*, aqueduct; *V*, remnants of the vermis, hypoplastic and upward rotated; *TH*, tentorial hiatus; *G*, vein of Galen; *D*, dura. (Photograph courtesy of Professor Jean-François Hirsch)

The patency of the foramina of Luschka and Magendie is variable. In cases where the foramina are atretic, they are covered by a well-organized membrane consisting of astrocytes with ependymal lining [77].

The pathological findings of Dandy-Walker variant and mega cisterna magna are similar to those of the classic DWM. In Dandy-Walker variant the cerebellar vermis is hypoplastic, but there is no enlargement of the posterior fossa; in mega cisterna magna both the posterior fossa and the cisterna magna are enlarged, but there is no hypoplasia of the vermis [2, 22].

Gardner [34] used the term “Dandy-Walker cyst” for cases of DWM in which the fourth ventricle was distended by an enclosed loculated cyst formed between the two layers of the rhombic roof. In Dandy-Walker cyst as described by Gardner, the outlet foramina are always atretic and the aqueduct is often obstructed [74]; the fluid aspirated from it may be yellow. The formation of the enclosed cyst may be explained [34] by the fact that the ependymal layer is more permeable to ventricular fluid than the outer pial layer.

With the increasing use of MRI and CT, agenesis of the vermis may prove to be no longer a rare condition. DWM should be distinguished from various conditions characterized by agenesis of the vermis, in which, usually, there is no enlargement of fourth ventricle, e.g., simple aplasia (usually of no clinical importance), Joubert syndrome (a recessively inherited condition characterized by episodic hyperpnea, abnormal eye movements, ataxia, and retardation, probably due to malformation of the brainstem nuclei) and tectocerebellar dysraphism with occipital encephalocele (a rare syndrome consisting of occipital encephalocele, aplasia of the vermis, and deformity of the tectum) [25, 30, 31, 81].

Pathogenesis and Etiology of DWM

The “Closed Foramina” Theory

The pathogenesis of DWM has been the subject of considerable debate for many years. Despite numerous reviews, the precise etiology and mechanism of this abnormality are incompletely understood. Dandy and Blackfan [23] believed that the disorder resulted from failure of the foramina of Luschka and Magendie to develop, or from inflammatory obstruction of these foramina, due to an intrauterine inflammatory process; they named this condition “atresia of the foramina of Luschka and Magendie”.

Taggart and Walker [83] agreed with the atretic theory and suggested a pathogenetic sequence as follows: atresia of the CSF outlets as primary defect, and occlusive hydrocephalus and hypoplasia of the cerebellar vermis due to pressure during embryonic brain development. They also reported the almost pathognomonic radiologic finding of high insertion of the confluent sinus.

Embryology

The accuracy of this theory was questioned by the subsequent observation of patency of the outlet foramina in some cases [37] and by embryological studies of cerebellar development that demonstrated that the vermis develops before the opening of the outlet foramina of the fourth ventricle. Thus, the failure of opening of the foramina appears to be the consequence and not the cause of cerebellar dysgenesis. The cerebellum and the roof of the fourth ventricle develop embryologically from the roof of the rhombencephalon [7,79,86], which is the most caudal of the three primitive encephalic vesicles (see Chap. 2 for details). It is rhombus-shaped and composed of an ependymal layer coated posteriorly by the pia mater. The formation of a transverse vascular fold, the plica choroidea, from which the choroid plexus will develop by apposition of mesodermal tissue, divides the roof in two parts: the anterior membranous area (AMA) cranially and the posterior membranous area (PMA) caudally. At about the 5th week of gestation a thickening occurs bilaterally to the AMA in the alar plates of the rhombencephalon, forming the rhombic lips, which are the primordia of the cerebellar hemispheres. The cerebellar vermis forms from the fusion of the developing hemispheres, beginning superiorly in the midline and continuing inferiorly as the hemispheres grow, until the end of the 15th week [53,85]. By the end of the 11th week the AMA is incorporated into the developing choroid plexus. Communication between the fourth ventricle and subarachnoid space of the cisterna magna (developed by cavitation of the primitive meninx) occurs through breaks in the tela choroidea derived from the PMA. Afterwards the tela choroidea shows a finger-like expansion, "Blake's pouch", a structure that disappears, leaving a median opening: the foramen of Magendie. This event is dated around the 4th month of gestation [86]. The formation of the foramina of Luschka occurs later.

Thus, lesions of the alar plates may cause alterations in the development of the vermis and persistence of the AMA, which bulging outward becomes the roof of a cystic enlarged fourth ventricle, producing DWM and its variant (Dandy-Walker complex

type A), whereas a defect of the PMA may produce the mega cisterna magna and persistent Blake's pouch (Dandy-Walker complex type B).

Dysraphic and Hydrodynamic Theories

Benda [9] in 1954, noting the failure of fusion of cerebellar hemispheres, proposed that the malformation represented a form of cerebellar rachischisis, like meningomyeloceles of the spinal cord. Gardner [32, 34] postulated a "hydrodynamic" theory: he proposed that the interplay between the distending forces created by the primitive posterior and anterior choroid plexus determined the size of the posterior fossa and the final position of the tentorium; hypertrophy of the posterior choroid plexus with increased CSF production during embryonic development would lead to pouching of the AMA, with subsequent cystic enlargement of the fourth ventricle, and to the high insertion of the tentorium.

Associated Malformations

DWM is often associated with other brain or systemic anomalies. Hart et al. [43] found associated brain malformations in 68% of their autopsy cases, while in clinical series this association occurs in about 45% [45, 71, 80]. The most frequent are [40, 45, 63, 71, 73, 76]: agenesis of the corpus callosum (see Fig. 5), aqueductal stenosis, rachischisis, ectopic brain or cerebellar tissue, holoprosencephaly, and neural tube defect. Extracerebral anomalies include: congenital heart defect, kidney malformations, polydactyly/syndactyly, cleft palate, perineal malformations, hypospadias, imperforate hymen, Klippel-Feil malformation, and facial hemangiomas. The frequent association of DWM with other midline abnormalities appears to support the concept of "midline as a developmental field" [38, 66, 67]. Several pleiotropic mutations seem to exert their effect predominantly on the midline structures, including CNS, the heart, the palate, the midface, the vertebrae, the genitalia, and the sacrococcygeal region.

Genetic Factors

DWM may be caused by many conditions affecting the brain development at an early stage: the malformations of the posterior fossa and the associated anomalies suggest a teratogenic influence between the 4th and 7th embryonic weeks [71, 81]. DWM can occur as a manifestation of certain mendelian condi-

tions (Warburg syndrome, Mohr syndrome, Meckel-Gruber syndrome), in cases of chromosomal aberrations (several duplication syndromes involving 5p, 8p, 8q; trisomy 9, duplication on 17q, Turner syndrome), in environmentally induced malformation syndrome (prenatal exposure to rubella, cytomegalovirus, toxoplasmosis, warfarin, alcohol, and maternal diabetes), and in multifactorial and sporadic disorders. This etiologic heterogeneity was discussed by Murray et al. [63]; they also estimated a recurrence risk of about 1%-10% in subsequent pregnancies for DWM not associated to a known mendelian disorder.

Pathophysiology of Hydrocephalus

Atresia of Foramina of Luschka and Magendie

Although Hart et al. [43] stated that hydrocephalus is essential to the diagnosis, it is not always in fact associated with DWM. Hirsch et al. [45] reported a 90% incidence of hydrocephalus in their clinical series, but they argued that these data could be an overestimation since children are referred to neurosurgeons only when they develop hydrocephalus and require surgical intervention.

The relevance of foraminal atresia as a pathogenetic factor has been doubted, chiefly because of two observations: that the foramina have occasionally been found to be patent, and that more than 80% of Dandy-Walker infants are not hydrocephalic at birth (Fig. 9).

Atresia in one or two foramina is frequent in otherwise normal brain, the others compensating for the absence. At autopsy [81] one or both the foramina of

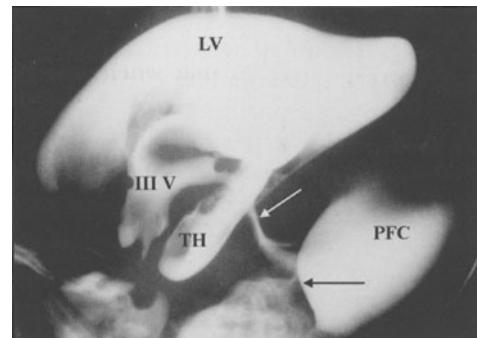


Fig. 10. Ventriculography in Dandy-Walker malformation: note the patency of the aqueduct (white arrow) and of the foramen of Luschka (black arrow). *VL*, Lateral ventricle; *III V*, third ventricle; *TH*, temporal horn; *PFC*, posterior fossa cyst

Luschka are not patent in about 20% of individuals. Barr [8] observed nonpatency of the foramina of Magendie in only 1% of autopsies. Furthermore, when patent, it appeared to have no regular outline, usually presenting as a large defect with free communication between the fourth ventricle and the cisterna magna. Its cross-sectional area averaged about 16 mm^2 in 89% of cases, 7 mm^2 in 7%, and 1 mm^2 in 3%. Even this small opening was adequate to handle the normal flow of about 500 ml of CSF per day. Hirsch et al. [45], who never found an open foramen of Magendie at surgery, ascribed to the patency of the foramina of Luschka, which open later in intrauterine life, the balance between the CSF secretion and CSF absorption at birth (Fig. 10).

Thus, the hydrocephalus in DWM cannot be considered simply a noncommunicating hydrocephalus caused by obstruction of the outlets of the fourth ventricle. In fact such obstruction may be total or partial (even with a valve mechanism which may permit the flow of dye but not of air on contrast studies) [28]. It should be considered multifactorial. Gibson [37] used the term "partial communicating" to refer to this kind of hydrocephalus.

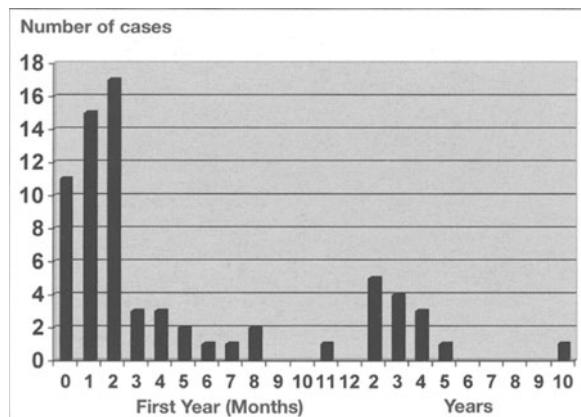


Fig. 9. Age of onset of hydrocephalus in a series of 61 patients

Aqueductal Stenosis

Many conditions may explain why hydrocephalus becomes established. In addition to obstruction of the outlet foramina, aqueductal stenosis, due to a primary developmental defect or secondary to herniation of the vermis or cyst through the tentorial hiatus [16, 74], could be an important, though probably overestimated pathogenetic factor in some cases. Upward herniation of contents of the posterior fossa, with subsequent aqueductal obstruction, may

follow shunting of the ventricular system or may be due to failure of the shunt from the cyst [16, 74]. Raimondi et al. [74] observed that when there is increased pressure under the tentorium, the upper vermis may rotate further anteriorly, acting as a valve for the fluid attempting to escape from the fourth ventricle. They called this condition "functional aqueductal stenosis". For this reason they recommended a combination of fourth and lateral ventricle shunts for the treatment of DWM. However, one should be aware of the fact that these reports, which have greatly influenced the evolution of treatment of this malformation, were presented in either the pre-CT [74] or the pre-MRI era [13], when great confusion still existed in the classification of the cystic collections of the posterior fossa, so that they were all included in the same surgical series. In fact, the rule in typical DWM (type A of Barkovich) is a clearly patent aqueduct with free communication between the third and fourth ventricles (Fig. 10). As a consequence, most authors [5, 16, 24, 28, 45, 56] recommend combined shunt only when lack of adequate communication between the dilated fourth ventricle and lateral ventricular system is suspected preoperatively.

Arachnoiditis

The obstruction of CSF flow may also be distal to the outlets of the fourth ventricle: basal arachnoiditis [23] may cause cisterna magna [33, 87], perimedullary cisterns [39], or incisural [16] block. Glasauer [39] noted at isotope cisternography that occasionally the subarachnoid space anterior to the medulla and basal cisterns was not patent. He ascribed this finding to an inflammatory process, while Palma et al. [70] observed abnormally developed subarachnoid space as a part of DWM. Russell [78] and Raimondi [74] also believed that subarachnoid pathways might be incapable of adequately handling CSF. This concept led to the idea that cyst fenestration and third ventriculostomy were of no therapeutic value in the management of DWM. Actually, subsequent reviews have shown that the opening of subarachnoid space may take days or even weeks after fenestration between the ventricular system and subarachnoid space, and thus no clinical tests can predict the patency of subarachnoid pathways after operation [46].

Venous Hypertension

Finally, the possible role of venous hypertension should not be underestimated: the severe malforma-

tion of the posterior fossa with elevation of the tentorium with the torcular Herophili and the transverse sinuses is obviously associated with lengthening of the venous sinuses and direct compression from the posterior fossa cyst without intermediate compliant cerebellar parenchyma when hydrocephalus occurs. The vascular abnormalities that are frequently observed can contribute to the pathophysiology of hydrocephalus, although no evidence is available so far (Fig. 11).

CSF dynamics should be studied in each case of DWM in order to recognize the main pathogenetic mechanism and choose the most rational treatment. In the past, pneumoencephalography, ventriculography, angiography, and radioisotopes studies have commonly been used for diagnosis [4, 16, 45, 70, 74, 80]. Today CT and MRI are the investigations more frequently used. Plain CT has been found to be insuf-



Fig. 11a, b. Three-month old girl with Dandy-Walker malformation and hydrocephalus. **a** MR angiography, view from above. Complete agenesis of the left transverse sinus; the straight sinus is shortened and verticalized, the sigmoid sinus is thinned. **b** View from behind, same finding as in **a**; note the thinned sigmoid sinus

ficient [4, 69] for the assessment of DWM. Many [69, 76, 90] advise contrast dynamic CT scan to study this condition; flow-sensitive phase-contrast cine MRI could be helpful, but to our knowledge there are no reports of its use in DWM. In our experience MRI with flow study of the aqueduct can be sufficient.

The presence of calvarium defect and occipital meningoceles at birth in patients with DWM has been interpreted as a compensation for increased pressure in the posterior fossa during fetal life (see Fig. 4) [10]. The treatment of DWM often leads to ossification of the defect; thus, surgical closure of occipital meningoceles in these patients may be delayed if skin ulceration is not present.

Syringomyelia

During the course of their disease, Dandy-Walker patients may develop a cavitation in the spinal cord [6, 19, 35, 41, 61, 89]. The pathogenesis of syringomyelia in the course of DWM could be multifactorial. Herniation of the lower pole of the huge enlarged cystic ventricle into the foramen magnum may cause crowding of the occipital foramen, altering the CSF flow dynamics by mechanisms similar to tonsil herniation in Chiari malformation (Fig. 12). An alternative mechanism which may explain the syringes communicating with the fourth ventricle through an enlarged central canal

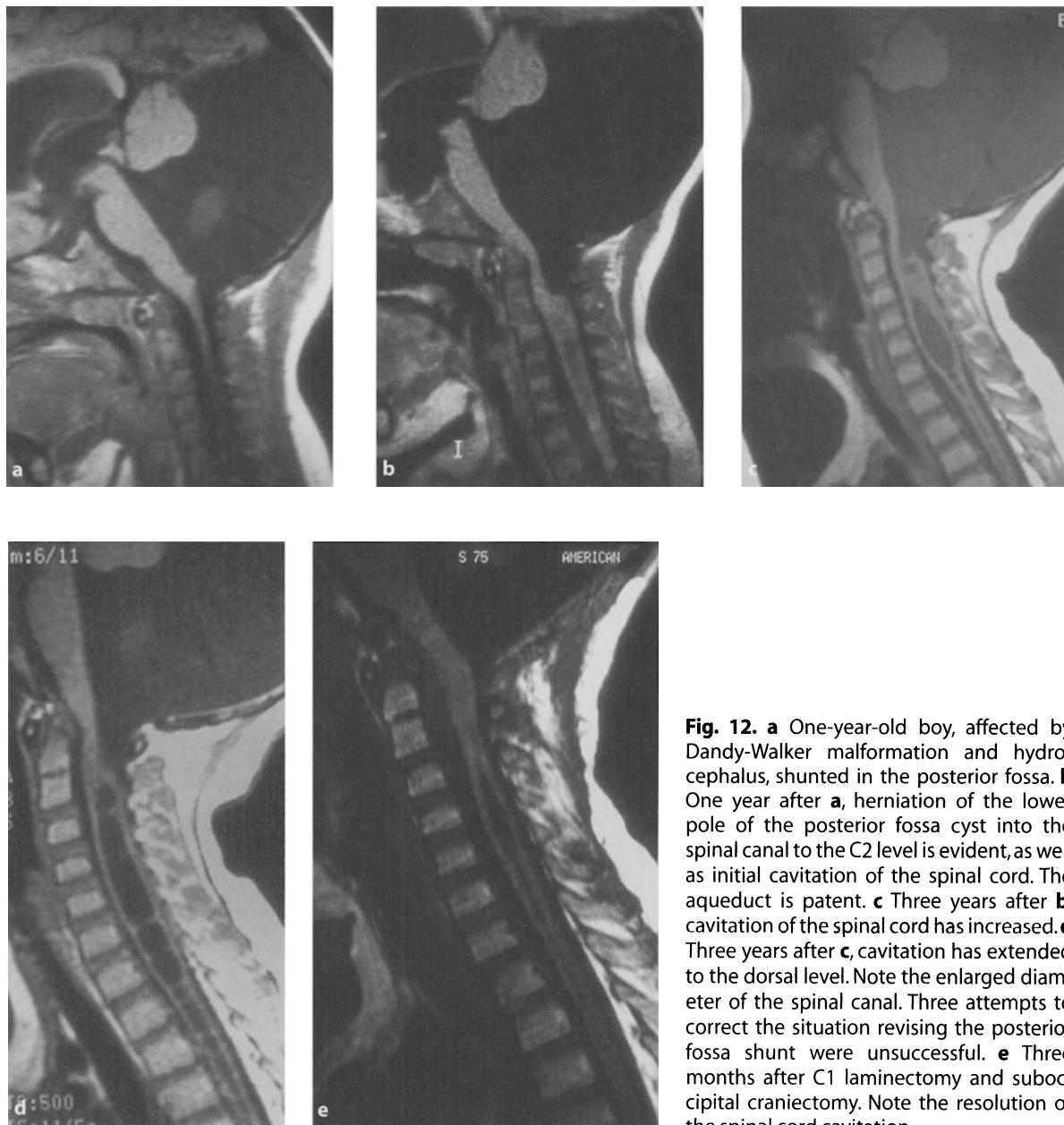


Fig. 12. **a** One-year-old boy, affected by Dandy-Walker malformation and hydrocephalus, shunted in the posterior fossa. **b** One year after **a**, herniation of the lower pole of the posterior fossa cyst into the spinal canal to the C2 level is evident, as well as initial cavitation of the spinal cord. The aqueduct is patent. **c** Three years after **b**, cavitation of the spinal cord has increased. **d** Three years after **c**, cavitation has extended to the dorsal level. Note the enlarged diameter of the spinal canal. Three attempts to correct the situation revising the posterior fossa shunt were unsuccessful. **e** Three months after C1 laminectomy and suboccipital craniectomy. Note the resolution of the spinal cord cavitation

was proposed by Milhorat et al. [61]. They stated that if uncontrolled hydrocephalus was due to obstruction distal to the fourth ventricle, the occurrence of syringomyelia would be the expression of participation of the central canal “in the hydrocephalus process like a fifth ventricle”. Usually the control of hydrocephalus and/or the fourth ventricle dilatation by shunt insertion (or shunt revisions in the case of shunt failure) leads to the resolution of the syringomyelia [41]. Failure to respond to shunting could be explained by adhesion formation between the herniated cyst and the cervicomedullary junction. When this event occurs, suboccipital decompression and duraplasty has been reported to be an effective treatment [19].

Clinical and Neuroradiological Features

Epidemiology and Clinical Features

The incidence of DWM has been estimated to be 1:25 000-1:30 000 births, and children with DWM account for between 1% and 4% of all cases of hydrocephalus [45, 68, 71]. A slight female predominance has been reported in most series [45, 68, 80]. Familial cases are very uncommon [45]. The symptoms in DWM are related to hydrocephalus, cerebellar and cranial nerve dysfunction, and the presence of associated anomalies. The majority of children present early in life: 80%-90% in the first year [45, 68, 80]. Clinical presentation tends to be somewhat age-specific.

Children under 1 year of age most often present with nonspecific symptoms and signs of hydrocephalus and increased intracranial pressure. Macrocrania is by far the most frequent presenting symptom. It is the consequence of hydrocephalus, but can be attributable also to the presence of an enlarged posterior fossa. In some cases the lambdoid suture may be disproportionately widened, characterizing the shape of the head.

In children beyond 1 year, DWM usually presents with delayed achievement of motor milestones, particularly walking and coordination. Spastic paraparesis is the most common motor deficit. Actually, psychomotor retardation is also a frequent feature at any age. Focal neurological deficits, such as nystagmus, cranial nerves palsies, truncal ataxia, explosive speech, and dysmetria, indicative of cerebellar or brainstem dysfunction, are relatively uncommon [80]. These symptoms, together with signs of quadrigeminal plate compression and hypothalamic insufficiency, may arise where there is persistent increased intracranial pressure, particularly

during shunt failures and in cases of expansion of the unshunted compartment (lateral ventricles or cyst) with a pressure gradient at the tentorium [74, 80]. The cerebellar deficits, which usually affect axial movement rather than movements of the extremities [16], tend to improve markedly after adequate control of the hydrocephalus. Seizures are quite common in DWM [11]: they are usually associated with supratentorial malformations (chiefly, heterotopia of the cerebral cortex), and together with hearing/visual problems correlate with poor intellectual development [11].

In older children and adults [26, 54], the classical picture may be indistinguishable from that of a posterior fossa tumor [28], with occipital headache, ataxic gait, vomiting, cranial nerve palsies, pyramidal tract signs, mental status changes, and increased intracranial pressure. The course ranges from weeks to years. Symptomatic cases may be precipitated by minor head trauma. However, DWM has been found incidentally or at autopsy [26, 28, 54, 82].

Radiology

Plain radiographs of the skull may show, although inconsistently, the characteristic features of DWM: enlargement and deepening of the posterior fossa associated with elevation of the groove for the transverse sinus and torcular, thinning of the occipital bone, and separation of the lambdoid suture. Absent posterior inferior cerebellar arteries or an abnormal course of their vermian branches, absent or small and anteriorly displaced cerebellar blush, and elongation of the vein of Galen are the most specific angiographic features, but are nowadays of historical value.

Ultrasonography may be helpful in the first year of life. It may demonstrate: a large cyst within the posterior fossa that is continuous with a dilated fourth ventricle; a small vermis; cerebellar hemispheres displaced anterolaterally; and divergence of the occipital horns of the lateral ventricles as the result of the elevated position of the tentorium [80].

At the present time CT and MRI are the most useful methods of diagnostic imaging. CT scans usually demonstrate a midline defect of the cerebellum that involves the caudal vermis. The fourth ventricle is seen to open into a large low-density area which may occupy the majority of the posterior fossa, displacing the hypoplastic cerebellar hemispheres against the petrous bone and rotating the posterior vermis rostrally [16]. The differential diagnosis against posterior fossa extra-axial cysts relies on demonstrating a compressed and anteriorly displaced fourth ventricle and the lack of communication between the low-density area and the small fourth ventricle [80].

MRI has the advantage of multiplanar imaging and better anatomic resolution. Axial images reveal findings similar to those defined by CT; sagittal MRI may delineate better the extension of the posterior fossa cyst either rostrally through the incisura or caudally into the cervical canal. MRI may also help in assessing the patency of the aqueduct and allows assessment of the degree of cerebellar dysgenesis and the extent of associated malformations, such as agenesis of the corpus callosum [42]. On the basis of CT and MRI findings it is also possible to characterize DWM according to the classification proposed by Barkovich et al. [7], although this morphological classification does not appear to help decision making in management [24].

Treatment

Cyst Membrane Excision

The therapeutic approach to DWM has varied through the years, but contemporary management remains controversial, too. Dandy and Blackfan [23] in 1921 and subsequently Taggart and Walker [83] advocated a direct approach to the posterior fossa cyst with membrane excision, in an attempt to establish communication between the cyst and the subarachnoid space. This form of therapy was based on the assumption that outlets of the fourth ventricle were blocked, resulting in expansion of the fourth ventricle and supratentorial hydrocephalus. Although the results were not good, with a failure rate of 75% and a mortality rate of 10% [29, 59], this was the only treatment available for several decades until the advent of ventricular shunt devices. The failure to control hydrocephalus was thought to be related to abnormality of the subarachnoid space and CSF dy-

namics, but it could be also explained by postoperative scarring, which recreated the adhesions removed during surgery. This procedure was mostly performed in the premicrosurgical era, when the anesthesiological and surgical techniques were probably responsible for the high morbidity and mortality rates [21]. Matson [59], though, did not abandon excision of the membrane as widely as possible in every patients, recommending shunting of the lateral ventricle if membrane excision failed to control the hydrocephalus. He reported, in a later publication [58] with a longer follow-up, a high failure rate of membrane excision alone, noting that 85%-90% of children required shunting, and made a distinction between early and late cases, limiting membrane excision to older patients.

A surgical approach via the posterior fossa and cyst fenestration has been re-evaluated in recent years [1, 51, 88]. The aim of fenestration is to eliminate the need to shunt the posterior fossa in order to reduce the high complication and revision rates, improving the patients' overall functional outcome. This technique does not simultaneously cure the hydrocephalus in patients who have developed aqueductal stenosis and still require ventriculoperitoneal shunt to drain the supratentorial compartment. However, in the case of shunt failure or occlusion of the fenestration, the symptoms are more gradual in onset and not acutely life-threatening like cystoperitoneal shunt obstruction. Moreover, Fischer [28] has stated that membrane excision may be protective against upward transtentorial herniation due to cyst enlargement. Villavicencio et al. [88] have performed open fenestration, with good results, in cases of symptomatic cystic dilatation of the fourth ventricle, after multiple cystoperitoneal shunt failures and revisions. Finally, the procedure can cure the hydrocephalus in selected cases (Fig. 13). This procedure is performed through a small suboccipital craniotomy with removal of the C1 lamina. The linear

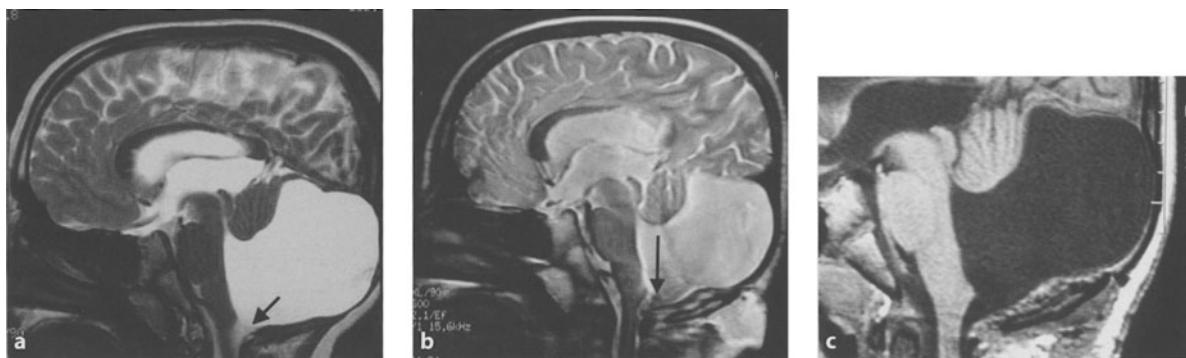


Fig. 13a-c. Ten-year-old boy with a ventriculoperitoneal shunt placed at birth, reoperated on several times for recurring shunt infection. Because of the large number of surgical procedures, microsurgical fenestration of the posterior fossa cyst was performed. **a** Preoperative MRI. **b** T2-weighted immediately postoperative MRI. Note the flow void at the level of the fenestration (arrow). **c** T1-weighted MRI 3 months after the fenestration. The patient is shunt-free

dural opening is made starting just rostral to the foramen magnum and extending to the level of C1. A large fenestration should be performed in the cyst wall, lysing all arachnoidal adhesions in order to communicate the cyst with the surrounding subarachnoid spaces of the cerebellopontine angle and spinal subarachnoid space.

Shunts: Ventriculoperitoneal and Y

Later reviews of several clinical series [80] led to the recognition that the failure rate was too high and that the primary mode of therapy should be shunting, but disagreement still exists as to the optimal position of the proximal end of the shunt: in the lateral ventricle [ventriculoperitoneal (VP) or ventriculoatrial shunts], in the fourth ventricle [cystoperitoneal (CP) shunt], or combined VP/CP shunt. Patency of the aqueduct is a prerequisite for single shunt, whether VP or CP. Some authors [11, 88] report that approximately half of shunted patients require a second shunt during the course of their disease, due to the presence of symptoms suggestive of increased pressure or CT evidence of expansion of the unshunted compartment (ventricles or cyst). This is definitely related to the confusion in classification and to the inclusion of cases (posterior fossa cysts, mega cisterna magna, and real DWM) with radically different pathophysiologies of hydrocephalus in the same surgical series. There are several reports on the surgical management of DWM where patients were mainly studied by CT scan, and some of the images obviously presented cases of posterior fossa cyst [51]. This trend to confusion and to generalization of treatment must be halted, because these diseases are different and their treatment should be individually tailored. The reported cases that are correctly studied and classified as DWM in accordance with the above-cited criteria clearly show that the aqueduct is patent in real DWM and should be considered as patent until the contrary is demonstrated [49].

Historically, Raimondi et al. [74], noted a high frequency of “functional aqueductal stenosis” in their series after placement of VP shunt alone, despite radiographic demonstration of anatomical patency, with progressive life-threatening enlargement of the cyst-like fourth ventricle, due to CSF production. For these reasons they advocated combined VP/CP shunting as first treatment of DWM, with the aim of decompressing the posterior fossa mass effect at the same time as decompressing the ventricles. They also recommended placing the VP/CP shunt with the aid of a Y-connector to minimize differential pressure gradients between the two compartments and, more

importantly, to reduce the risk of single shunt failure, which may result in transtentorial upward or downward herniations. Combined shunt as first treatment has been advocated by several authors since [48, 68, 84]. Osenbach and Menezes [68] reported an unusually high success rate of 92% in children initially treated in this fashion, based on control of hydrocephalus, reduction of intracranial pressure, and reduction in the size of the posterior fossa cyst without increase in shunt-related complications, compared to patients with a single shunt.

Shunts: Posterior Fossa

However, in cases of aqueductal patency, many authors [5, 24, 45, 56, 72] have felt that equivalent results to a double-shunt system could be obtained with cystoperitoneal shunt alone. They have also observed a lower rate of obstruction than with VP or VP/CP shunts, and this is the preferred shunting procedure in their experience. CP shunt appears to encourage the normal flow of CSF through the aqueduct, with a lower incidence of secondary aqueductal stenosis. Moreover, the lack of collapse of the cyst around the shunt tubing minimizes the risk of malfunction [80], although in cases of entrapped fourth ventricle it has been reported [60] that the posterior fossa choroid plexus produces a sufficient amount of CSF for life-threatening cyst enlargement, but an insufficient amount to maintain a functioning shunt.

The CP shunt, on the other hand, is technically the most difficult to position and secure, and this is reflected by a 21.5 % incidence of poorly positioned CP shunts and 9% risk of shunt migration [24].

In a series of 74 patients affected by DWM treated at the Hôpital Necker-Enfants Malades in Paris between 1970 and 1996, hydrocephalus was observed in 61 cases (82%) [20]. The diagnosis of hydrocephalus was more frequent at birth (congenital hydrocephalus in 10 cases) or during the first 3 months of life (Fig. 9). The hydrocephalus was treated in 9 cases by direct surgical approach to the posterior fossa with membrane excision, in 28 cases by infratentorial shunt, in 19 cases by supratentorial shunt, and in 5 cases by third ventriculostomy. The modalities of shunt malfunction are shown in Figs. 14 and 15. The failure rate of supratentorial shunts versus infratentorial shunts shown in Fig. 16 seems to suggest that supratentorial shunts fail less frequently than infratentorial shunts in the long term. The most remarkable thing is that in only two patients was it necessary to shunt both compartments: both of them had undergone open surgery for cyst wall removal and one had suffered severe ventriculitis. Thus, in this series the overall incidence of secondary

(or “functional”) aqueductal stenosis was 2/47 cases (4%), which is very far from the data reported in the literature. As seen above, this difference could be related to two factors: inclusion in a Dandy-Walker series of patients in reality affected by posterior fossa cystic lesions not communicating with the ventricular system; in such cases, shunting of the supratentorial ventricular system would obviously lead to enlargement of the excluded, infratentorial CSF collection. The second factor could be the trend to implant low-pressure or very-low-pressure valves in cases of large cystic collection. Implantation of such a valve in a patient with DWM could create a significant pressure gradient between the supra- and infratentorial compartment, facilitating transtentorial herniation of the medial wall of the ventricular trigones [64] and creating the conditions for mesencephalic deformation with possible secondary aqueductal stenosis. Therefore, in cases where a shunt is required, we think that implantation of a flow-regulating or antisiphon valve should be preferred to differential middle- or high-pressure valves. Low-pressure valves are certainly contraindicated.

The position of the proximal catheter still remains a matter of debate. The posterior fossa cyst still looks the more logical site, because it maintains a downstream flow in the aqueduct and, because of the significant displacement of the tentorium, placement of the burr hole is easier. Surgical placement of a CP shunt is usually performed through a burr hole drilled into the suboccipital area just lateral to the midline. After coagulation and opening of the dura, a ventricular catheter is passed at a distance previously measured on CT or MRI to place the catheter tip within the cyst. The tube can be secured to the dural edges to avoid migration during wound closure, and then tunneled to the lateral part of the neck, where it can be connected in a Y fashion to the supratentorial shunt if a double shunt system is required.

This “blind” procedure exposes the patient to complications. Lee et al. [52] reported in 12 shunted patients a 42% morbidity rate directly related to the placement of the proximal catheter. The complications included injury of the pons with appearance of new neurological deficits (cranial nerves palsies, internuclear ophthalmoplegia, weakness and ataxia) in the immediate postoperative periods, intracystic hemorrhage (which resulted in shunt failure several days after surgery), and embedding of the catheter tip in the brainstem parenchyma (without new neurological deficits). With the aim of avoiding these complications Lee et al. [52] have modified their technique by altering the trajectory of the ventricular catheter while cannulating the posterior fossa. They perform a 2×3 cm craniotomy just medial and inferior to the junction of the transverse and lateral sinus, so that the catheter, under direct ultrasound guidance, enters the cyst par-

allel to the floor of the fourth ventricle rather than directly perpendicular. If a posterior fossa approach is not desirable, the fourth ventricular catheter can be placed through a right parietal burr hole utilizing the stereotactic transtentorial hiatus insertion technique developed by Montes et al. [62]. In cases of ventricular dilatation, cannulation of the aqueduct under neuroendoscopic control is a better alternative [49].

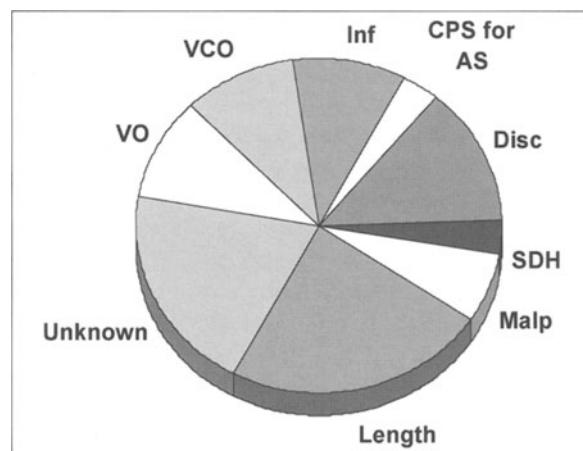


Fig. 14. Modalities of dysfunction of supratentorial shunts in 19 cases of Dandy-Walker malformation. Note that in only one case was it necessary to add a shunt into the posterior fossa cyst for aqueductal stenosis. Inf, Infection; CPS, cystoperitoneal shunt; AS, aqueductal stenosis; Disc, disconnection; SDH, subdural hematoma; Malp, malposition; Length, lengthening of distal catheter; VO, valve obstruction; VCO, ventricular catheter obstruction

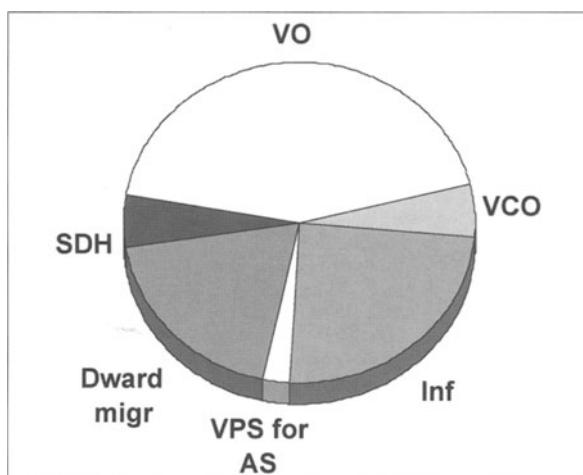


Fig. 15. Modalities of dysfunction of infratentorial shunts in 28 cases of Dandy-Walker malformation. Note that in only one case was it necessary to add a shunt into the supratentorial ventricular system for aqueductal stenosis. VO, Valve obstruction; VCO, ventricular catheter obstruction; Inf, infection; VPS, ventriculoperitoneal shunt; AS, aqueductal stenosis; Dward migr, downward migration; SDH, subdural hematoma

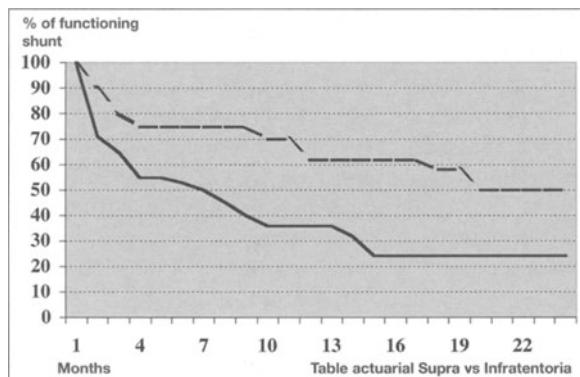


Fig. 16. The actuarial failure rate of supratentorial shunts versus infratentorial shunts in a series of 47 patients with Dandy-Walker malformation (28 cystoperitoneal shunts and 19 ventriculoperitoneal shunts) seems to suggest that supratentorial shunts fail less frequently than infratentorial shunts in the long term

In addition, a CP shunt, whether alone or combined with a VP shunt, carries the risk of failure or overdrainage. Overdrainage may result in posterior fossa subdural hematomas [11], brainstem tethering [55], and chronic cerebral herniation [64]. In patients with DWM, the high position of the tentorium, the wide incisura, and the large posterior fossa may create a predisposition to chronic downward transincisural herniation of the cerebral hemispheres, which may develop when the infratentorial compartment is drained. This predisposition is aggravated by the increase in supratentorial volume due to VP shunt malfunction or post-traumatic or postinfection cerebral edema. Naidich et al. [64] observed that, once established, the herniation may persist despite multiple shunt revisions and restoration of normal pressure. This appears to be a bad prognostic factor. According to Liu et al. [55], brainstem tethering should be suspected if focal cranial nerve palsies or occipital pain develop in children with functional CP or complex shunt: reduction of the cyst size by drainage in the presence of scars secondary to infection may produce traction on the brainstem and subsequent brainstem dysfunction. Sagittal MRI may confirm the diagnosis and an aggressive surgical approach is warranted [55]. Posterior fossa craniectomy with cyst fenestration and untethering may improve neurological deficits and eliminate the need for CP shunt [55]. The high incidence of transtentorial herniations reported in the literature is probably due to the use of low- or very-low-pressure valves to drain the cyst, inducing overdrainage [21].

Because of the frequency and importance of CP shunt complications, Bindal and coworkers [11] believe that CP shunting carries an additional risk to patients and is best avoided if possible. They, together



Fig. 17. All the pitfalls of shunt surgery in Dandy-Walker malformation are summarized in this image. The burr hole is dangerously close to the transverse sinus. The catheter did not enter the lateral ventricle, slid over the tentorium and the posterior fossa cyst, and failed to enter the contralateral ventricle

with Fischer [28], Pascual-Castroviejo et al. [71], and Marinov et al. [57], recommend VP shunting as the first procedure in the absence of evidence of aqueductal stenosis. This procedure presents the clear advantage of a long track through the parenchyma, with very small risk of CSF leaks around the dural hole compared to the catheter into the posterior fossa cyst. Nevertheless, the distorted anatomy and the elevation of the tentorium can lead to an unusually high rate of proximal displacement (Fig. 17). A policy of close follow-up with clinical examinations and routine imaging studies is recommended for all types of shunt system.

Third Ventriculostomy

Whatever shunting procedure is adopted, the risk of complications remains very high (50%-59%) [24], so alternatives to shunting have been investigated. Third ventriculostomy under either radioscopic or endoscopic control has been successfully performed [5, 17, 21, 45]. Conditions allowing a safe and successful third ventriculostomy are: sufficient dilatation of the third ventricle, permeability of the subarachnoid space, and absence of other CNS malformations, such as agenesis of the corpus callosum, which might allow the escape

of CSF into the convexity of the subarachnoid space [21, 45]. However, patients with DWM without associated CNS anomalies are usually good candidates for endoscopic third ventriculostomy.

Based on the experience of the senior author [21], considering the severe complications observed with traditional extracranial shunts we advocate third ventriculostomy as the first treatment option in DWM. The aim of the procedure (like cyst fenestration) is to create a communication between the ven-

tricular system and the subarachnoid space. Since this procedure is minimally invasive, with no dissection, minimal surgical trauma, and reduced risk of postoperative adhesion compared to posterior fossa exploration and cyst fenestration, endoscopic third ventriculostomy should be suggested for all cases where the anatomy allows, giving the patient the chance to remain “shunt-free” (Fig. 18), even if some cases may fail to respond adequately due to poor development of the subarachnoid space [46]. Hirsch et

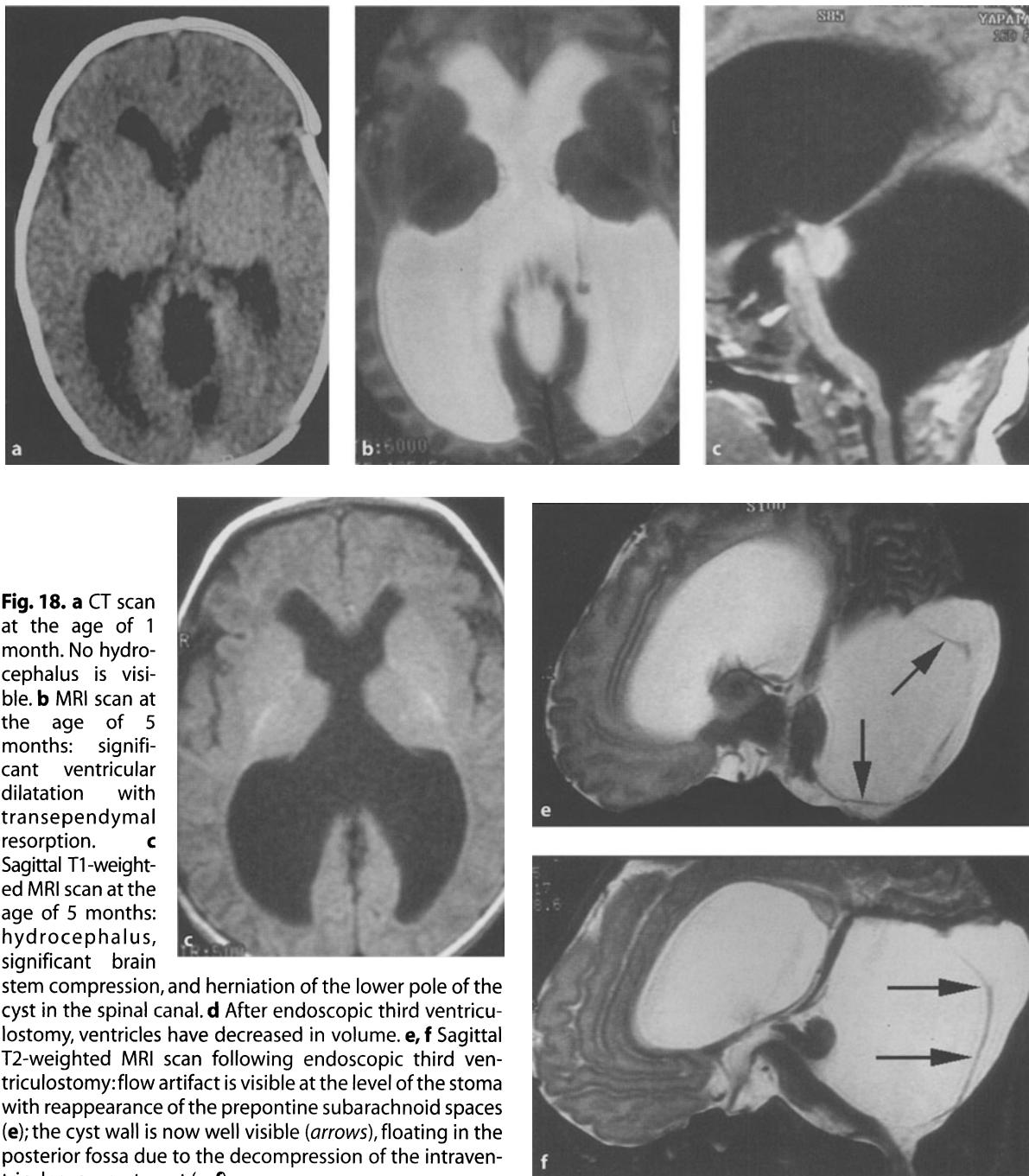


Fig. 18. **a** CT scan at the age of 1 month. No hydrocephalus is visible. **b** MRI scan at the age of 5 months: significant ventricular dilatation with transependymal resorption. **c** Sagittal T1-weighted MRI scan at the age of 5 months: hydrocephalus, significant brain stem compression, and herniation of the lower pole of the cyst in the spinal canal. **d** After endoscopic third ventriculostomy, ventricles have decreased in volume. **e, f** Sagittal T2-weighted MRI scan following endoscopic third ventriculostomy: flow artifact is visible at the level of the stoma with reappearance of the preopticine subarachnoid spaces (**e**); the cyst wall is now well visible (arrows), floating in the posterior fossa due to the decompression of the intraventricular compartment (**e, f**)

al. [45] and Hoffmann et al. [47] reported a 50% success rate, while Cinalli [21] reported a long-term resolution of hydrocephalus in three of a total of four patients operated on with the endoscopic technique as a first option.

Actually the anatomical modifications of the interpeduncular cistern and of the third ventricle, and above all the orientation of the floor, the position of the tip of the basilar artery, which is much higher than normal, and the displacement of the brainstem against the clivus, make this procedure difficult to perform. On both MRI and during the procedure, the first impression is often that perforation of the floor of the third ventricle would be impossible or too hazardous; but waiting some minutes and allowing the CSF to leak slowly through the endoscope usually allows a slow but progressive decompression of the cyst, reducing the mass effect on the brainstem and recreating the space for a safe third ventriculostomy. Thus, the ultimate decision to perforate the floor should be taken during surgery, and this will depend mainly on the attitude and experience of the surgeon. Isolated cases will probably show better results than those associated with other CNS malformations.

Outcome and Prognosis

Overall mortality in DWM has been reduced from 40%-50% in the pre-CT era [28, 48, 74, 84] to 10%-20% today [5, 57, 90], thanks chiefly to improvements in anesthesiological and surgical techniques, aggressive shunt management, and advances in neuroimaging. The major causes of death still remain infectious, uncontrolled hydrocephalus and shunt malfunction or shunt complications.

Subnormal intellectual development and/or poor motor function have been reported in up to 50% of children, possibly related to the presence of associated CNS anomalies, such as callosal agenesis and cerebral gyral anomalies [5, 11, 21, 40, 56]. Golden et al. [40] have suggested that if DWM is isolated, i.e., unaccompanied by other CNS or visceral anomalies, the outcome should be relatively favorable, with many surviving children who manifest normal intellectual and neurological development. By contrast, children with other anomalies appear to die at a young age or tend to reach fewer intellectual milestones. Thus, seizures, significant hearing and visual problems, which may indicate the presence of CNS anomalies, and systemic anomalies are statistically related to poor outcome [11], while the reestablishment of posterior fossa architecture after shunting (on CT scans) [36] indicates a good prognosis. In the past, no correlation was

found between cerebellar size and intellectual disorders or cerebellar function [36] or between time of placement and type of shunt used and neurological development [11, 36, 40]. The present authors agree with Carmel et al. [16] and Osenbach and Menezes [68], who stated: "In the absence of major CNS malformations, early and adequate treatment of hydrocephalus is the single most important factor in producing the potential for normal intellectual development". The recent works of Klein and Boddaert et al. [12, 50], based on careful analysis of patients studied by MRI, seem to show the direction of further research for an accurate assessment of intellectual prognosis, possibly in utero. They showed a precise relationship between the degree of vermian malformation and intellectual outcome: patients who presented more complete lobulation of the vermis, with the two main fissures (primary and secondary fissure) and the three main lobes visible, were likely to have a good intellectual prognosis (IQ>85) (see Fig. 2).

With the increasing availability of prenatal ultrasonography, many cases of DWM are diagnosed in utero: the prognosis ranges from normal development to severe disability or death, and appears to be related to abnormal karyotype and associated anomalies [18, 27]; thus, amniocentesis and a detailed ultrasonographic search for associated anomalies or a fetal MRI should be recommended, as well as postnatal cranial neuroimaging [18, 27].

References

1. Almeida GM, Matushita H, Mattosinho-França, et al: Dandy-Walker Syndrome: posterior fossa craniectomy and cyst fenestration after several shunt revisions. *Child's Nerv Syst* 6: 335-337, 1990
2. Altman NR, Naidich TP, Braffmann BH: Posterior fossa malformations. *AJNR Am J Neuroradiol* 13: 691-724, 1992
3. Arai H, Sato K: Posterior fossa cysts: clinical, neuroradiological and surgical features. *Child's Nerv Syst* 7: 156-164, 1991
4. Archer CR, Darwish H, Smith K: Enlarged cisterna magna and posterior fossa cysts simulating Dandy-Walker syndrome on computed tomography. *Radiology* 127: 681-686, 1978
5. Asai A, Hoffman HJ, Hendrick EB, Humphreys RP: Dandy-Walker syndrome: experience at the Hospital for Sick Children, Toronto. *Pediatr Neurosci* 15: 66-73, 1989
6. Baker GS, Rydell RE: Dandy-Walker Malformation. Association with syringomyelia. *Minn Med* 54: 889-893, 1971
7. Barkovich AJ, Kjos BO, Norman D, et al: Revised classification of posterior fossa cysts and cyst-like malformations based on the results of multiplanar MR imaging. *AJNR Am J Neuroradiol* 10: 977-988, 1989
8. Barr: Observations on the foramen of Magendie in a series of human brains. *Brain* 71: 281, 1948
9. Benda CE: The Dandy-Walker syndrome or the so-called atresia of the foramen of Magendie. *J Neuropathol Exp Neurol* 13: 14-29, 1954

10. Bindal AK, Storrs BB, McLone DG: Occipital meningoceles in patients with the Dandy-Walker syndrome. *Neurosurgery* 28: 844-847, 1991
11. Bindal AK, Storrs BB, McLone DG: Management of Dandy-Walker syndrome. *Pediatr Neurosurg* 16: 163-169, 1990-1991
12. Boddaert N, Klein O, Ferguson N, et al: Intellectual prognosis of the Dandy-Walker malformation in children: the importance of vermian lobulation. *Neuroradiology* 45:320-324, 2003
13. Boltshauser E: Cerebellar imaging – an important signpost in pediatric neurology. *Child's Nerv Syst* 17:211-216, 2001
14. Brown J: The Dandy-Walker syndrome. In: Vincken PJ, Bruyn GW (Eds) *Handbook of clinical neurology*, vol 30. Amsterdam, North Holland Publishing p 623, 1977
15. Calabro' F, Arcuri T, Jenkins JR: Blake's pouch cyst: an entity within the Dandy-Walker continuum. *Neuroradiology* 42:290-295, 2000
16. Carmel PW, Antunes JL, Hilal SK, et al: Dandy-Walker syndrome: clinico-pathological features and re-evaluation of modes of treatment. *Surg Neurol* 8: 132-138, 1977
17. Cartmill M, Jaspan T, McConachie N, et al: Neuroendoscopic third ventriculostomy in dysmorphic brain. *Child's Nerv Syst* 17: 391-394, 2001
18. Chen FP, Chu KK: Prenatal diagnosis of Dandy-Walker malformation: report of a case. *J Formos Med Assoc* 93: 967-970, 1994
19. Cinalli G, Vinikoff L, Zerah M, et al: Dandy-Walker malformation associated with syringomyelia. *J Neurosurg* 86: 571, 1997
20. Cinalli G, Sainte-Rose C, Zerah M, et al: La malformation de Dandy-Walker. Proceedings of the French Society of Neurosurgery. Fort-de-France, Martinique, 19-24 January 1997
21. Cinalli G: Alternatives to shunting. *Child's Nerv Syst* 15: 718-731, 1999
22. Costa C, Hauw JJ: Pathology of the cerebellum, brain stem, and spinal cord. In: Duckett S (ed) *Pediatric neuropathology*. Williams & Wilkins, Baltimore, pp 217-238, 1995
23. Dandy WE, Blackfan KD: Internal hydrocephalus. An experimental, clinical and pathological study. *Am J Dis Child* 8: 406-482, 1914
24. Domingo Z, Peter J: Midline developmental abnormalities of the posterior fossa: correlation of classification with outcome. *Pediatr Neurosurg* 24: 111-118, 1996
25. Egger J, Bellman MH, Ross EM, Barairser M: Joubert-Boltshauer syndrome with polydactyly in siblings. *J Neurol Neurosurg Psychiatry* 45: 737-739, 1982
26. Engelhard HH, Mayer JR: Adult-onset presentation of Dandy-Walker variant in siblings. *Surg Neurol* 44: 43-47, 1995
27. Estroff JA, Scott MR, Benacerraf BR: Dandy-Walker variant: prenatal sonographic features and clinical outcome. *Radiology* 185: 755-758, 1992
28. Fischer EG: Dandy-Walker Syndrome: an evaluation of surgical treatment. *J Neurosurg* 39: 615-621, 1973
29. Fowler FD, Alexander E: Atresia of the foramina of Luschka and Magendie. *Am J Dis Child* 92: 131-137, 1956
30. Friede RL, Boltshauer: Uncommon syndromes of cerebellar aplasia. I: Joubert syndrome. *Dev Med Child Neurol* 20: 758-763, 1978
31. Friede RL: Uncommon syndromes of cerebellar aplasia. II: Tecto-cerebellar dysraphia with occipital encephalocele. *Dev Med Child Neurol* 20: 764-772, 1978
32. Gardner WJ, Abdullah AF, McCormack LJ: The varying expression of the embryonal atresia of fourth ventricle in adult. Arnold-Chiari malformation, Dandy-Walker syndrome, "arachnoid cyst" of cerebellum, and syringomyelia. *J Neurosurg* 14: 591-607, 1957
33. Gardner WJ, Smith JL, Padget DH: The relationship of Arnold-Chiari and Dandy-Walker malformations. *J Neurosurg* 36: 481-486, 1972
34. Gardner WJ: Hydrodynamic factors in Dandy-Walker and Arnold-Chiari malformations. *Child's Brain* 3: 200-212, 1977
35. Gardner WJ: Hydrodynamic mechanism of syringomyelia: its relationship to myelocele. *J Neurol Neurosurg Psychiatry* 28: 247-269, 1965
36. Gerszten PC, Albright AL: Relationship between cerebellar appearance and function in children with Dandy-Walker syndrome. *Pediatr Neurosurg* 23: 86-92, 1995
37. Gibson JB: Congenital hydrocephalus due to atresia of the foramen of Magendie. *J Neuropathol Exp Neurol* 14: 244-262, 1955
38. Gilbert-Barness E, Debich-Spicer D, Cohen MM Jr, et al: Evidence for the "midline" hypothesis in associated defects of laterality formation and multiple midline anomalies. *Am J Med Genet* 101: 382-7, 2001
39. Glasauer FE: Isotope cisternography and ventriculography in congenital anomalies of the central nervous system. *J Neurosurg* 43: 18-26, 1975
40. Golden JA, Rorke LB, Bruce DA: Dandy-Walker syndrome and associated anomalies. *Pediatr Neurosci* 13: 38-44, 1987
41. Hammond CJ, Chitnavis B, Penny CC, et al: Dandy-Walker complex and syringomyelia in an adult: case report and discussion. *Neurosurgery* 50: 191-194, 2002
42. Hanigan WC, Wright R, Wright S: Magnetic resonance imaging of the Dandy-Walker malformation. *Pediatr Neurosci* 12: 151-156, 1986
43. Hart MN, Malamud N, Ellis WG: The Dandy-Walker syndrome. A clinico-pathological study based on 28 cases. *Neurology* 22: 771-780, 1972
44. Harwood-Nash DC, Fitz CR: Neuroradiology in infants and children, vol 3. Mosby, St Louis, pp 1014-1019, 1976
45. Hirsch JF, Pierre-Kahn A, Renier D, et al: The Dandy-Walker malformation. A review of 40 cases. *J Neurosurg* 61: 515-522, 1984
46. Hirsch JF: Percutaneous ventriculocisternostomies in non-communicating hydrocephalus. *Monogr Neurol Sci* 8: 170-178, 1982
47. Hoffman HJ, Harwood-Nash D, Gilday DL, Craven MA: Percutaneous ventriculostomy in the management of non-communicating hydrocephalus. *Neurosurgery* 7: 1330-1337, 1980
48. James HE, Kaiser G, Schut L, et al: Problems of diagnosis and treatment in the Dandy-Walker syndrome. *Child's Brain* 5: 24-30, 1979
49. Kawaguchi T, Jokura H, Kusaka Y, et al: Intraoperative direct neuroendoscopic observation of the aqueduct in Dandy-Walker malformation. *Acta Neurochir* 75: 63-67, 2003
50. Klein O, Pierre-Kahn A, Boddaert N, Parisot D, Brunelle F: Dandy-Walker malformation: prenatal diagnosis and prognosis. *Child's Nerv Syst* 19:484-489, 2003
51. Kumar R, Jain MK, Chabra DK: Dandy-Walker syndrome: different modalities of treatment and outcome in 42 cases. *Child's Nerv Syst* 17: 348-352, 2001

52. Lee M, Leahu D, Weiner HL, et al: Complications of fourth ventricle shunts. *Pediatr Neurosurg* 22: 309-314, 1995
53. Lemire RJ, Loeser JD, Leech RW, et al: Normal and abnormal development of the human nervous system. Harper & Row, Hagerstown, MD, pp 144-164, 1985
54. Lipton HL, Preziosi TJ, Moses H: Adult onset in Dandy-Walker syndrome. *Arch Neurol* 35: 672-675, 1978
55. Liu JC, Ciacci JD, George TM: Brainstem tethering in Dandy-Walker syndrome: a complication of cystoperitoneal shunting. *J Neurosurg* 83: 1072-1074, 1995
56. Maria BL, Zinreich SJ, Carson BC, et al: Dandy-Walker syndrome revisited. *Pediatr Neurosci* 13: 45-51, 1987
57. Marinov M, Gabrovski S, Undjian S: The Dandy-Walker syndrome: diagnostic and surgical consideration. *Br J Neurosurg* 5: 475-483, 1991
58. Matson DD: Neurosurgery of infants and childhood, 2nd edn. Charles C Thomas, Springfield, Ill, pp 259-268, 1969
59. Matson DD: Prenatal obstruction of the fourth ventricle. *Am J Roentg* 76: 499-506, 1956
60. McLone DG, Naidich TP, Cunningham T: Posterior fossa cysts: management and outcome. *Concept Pediatr Neurosurg* 7: 134-141, 1987
61. Milhorat TH, Capocelli AL, Anzil AP, et al: Pathological basis of spinal cord cavitation in syringomyelia: analysis of 105 autopsy cases. *J Neurosurg* 82: 802-812, 1995
62. Montes JL, Clarke DB, Farmer JP: Stereotactic transtentorial hiatus ventriculoperitoneal shunt for the sequestered fourth ventricle. Technical note. *J Neurosurg* 80: 759-761, 1994
63. Murray JC, Johnson JA, Bird TD: Dandy-Walker malformation: etiologic heterogeneity and empiric recurrence risks. *Clin Genet* 28: 272-283, 1985
64. Naidich TP, Radkowski MA, McLone DG, et al: Chronic cerebral herniation in shunted Dandy-Walker malformation. *Radiology* 158: 431-434, 1986
65. Nieuwenhuis R, Voogd J, van Huijzen: The human central nervous system. A synopsis and atlas, 3rd edn. Springer, Berlin Heidelberg New York, pp 18-19, 1988
66. Opitz JM, Gilbert EF: CNS anomalies and the midline as a "developmental field". *Am J Med Genet* 12: 443-455, 1982
67. Opitz JM: The developmental field concept. *Am J Med Genet* 21: 1-11, 1985
68. Osenbach RK, Menezes AH: Diagnosis and management of the Dandy-Walker malformation: 30 years experience. *Pediatr Neurosurg* 18: 179-189, 1992
69. Özgen T, A_ikgöz B: CSF dynamics in Dandy-Walker syndrome. *Acta Neurochir (Wien)* 104: 54-58, 1990
70. Palma A, Nazar N, Castro M, et al: Dandy-Walker malformation and the contribution of radioisotopic studies of cerebral spinal fluid dynamics to its diagnosis. *Acta Neurochir* 61: 319-324, 1982
71. Pascual-Castroviejo I, Velez A, Pascual-Pascual SI, et al: Dandy-Walter malformation: analysis of 38 cases. *Child's Nerv Syst* 7: 88-97, 1991
72. Peter JC, Fieggen G: Congenital malformations of the brain: a neurosurgical perspective at the close of the twentieth century. *Child's Nerv Syst* 15: 635-645, 1999
73. Pierquin G, Deroover J, Levi S, Masson T, et al: Dandy-Walker malformation with postaxial polydactyly: a new syndrome? *Am J Med Genet* 33: 483-484, 1989
74. Raimondi AJ, Samuelson G, Yarzagbaray L, et al: Atresia of the foramen of Luschka and Magendie: the Dandy-Walker cyst. *J Neurosurg* 31: 202-216, 1969
75. Raybaud C: Cystic malformations of the posterior fossa. Abnormalities associated with the development of the roof of the fourth ventricle and adjacent meningeal structures. *J Neuroradiol* 9: 103-133, 1982
76. Ritscher D, Schinzel A, Boltshauer E, et al: Dandy-Walker (like) malformation, atrio-ventricular septal defect and a similar pattern of minor anomalies in two sisters: a new syndrome? *Am J Med Genet* 26: 481-49, 1987
77. Roessmann U: Congenital malformations. In: Duckett S (Ed) *Pediatric neuropathology*. Williams & Wilkins, Baltimore, pp 123-148, 1995
78. Russell DS: Observations on the pathology of hydrocephalus. His Majesty's Stationery Office, London, 1949 (Medical Research Council, special report series no. 265)
79. Sarnat HB: Cerebral dysgenesis. Embryology and clinical expression. Oxford University Press, New York Oxford, pp 275-329, 1992
80. Sawaya R, McLaurin RL: Dandy-Walker syndrome. Clinical analysis of 23 cases. *J Neurosurg* 55: 89-98, 1981
81. Shaw CM, Alvord EC: Hydrocephalus. In: Duckett S (ed) *Pediatric neuropathology*. Williams & Wilkins, Baltimore, pp 149-211, 1995
82. Stoll C, Huber C, Alembik Y, et al: Dandy-Walker variant malformation, spastic paraparesia and mental retardation in two sibs. *Am J Med Genet* 37: 124-127, 1990
83. Taggart JK, Walker AE: Congenital atresia of the foramen of Luschka and Magendie. *Arch Neurol Psychiatry* 48: 583-612, 1942
84. Tal Y, Freigang B, Dunn HG, et al: Dandy-Walker syndrome analysis of 21 cases. *Dev Med Child Neurol* 22: 189-201, 1980
85. Ten Donkelaar HJ, Lammens M, Wesseling P, et al: Development and developmental disorders of the human cerebellum. *J Neurol* 250: 1025-1036, 2003
86. Tortori-Donati P, Fondelli MP, Rossi A, et al: Cystic malformations of the posterior cranial fossa originating from a defect of the posterior membranous area. Mega cisterna magna and persisting Blake's pouch: two separate entities. *Child's Nerv Syst* 12: 303-308, 1996
87. Udarhelyi GB, Epstein MH: The so-called Dandy-Walker Syndrome: analysis of 12 operated cases. *Child's Brain* 1: 158-182, 1975
88. Villavicencio AT, Wellos JC, George TM: Avoiding complicated shunt systems by open fenestration of symptomatic fourth ventricular cysts associated with hydrocephalus. *Pediatr Neurosurg* 29: 314-319, 1998
89. Vuia O, Pascu G: The Dandy-Walker syndrome associated with syringomyelia in an infant. *Confin Neurol* 33: 33-40, 1971
90. Wolpert SM, Scott RM, Runge VM, et al: Difficulties of diagnosing congenital posterior fossa fluid collection after shunting procedures. *AJNR Am J Neuroradiol* 8: 653-656, 1986

Hydrocephalus and Aqueductal Stenosis

GIUSEPPE CINALLI¹, PIETRO SPENNATO², EMILIO CIANCIULLI³ AND MARIA D'ARMIENTO⁴

Introduction

The cerebral aqueduct was described by Vesalius in 1542 as a short tube “so that the animal spirit may flow continuously into the dorsal marrow” [32]. Actually, the aqueduct of Sylvius connects the third and fourth ventricle: it is a narrow, irregular channel, situated in the dorsal midbrain, with posterior commissure and lamina tecti behind, oculomotor and trochlear nerves nuclei, and medial longitudinal fasciculus and red nuclei in front. It forms a gentle concave curve to the base of the skull and is surrounded by the periaqueductal gray matter. In fixed brain specimens two areas of relative constriction have been found: one is at the level of the superior colliculus, the other at the level of the intercollicular sulcus; in cross section the lumen is highly changeable, probably owing to the influence of different nuclear masses or fiber tracts surrounding it at different levels. The lumen is usually triangular with the apex directed ventrally at the two constrictions and ovoid in the central dilated area, which has been referred to as the ampulla of the aqueduct or the ventricle of the midbrain [8]. The length of the aqueduct increases rapidly during infancy, measuring about 12.8 mm at birth, 17.4 mm at six months, 18 mm at 1 year, and thereafter hardly increases [32]. The lumen varies considerably between different individuals and along the length of aqueduct, the narrowest part usually being at the level of the superior constriction. Emery and Staschak [32] reported a mean value of 0.5 mm² cross-sectional area in children, and Woollam and Millen [96] a mean of 0.8 mm² (range 0.2–1.8 mm²) in the normal adult. It is not known how much narrowing must occur to produce hydrocephalus: in nonhydrocephalic subjects cross-sectional areas as narrow as 0.1 mm² have been reported [32, 45, 81]. Alvord [1] suggested that normal aqueduct was 10–100 times larger than was necessary to conduct the cerebrospinal fluid (CSF) from the third to the fourth ventricle.

The ependymal lining often presents individual variations, being absent for short distances (denuded areas) on one or both sides or thicker than one cell layer. It can also be wrinkly and form small diverticula. At variable short distances from the wall of the main aqueduct, small accessory aqueductules or clusters of ependymal cells can be found [8]. The subependymal glial plate also presents numerous variations in position and cell density: it may be situated only dorsally, only ventrally, only laterally, or it may surround the entire aqueduct. In some instances a true subependymal cellular plate is not discernible, but the ependymal wall of the aqueduct is bordered by the continuance of the brainstem glia [8]. Moreover, in areas lacking in ependyma, glia can overgrow. If this proliferation is excessive, glia can protrude into the lumen and even bridge the canal.

At the three-vesicle stage of intrauterine life, the aqueduct is as large as other portions of neural tube. Its adult configuration results from the gradual narrowing that occurs during fetal development due to thickening of surrounding nuclear masses and fiber tracts of the mesencephalon. The aqueduct, due to its length and narrowness, is particularly exposed to obstructive lesions and has been considered the most common site of intraventricular blockage of CSF since Bourneville and Noir [14] first noted in 1900 the association between hydrocephalus and stenosis of the aqueduct. Later, in 1920, Dandy [26] coined the term “noncommunicating hydrocephalus” to indicate hydrocephalus due to aqueductal stenosis.

Aqueductal stenosis has been classified in various ways; however, the first and most important distinction is between aqueductal stenosis secondary to compression from mass lesions (particularly tectal tumors and vascular malformations) and stenosis due to intrinsic pathology of the aqueduct itself, so-called “nontumoral aqueductal stenosis.” In this chapter we will be specifically concerned with the nontumoral or “benign” form of aqueductal stenosis.

¹Department of Pediatric Neurosurgery, Santobono-Pausilipon Children's Hospital, Naples; ² Department of Neurosurgery, Second University of Naples; ³ Department of Pediatric Neuroradiology, Santobono-Pausilipon Children's Hospital, Naples; ⁴ Department of Biomorphological and Functional Sciences, Section of Pathology, Federico II, University of Naples, Italy

Pathological Findings

The appearance of the aqueduct in cases of aqueductal stenosis is highly variable. Although the type of obstruction is classically categorized as congenital or acquired, a complete correlation between pathological findings, age at clinical onset, and etiology has never been demonstrated. Russell [81] in her histopathological classification in 1949 subdivided nontumoral aqueduct anomalies into four types:

1. *Stenosis.* In this form the aqueduct is narrowed or obliterated and ependyma lines the lumen without gliosis of the surrounding tissue. In cases of “simple stenosis” an abnormally small aqueduct with normal cells is present. In cases of “congenital atresia” the aqueduct may not be discernible on gross inspection (Fig. 1). Microscopic examination can reveal clusters of ependymal nests and channels or aqueductules scattered throughout the midbrain. Congenital atresia is very rare; it is the form most probably due to “developmental” errors, in which abnormal infolding of the neural plate results in narrowing of the neural tube with cleaning of the lumen and the creation of small ependymal nests [45].
2. *Forking.* This form is characterized by splitting of the aqueduct into two or more separate irregular channels (Fig. 2). These channels can communicate each other, can enter the ventricle indepen-

Fig. 1. Stenosis of the aqueduct showing a greatly reduced ependymal channel with gliosis in the surrounding midbrain

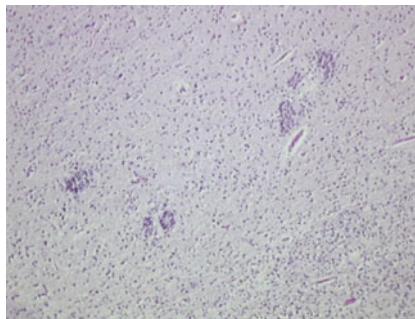
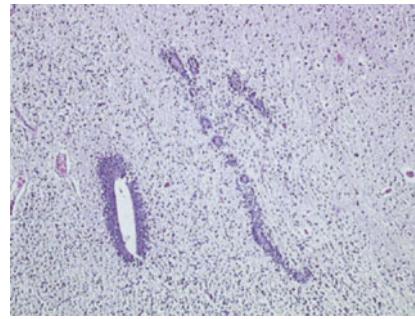


Fig. 2. Forking of the aqueduct with two relatively small channels lined by ependymal cells and no surrounding gliosis



dently, or can end blindly. Although a “simple” forking (a ventral channel of the normal aqueduct) can be found also in nonhydrocephalic subjects, this condition usually reduces the aqueductal lumen. It results from incomplete fusion of the median fissure.

3. *Septum formation.* In this form the aqueduct is totally or in part obstructed by a thin, translucent membrane. This is usually located at the lower end of the aqueduct and is composed of loose-textured fibrillary neuroglia. Small ependymal canaliculi or scattered clumps of ependymal cells can be found on the septum or in the brain adjacent to its attachment: they lead to incomplete flow of CSF, delaying the onset of symptoms [90]. Turnbull and Drake [90] consider that septum formation results from the same process that produces other forms of aqueductal stenosis: when the glial overgrowth is restricted to the lower end of the aqueduct, it gradually becomes a tiny sheet from prolonged pressure and dilatation of the canal above.
4. *Gliosis.* Gliotic stenosis is characterized by proliferation of glial cells and overproduction of glial fibers, which are arranged in tangled fasciculi or large bands [8]. Gliosis completely fills the area of pre-existing aqueduct or leaves a narrow lumen or several little channels that are not outlined by ependyma (Fig. 3). Instead, scattered residual nests of ependyma outline gliosis. Some authors [8] consider this kind of stenosis an expression of developmental disorders because of its association with other developmental alterations (presence of aqueductules, absence of ependyma, variations in position and cell density of the glial plate, protrusion of glia into the lumen of aque-

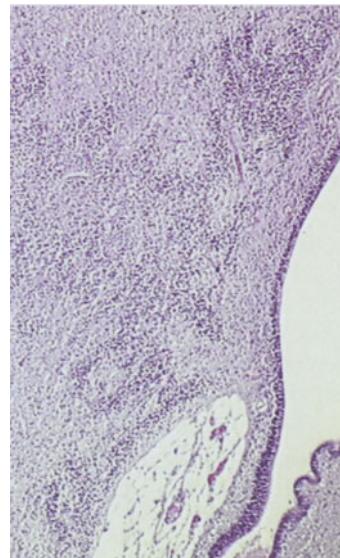


Fig. 3. Gliosis showing dense fibres in the area of original outline of the channel

duct) observed in a smaller degree in “normal” patients. The majority of the investigators [45, 81] anyway favor an acquired condition as the cause of gliosis. They assume that glial proliferation in reaction to an irritant, whether toxic, inflammatory, or traumatic, is responsible for the obliterating reactive gliosis. Gliotic stenosis may be present in only one part of the aqueduct, thus creating a long aqueductal stenosis (≥ 5 mm) or a short aqueductal stenosis (< 5 mm) [82].

In many cases aqueductal stenosis is incomplete, at least at birth, but it can give rise to late complications. Many hypotheses have been advanced to explain this phenomenon. According to Lapras et al. [53], occlusion may be completed by slow spontaneous evolution, or be triggered by a cranial trauma, or a small subarachnoid hemorrhage, or a viral infection with benign meningitis. Partial stenosis can also be completed by a functional mechanism [53]: accumulation of fluid produces progressive enlargement of the lateral and third ventricle, with distortion of the brainstem and kinking of the aqueduct. Oi et al. [69], studying a group of 20 patients with onset of symptoms in adulthood despite the signs of congenital aqueductal stenosis (such as macrocrania and radiological findings of chronically elevated intracranial pressure), hypothesized that CSF dynamics could change over time under disturbed conditions: arrested hydrocephalus could change to progressive hydrocephalus and vice versa. In fact, due to the high compensatory capacity of the brain and skull during the neonatal and infantile periods, progression of the hydrocephalic state can be compensated. In arrested hydrocephalus the pattern of CSF circulation can be re-established via three mechanisms [47]: (1) re-establishment of the normal CSF circulation, (2) utilization of an alternative CSF pathway, or (3) changes in CSF production. The authors recommended further studies to establish which of these mechanisms fails when arrested hydrocephalus becomes progressive in cases of late-onset hydrocephalic state.

The mechanism of aqueductal occlusion is also controversial. Oi et al. [70] in their experimental models characterized two types of mutant hydrocephalic rats that developed stenosis of aqueduct and subsequent hydrocephalus with different mechanisms. In the first type [97] (LEW/Jms), encephalodysgenetic changes of the ependymal layer, with reduction in the number of ependymal cells and alterations in cell alignment, were present; in the other (HTX), the ependymal layer and cells were well developed, but hypercellularity in the periaqueductal region and secondary occlusion of the aqueduct were present instead. Raimondi et al. [74], investigating congenital hydrocephalus in a murine mutant (hy-3/hy-3), found that aqueductal stenosis developed during progression of ventricular dilatation,

through multiple stages: dilatation of the lateral ventricle with an open aqueduct, cerebral edema and compression of the brainstem, brainstem edema, ependymal changes, and aqueductal occlusion. Nugent et al. [68] believed that, although hydrocephalus as the result of aqueductal stenosis does occur, some cases of communicating hydrocephalus slowly progress to the point that the lateral ventricles cause functional or dynamic closure of the aqueduct, superimposing an obstructive component on advanced communicating hydrocephalus and accelerating neurological deterioration.

Etiology

In about three-quarters of patients with aqueductal stenosis the etiology of the disorder is not known [45]. In the remaining cases it can be attributed to different causes.

- Infection and hemorrhage.* Bacterial meningitis, both intrauterine and infantile, is the most common cause of acquired gliotic obstruction: the lumen can be filled during the acute or subacute phase by a fibrinopurulent exudate that successively organizes. The stenosis can also develop gradually from proliferation and fusion of glial nodules in diffuse nodular ependymitis [45]. Aqueductal stenosis can also occur as a noninflammatory sequela of a preceding viral infection of ependyma (see Chap. 15). Aqueductal stenosis can be observed following organization of clots following intraventricular hemorrhage at any age (Fig. 4) (see Chap. 8).
- Intoxications and deficiencies.* In experimental models many substances, such as trypan blue, salicylate, and cuprizone, administered to the mother in early gestation, were able to induce aqueductal stenosis [45]. Similar lesions were induced in rabbits by vita-

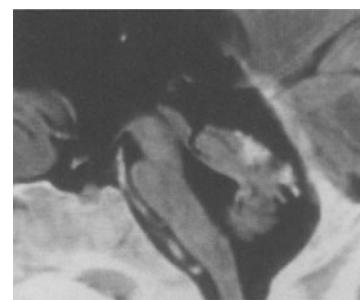


Fig. 4. Hydrocephalus and aqueductal stenosis following intraventricular hemorrhage of the premature. Note the blood clots still visible in the supracerebellar cistern

- min A deficiency and in rats born to mothers fed with a diet deficient in vitamin B or folic acid [45].
3. *Genetic factors.* In 1949 Bickers and Adams [11] and in 1961 Edwards [31] described an X-linked syndrome characterized by congenital hydrocephalus, stenosis of the aqueduct, adducted thumbs, and spastic paraparesis. This syndrome has been named Bickers-Adams-Edwards syndrome. Pathological findings in X-linked hydrocephalus are similar to those that occur in sporadic aqueductal stenosis, and thus the stenosis was thought to be the primary cause of hydrocephalus. Subsequent observations [52] suggested that the reduction of the aqueduct diameter was produced secondarily by lateral compression of the lateral and third ventricles. The patency of aqueduct was also demonstrated in some cases by MR images [98] (for further details see Chap. 1). Nontumoral aqueductal stenosis has been described in association with neurofibromatosis (Fig. 5) [85].
4. *CNS malformations.* Aqueductal stenosis has been reported in association with different CNS malformations, such as Arnold-Chiari, spina bifida (Fig. 6), Dandy-Walker, retrocerebellar, and supracollic-

ular cysts (Fig. 7) [61, 45]. The pathogenesis of the stenosis appears to result from long-standing hydrocephalus [95], which causes axial herniation and entrapment of the midbrain and secondary compression of the ependymal surfaces of the aqueduct, leading to aqueductal obstruction. In cases of “brainstem cerebellum deformity” or other lesions affecting the posterior cranial fossa, the aqueductal stenosis may be related to transtentorial upward displacement of the cerebellum with compression of the quadrigeminal plate and secondary modifications of the aqueductal ependyma (see Chap. 9).

5. *Tumoral aqueductal stenosis.* Obstruction of the aqueduct has to be distinguished from small subependymal tectal tumors that can cause progressive aqueductal stenosis in children and adults (Figs. 8, 9). Unlike the majority of brainstem tu-



Fig. 5. Stenosis of the lower third of the aqueduct in a 9-year-old girl affected by type I neurofibromatosis with hemifacial hypertrophy. Note the membranous occlusion, the dilatation of the upper part of the aqueduct, and the altered signal in the anterior part of the vermis that has remained stable for 6-year follow-up. The patient was treated by third ventriculostomy



Fig. 6. Twelve-year-old girl affected by myelomeningocele and hydrocephalus. Note the thickening and altered profile of the tectal plate and the lack of visibility of the aqueduct

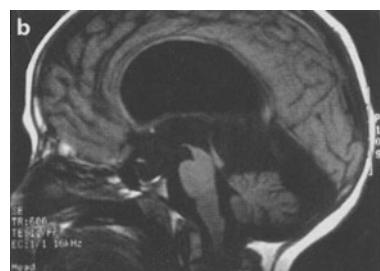
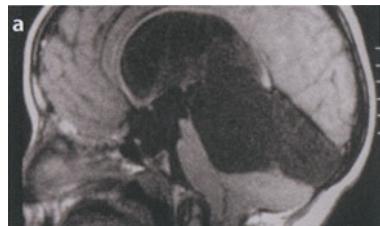


Fig. 7. a Nine-year old boy presenting with chronic headache and endocrine disturbances. Large arachnoid cyst of the quadrigeminal cistern with hydrocephalus. **b** Six months following endoscopic ventriculocystostomy and third ventriculocisternostomy. The cyst has decreased as well as the mass effect on the cerebellum and brainstem. Note the residual aqueductal stenosis, related to the long-term compression of the mesencephalic region

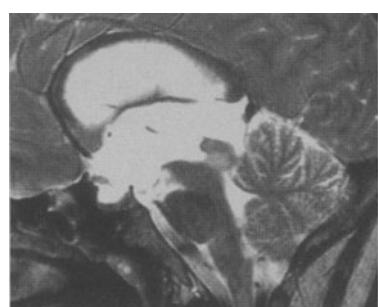


Fig. 8. Seven-year old boy presenting with triventricular hydrocephalus. A small, hyperintense lesion is evident in the middle third of the aqueduct, with mild mass effect on the tectal plate



Fig. 9. Thirteen-year old girl presenting with triventricular hydrocephalus. Altered, hyperintense signal of the peri-aqueductal region

mors, which are intrinsic, infiltrative, and biologically aggressive, gliomas of the tectal plate have been reported [20, 72] to be particularly indolent, often remaining stable in size for several years (Fig. 10). These tumors characteristically present with late-onset aqueductal stenosis, often without associated brainstem signs, and they enlarge slowly, if at all, over time. The management of hydrocephalus usually warrants a favorable long-term prognosis [72].

6. *Aqueductal stenosis and vascular malformations.* Obstruction of the aqueduct by vascular malformations is rare at any age [45]. Aneurysms of the vein of Galen [80] may compress the quadrigeminal plate, inducing aqueductal stenosis. Abnormal draining veins of midbrain arteriovenous malformations may also cross the aqueduct and obstruct the CSF flow [12]. In adults aqueductal stenosis may be caused by large fusiform aneurysms of the basilar artery [45].

Pathophysiology of Hydrocephalus in Aqueductal Stenosis

The circulation of CSF through the aqueduct is not a unidirectional flow, but a systolic and diastolic to-and-fro displacement of CSF. The pulsation of CSF in this essentially closed system seems to be brought about in the first place by the distensibility of the lumbar sac [59] and emptying of veins in spinal and cranial cavities. MRI studies [33, 73] suggested that during systolic expansion a craniocaudal displacement of CSF occurs

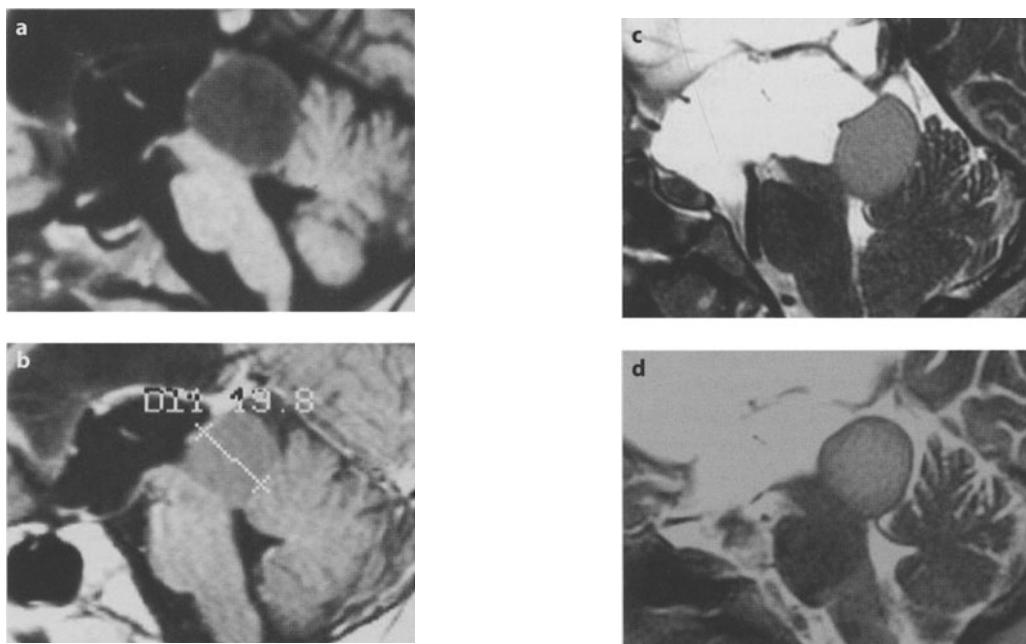


Fig. 10. **a** One-year old baby girl presenting with obstructive triventricular hydrocephalus due to a large tumor of the tectal plate. Ventriculoperitoneal shunt was implanted and the parents refused surgery on the tumor. **b** Six years later, follow-up MRI showed shunt malfunction with mild increase of the ventricular system and no increase of the tectal mass. The patient was asymptomatic and the parents refused shunt revision. Note the deformation of the third ventricular floor, which bulges downward into the interpeduncular cistern. **c** Four years after **b**, follow-up MRI shows increased dilatation and deformation of the third ventricle, with severe flattening of the midbrain, erosion of the posterior clinoid processes, and the floor of the third ventricle bulging into the prepontine cistern. **d** Three months following endoscopic third ventriculostomy and shunt removal. The midbrain has a more normal shape and the floor of the third ventricle is in the normal position with a flow void artifact

in the aqueduct, basal cisterns, and cervical subarachnoid space, while the fourth ventricle and cisterna magna act as mixing chambers showing craniocaudal and craniocervical displacement simultaneously in systolic and diastolic time segments of the cardiac cycle. During diastole the decrease in brain blood volume and recoil of CSF displaced in the lumbar sac reverses the CSF displacement. The net outward movement is equivalent to CSF production ($0.0067 \text{ ml} \cdot \text{s}^{-1}$). The presence of a net outward flow of CSF implies that there is a net outward pressure driving its flow. Several authors have attempted to measure the pressure gradient between the ventricles and the pericerebral subarachnoid spaces. The pressure drop in the aqueduct is too small to be measured by the pressure transducers in clinical use. Jacobson et al. developed a computer model of the flow dynamics in normal [43] and stenotic [42] aqueduct. Comparing the flow through the aqueduct with flow through a cylinder of comparable dimensions, with an inlet area of 1.56 mm^2 , they observed that flow increased linearly with the pressure at the inlet (laminar flow) and calculated that 1 Pa (0.0075 mmHg) of steady pressure caused a volume flow rate of CSF of $0.0060 \text{ ml} \cdot \text{s}^{-1}$. Therefore, the pressure drop required to move $0.0067 \text{ ml} \cdot \text{s}^{-1}$ is 1.1 Pa and that required to move the CSF produced above the aqueduct (assuming that this is half of the total [43]), is 0.55 Pa. Comparing these data with the transmantle pressure of 27 Pa (from lateral ventricles to the subarachnoid space) measured by Conner et al. [24], it was evident that the pressure drop across the aqueduct is small, less than 5% of the total. Even with application of an unsteady pressure, producing a pulsatile flow similar to the physiological CSF pulse, CSF remained laminar at all times and flow continued to follow the wall even when the direction of flow reversed, without recirculation of fluid. In the same study the authors [43] also discovered that the shape of the aqueduct, despite its complexity, is important in minimizing the pressure drop for a given flow rate. In fact, it seems to guide a core of fluid centrally away from the wall, which could slow it down.

Therefore changes in aqueductal size and shape will alter the volume flow rate and the flow pattern. As the aqueduct narrows, the flow decreases for a given pressure difference, the velocity increases up to a maximum of ten times the normal velocity, and the wall shear stresses increase [42]. This velocity may potentially cause a flow void on MRI imaging, falsely leading to the diagnosis of a patent aqueduct. Increasing pressure within the duct may be responsible for gliosis with further narrowing [42], or alternatively may dilate the duct, disrupting the ependymal continuum. Changing the structural anatomy (for example in forking of the aqueduct) also changes the flow pattern significantly: it becomes turbulent and flow stasis occurs just distal to fork. In the computer model [42], to achieve normal

physiological CSF flow through two narrow ducts with inlet areas of 0.49 and 0.15 mm^2 , pressure of 10 and 120 Pa are required, respectively. Therefore, significant stenosis may occur without necessarily increasing the intracranial pressure to abnormal levels, but the increased wall shear stresses may result in ongoing damage of the aqueduct. The drop in pressure required when the cross-sectional area is as little as 0.15 mm^2 , though it may not contribute significantly to the total intracranial pressure (120 Pa or 0.9 mmHg), is significant and measurable in vivo. Any measurable pressure difference between the third and fourth ventricle is pathological [42]. More severe stenosis results in a detectable increase in intracranial pressure. Kaufmann and Clarke [50], in their study on simultaneous supratentorial and infratentorial intracranial pressure monitoring in patients with head injury or an intracranial space-occupying lesion, observed that when intraventricular CSF pressure exceeds the cervical subarachnoid pressure by more than 10 mmHg, fatal transtentorial and/or tonsillar herniation occurs. In noncommunicating hydrocephalus, too, the pressure gradient cannot exceed the critical value of 10 mmHg, because the intraventricular pressure is partially transmitted through the brain parenchyma to the supratentorial subarachnoid spaces, which communicate freely with the infratentorial compartment, contributing to infratentorial pressure [22, 56]. Recent studies, however, seem to show that the transmantle pressure in the supratentorial compartment does not in fact exceed the maximum possible hydrostatic pressure difference [87]. Thus, in aqueductal stenosis the only measurable pressure gradient develops only between the supratentorial and the infratentorial compartment [10], leading to the typical anatomical deformations of the third ventricle observed in obstructive triventricular hydrocephalus. Past [10, 29] and recent [63] studies have stressed the importance of CSF pulsation in the development of hydrocephalus. Mise et al. [63] observed that in experimental aqueductal stenosis, the systolic displacement of CSF is impaired. The CSF pulse during systole may lead to periventricular edema and partial displacement of blood from parenchymal vessels and to accumulation of CSF in third and lateral ventricles. This could lead to ischemia, tissue damage, and ventricular dilatation.

Anatomical and Radiological Findings

The presence of a pressure gradient at the tentorium [22, 46] is specific to hydrocephalus due to aqueductal stenosis and causes the application of the most

important stress on an anatomical structure located at the level of the tentorial hiatus: the floor of the third ventricle herniates downward into the interpeduncular cistern (Figs. 10, 11), the suprapineal recess herniates backward in the quadrigeminal cistern (Figs. 11, 12) and the midbrain is pushed down and flattened. The most severe deformation is observed at the level of the periaqueductal region, with ballooning and funneling of the aqueduct above the obstruction (Figs. 5, 11), depression of its floor, severe

compression of the periaqueductal gray matter, and stretching of the posterior commissure [22, 46, 54]. As described by Johnson and Yates [46], when an increase in pressure occurs above the tentorium, the hemispheres, driven by the depth of the temporal fossa and cavernous sinus in front and the depth of the occipital fossa behind, slide along the middle section of the tentorium and compress the posterior half of the midbrain from both sides, inducing a pear-shaped deformation. Moreover, because the ventricular enlargement in many cases of aqueductal stenosis progresses slowly, with late onset of symptoms of raised intracranial pressure, the diagnosis may be retarded and the ventricular dilatation may be massive. As a result of long-standing CSF pulsations against the thinnest segment of the ventricular walls, focal enlargement of the ventricular system may occur, leading to the formation of pulsion diverticula, subependymal dissection (Fig. 13) and spontaneous

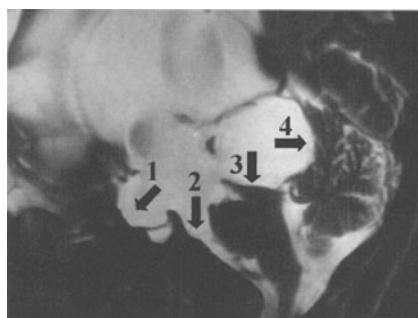


Fig. 11. Complex deformation of the third ventricle induced by the chronic pressure gradient between the supratentorial and infratentorial compartment: the suprachiasmatic recess is dilated with compression of the chiasm on the skull base (arrow 1), the floor of the third ventricle is deformed and bulges into the preopticine cistern (arrow 2), the midbrain is compressed and flattened (arrow 3), and the suprapineal recess is enormously dilated and bulges into the quadrigeminal cistern, compressing the upper vermis (arrow 4)

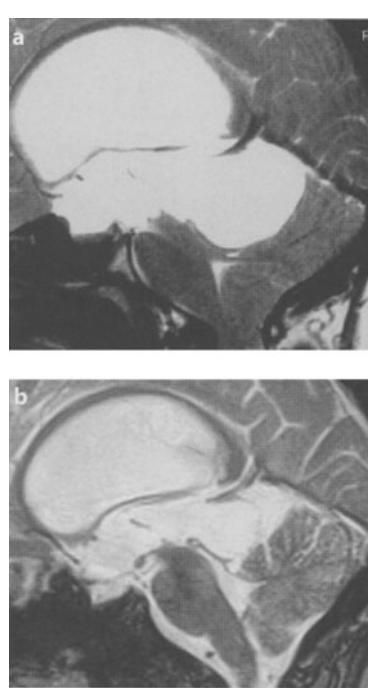


Fig. 12. **a** Dilatation of the suprapineal recess with cerebellar compression, chronic tonsillar herniation, and severe deformation of the midbrain and third ventricular floor in a 12-year-old girl affected by aqueductal stenosis. **b** Two months following third ventriculostomy: significant reduction of the suprapineal recess, resolution of the chronic tonsillar herniation and midbrain deformity, and normal position of the third ventricular floor

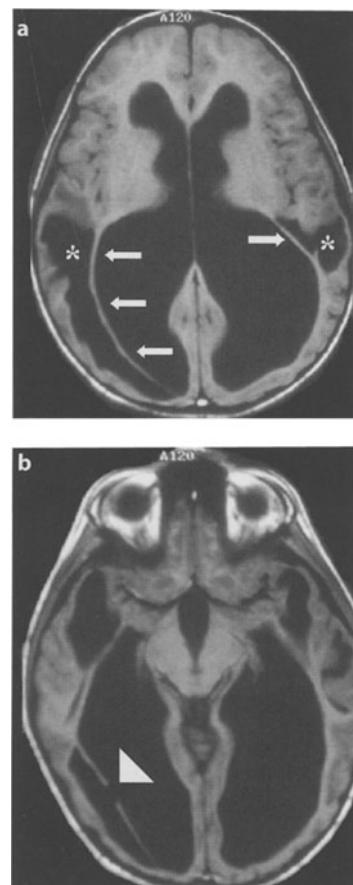


Fig. 13. **a** Nine-year-old boy presenting with papilledema, visual field defect, and triventricular hydrocephalus with aqueductal stenosis. Large areas of subependymal dissection (asterisks) are visible below the ependyma (arrows). **b** Disruption of the ependymal layer (arrowhead)

ventriculostomies (Fig. 14). The latter occur when rupture of the ventricular walls, most often at the level of the lamina terminalis and of the posterior wall of the third ventricle, leads to free communication between the ventricle and subarachnoid space, in some cases leading to spontaneous compensation of hydrocephalus. Less frequently, ventricles may open into the subdural space or even into the frontal, sphenoidal sinuses or ethmoidal cells, whose wall have been progressively thinned by chronic increased intracranial pressure [17, 54], with subsequent rhinoliquorrhea. These events are rare and



Fig. 14. Nine-year old boy presenting with mild ventricular enlargement incidentally discovered on a CT scan performed for mild head trauma. The patient had only mild macrocrania. This CT scan performed immediately after intraventricular injection of contrast medium showed contamination of the quadrigeminal cistern through a spontaneous ventriculostomy at the level of the suprapineal recess

may follow mild head injury. Subependymal dissection may originate from spontaneous or iatrogenic ruptures of the ependymal layer, with CSF entering the subependymal space and dissecting the ependymal layer from the periventricular white matter. The latter can present severe damage, with formation of enlarging CSF-filled cavities (Fig. 15).

Diverticula are cystic spaces lined by pia mater that are walled off from the subarachnoid spaces and communicate only with the ventricles [65]. The most frequent sites [94] of ventricular rupture and formation of diverticula are the medial wall of the trigone of the lateral ventricles (atrial diverticula) and posterior wall of the third ventricle (expansion of the suprapineal recess). Atrial diverticula [64] occur at the weakest point of the trigone where the wall is formed by the splenium of corpus callosum above, the crura of fornix inferiorly, and the alvei and fimbriae of the hippocampus which connect the splenium with the crura. With progressive hydrocephalus and progressive expansion of the atria, the splenium is thinned, elevated, and displaced posteriorly; the crura of fornix are depressed, thinned, and displaced medially; and the alvei are displaced medially and stretched between the elevated corpus callosum and depressed fornix. With greater atrial dilatation, the alveus and crus become an extremely thin alveocrural sheet. This may be denuded of ependyma and may split or shear, creating unilateral or bilateral diverticulum ostia 5–20 mm in diameter, bordered by splenium posterolaterally and crura anteromedially [65]. After the ostium forms, CSF pushes through the mantle remnant and bulges the pia inferomedially to form a pulsion diverticulum. With progressive enlargement, the pial diverticulum and displaced arachnoid surrounding it bulge downward through the incisura and behind the

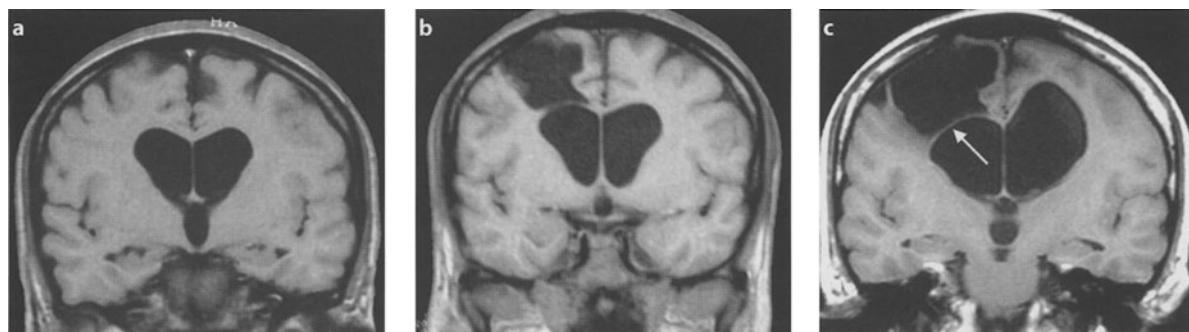


Fig. 15a-c. Forty-year-old woman presenting with chronic headache and triventricular dilatation due to aqueductal stenosis. Intracranial pressure monitoring with right frontal intraventricular catheter revealed mild increase of the baseline intracranial pressure (16–18 mmHg). The patient refused operation. **a** MRI coronal slice before intracranial pressure monitoring. **b** One year after intracranial pressure monitoring, a large intraparenchymal cavity lined by ependyma reaches the subdural space of the frontal convexity. **c** Ten years after intracranial pressure monitoring, increased ventricular dilation and enlargement of the frontal cavity lined by ependyma (arrow). The patient presents gait and sphincter disturbances and chronic headaches, but still refuses operation

midbrain to form an incisural and subtentorial "cyst" within the ambient and superior vermian cisterns (Figs. 16, 17). The diverticulum typically displaces the quadrigeminal plate, pineal gland, fourth ventricle, and vermis inferiorly, and straight sinus, tentorium, vein of Galen, and occipital lobes superiorly [65]. It can be confused (especially on CT scan) with dilated fourth ventricle associated with fourth ventricle obstruction or entrapped fourth ventricle, or "primary arachnoid cyst" of incisura [65]. In this case a differential diagnosis is very important, because arachnoid or ependymal cyst of the incisura can cause hydrocephalus, and extirpation, fenestration, or direct shunting of the cyst can resolve the hydrocephalus; whereas only a few patients with diverticulum may benefit from a direct surgical approach [64, 58], while treatment of the hydrocephalus (shunting or third ventriculostomy) is less dangerous and more effective in inducing regression of diverticulum [94] (Fig. 12). MRI, flow-sensitive phase contrast MRI [79] and, in more difficult cases, metrizamide CT ventriculography [65] may be useful to demonstrate direct continuity between the lateral ventricle and an incisural cyst.

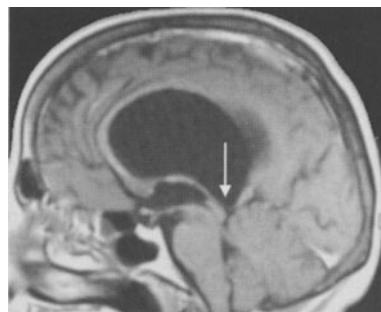


Fig. 16. Early stage of formation of an atrial diverticulum in aqueductal stenosis. The medial wall of the lateral ventricle is pushed downward through the tentorial incisura toward the quadrigeminal cistern by the pressure gradient between the supratentorial and the infratentorial compartment

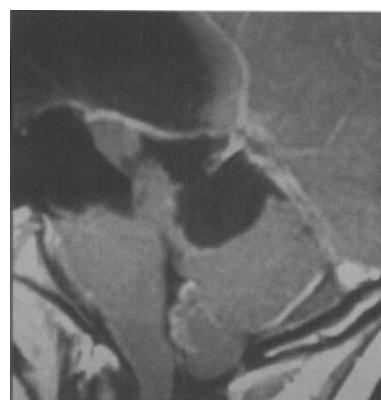


Fig. 17. Late stage of formation of an atrial diverticulum in aqueductal stenosis. The diverticulum fills the quadrigeminal cistern, compressing the cerebellum

The suprapineal, lamina terminalis, and infundibular recesses are the weakest part of the third ventricle. Their walls are not covered by neural or vascular structures, unlike the lateral and inferior third ventricular walls, which are bordered by the two thalamus laterally and the midbrain inferiorly. In normal subjects, the suprapineal recess is merely a diverticulum of the ependymal roof [83] and, in cases of aqueductal stenosis, may become markedly dilated to fill the quadrigeminal and superior vermian cisterns, displacing the vermis and cerebellar hemispheres downwards, and dislodging and compressing the dorsal midbrain and posterior commissura.

Clinical Features

Aqueductal stenosis is responsible for 6%-66% of cases of hydrocephalus in children (more than 50% presenting in the first year of life) and 5%-49% in adults [41, 45, 76]. Tisell et al. [89] reported an incidence of aqueductal stenosis of 3.7 per million per year in the adult Swedish population; Ceddia et al. [19] reported an incidence of congenital hydrocephalus of 0.3-2.5 per thousand live births, in 20% of cases associated with aqueductal stenosis. There is a slight male prevalence and there are two peaks of distribution for age: one in the first year of life, the second during adolescence [41].

In 1950 Beckett, Netsky, and Zimmermann [8] characterized three types of natural clinical course of aqueductal stenosis, despite the histological similarity of the lesions at autopsy: in the first group there were no signs or symptoms during life, in the second group the patients showed progressive mental deficiency, had intermittent bouts of headache, nausea, and vomiting, and died during one of the repeated attacks; in the third group patients developed a sudden block of the ventricular system, resulting in death with increased intracranial pressure.

The symptomatology of aqueductal stenosis, in fact, is highly variable, according predominantly to the patient's age. In first year of life the clinical presentation usually consists of fairly acute onset and rapid enlargement of the circumference of the head [76, 93]. In older children, adolescents and adults, only in a small percentage (15%) is the onset acute (presence of symptoms for 1 to 4 weeks [36, 76]) with headache, nausea and vomiting, visual disturbances, seizures, changes in mental state, and coma. More often the onset is subacute (symptoms for less than 6 months [36, 76]) or chronic (more than 6 months), characterized by an intracranial hypertension syndrome progressively taking hold [93]. Some patients

with a chronic history of symptoms such as retarded psychomotor development, school difficulties, temporary headache, endocrine disturbances, and growth retardation, may show acute progression of symptoms as the result of further decompensation of the hydrocephalic state. In some circumstances the causes of late decompensation may be identified in slight cranial trauma, hyperpyretic crises, or subarachnoid hemorrhage [30, 36, 76, 93]. As already discussed, the clinical presentation of aqueductal stenosis in adulthood and in the elderly may be correlated with the presence of aqueductal narrowing and hydrocephalus since early life (late-onset idiopathic aqueductal stenosis [36]). Such patients often report a history of recurrent headache during childhood and adolescence and present cranial enlargement and characteristic changes in the sella turcica, especially elongation of the anterior wall, on skull films [57]. When aqueductal stenosis decompensates in the elderly, it usually does so in a normal-pressure-hydrocephalus fashion [39, 57, 91], with the classic triad of gait disturbances, dementia, and incontinence.

In about 15% of cases [39] patients experience seizures during the course of their illness. There appears to be a predilection for development of temporal lobe and generalized seizures [57]. The appearance of seizures is related to the distress of the cerebral cortex due to increased intracranial pressure; often seizures do not regress with the treatment of hydrocephalus.

Headache has the characteristics of that associated with raised intracranial pressure, with exacerbation during coughing, sneezing, straining, and stooping. The site is variable and it is usually described as occurring in attacks. These may last for seconds or minutes or may continue for days. During attacks nausea, vomiting, drowsiness, sensation of weakness in the legs and even falls may occur. Headache and drop attacks are thought to be due to sudden changes in pressure relationships [57]. Visual disturbances are related to papilledema, with reduction of visual acuity in many cases. The chronic compression of the optic chiasm exerted by an enlarged third ventricle explains the presence of visual field defects. Unilateral or bilateral blurring of vision are frequent and have been variably attributed to compression of the chiasm, ischemia of the occipital lobes, or paralysis of the fixing and following reflexes, due to dorsal midbrain dysfunction rather than to impairment of the visual sensory pathway [21]. Endocrine manifestations have been reported to occur in 10% of adolescents and adults with aqueductal stenosis [37, 78]. The chronic compression of the hypothalamo-hypophyseal axis by an enlarged anterior third ventricle that, in some cases, may bulge into the sella turcica and erode the clinoids [4], may explain both hypophyseal hypo-

function and hyperfunction. In fact, diencephalo-hypophyseal compression can reduce secretion of hypophyseal hormones or hypothalamic inhibitor hormones, resulting in an increase in hypophyseal hormones. In the report of Rotilio et al. [78], endocrine findings in males have been (in order of frequency): obesity, hypogonadism (with impotence and infertility), diabetes insipidus, precocious puberty, and, more rarely, lethargy, gigantism, and acromegaly; in females they have been: amenorrhea, obesity, and, more rarely, diabetes insipidus, hypertrichosis, acromegalic features, and dwarfism. These abnormalities in many cases reverse after treatment of hydrocephalus. Ocular disorders, although rarely observed at the primary presentation, are quite frequent and specific to aqueductal stenosis in the case of shunt malfunction [21, 22]. These can range from paresis of upward gaze to the complete syndrome of aqueduct of Sylvius, a combination of impairment of upward gaze, abnormality of the pupils (better reaction to accommodative stimulus than to light stimulus), convergence spasm, nystagmus retractorius on attempted upward gaze, and upper lid retraction (Collier's sign) [7, 21]. This syndrome is also described as Koerber-Salus-Elshnig [21, 22, 40, 67], pretectal [12] or dorsal midbrain syndrome [6, 7]. Classically attributed to compression of the tectum and posterior commissure between the dilated suprapineal recess of the third ventricle above and the dilated rostral aqueduct below [5, 13], ocular signs are in fact related to the severe deformation of the periaqueductal region with consequent compression of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), a group of cells in the pre-rubric field of the mesencephalic reticular formation, which is considered the location of vertical gaze [16]. With further progression of hydrocephalus in addition to tegmental involvement, signs of ventral midbrain involvement may appear, causing the global rostral midbrain dysfunction [7], characterized by: (1) parkinsonian-like state with tremor, bradykinesia, masked face, and cogwheel rigidity, (2) spastic quadriparesis, and (3) alteration of level of consciousness [7]. Parkinsonian features may also be the presenting symptoms of obstructive hydrocephalus or may be manifest during shunt failure [44] as a result of compression of the striatum and midbrain. Some authors [25, 28, 71] have suggested that the dysfunction of "ascending" tracts (cortico-striato-pallido-thalamo-cortical motor loop and/or nigro-striatal fibers) play an important role in the pathophysiology of parkinsonism in hydrocephalus. The degree of reversibility of symptoms in response to shunt should reflect the extent of permanent neuronal damage. The functional impairment of the riMLF and of the whole dorsal midbrain during shunt malfunction is explained by the severe and acute deformation of the

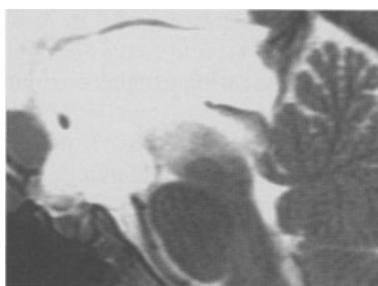


Fig. 18. Eleven-year old girl, shunted at birth for aqueductal stenosis, presenting with shunt malfunction and Parinaud sign. The floor is severely deformed; the midbrain and the periaqueductal region present diffuse hyperintensity

midbrain due to the formation of a pressure gradient between the supratentorial and the infratentorial compartment. In this acute phase, MRI shows marked hyperintensity on sagittal T2-weighted images, probably representing focal edema (Fig. 18). These changes are usually rapidly reversible following third ventriculostomy [22].

Compromise of the nigro-striatal dopaminergic pathway in aqueductal stenosis could explain the presence of other symptoms, such as blepharoclonus [37] and akinetic mutism. This is a condition characterized by unresponsiveness with the appearance of alertness [18]. Typically, the patient may look at the examiner, but remain mute. Commands may be carried out in a feeble, slow, and incomplete manner and painful peripheral stimulation produces slow withdrawal of the limb without manifestation of emotion [9]. This rare syndrome may develop after multiple shunt revisions for shunt failure [2, 9, 62, 77] and may respond to dopamine agonists, such as levodopa [9] and bromocriptine [77], with ephedrine added due to the possible damage to noradrenergic fibers [2].

duct has the same signal intensity as CSF. On the first and second echoes of the T2-weighted images, as a result of rapid CSF flow pulsations [55], the signal becomes hypointense compared with ventricular CSF (Fig. 19). "Flow void" often appears, extending superiorly into the third ventricle and through the aqueduct into the superior aspect of the fourth ventricle; its presence has been considered the most important sign for diagnosis of patent aqueduct [15, 23]. However, flow void is not always present: Sherman et al. [84] noted it in 67% of subjects without ventriculomegaly.

In normal subjects, the aqueduct is poorly visualized in the sagittal plane: this may be explained by distortion or displacement of the aqueduct out of the plane of section. For this reason, Kemp et al. [51] advise 3-mm-thick contiguous sections for specific evaluations of the aqueduct. If the aqueduct is not seen in either the sagittal plane or the axial plane, a long segment of obstruction is present. In cases of aqueductal stenosis in which the aqueduct remains visible, the obstruction is presumably caused by a membrane [55]. Hydrocephalus caused by obstruction at the aqueduct level is frequently, but not always, associated with loss of flow void [51]. Narrowing of the aqueduct is likely to cause either pronounced flow – since the same amount of CSF has to pass through a narrowed duct – or absence of flow. Only in the latter situation will the flow void be absent. Other methods have been introduced to better assess the CSF flow dynamics through the aqueduct, in particular gradient echo rapid MRI (GRE) and, above all, cardiac-gated cine-MRI (see Chap. 27). Failure to demonstrate flow in the aqueduct by cine-MRI technique is a pathological finding [73]: it has been observed in cases of aqueductal stenosis, of midbrain and aqueduct compression by a mass, and in the presence of a third ventricular mass lesion resulting in lack of propagation of the fluid wave. It has been reported [49] that in patients with aque-

Neuroradiological Findings

On CT scan, a diagnosis of aqueductal stenosis can be only presumptive [66]: dilatation of only the lateral and third ventricles suggests obstruction at or near the aqueduct. An MRI being mandatory for all cases of hydrocephalus, this will easily confirm the status of the aqueduct and, if stenosis is present, the primary or secondary nature of the obstruction. Since the advent of MRI, it has been possible to visualize the entire length of the aqueduct noninvasively. The optimal view for evaluation of anatomical details is a midline sagittal section using T1- and T2-weighted sequences [51]. On these images the aque-



Fig. 19. Neonatal communicating hydrocephalus. The flow void is evident in the aqueduct

ductal stenosis, turbulent flow in the third ventricle may be discernible. Moreover, in cases of long-standing hydrocephalus both MRI and cine-MRI may be helpful in the detection and correct interpretation of ventricular diverticula, third ventricle bulging in the chiasmatic and interpeduncular cisterns and cystic expansion of the suprapineal recess, and focal or diffuse abnormality of the morphology (dorsal flattening and thinning) and signal characteristics (hypointensity in T1- and hyperintensity in T2-weighted images) of the corpus callosum [88].

Prognosis and Intellectual Outcome

The long-term outcome of children with aqueductal stenosis, even if they receive prompt surgical intervention, is not always favorable [38, 92]. Furthermore, children treated with shunts become shunt-dependent: shunt malfunction is often associated with a temporary increase in intracranial pressure, which may lead to progressive psychological deterioration [53]. It has been observed [48] that shunt malfunction may be more dangerous, with more acute and massive intracranial pressure rises, in hydrocephalus due to aqueductal stenosis than in communicating hydrocephalus, because of a reduction in brain compliance [22, 56]. Moreover, shunt infections are closely related to poor intellectual development [60]. Villani et al. [92] reported a global mortality rate for children with aqueductal stenosis treated with shunts, who were followed for a period of 5–25 years (mean 15.2 years), of 28.8%, with a death rate of 1.2% per year. These data included a mortality rate of 7.7% after shunt revisions.

In most series [38, 41, 75, 92] the older the children at the time of clinical presentation, the more favorable the neurodevelopmental prognosis, if associated with prompt surgical treatment. Renier et al. [75], in their series of 108 children with congenital hydrocephalus (premature newborn and spina bifida patients excluded), observed a significant difference in outcome between infants with aqueductal stenosis and those with communicating hydrocephalus: the 10-year survival was 80% in aqueductal stenosis and 60% in communicating hydrocephalus. The mean intelligence quotient (IQ) was 67 in aqueductal stenosis, with 46% of children at or above 80, whereas in communicating hydrocephalus the mean IQ was 52, with only 20% of children at or above 80. The authors also noted a better outcome in postnatal hydrocephalus [41], with the same difference in intellectual outcome between hydrocephalus due to aqueductal stenosis and that due to communicating hydrocephalus. The

mean postoperative IQ score was 77 in aqueductal stenosis, with 59% of patients over 80, versus a mean IQ of 70 in communicating hydrocephalus, with 48% of patients scoring over 80. These better results were ascribed [75] to the presence of patients with late-onset hydrocephalus, in whom aqueductal stenosis progresses slowly. These data are in disagreement with those of Hanigan et al. [38] and McCollough and Balzert-Martin [60], who found that children with aqueductal stenosis have significantly lower IQs than children with communicating hydrocephalus. The poorest results were found in children with X-linked aqueductal stenosis [75, 98], where the obstruction of CSF flow is only partly responsible for the very low IQ. Obviously, the presence of associated malformations is associated with a low survival rate and poor mental developmental.

In the series published by Villani et al. [92], 68% of patients with follow-up longer than 15 years were designated as "normal" at the neurodevelopmental evaluation (attending normal school courses or having regular jobs), 24% as "moderately disabled", and 8% as "severely disabled". However, the 39% of patients designated as "normal" had functional motor skills abnormal for the presence of neurological deficits such as paraplegia, visual disturbances, and mild hemiparesis. The incidence of epilepsy paralleled the degree of mental and motor abnormalities [86], such as hypothalamus-hypophyseal dysfunction.

Many prognostic factors have been studied. Among these, the most significant are head circumference at birth [75], the value (score) of the first IQ assessment [75], and the relevance of postoperative frontal cortical mantle width on MRI or CT scan after surgery [38, 75, 92]. Failure in re-expansion of the cortical mantle (less than 20 mm) indicates, in fact, irreversible damage and poor mental neurodevelopment, as do increased head circumference above 4 standard deviations and low first IQ or development quotient assessment. As observed by some authors [27, 34], children with aqueductal stenosis have a tendency to show poorer development of nonverbal cognitive skills than of language development. These discrepancies are related to greater posterior thinning than anterior thinning of the cerebral white matter, in particular of the corpus callosum and internal capsule. The study published by Fletcher et al. [34] revealed that measurements on MRI of internal capsule and corpus callosum correlate well with the acquisition of nonverbal skills independently of the side of major compromise in cases of ventricular asymmetry.

In older children the duration of symptoms also affects the prognosis: chronic symptoms and delayed diagnosis usually correlate with partial regression of

symptomatology [30]. Older children with acute onset of symptoms and prompt surgery have the best prognosis: if a successful endoscopic third ventriculostomy can be performed, these children may be considered healed.

References

1. Alvord EC: The pathology of hydrocephalus. In: Fields WS, Desmond MM (ed) Disorders of the developing nervous system. Thomas, Springfield, pp 343-419, 1961
2. Anderson B: Relief of akinetic mutism from obstructive hydrocephalus using bromocriptine and ephedrine. *J Neurosurg* 76: 152-155, 1992
3. Atlas SW, Mark AS, Fram EK: Aqueductal stenosis: evaluation with gradient-echo rapid MR imaging. *Radiology* 169: 449-453, 1988
4. Avman N, Gökalp HZ, Arasil E, et al: Symptomatology, evaluation and treatment of aqueductal stenosis. *Neurol Res* 6: 194-198, 1984
5. Azar-Kia B, Palacios E, Churchill R: Aqueductal stenosis and Parinaud's syndrome. *Illinois Med J* 148:532-533, 1975
6. Baloh RW, Furman JM, Yee RD: Dorsal midbrain syndrome: clinical and oculographic findings. *Neurology* 35: 54-60, 1985
7. Barrer SJ, Schut L, Bruce DA: Global rostral midbrain dysfunction secondary to shunt malfunction and hydrocephalus. *Neurosurgery* 7: 322-325, 1980
8. Beckett RS, Netsky MG, Zimmerman HM: Developmental stenosis of the aqueduct of Sylvius. *Am J Pathol* 26: 755-787, 1950
9. Berger L, Gauthier S, Leblanc R: Akinetic mutism and parkinsonism associated with obstructive hydrocephalus. *Can J Neurol Sci* 12: 255-258, 1958
10. Bering EA: Choroid plexus and arterial pulsation of the choroid plexus as a cerebrospinal fluid pump. *Arch Neurol Psychiatr* 73: 165-172, 1955
11. Bickers DS, Adams RD: Hereditary stenosis of aqueduct of Sylvius as a cause of congenital hydrocephalus. *Brain* 72: 246-262, 1949
12. Blackmore CC, Mamourian AC: Aqueduct compression from venous angioma: MR findings. *AJNR Am J Neuroradiol* 17: 458-460, 1996
13. Bleasel AF, Ell JJ, Johnston I: Pretectal syndrome and ventricular shunt dysfunction. *Neuro-Ophthalmol* 12: 193-196, 1992
14. Bourneville, Noir J: Hydrocephalie. *Prog Med Paris* 12 :17-23, 1900
15. Bradley WG, Cortman KE, Burgioine B: Flowing cerebrospinal fluid in normal and hydrocephalic states: appearance on MR images. *Radiology* 159: 601-616, 1986
16. Büttner-Ennever JA, Büttner U, Cohen B, et al: Vertical gaze paralysis and the rostral interstitial nucleus of the medial longitudinal fasciculus. *Brain* 105: 125-149, 1982
17. Cabezudo JM, Vaquero J, Garcia-de-Sola R, et al: Direct communication between the lateral ventricle and the frontal sinus as a cause of CSF rhinorrhea in aqueductal stenosis. *Acta Neurochir* 57: 95-98, 1981
18. Cairns H, Oldfield RC, Pennybacker JB, et al: Akinetic mutism with an epidermoid cyst of the third ventricle. *Brain* 64: 273-290, 1941
19. Ceddia A, Di Rocco C, Iannelli A, et al: Idrocefalo neonatale ad eziologia non tumorale. *Minerva Pediatr* 44: 445-450, 1992
20. Chapman PH: Indolent gliomas of the midbrain tectum. *Concepts Pediatr Neurosurg* 10: 97-107, 1990
21. Chatta AS, Delong GR: Sylvian aqueduct syndrome as a sign of acute obstructive hydrocephalus in children. *J Neurol Neurosurg Psychiatry* 38: 288-296, 1975
22. Cinalli G, Sainte-Rose C, Simon I, et al: Sylvian aqueduct syndrome and global rostral midbrain dysfunction associated to shunt malfunction. *J Neurosurg* 90: 227-236, 1999
23. Citrin CM, Sherman JL, Gangarosa RE, et al: Physiology of the CSF flow-void sign: modification by cardiac gating. *AJNR Am J Neuroradiol* 7: 1021-1024, 1984
24. Conner ES, Foley L, Black PM: Experimental normal-pressure hydrocephalus is accompanied by increased transmantle pressure. *J Neurosurg* 61: 322-327, 1984
25. Curran T, Lang AE: Parkinsonian syndromes associated with hydrocephalus: case reports, a review of the literature and pathophysiological hypotheses. *Mov Disord* 9: 508-520, 1994
26. Dandy WE: Diagnosis and treatment of hydrocephalus resulting from strictures of the aqueduct of Sylvius. *Surg Gynecol Obstet* 31:340-358, 1920
27. Dennis M, Fitz CR, Netley CT, et al: The intelligence of hydrocephalic children. *Arch Neurol* 38: 607-615: 1981
28. DeVera Reyers JA: Parkinsonism-like syndrome caused by posterior fossa tumour. *J Neurosurg* 33: 599-601, 1970
29. Di Rocco C, Di Trapani G, Pettorossi VE, et al: On the pathology of experimental hydrocephalus induced by artificial increase in endoventricular CSF pulse pressure. *Childs Brain* 5: 81-95, 1979
30. Di Rocco C, Iannelli A, Tamburrini G: Idrocefalo da stenosi dell'acquedotto ad insorgenza tardiva. *Minerva Pediatr* 47: 511-520, 1995
31. Edwards JH: The syndrome of sex-linked hydrocephalus. *Arch Dis Child* 36: 486-493, 1961
32. Emery JL, Staschak MC: The size and form of cerebral aqueduct in children. *Brain* 95: 591-598, 1972
33. Enzmann DR, Pelec NJ: Normal flow pattern in intracranial and spinal cerebrospinal fluid defined with phase-contrast cine-MR imaging. *Radiol* 178:467-474, 1991
34. Fletcher JM, Bohan TP, Brandt ME, et al: Cerebral white matter and cognition in hydrocephalic children. *Arch Neurol* 49: 818-824; 1992
35. Fram E, Hedlund L, Dimick R, et al: Parameters determining the signal of flowing fluid in gradient refocused imaging: flow velocity, TR and flip angle. *Proc Int Soc Mag Reson Med* 1: 84-85, 1986
36. Fukuhara T, Luciano M: Clinical features of late-onset idiopathic aqueductal stenosis. *Surg Neurol* 55: 132-137, 2001
37. Gatto M, Micheli F, Pardal MF: Blepharoclonus and parkinsonism associated with aqueductal stenosis. *Mov Disord* 5: 310-313, 1990
38. Hanigan WC, Morgan A, Shaaban A, et al: Surgical treatment and neurodevelopment outcome for infants with idiopathic aqueductal stenosis. *Child's Nerv Syst* 7: 386-390, 1991
39. Harrison MJG, Robert CM, Uttley D: Benign aqueductal stenosis in adults. *J Neurol Neurosurg Psychiatry* 37: 1322-1328, 1974
40. Hatcher MA, Klintworth GK: The sylvian aqueduct syndrome. A clinicopathological study. *Arch Neurol* 15: 215-222, 1966

41. Hirsch JF, Hirsch E, Sainte-Rose C, et al: Stenosis of the aqueduct of Sylvius (etiology and treatment). *J Neurosurg Sci* 30: 29-39, 1986
42. Jacobson EE, Fletcher DF, Morgan MK, et al: Computer modelling of the CSF flow dynamics of aqueductal stenosis. *Med Biol Eng Comput* 37: 59-63, 1999
43. Jacobson EE, Fletcher DF, Morgan MK, et al: Fluid dynamics of the cerebral aqueduct. *Pediatr Neurosurg* 24: 229-236, 1996
44. Jankovic J, Newmark M, Peter P: Parkinsonism and acquired hydrocephalus. *Mov Disord* 1: 59-64, 1986
45. Jellinger G: Anatomopathology of nontumoral aqueductal stenosis. *J Neurosurg Sci* 30: 1-16, 1986
46. Johnson RT, Yates PO: Clinico-pathological aspects of pressure changes at tentorium. *Acta Radiol* 46: 242-249, 1956
47. Johnston IH, Kowman-Giles R, Whittle IR: The arrest of treated hydrocephalus in children. A radionuclide study. *J Neurosurg* 61: 752-756, 1984
48. Jones RFC, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26: 86-92, 1990
49. Kadokawa C, Hara M, Numoto M, et al: Cine magnetic resonance imaging of aqueductal stenosis. *Child's Nerv Syst* 11: 107-111, 1995
50. Kaufmann GE, Clark K: Continuous simultaneous monitoring of intraventricular and cervical subarachnoid cerebrospinal fluid pressure to indicate development of cerebral or tonsillar herniation. *J Neurosurg* 33: 135-140, 1970
51. Kemp SS, Zimmerman RA, Bilaniuk LT, et al: Magnetic resonance imaging of the cerebral aqueduct. *Neuroradiology* 29: 430-436, 1987
52. Landrieu O, Ninane J, Ferriere G, et al: Aqueductal stenosis in X-linked hydrocephalus: a secondary phenomenon? *Dev Med Child Neurol* 21: 637-652, 1979
53. Lapras C, Bret P, Patet JD, Huppert J, et al: Hydrocephalus and aqueductal stenosis. Direct surgical treatment by interventriculostomy (aqueduct cannulation). *J Neurosurg Sci* 30: 47-53, 1986
54. Lapras C, Bret P, Tommasi M, et al: Les sténoses de l'aqueduc de Sylvius. *Neurochirurgie* 26 (Suppl 1): 1-152, 1980
55. Lee BCP: Magnetic resonance imaging of peri-aqueductal lesions. *Clin Radiol* 38: 527-533, 1987
56. Lim ST, Potts DG, Deonarine V, et al: Ventricular compliance in dogs with and without aqueductal obstruction. *J Neurosurg* 39: 463-473, 1973
57. Little JR, Houser OW, MacCarty CS: Clinical manifestations of aqueductal stenosis in adults. *J Neurosurg* 43: 546-552, 1975
58. MacFarlane WV, Falconer MA: Diverticulum of the lateral ventricle extending into posterior cranial fossa: report of case successively relieved by operation. *J Neurol Neurosurg Psychiatry* 10: 101-106, 1947
59. Martins AN, Wiley JK, Myers PW: Dynamics of the cerebrospinal fluid and spinal dura mater. *J Neurol Neurosurg Psychiatry* 35: 468-473, 1972
60. McCullough DC, Balzer-Martin LA: Current prognosis in overt neonatal hydrocephalus. *J Neurosurg* 57: 378-383, 1982
61. McFarlane A, Maloney AFJ: The appearance of aqueduct and its relationship with hydrocephalus in the Arnold-Chiari malformation. *Brain* 80: 479-491, 1957
62. Messert B, Henke TK, Langheim W: Syndrome of akinetic mutism associated with obstructive hydrocephalus. *Neurology* 16: 635-649, 1966
63. Mise B, Klarica M, Bulat M, et al: Experimental hydrocephalus and hydromyelia: a new insight in mechanism of their development. *Acta Neurochir* 138: 862-869, 1996
64. Mott M, Cummins B: Hydrocephalus related to pulsion diverticulum of lateral ventricle. *Arch Dis Child* 49: 407-410, 1974
65. Naidich TP, McLone DG, Hahn YS, et al: Atrial diverticula in severe hydrocephalus. *AJR Am J Neuroradiol* 3: 257-266, 1982
66. Naidich TP, Schott LH, Baron RL: Computed tomography in evaluation of hydrocephalus. *Radiol Clin North Am* 20: 143-167, 1982
67. Nashold BS, Gills JP: Ocular signs from brain stimulation and lesions. *Arch Ophthalmol* 77: 609-618, 1967
68. Nugent GR, Al-Mefty O, Chou S: Communicating hydrocephalus as a cause of aqueductal stenosis. *J Neurosurg* 51: 812-818, 1979
69. Oi S, Shimoda M, Shibata M, et al: Pathophysiology of long-standing overt ventriculomegaly in adults. *J Neurosurg* 92: 933-940, 2000
70. Oi S, Yamada H, Sato O, et al: Experimental models of congenital hydrocephalus and comparable clinical problems on the fetal and neonatal period. *Child's Nerv Syst* 12: 292-302, 1996
71. Oliver R: Parkinsonism due to midbrain compression. *Lancet* 2: 817-819, 1959
72. Pollack IF, Pang D, Albright AL: The long-term outcome in children with late-onset aqueductal stenosis resulting from benign intrinsic tectal tumors. *J Neurosurg* 80: 681-688, 1994
73. Quencer RM, Donovan Post MJ, Hinks RS: Cine MR in the evaluation of normal and abnormal CSF flow: intracranial and intraspinal studies. *Neuroradiology* 32: 371-391, 1990
74. Raimondi AJ, Clark SJ, McLone DG: Pathogenesis of aqueductal occlusion in congenital murine hydrocephalus. *J Neurosurg* 45: 66-77, 1976
75. Renier D, Saint-Rose C, Pierre-Kahn A, et al: Prenatal hydrocephalus: outcome and prognosis. *Child's Nerv Syst* 4: 213-222, 1988
76. Robertson JA, Leggate JRS, Miller JD, et al: Aqueductal stenosis—presentation and prognosis. *Br J Neurosurg* 4: 101-106, 1990
77. Ross ED, Stewart RM: Akinetic mutism from hypothalamic damage: successful treatment with dopamine agonists. *Neurology* 31: 1435-1439, 1981
78. Rotilio A, d'Avella D, de Blasi F, et al: Disendocrine manifestations during non tumoral aqueductal stenosis. *J Neurosurg Sci* 30: 71-76, 1986
79. Rovira A, Capellades J, Grive E, et al: Spontaneous ventriculostomy: report of three cases revealed by flow-sensitive phase-contrast cine MR imaging. *AJR Am J Neuroradiol* 20: 1647-1652, 1999
80. Russell DS, Nevin S: Aneurysm of the great vein of Galen causing internal hydrocephalus: report of two cases. *J Pathol Bacteriol* 51: 447-448, 1940
81. Russell DS: Observations on the pathology of hydrocephalus. Medical Res Council, special report series No. 265. His Majesty's Stationery Office, London, 1949
82. Schroeder HWS, Gaab MR: Endoscopic aqueductoplasty: technique and results. *Neurosurgery* 45: 508-518, 1999
83. Shallat RF, Pawl RP, Jerva MJ: Significance of upward gaze palsy (Parinaud's syndrome) in hydrocephalus due to shunt malfunction. *J Neurosurg* 38: 717-721, 1973

84. Sherman JL, Citrin CM, Gangarosa RE, et al: The MR appearance of CSF flow in patients with ventriculomegaly. *AJNR Am J Neuroradiol* 7: 1025-1031, 1986
85. Spadaro A, Ambrosio D, Moraci A, et al: Aqueductal stenosis as isolated localization involving the central nervous system in children affected by von Recklinghausen disease. *J Neurosurg Sci* 30: 87-93, 1989
86. Stellman GR, Bannister CM, Hillier V: The incidence of seizures disorders in children with congenital and acquired hydrocephalus. *Z Kinderchir* 41 [Suppl 1]: 38-41, 1986
87. Stephensen H, Tisell M, Wikkelso C: There is no transmantle pressure gradient in communicating or noncommunicating hydrocephalus. *Neurosurgery* 50: 763-771, 2002
88. Suh DY, Gaskill-Shipley M, Nemann MW, et al: Corpus callosal changes associated with hydrocephalus: a report of two cases. *Neurosurgery* 41: 488-494, 1997
89. Tisell M, Edsbagge M, Stephenson H, et al: Elastance correlates with outcome after endoscopic third ventriculostomy in adults with hydrocephalus caused by primary aqueductal stenosis. *Neurosurgery* 50: 70-77, 2002
90. Turnbull IM, Drake CG: Membranous occlusion of the aqueduct of Sylvius. *J Neurosurg* 24: 24-33, 1966
91. Vanneste J, Hyman R: Non-tumoral aqueductal stenosis and normal pressure hydrocephalus in the elderly. *J Neurol Neurosurg Psychiatry* 49: 529-535, 1986
92. Villani R, Tomei G, Gaini SM, et al: Long-term outcome in aqueductal stenosis. *Child's Nerv Syst* 11: 180-185, 1995
93. Vindigni G, Del Fabro P, Facchini P, et al: On the neurological complications of internal and external shunt in patients with non-neoplastic stenosis of the aqueduct. *J Neurosurg Sci* 30: 83-86, 1986
94. Wakai S, Narita J, Hashimoto K, et al: Diverticulum of the lateral ventricle causing cerebellar ataxia. Case report. *J Neurosurg* 59: 895-898, 1983
95. Williams B: Cerebrospinal fluid pressure-gradients in spina bifida cystica, with special reference to Arnold-Chiari malformation and aqueductal stenosis. *Dev Med Child Neurol Suppl* 35: 138-150, 1975
96. Woollam DH, Millen JW: Anatomical considerations in the pathology of stenosis of the cerebral aqueduct. *Brain* 76: 104-112, 1953
97. Yamada H, Oi S, Tamaki N, et al: Prenatal aqueductal stenosis as a cause of congenital hydrocephalus in the inbred rat LEW/Jms. *Child's Nerv Syst* 7: 218-222, 1991
98. Yamasaki M, Arita N, Hiraga S, et al: A clinical and neuroradiological study of X-linked hydrocephalus in Japan. *J Neurosurg* 83: 50-55, 1995

Shunt Hardware and Surgical Technique

HOWARD J. GINSBERG, JAMES M. DRAKE

Introduction

Hydrocephalus is one of the most common complications of virtually any insult to the neonatal, infant, or child's nervous system. It occurs in approximately 1 in 2000 births, and is associated with approximately one-third of all congenital malformations of the nervous system [15]. It is also a common complication of intraventricular hemorrhage, brain tumors, infections, and head injury [4]. The etiology of hydrocephalus in 345 children undergoing a first shunt insertion in the randomized shunt design trial [31, 32] has been analyzed in detail elsewhere [33]. The median corrected age of the patients was 55 days, indicating that this is very much a problem seen most commonly in infancy. An estimated 33 000 shunts are placed in patients of all ages annually in the United States, with an estimated shunt prevalence of more than 56 000 in children less than 18 years old [15].

The insertion of a cerebrospinal fluid (CSF) shunt is the commonest procedure performed in most neurosurgical centers, and forms the overwhelming majority in pediatric centers. Few topics generate as much discussion and controversy as the question of which is the best shunt system for a particular pa-

tient. There is often some confusion about just what a particular shunt device does or how it works. Much of what neurosurgeons know about shunts comes from advertisements or displays by vendors, and also from ingenious neurosurgical inventors who believe strongly in the merits of their own design. We believe that knowledge of the principles of shunt function will allow neurosurgeons to select intelligently among the myriad designs and understand some of the fascinating complications of these remarkable devices.

History

A mere half century ago, a diagnosis of hydrocephalus carried a terminal or intellectually devastating prognosis. Our earliest ancestors must have recognized the overt clinical manifestations of untreated infantile hydrocephalus, but early attempts at treatment were doomed due to a lack of understanding of CSF physiology and the absence of sterile technique. Drainage of CSF into various intra- and extracranial spaces (Table 1) has been investigated since the turn of the century [25, 85], and virtually no

Table 1. Distal sites used for CSF conversion

Head and neck region	Abdominal region	Thoracic region
Subgaleal region	Peritoneal cavity	Thoracic duct
Superior sagittal sinus	Omental bursa	Spinal epidural space
Internal jugular vein	Stomach	Bone marrow
Common facial vein	Gall bladder	Pleural cavity
Subdural space	Ileum	Right atrium
Subarachnoid space	Ureter	Superior vena cava
Mastoid antrum	Fallopian tube	
Salivary gland ducts		

imaginable site has remained untried. It was not until the development of compatible biomaterials and one-way valves that the modern era of shunt surgery began. Nulsen and Spitz [73] were first to report the successful use of a ventriculojugular shunt with a spring and stainless steel ball valve. In 1955 Pudenz introduced silicone as a shunt tubing material while investigating the feasibility of shunting CSF into the circulatory system of animals. The first child to receive a silicone ventriculoatrial shunt survived 2 years, only to die later from shunt obstruction. Silicone has since become the material of choice for implanted shunts. Ventriculoatrial, ventriculoperitoneal, and lumboperitoneal shunting procedures became widespread in the 1970s and the management of their complications became a major focus.

All current ventricular CSF shunt systems contain a proximal ventricular catheter, a one-way valve, and a distal catheter terminating in the peritoneum, venous system, or, less commonly, the pleural space. Ventriculoperitoneal shunting, which was first reported in 1908 [57] and subsequently fell out of favor, has now become the procedure of choice in the initial treatment of obstructive hydrocephalus.

CSF Shunt Hydrodynamics

The hydrodynamics of shunt systems is concerned with the flow of CSF in silicone tubing and valves, or, more precisely, the resistance to flow and the driving pressure. In order to appreciate the difference between the many valves available on the market, it is important to have a basic understanding of hydrodynamics. The clinical importance of shunt hydrodynamics has been emphasized in numerous publications [3, 7, 22, 23, 36, 37, 44, 47, 55, 66, 70, 80, 81, 83, 87, 90, 92, 98, 106, 110, 112]. The transformation of the open-ended tube into the modern shunt systems on the market today is a testament to an improved understanding of hydrodynamics.

An ideal shunt system would be one that mimics the normal brain's reabsorption of CSF into the venous system via the arachnoid granulations, controls intracranial pressure, and reconstitutes the cerebral mantle [23]. The fact that there are so many shunt products on the market and new ones continually being developed implies that the ideal shunt is far from realized [49, 91].

Most cases of hydrocephalus are due to a pathological increase in the hydrodynamic resistance to the outflow of CSF [3]. A shunt system provides a low-resistance pathway for CSF diversion. Resistance is therefore a particularly important concept.

Flow in shunt systems can be related to resistance and the pressure gradient by the following simple equation:

$$Q = \Delta P/R$$

Where Q is the flow rate, R is the resistance to flow, and ΔP is the driving pressure. Shunt flow rates have been documented in vivo [55] from 0.6 to 116 ml/h, although pumping a shunt valve can produce peak flow rates [6] up to 2000 ml/h. R is made up of: R_T , which is resistance from the shunt tubing, plus R_V , which is resistance from the valve components. R_T is dependent on a number of factors including the length and inner diameter of the shunt tubing and the viscosity of the CSF as described by Poiseuille's law:

$$\frac{8 L}{R_T = \pi r^2}$$

where η is the coefficient of absolute viscosity, L is the length, and r is the inner radius of the shunt tubing. It is important to note that viscosity is highly dependent on temperature, and any shunt testing should use fluid at 37 °C, otherwise erroneous pressure-flow characteristics will be obtained (η_{water} at 37 °C is 0.6915 cP whereas at room temperature (22 °C) it is 0.9548 cP – a difference of 38%). Flow through shunt systems under normal physiological conditions is usually laminar (Reynolds number typically <1), even at sharp corners and through narrow valves, because of the relatively low flow rates. R_T will remain constant at any flow rate, thus producing a linear pressure versus flow curve for the tubing (Fig. 1). R_V is much more complicated because of the complex geometry and moving parts. In many cases the resistance is not constant in the range of physiologic flow rates and thus a curved pressure versus flow relationship is seen. Studies in

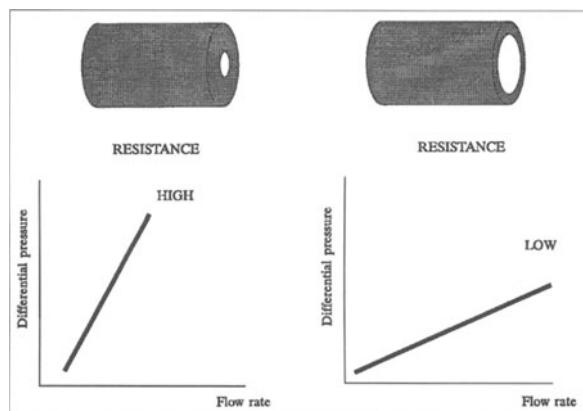


Fig. 1. Linear pressure versus flow curve for valveless tubing with constant resistance

our laboratory and by others show that a 90-cm-long distal catheter provides an additional resistance to flow roughly equivalent to the resistance provided by a differential pressure valve, and may in fact provide up to 94% of the total resistance of a shunt system [6, 23]. Care must therefore be taken when shortening a distal catheter as this can significantly alter the shunt's pressure flow characteristics.

The resistance of a shunt system ($R_T + R_V$) plays an important role in defining the intraventricular pressure with a given rate of CSF production and absorption, and is therefore at least as important in the choice of shunt as the opening pressure. Resistance to bulk flow of CSF across the arachnoid granulations in the absence of hydrocephalus is approximately 60 cmH₂O/ml per minute. Resistance of a typical low-pressure shunt system flowing at 25 ml/h is approximately 8 cmH₂O/ml per minute, a much lower value.

The pressure gradient driving the flow in a ventriculoperitoneal shunt system is determined by [83]:

$$\Delta P = IVP + \rho gh - OPV - DCP,$$

where IVP is the intraventricular pressure, ρgh (density×gravitational constant×vertical height difference between proximal and distal ends) is the hydrostatic pressure, OPV is the opening pressure of the valve, and DCP is the distal cavity pressure (Fig. 2). If the distal catheter is placed in the venous system, the DCP is obviously the venous pressure. If the catheter is placed in the peritoneal cavity the DCP becomes the intra-abdominal pressure, which is usually zero relative to the atmosphere, but can climb transiently during straining.

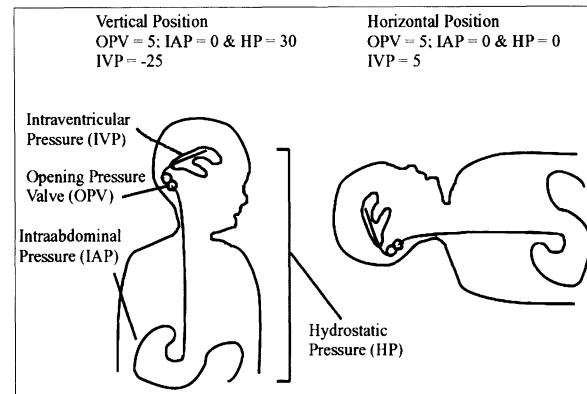


Fig. 2. Compartment pressures and the effect of position. Hydrostatic pressure predominates in the upright position. (Reproduced from [28], Fig. 2-5, with permission)

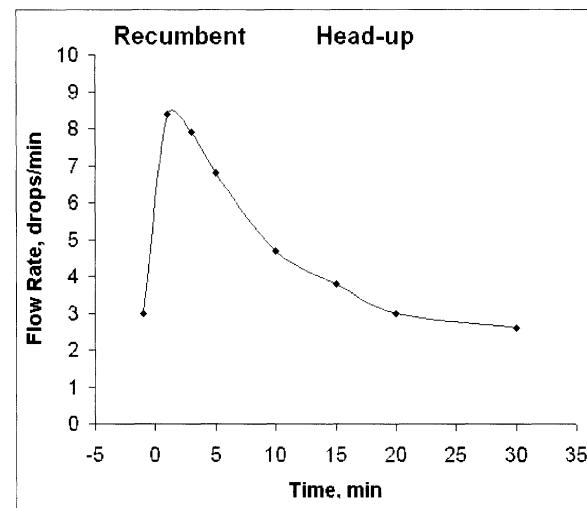


Fig. 3. Change in CSF flow rate when moving from supine to upright position in dogs. (Adapted from [112], with permission)

Siphoning

Siphoning occurs when there is a difference between the height of the ventricular catheter and the distal catheter. A rapid increase in flow rate occurs and is due to a pressure differential equal to ρgh that is generated when the patient moves from the recumbent to the upright position [28]. A canine study revealed that upon the dogs' assuming the upright position, the flow rate rapidly increases and then progressively decreases until it becomes stabilized [112] (Fig. 3). Transient flow rates up to 170 times the normal rate of CSF production can be achieved in simulations [5]. This siphoning effect does not occur in the normal brain since there is no posture-related change in the CSF-sagittal sinus pressure gradient [23]. Since the head is not open to atmospheric pressure, in a shunted patient fluid will flow until the intracranial pressure drops to negative ρgh (Fig. 4) to balance the

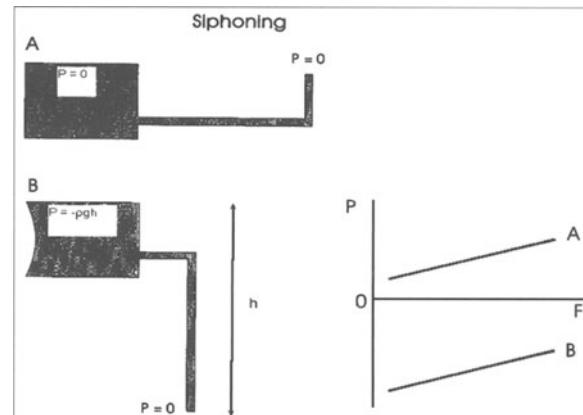


Fig. 4. Changes in intraventricular pressure that occur with siphoning. (Reproduced from [28], Fig. 2-4, with permission)

siphon effect. This of course has the danger of causing low-pressure symptoms [35], tearing bridging veins, causing a subdural hematoma [67,79], and prematurely closing cranial sutures [56, 62] or causing slit-ventricle syndrome [86]. Low-pressure symptoms were reported by Pudenz and Foltz to occur in 10%-12% of patients, indicating that many patients will tolerate this siphoning effect without malady. It is important to understand that the hydrostatic pressure generated in the upright position (25-50 cmH₂O) is significantly higher than the opening pressure of a typical low-pressure (1-4 cmH₂O) or high-pressure valve (8-10 cmH₂O). Raising the opening pressure of the valve by δ cmH₂O simply decreases the magnitude of the negative intraventricular pressure generated from siphoning by δ cmH₂O. Thus, changing the shunt valve to one with a higher opening pressure may delay ventricular collapse, but will not prevent it, in those that are prone to slit-ventricle syndrome [48, 52].

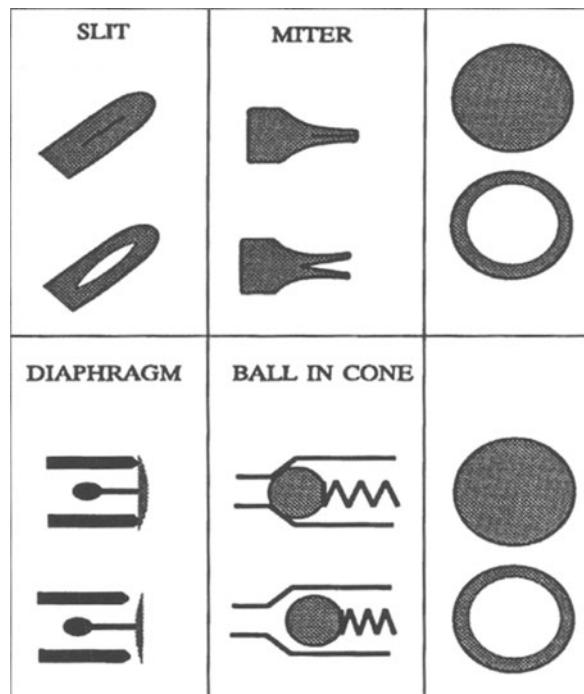


Fig. 5. General categories of differential-pressure valve. (Reproduced from [28], Fig. 2-7, with permission)

Shunt Valves

The valves most commonly used in practice today include differential pressure regulators (static and programmable), flow regulators, siphon-resistive devices, and gravity-actuated valves.

Differential-Pressure Valves

Numerous differential-pressure one-way valves have been developed in four broad categories: slit valves, miter valves, diaphragm valves, and ball-in-cone valves (Fig. 5) [28, 84]. These devices all attempt to achieve the same goal of keeping the intraventricular pressure from climbing too high or falling too low. Differential-pressure valves are defined by their opening or closing pressure. As the intraventricular pressure climbs above the valve opening pressure, the valve opens to allow egress of CSF at a rate determined by the resistance of the entire shunt system, until the pressure falls below the closing pressure and the flow of CSF ceases. Although it has not been demonstrated *in vivo*, it is possible that the valve opens and closes with each cardiac cycle. The opening pressure is not necessarily the same as the valve closing pressure due to the phenomenon of hysteresis [23, 28]. Hysteresis occurs because of a slight change in the mechanical properties of the valves depending on whether they are opening or closing and occurs most frequently with slit and miter valves. Most manufacturers provide differential-pressure valves with

various opening pressure ranges in three or four categories: very low (<1 cmH₂O), low (1-4 cmH₂O), medium (4-8 cmH₂O) and high (>8 cmH₂O). Two different differential-pressure valves may have the same opening pressure and completely different resistance values and will therefore behave very differently.

Slit valves may be at the proximal end (Holter-Hausner valve) or at the distal end of a shunt (Codman Unishunt). Simple distal slit valves offer the lowest resistance to flow, and in fact no significant difference in resistance can be measured between a tube with a distal slit valve and an equally long open-ended tube.

The diaphragm valve is probably the most commonly produced type of differential-pressure valve. Generally speaking, these valves involve the deflection of a silicone membrane in response to pressure in order to allow flow of CSF.

Programmable Valves

Programmable valves are more appropriately called externally adjustable differential pressure valves. They act in the same fashion as nonadjustable differential-pressure valves, except that the surgeon has the option of altering the opening pressure with an external device, obviating the need for surgical shunt revision [63]. This provides increased convenience and mar-

ginally decreased risk, but it is not clear that the benefit outweighs the increased cost for use in all patients. Several authors have reported clinical success and complications associated with these devices [1, 12, 18, 63, 88]. It has been suggested that this type of shunt is well suited for difficult-to-manage cases of overdrainage (e.g., slit ventricles, subdural collections) or underdrainage (e.g., persistent symptoms of hydrocephalus). It has also been suggested that externally adjustable shunts are particularly useful in gradually decreasing the size of arachnoid cysts and the size of the ventricles in normal-pressure hydrocephalus [12, 14, 18]. It is important to note that these programmable valves are also susceptible to siphoning.

The Codman Medos programmable valve (Codman, Randolph, Mass.) (Fig. 6) has an adjustable ball-spring mechanism. A cam and stepper motor assembly (akin to a spiral staircase) is used to adjust the tension on the spring. The opening pressure can be read from radiopaque markers and can be adjusted from 3 to 20 cmH₂O in 1-cmH₂O increments. The motor assembly is adjusted with an externally applied magnetic field from the valve programmer. In adjusting the pressure over the total range from 3 to 20 cmH₂O, the spring moves by less than 1 mm [8, 78]. The Sophy programmable pressure valve (Sophysa, France) is also a ball-spring type of valve, where a semicircular spring can be adjusted for various tensions by rotation with magnets. This device has eight possible positions in the range of 5–17 cmH₂O opening pressure. Since both of these valves contain magnets, they will produce an artifact on MRI scans and may possibly be reprogrammed by a magnetic field [11, 38, 74, 111].

Flow-Regulating Valves

Flow-regulating devices are designed to increase the hydrodynamic resistance as the pressure gradient increases, in an attempt to keep the flow rate constant. It is in fact the differential pressure that controls the resistance, and perhaps these valves should be more descriptively called pressure-controlled, variable resistance, constant flow valves. These devices produce pressure flow curves with a sigmoid shape (Fig. 7). This is accomplished by the Cordis Orbis Sigma valve with a contoured synthetic ruby flow-control pin that fits inside a moveable synthetic ruby ring (Fig. 8). As the pressure increases

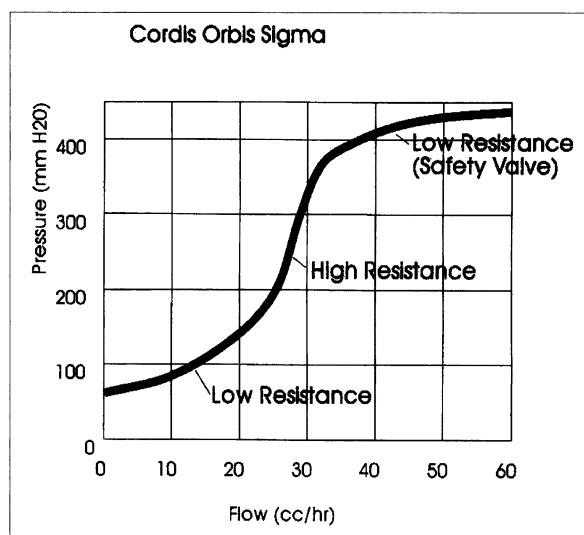


Fig. 7. Pressure versus flow rate for Cordis Orbis Sigma valve. (Reproduced from [28], Fig. 4-25B, with permission)

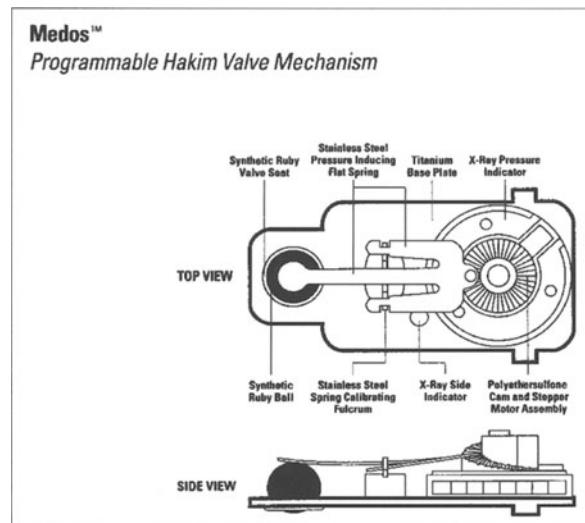


Fig. 6. Schematic diagram of Codman Medos Programmable valve. (Reproduced from [28], Fig. 4-22, with permission)

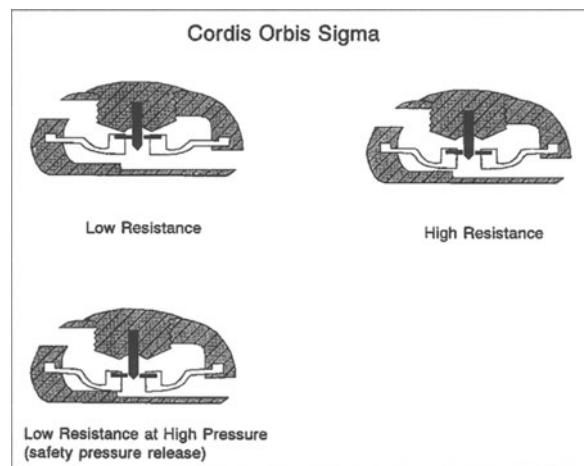


Fig. 8. Schematic diagram of Cordis Orbis Sigma valve. (Reproduced from [28], Fig. 4-25A, with permission)

es the ruby ring is deflected downward, and since the ruby pin is tapered, the flow aperture decreases, which increases resistance and reduces flow. If the pressure increases further, beyond a predetermined threshold, the ruby ring is deflected further downward until resistance is lowered to allow a rapid increase in flow rate. Sainte-Rose et al. [90] describe three stages as follows: the first stage consists of a medium-pressure low-resistance valve that operates as a conventional differential-pressure valve until the flow through the shunt reaches a mean value of 20 ml/h. A second stage consists of a variable-resistance flow regulator that maintains flow between 20 and 30 ml/h at differential pressures of 8–35 cmH₂O. The third stage is a safety device that operates at differential pressures above 35 cmH₂O (inducing a rapid increase in CSF flow rate) and therefore prevents excessive intracranial pressure. Flow-regulating valves are less likely to be associated with siphoning and overdrainage and have been shown to improve symptomatic low intracranial pressure in shunted individuals [35]. However, flow-regulating valves typically have very small orifices, which makes the valve itself a likely site of obstruction [33], and the high resistance offered has a propensity to cause fluid collections postoperatively under the scalp in young children unless they are nursed upright with a compressive dressing.

Antisiphon Devices

One strategy developed to avoid the complication of overdrainage is the siphon-resistive or antisiphon device (ASD). This device, which is typically placed under the scalp, has a small diaphragm that reduces the flow of CSF when the pressure inside the shunt falls below atmospheric pressure (Fig. 9). The PS Medical siphon control device, which contains two membranes, is designed to be closed in its resting

position and can only be forced open when the internal shunt pressure exceeds atmospheric pressure. The PS Medical Delta valve consists of a siphon-control device just distal to a differential-pressure valve. The ASD can theoretically be placed anywhere along the length of the shunt, giving the surgeon some control over the ventricular pressure at which the ASD closes [59, 105]. The more distally the ASD is placed, the more negative pressure is required inside the ventricle in order to reduce flow by the same degree. An ASD placed at the distal end of a peritoneal catheter will have no effect whatsoever. Portnoy et al. [79] were the first to report successful obliteration of symptomatic low intracranial pressure using an ASD in 11 of 13 patients, although 6 patients still developed a subdural hematoma. Gruber et al. [40] reported the results of placing an ASD in 41 children (31 previously shunted and 10 with primary shunts). They reported a marked decrease in slit-ventricle syndrome and patient complaints regarding low-pressure symptoms during the daytime or after excessive activity. Four cases of severe neurological deterioration after ASD implantation, in the absence of shunt obstruction, have been reported [68]. Symptoms resolved with removal of the ASD. The fact that these four patients suffered from signs of intracranial hypertension suggests that the ASD in those cases either remained closed or failed to open once siphoning ceased, or did not open at all. Drake et al. [29] demonstrated that raised tissue compartment pressure from scar tissue overlying an ASD can lead to functional obstruction, and was the likely cause in those cases.

Gravity-Actuated Valves

Gravity-actuated valves attempt to prohibit or reduce siphoning by increasing opening pressure with the assistance of gravity when a patient sits or stands. The Cordis Horizontal-Vertical valve is one such device, designed for use with lumboperitoneal shunts (Fig. 10). This device has an inlet valve and an outlet valve. The inlet valve is a ball-spring valve and does not markedly change resistance with position. The outlet valve has a synthetic ruby ball that sits in a conical seat, and there are three stainless steel balls sitting on top of the ruby ball. In the upright position the weight of the steel balls acts to weigh down the ruby ball into its seat, thus creating high resistance. In the recumbent position, the balls fall away from the seat to allow flow at a low resistance. It is therefore extremely important to ensure that gravity-actuated valves are secure and in the proper position.

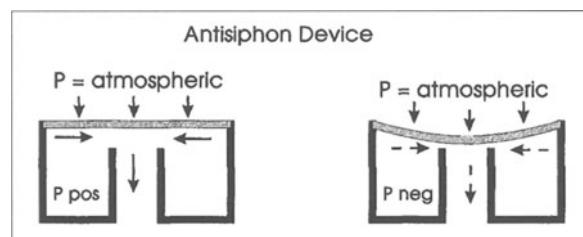


Fig. 9. Mechanism of siphon-resistive devices. As the pressure inside the container falls, atmospheric pressure pushes the membrane toward the orifice, narrowing it and increasing resistance. (Reproduced from [28], Fig. 2-9, with permission)

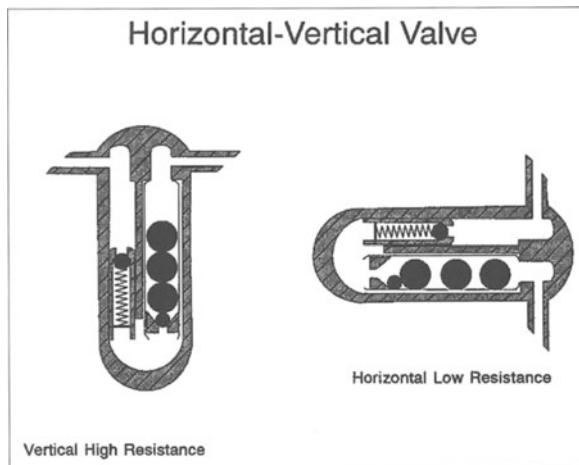


Fig. 10. Schematic diagram of Cordis Horizontal-Vertical valve. (Reproduced from [28], Fig. 4-30A, with permission)

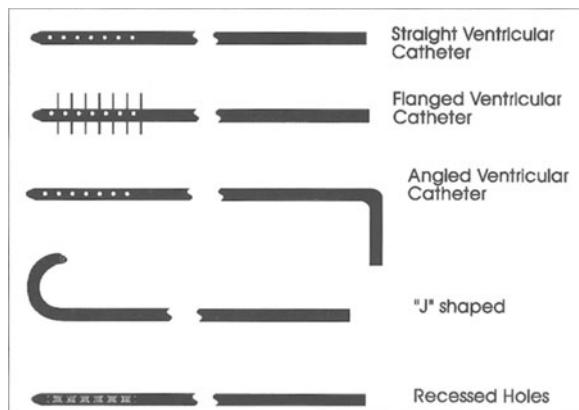


Fig. 11. Various ventricular catheter designs. (Reproduced from [28], Fig. 4-1, with permission)

Proximal and Distal Catheters

All ventricular and distal catheters currently in use are made from synthetic silicone rubber. Most of these catheters are impregnated with barium along their entire length or separated tantalum markers for radiographic visualization. Ventricular catheters are designed to be stiff enough so that they are kink-resistant, and compliant enough to prevent brain injury if the ventricles collapse onto the catheter. Various lengths, shapes, inner/outer diameters, and wall thicknesses are available. Inner diameters from 1.0 to 1.6 mm are available, the smallest being designed for neonates. It is important to note that changing the diameter of tubing from 1.3 mm to 1.0 mm results in a nearly three-fold increase in resistance. Straight catheters, angled catheters, and catheters with flanges and recessed holes have been produced (Fig. 11). Flanged catheters were designed to keep the choroid plexus away from the draining holes in order to diminish the likelihood of mechanical obstruction from choroid plexus [42]. However, they do not decrease the incidence of ventricular catheter occlusion [92], and in fact close inspection of explanted flanged catheters demonstrates that the flanges can act like scaffolding for choroid plexus to attach onto. The size and number of drainage holes in a ventricular catheter is variable, although most of the holes are redundant [39]. There is some resistance to flow from the ventricular catheter and its holes, and this resistance increases as the number of holes decreases due to partial obstruction. We have shown in our laboratory that there is no significant increase in the total resistance of a shunt system even if only a single 500-mm hole allows CSF to flow [39].

Distal shunt tubing is either open-ended or closed at the tip with slit valves near the distal end. Some have both open ends and slits; in the event that the open-ended tip becomes obstructed, the slits provide an alternate pathway for CSF flow. With the exception of the distal ends of these catheters, they are simply silicone rubber tubes.

Brain Biomechanical Model

Behind every shunt design is some concept of a mathematical model of CSF production, absorption, and intracranial pressure. Several mathematical and computer biomechanical models applicable to the hydrocephalic brain have been developed with varying degrees of sophistication (see Chap. 3) [30, 41, 45, 46, 58, 65, 71, 72, 76, 96, 97, 99, 100, 104, 112].

Unblocking Shunts

Mechanical obstruction is the most common cause of shunt failure [33, 93], and the ventricular catheter is the most likely site of obstruction. In the pediatric population, the ventricular catheter is obstructed in up to 90% of mechanical shunt failures [108]. The catheters are most commonly blocked by ingrowth of choroid plexus, due to flow of CSF drawing the plexus in, and glial tissue from astrocyte proliferation [21]. Less commonly, ventricular catheters are obstructed with connective tissue, clotted blood, ependymal cells, necrotic brain tissue, lymphocytes, multinucleated giant cells, neutrophils, and foreign materials

(hair, fiber, etc.). Despite modifications in ventricular catheter position [2, 13, 92] and design [42], including changes in shape and material, no significant improvement has been shown. The current treatment for mechanical shunt failure is surgical replacement of the obstructed shunt components. A 31% risk of visible hemorrhage has been reported for shunt revision surgery, visualized during surgery or diagnosed by postoperative CT scan [16]. Although most of these hemorrhages are not clinically significant, they can reduce the time to subsequent shunt revision by 70%. It may therefore be advantageous to leave the ventricular catheter *in situ* and simply recanalize it. Additional advantages of this procedure include avoiding replacement of ventricular catheters when the ventricles are small, and reducing the incidence of intraventricular hemorrhage caused by removing an adherent catheter.

In 1988 Chambi and Hendrick [18] reported the use of electrocautery for removal of adherent ventricular catheters, which is probably a routine part of shunt revision in most centers. It has since been shown that electrocautery can be used inside a ventricular catheter to reestablish flow during open shunt revision [51] or percutaneously via a Rickham reservoir [75]. Pattisapu [75] inserts a wire and fiberoptic endoscope through a Rickham reservoir and into the ventricular catheter. He cauterizes the obstructing tissue under direct endoscopic vision. Eighty-five percent of patients have maintained a patent shunt with a mean follow-up of 20 months in this study. The use of fiberoptic delivery of laser energy to remove occlusions has been investigated experimentally [19]. A 300-ms pulse of a 2.09-fm wavelength laser was used to create short-lived vapor bubbles at the fiber tip in order to expel tissue blocking the inflow holes. Our group is currently investigating the use of percutaneous ultrasonic cavitation to recanalize blocked ventricular catheters. Using a custom-designed prototype (Cyberonics, Erie, Pa, USA), ultrasound is passed down a wire that is placed inside the ventricular catheter and bubbles are formed at the tip. These bubbles subsequently collapse and create minute shockwaves, which act quite locally to break up the debris. This system can effectively clean explanted ventricular catheters, but has not yet been subjected to clinical trials. Ultrasound cleans more quickly and thoroughly than electrocautery and does not damage silicone the way a laser system may. We have also shown that only a single hole need be reopened in order to restore appropriate hydrodynamics to most shunt systems. At this point, it is not clear whether ventricular catheter cleaning will offer any short- or long-term benefits to patients over traditional shunt revision, but it clearly deserves further investigation.

The Future of Shunt Design

Improvements in mathematical and computer models of CSF hydrodynamics along with sophisticated in vitro testing techniques may prove to be the keys to further refining shunt design. The ideal shunt, which mimics the normal process of CSF absorption, has not yet been built. In order to achieve this ideal, it will probably be necessary to incorporate a sensor into a shunt system with servo-feedback to the valve; this idea was first alluded to by Salomón Hakim [43] in 1973. It is conceivable that a shunt, with the aid of miniature embedded microprocessors, could constantly control the intracranial pressure by accordingly adjusting the valve. With the aid of nanotechnology, it is now possible to design and build microscopic machines and switches that can be manipulated electronically. The increased sophistication and cost should be offset by a decreased incidence of complications. It is also possible that a more physiological shunt could have a positive impact on the developing brain, although this would require a very carefully designed long-term outcome study.

Another future direction in the treatment of hydrocephalus is in reducing the morbidity of the overall management of shunt complications. With the advent of noninvasive techniques for diagnosing shunt patency in difficult cases and determining shunt performance, patients will no longer be subjected to invasive tests and unnecessary operations. No matter how sophisticated the shunt system is, shunt failure will always remain a problem in some cases. The treatment of shunt occlusion by minimally invasive means is currently being explored and promises an overall improvement in the care of shunt patients and a decrease in the cost of that care. We envision a future where a patient receives only one shunt in his/her lifetime, which is sophisticated enough to control intracranial pressure within normal physiological limits, can be adjusted and monitored noninvasively, and can be treated minimally invasively for shunt obstruction.

Treatment with CSF Shunts

Shunt Selection

There are currently no data on which to recommend one particular shunt over another. In fact, a recent randomized trial on CSF shunt design which com-

pared a standard valve to the Delta valve and the Orbis Sigma valve failed to show any difference in terms of overall shunt failure [33]. However, there are important considerations to be taken into account when considering the individual patient. These include age, weight, skin thickness, head size, size of the ventricles, pathogenesis of hydrocephalus, the acuteness of the illness, the presence of internal lines or gastrostomy, tracheotomy openings, status of the distal drainage site, and plans for further surgery.

For example, a premature infant with thin skin stretched further by a rapidly expanded head cannot handle adult-size equipment without the risk of skin erosion. If the same infant has blood in the ventricles, then immediate implantation of a valve with a narrow, flow-limiting orifice might increase the risk of early obstruction. If one ventricle is significantly larger than the other, then placing the ventricular catheter on that side is easier. In patients with very large ventricles, and large skulls with fused sutures, placing a flow-limiting or siphon-reducing device might decrease the risk of subdural hemorrhage.

If there are loculations within the ventricular system, then fenestrating them endoscopically at the time of shunt insertion would at least attempt to keep the number of shunts at one. If a patient is expected to have a number of subsequent and important MRI studies, metallic shunt components or magnetic programmable valves might interfere with the interpretation of these images. Finally, if a patient is scheduled to have further intra-abdominal surgery – for example, to close a colostomy, or to reconstruct the bladder – this might influence the choice of site of distal drainage.

For most routine cases, it is probably better to use what one is quite familiar with. In this setting the authors prefer a two-piece system, with a non-flanged ventricular catheter, connected to a flat-bottomed valve with a reservoir, with open-ended distal tubing.

Surgical Technique

Initial Shunt Insertion

While shunt surgery is often regarded with some disdain by staff and trainee neurosurgeons alike – “plumbing” – it has the highest failure rate of any neurosurgical procedure, and nothing is less forgiving of any technical errors than a shunt operation. It is true that shunts often fail because of tissue occluding the upper or lower end. But parenchymal ventricular catheters, extraperitoneal

distal catheters, and spontaneously disconnected or migrated shunts have happened in virtually every neurosurgical service. These complications are avoidable. The authors believe that shunt surgery should command great respect, require meticulous attention to detail, and be carried out in a skilled and expeditious fashion.

Patient Preparation

Body wash and shampoo, the night before and again prior to surgery, with an antiseptic solution, e.g., chlorhexidine, is recommended. In the operating room, the patient is positioned under general endotracheal anesthesia, with the head rotated to the side opposite the shunt, and the neck extended so that there is almost a straight line between the scalp and abdominal incisions. A number of meta-analyses have shown that prophylactic antibiotics are effective [61], and they are strongly recommended. Cloxicillin 50 mg/kg 30 min prior to surgery is often used. For patients in whom an abdominal trocar is being used, the bladder should be emptied either by a Credé maneuver, or by urinary catheter. Hair is clipped (not shaved) in the operating room if desired to assist with skin closure and bandage application. However, hair removal has never been shown to reduce the risk of infection [50].

Surgery

The patient should be positioned so there is a flat plane between the upper and lower incision sites, so that the shunt can be passed easily. For an occipital burr hole, this means rotating the head to the opposite side, and extending the neck, usually with a rolled towel (Fig. 12). The site of the burr hole and



Fig. 12. Patient positioning and marking of incisions

abdominal incisions should be selected and marked prior to draping before the surface landmarks are obscured. Occipital burr holes are usually on the flat part of the occiput 3 to 4 cm from the midline along the course of the lambdoid suture. In patients with Dandy-Walker malformation or huge arachnoid cysts of the posterior fossa, the transverse sinus can be placed much higher than in normal subjects. In these patients the position of the transverse sinus should be identified preoperatively by MRI, and the placement of the burr hole should be modified according to the results of this exam. Frontal burr holes are along the coronal suture 2 to 3 cm from the midline. The issue of frontal vs. occipital burr hole controversy has never been resolved [13].

The skin is meticulously prepped with a slow-release iodine solution. Disposable adhesive drapes are used to cover entirely the patient and the operating table, except for a small band of skin from the burr hole site to the abdomen (Fig. 13). The drapes may need to be stapled to the hair-bearing areas of the scalp. Small skin incisions are adequate. It is better to position them so that the hardware is not afterwards directly underneath. The burr hole need not be a standard size, and a twist drill is adequate unless a burr hole reservoir or intraoperative ultrasound is being used. In infants, particularly if premature, an opening between the splayed sutures at either frontal or occipital sites is all that is required. The dura does not need to be opened widely, and in patients with thinned cortical mantles, a wide dural opening may allow CSF to escape around the ventricular catheter into the subcutaneous tissues, promoting a CSF leak. The brain and pia is cauterized and nicked.

The abdominal incision is simultaneously opened by an assistant; the method and site are unimportant. Paraumbilical and upper midline sites are com-

mon. One needs to be sure that the peritoneum has truly been opened and not just the preperitoneal space. Passing a blunt dissector easily well into the abdominal cavity verifies this (Fig. 14). A purse string suture around the peritoneum tends to prevent omentum from herniating but is not absolutely necessary. The authors prefer to use abdominal trocars in "virgin" bellies from a paraumbilical location. Opening the rectus sheath through a tiny incision and visualizing the posterior wall of the sheath facilitates placement. The posterior sheath is then "picked up" by the tip of the trocar, and then the tip is angled inferiorly and off the midline to avoid hitting the great vessels (Fig. 15). A gentle "pop" is felt as the peritoneum is penetrated. A blunt instrument can also be passed along the trocar sheath to verify peritoneal entry.

Care must be taken when tunneling. If the metal tube is too deep, either the chest or even the posterior fossa can be entered. One has to be particularly careful in patients who have had an occipital craniectomy, for it is possible to pass the device into

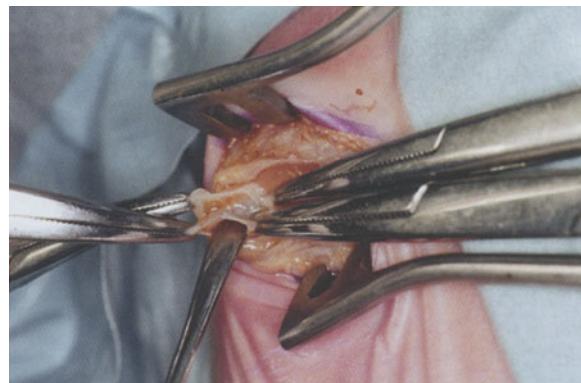


Fig. 14. Passing a blunt dissector into the peritoneal cavity



Fig. 13. Draping

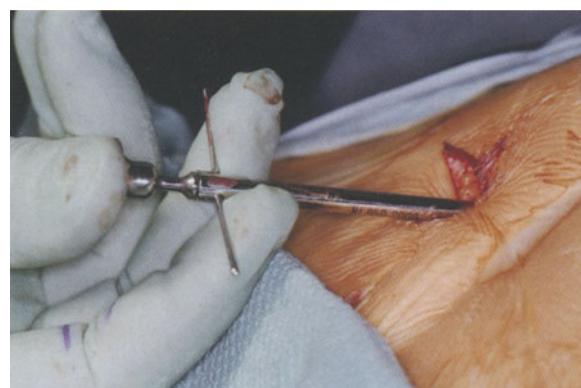


Fig. 15. Using an abdominal trocar

the bone opening by mistake. If the tunneling device is too superficial, then a skin laceration, which may be initially unrecognized, can occur. A gentle curve to the tunneling instrument allows one to direct the tip posteriorly when coming over the anterior chest into the neck, and by then rotating 180° the tip anteriorly toward the occiput (Fig. 16). Significant resistance is usually felt at the posterior nuchal line. Firm pressure, making sure that the pointed central stylet has not backed out, and guarding against plunging will usually allow this fascia to be penetrated. If one is using excessive force, then a separate incision should be made in the neck.

If passing to a frontal burr hole, an intervening incision is needed over the occiput. There appears to be no logical reason to tunnel down the back of the patient. Not only is it awkward, but with time a fibrous cord like a bow string forms, which is unsightly and can even affect neck mobility. The cord also remains if the shunt hardware is removed. The tunneling device is rigid enough when in place to compress the chest of small children so that the anesthetist typically notes an increase in airway pressure. It should not be left in place too long. It can also tear the scalp, particularly in small infants, where one is trying to bring the straight tunneling tube around the curved skull.

The peritoneal tubing, with or without the attached valve, is then passed along the tube, attaching suction to the distal end and irrigating. The valve should then be attached and irrigated to fill it with fluid, usually the antibiotic solution soaking the shunt equipment. It is not necessary to test the opening pressure of the shunt in the operating room. Merely handling the valve will change its performance characteristics for days, and air bubbles can also affect these measurements. It is important to connect the valve in the right direction!



Fig. 16. Tunneling device

The ventricular catheter trajectory is then determined according to external landmarks (Fig. 17). From a frontal burr hole, the intersection of the planes through the pupil and the external auditory meatus (traditional landmarks for the foramen of Monro) or simply being perpendicular to the skull are the preferred techniques. From the occipital location, a target at the midpoint of the forehead just at the normal hair line will ensure the catheter proceeds into the frontal horn instead of the temporal horn. There is, however, no proven ideal location for the ventricular catheter. Very recent evidence from the pediatric shunt design trial suggests that frontal or occipital locations are better than in the body of the ventricle or in the third ventricle [107]. Hitting small ventricles is easier from a frontal location. In these patients either ultrasound or even stereotaxis may assist with successful ventricular cannulation. The present authors routinely use ultrasound either through the shunt burr hole or, in infants, through the open fontanelle (Fig. 18). An endoscopic



Fig. 17. Cannulating the ventricle according to landmarks



Fig. 18. Using ultrasound guidance to place the ventricular catheter

stylet can also be used to place the shunt (Fig. 19). With these techniques the surgeon is as certain as possible that the catheter is in a good position at the end of the procedure, and not in one of the “unusual” sites such as the sylvian fissure, quadrigeminal cistern, etc. The ventricular catheter can usually be felt to “pop” once the ependyma is breached with concomitant gush of CSF. If the surgeon is unsure, gently irrigating the catheter may show pulsatile CSF flow into and out of the catheter. Withdrawing vigorously will simply draw brain tissue into the catheter, and plug the shunt if one is in the parenchyma. While there is no official limit on the number of passes, after two the present authors prefer to use ultrasound. A little fresh blood which clears is not unusual, and is one reason for recommending a separate ventricular catheter, for blood and debris can be cleared prior to attaching it to the valve. Extensive hemorrhage should prompt extensive irrigation until it clears. Installing a narrow-orifice, high-resistance valve in this setting will likely result in rapid occlusion.

There are a number of ways of getting the ventricular catheter around the burr hole corner. All are somewhat awkward. Simply bending the catheter, using the forces of the brain, burr hole, and dura is fine, but the inherent stiffness of the catheter tends to move the tip in the opposite direction. In patients with large ventricles and thin cortical mantles, the catheter can take an almost vertical trajectory. Right-angled guides avoid this. When attaching burr hole reservoirs (usually with contained valves), the ventricular catheter must be withdrawn then readvanced. The attachment site is usually below the cortical surface, where it becomes adherent, and losing the catheter at a subsequent revision is quite possible.

When using a flat-bottomed valve, a pocket must be created along the distal path. This pocket must be exactly along the course of the catheter or the valve will bind during the attempt to slide it along (Fig. 20). This can be an enormous nuisance, particularly if the ventricular catheter is already connected. When attaching the ventricular catheter to the valve, one should avoid using metal instruments forcefully directly on the tubing, as they can lacerate it and it may subsequently leak or break. We put silicone sleeves over forceps and snaps (Fig. 21), or use a clean gauze sponge. Similarly, when tying the catheter over the connector, it is vital to have the tie directly over the neck of the connector, tight enough not to allow spontaneous disconnection, but not too tight to lacerate the tubing. The valve system is then placed into its pocket by gently tugging on the peritoneal catheter from below (Fig. 22). The shunt system should then be secured to the pericranium (Fig. 23). It is incredible how unsecured systems can migrate. Post-fossa catheters are particularly difficult to secure, and have a high tendency to move. A three-way connector in this site also seems to come under excessive stress with neck motion, and be prone to fracture.

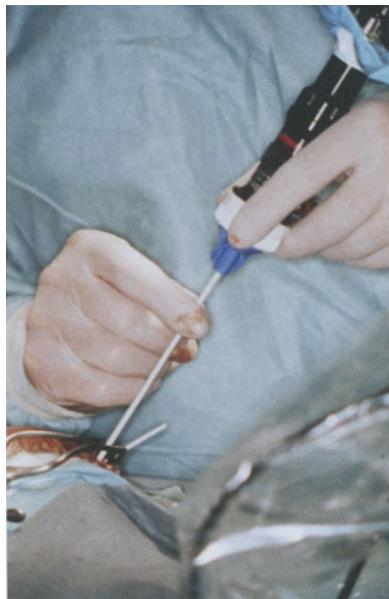


Fig. 19. Using a shunt scope to place the ventricular catheter

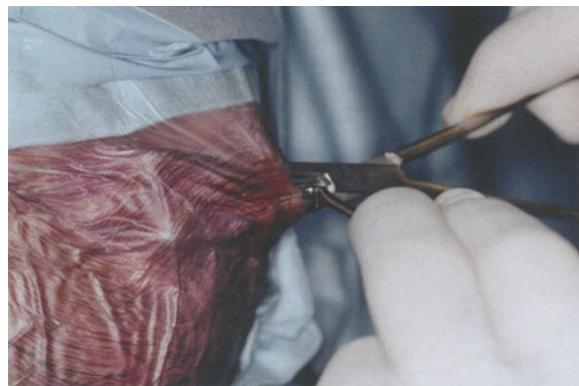


Fig. 20. Making the subcutaneous pocket for the valve



Fig. 21. Silastic sleeved forceps coaxing the tubing onto the connector



Fig. 22. Placing the valve into its pocket

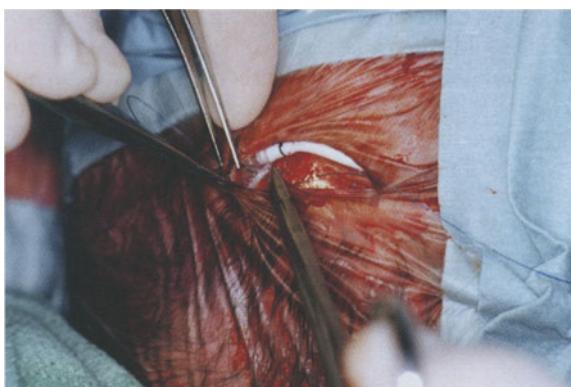


Fig. 23. Suturing the valve to the pericranium

Once in place, the system should be checked that it is flowing, either spontaneously or with gentle pumping of the reservoir. If there is any doubt, the system should be disconnected to verify that both ends are patent. This avoids having the patient return from the recovery room directly back to the operating room. The distal catheter is then inserted, making sure that it goes easily. If the catheter keeps backing out of the abdomen, it may be coiling up in the preperitoneal space. Ensure that one is truly intraperitoneal. The purse string suture is then tied snugly, and the abdominal layers reapproximated.

Skin closure is critical. Any CSF leak predisposes to wound breakdown or infection. Normally the skin is closed in two layers, with careful apposition of the skin edges. The fragile skin of premature infants may fray, and will leak CSF through large needle holes. An occlusive dressing, which will also resist attempts by small children to remove it, is also recommended for 48 h. Positioning in the postoperative period is also important. In patients with large ventricles, early mobilization may risk a subdural hemorrhage. In patients with high-resistance valves, deliberately placing

them in an upright posture may promote CSF drainage and prevent accumulation under the skin.

The postoperative hospital stay is typically 2 or 3 days. Prophylactic antibiotics are normally given intravenously preoperatively, and sometimes for only a few doses postoperatively. Prolonged antibiotic treatment in the postoperative period in an uncomplicated shunt patient is unwarranted. Shunted patients typically have immediate resolution of acute symptoms. In infants a sunken fontanelle with standard valves is typical. Low-pressure headache can occur in older patients, particularly if the hydrocephalus is long-standing. An initial postoperative CT or MRI study, unless there was some particular problem intraoperatively, is unlikely to be very helpful. Normally the patients are followed up approximately 3 months postoperatively, with a CT or MRI scan at this time, and at 1 year, with repeat imaging – the ventricles do not reach their final size until 1 year postoperatively on average, at least in children [108].

Ventriculopleural Shunts

Pleural shunts are a second choice to peritoneal. Contraindications include previous chest surgery and adhesions, active pulmonary disease including infection, and borderline pulmonary function where a significant pleural effusion might push the patient into respiratory failure. Infants are more likely to develop a significant effusion temporarily. The pleural space can be entered at a variety of sites. Along the anterior axillary line in the fourth to sixth interspace is often convenient. A muscle-splitting approach along the upper border of the rib (to avoid the neurovascular bundle) will reveal the translucent pleura and the lung moving with ventilation.

The pleura is opened sharply, like the peritoneum. There is no need to ask the anesthetist to collapse the lung; it will move away slightly as atmospheric pressure enters the chest cavity. The distal catheter is then introduced gently, being careful to guide it along the chest wall, not into the lung parenchyma. The catheter may need to be cut to length to avoid putting excess tubing, even allowing for growth, into the chest. There is no need to place a purse string suture, and a Valsalva maneuver by the anesthetist will inflate the lung adequately. Rapidly closing the muscles with a few sutures will avoid further air entry into the chest.

A small pneumothorax will be seen on the mandatory postoperative film. It will resolve over the next few days, while the CSF will usually accumulate as a small pleural effusion, especially in infants. These patients need to be monitored for any evidence of respiratory distress, and with serial chest X-rays [10, 94]. Usually the intrapleural fluid

disappears over the next several weeks. In patients in whom the pleural fluid progressively accumulates, leading to respiratory distress, with significant shift of the mediastinum, percutaneous drainage of the fluid and moving the distal tubing to another site is required.

Ventriculocardiac Shunts

Cardiac shunts are third choice amongst the distal sites, due to the serious complications of cor pulmonale and shunt nephritis [60, 64]. Catheter embolization is also a possibility. With growth the shunts tend to block as they pull out of the right atrium, so that a small child might need several revisions for growth-related failure. The shunt tip should lie in the superior vena cava just above the tricuspid valve. There are a number of ways of achieving this. Entrance to the jugular vein is usually achieved via the common facial vein, which is tied proximally and held with a stay suture distal to the venotomy site. The catheter is then advanced down the jugular vein into the superior vena cava, which is much easier to do on the right side. Percutaneous methods both into the jugular and subclavian vein have also been described [26]. Positioning the tip can be done under fluoroscopy, or even ultrasound [69, 99, 100, 103]. Fluoroscopy is useful as on occasion the catheter can be seen traveling out of the subclavian vein. Alternatively, one can use the tip of the catheter as an ECG lead and look for a change in P-wave polarity.

Shunt Revision

The surgery for shunt revision is not that different from an initial shunt insertion, but there are a few important points. Unless one is planning on removing the shunt for an infection, the patient should be prepped and draped as for a shunt insertion, including upper and lower incisions. This remains the case even when one strongly suspects one or other end of the shunt, since these suspicions can turn out to be wrong.

The present authors normally explore the upper end of the shunt first, since one can test both ends from the same location, and piecemeal replacement of the lower end from an abdominal site using connectors is to be discouraged. Once the skin is incised, cutting cautery can be used to expose the shunt hardware easily with minimal bleeding (Fig. 24). Care must be taken with burr hole reservoir systems, particularly where there is a tie on the ventricular catheter which resides below the pial

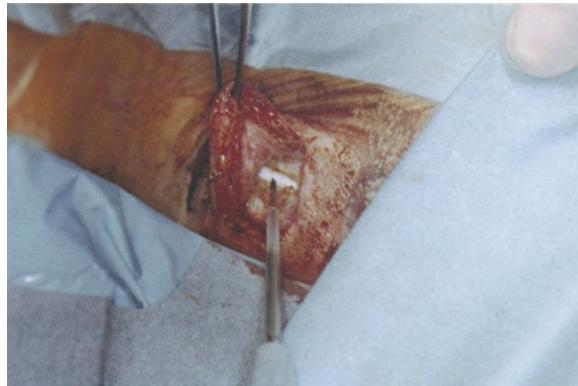


Fig. 24. Dissecting the shunt apparatus during a shunt revision with cutting cautery, which will not harm the Silastic material

surface. This becomes stuck, and it is easy to lose the catheter when it separates. These lost catheters are extremely difficult to find, and one should probably introduce a ventriculoscope into the ventricle, rather than searching blindly in the parenchyma. For this reason the authors rarely recommend burr hole systems. The equipment should then be inspected carefully for signs of damage, CSF egress, or infection.

Disconnecting the ventricular catheter from the valve will allow patency of the upper end to be determined, as well as the opportunity to take a CSF sample. Slow drops from the upper end often indicate an incomplete, but clinically significant ventricular catheter obstruction, as evidenced by the gush of high-pressure CSF when the catheter is replaced. If there is doubt, the catheter can be gently manipulated, or a manometer using clear silicone tubing and a straight connector attached, to demonstrate free to-and-fro flow.

The lower end is then tested by connecting the clear silicone tubing manometer to the valve and watching for spontaneous drainage. The distal system may need to be irrigated, but if flow is poor, the lower end should probably be explored. It is possible to re-open the same lower end incision, and using the cutting cautery, expose the tubing as well as its fibrous tract. Stay sutures on the tract allow the tubing to be removed from the abdomen, and then the same or a new catheter can be passed down the same tract, avoiding a separate laparotomy.

If the upper end of the shunt is the culprit, then the ventricular catheter should be gently removed and a new catheter introduced in rapid sequence, being careful not to lose too much CSF as the ventricles will collapse. The standard landmarks are again employed, but as with an initial shunt insertion, ultrasound, endoscopy, or stereotaxis can be employed

as aids. For preference the metal stylet should be used to direct the catheter, although with very small ventricles, sliding the limp catheter down the old tract may suffice. One has no control over the trajectory of the catheter without the stylet, and astonishing catheter positions can result.

If the ventricular catheter is stuck, gently rotating the catheter may free it. Otherwise the metal stylet can be advanced down the lumen to the tip and cautery applied to the metal stylet while rotating the ventricular catheter (Fig. 25) [101]. Badly stuck catheters should probably be left in place rather than produce a serious intraventricular hemorrhage. If hemorrhage does occur, manifested as frankly bloody CSF, the ventricle should be copiously irrigated with warm irrigation fluid. Failure of the CSF to clear should prompt placement of an external ventricular drain, and the shunt revision should be abandoned.

Lower-end obstruction is less common, and its cause should always be sought. Distal slit valves may accumulate debris, which forms a column inside the shunt, eventually blocking the slits. Unclogging the tip or just cutting it off may suffice. If the peritoneal catheter has fractured, or is too short, the authors would recommend replacing the entire aging system rather than piecing it together, as the latter may result in further disruption in short order. Connectors should not be placed anywhere along the path of the peritoneal catheter below the skull in growing children. They become adherent to the surrounding tissues, and the catheter breaks with growth. If there appears to be an outflow problem into the peritoneum, the catheter should be removed to another site rather than placing it down the same tract. If the problem is the valve, or if one is changing a valve onto the same peritoneal catheter, care should be taken when pulling the peritoneal catheter up into the wound and then

repassing it back down from above, since it is possible for the catheter to kink or coil out of site, impeding shunt flow. It is preferable to expose the valve rather than extract and reinsert blindly.

Management of the "Difficult Shunt Patient"

"Difficult shunt patients" seem to fall into two general categories. One category is patients with intractable symptoms, usually headache, where doubt about the functional status of the shunt exists [24, 53, 102]. The other is patients who present repeatedly with shunt malfunction for no apparent reason. Both can be exasperatingly difficult to manage. The patients often otherwise lead normal lives and are completely disabled or continuously in hospital with their shunt problem.

A detailed history including all the previous shunt surgeries is mandatory. Previous operating room notes from the hospitals where the surgery was done should be sought. The relevant imaging studies, which should be related to the patient's clinical status at the time they were obtained, should also be carefully studied. This whole process often requires creating a spreadsheet or log to keep track of the multiple interventions. All culture reports should also be sought, looking for an unrecognized or partially treated infection. A thorough physical exam, including the shunt equipment, follows. Current imaging should be complete, including plain X-rays of the shunt equipment.

In patients with chronic headache, a notion of whether the headache is postural can often be obtained by history. Other exacerbating and relieving symptoms as well as concomitant features should be sought. Determining the functional status of the shunt by pumping the reservoir is notoriously unreliable [77]. If the shunt's functional status is still uncertain by standard imaging, a flow study using a radioisotope or other contrast agent should be done. If the reservoir is above the valve, then reflux into the ventricles will confirm that the upper end is patent. Otherwise it may be more difficult to decide which end is blocked. Sitting the patient up or pumping the reservoir helps to see what effect these manipulations have on the shunt system. Collection of contrast in a localized cyst in the abdomen can also be seen with this technique and confirmed with ultrasound. It should be noted that these flow studies are not infallible, and both false-positive and false-negative results are possible.

If all information suggests the shunt is working, then intracranial pressure monitoring is usually the next step. Using a separate intraparenchymal probe is



Fig. 25. Applying cautery to the ventricular catheter stylet in order to free a stuck ventricular catheter

warranted since it will provide the most accurate information. The patient should be monitored for 48–72 h to ensure that prolonged periods of sleep and wakefulness in various postural positions are recorded. The patient or family should also keep a timed log to record any headaches, so that they can be related to the pressure recordings. Slightly negative intracranial pressure in the upright position is normal. In patients with symptomatic postural hypotension, large negative pressures associated with headache are what is sought. Patients with slit ventricle syndrome usually have plateau waves of 20 or 30 min with pressures frequently greater than 20 mmHg, and usually when asleep at night.

Patients with postural hypotension usually respond to placement of either a siphon-reducing device or a flow-limiting valve. Verification that both ends of the shunt are functioning properly at surgery is mandatory before replacing the valve. Leaving the pressure monitor in place for a few days will ensure that the new valve is functioning as expected. If the patient continues to have headache, the relationship to the new pressure profile can help to sort this out.

Patients with slit ventricle syndrome are more difficult deal with [20, 27, 34, 95, 109]. In patients in whom the pressure monitoring is normal or bears no relationship to headache, surgical restraint is wise. Assessment by a chronic pain or headache specialist team consisting of physicians, psychiatrists, or psychologists is important, particularly if the patients are dependent on narcotic analgesics. Various forms of psychotherapy may dramatically improve the patients' condition.

In patients with repetitive obstruction for no apparent reason, every search for a possible indolent infection should be sought, including anaerobic cultures. Encysted fluid collections in the abdominal cavity, even in the absence of positive cultures, strongly point to an infection. If there is any doubt, the whole shunt system, including any retained hardware (the exception being fragments in the chest wall not in communication with the abdomen) should be removed and an external drain placed. A new system should be placed at new sites both in the head and abdomen.

If there are repetitive proximal obstructions, the ventricular catheter may be traveling down a sheath of gliotic tissue to the same site, only to be re-plugged. Placing the ventricular catheter under ultrasound or endoscopic guidance into a completely different site (even the opposite ventricle) will get around this problem. If the patients have slit ventricles when the shunt is functioning, then changing the valve to a flow-limiting one may slightly expand the ventricles and possibly lead to a reduced rate of obstruction. Another possibility is to place a pro-

grammable shunt, so that the opening pressure can be changed once it is implanted [89]. Finally, particularly if the patient has a history of aqueduct stenosis, an endoscopic third ventriculostomy may render the patient shunt-free entirely, as discussed in chapters 25 and 26 [9].

References

- Aihara N, Takagi T, Hashimoto N, et al: Breakage of shunt devices (Sophys programmable pressure valve) following implantation in the hypochondriac region. *Child's Nerv Syst* 13:636–638, 1997
- Albright AL, Haines SJ, Taylor FH: Function of parietal and frontal shunts in childhood hydrocephalus. *J Neurosurg* 69:883–886, 1988
- Andersson H, Logren J: Hydrodynamic evaluation of shunt performance in hydrocephalus. *Dev Med Child Neurol Suppl* 4:30–34, 1968
- Aronyk KE: The history and classification of hydrocephalus. *Neurosurg Clin North Am* 4:599–609, 1993
- Aschoff A: Overdrainage and shunt technology. A critical comparison of programmable, hydrostatic and variable-resistance valves and flow-reducing devices. *Child's Nerv Syst* 11:193–202, 1995
- Aschoff A, Benesch C, Kremer P, et al: The solved and unsolved problems of hydrocephalus valves: A critical comment. *Advances in Neurosurgery*, vol 21. Springer, Berlin Heidelberg New York, pp 103–114, 1993
- Aschoff A, Kramer P, Benesch C, et al: Shunt technology and overdrainage – a critical review of hydrostatic, programmable and variable-resistance valves and flow-reducing devices. *Eur J Pediatr Surg* 1 Suppl 1:49–50, 1995
- Aschoff A, Benesch C, Kremer P, et al: Forty-four "programmable" valves in bench-test. *Child's Nerv Syst* 12:503, 1996
- Baskin JJ, Manwaring KH, Rekate HL: Ventricular shunt removal: the ultimate treatment of the slit ventricle syndrome. *J Neurosurg* 88:478–484, 1998
- Beach C, Manthey DE, et al: Tension hydrothorax due to ventriculopleural shunting. *J Emerg Med* 16:33–36, 1998
- Benesch C, Friese M, Aschoff A: Four year follow up study of 146 patients with programmable Medos Hakim valve shunt system. *Child's Nerv Syst* 10:475, 1994
- Belliard H, Roux FX, Turak B, et al: [The Codman Medos programmable shunt valve. Evaluation of 53 implantations in 50 patients]. *Neurochirurgie* 42:139–145, 1996
- Bierbauer KS, Storrs BB, McLone DG, et al: A prospective, randomized study of shunt function and infections as a function of shunt placement. *Pediatr Neurosurg* 16:287–291, 1990
- Black PM, Hakim R, Bailey NO: The use of the Codman-Medos Programmable Hakim valve in the management of patients with hydrocephalus: illustrative cases. *Neurosurg* 34:1110–1113, 1994
- Bondurant CP, Jimenez DF: Epidemiology of cerebrospinal fluid shunting. *Pediatr Neurosurg* 23:254–258; discussion 259, 1995
- Brownlee RD, Dold ON, Myles ST: Intraventricular hemorrhage complicating ventricular catheter revision: incidence and effect on shunt survival. *Pediatr Neurosurg* 22:315–320, 1995

17. Chambi I, Hendrick EB: A technique for removal of an adherent ventricular catheter. *Pediatr Neurosci* 14:216-217, 1988
18. Chidiac A, Pelissou-Guyotat I, Sindou M: [Practical value of transcutaneous pressure adjustable valves (Sophy SU 8) in the treatment of hydrocephalus and arachnoid cysts in adults (75 cases)]. *Neurochirurgie* 38:291-296, 1992
19. Christens-Barry WA, Guarnieri M, Carson BS: Fiberoptic delivery of laser energy to remove occlusions from ventricular shunts: technical report. *Neurosurgery* 44:345-350, 1999
20. Coker SB: Cyclic vomiting and the slit ventricle syndrome. *Pediatr Neurol* 3:297-299, 1987
21. Collins P, Hockley AD, Woollam DHM: Surface ultrastructure of tissues occluding ventricular catheters. *J Neurosurg* 48:609-613, 1978
22. Czosnyka M, Maksymowicz W, Batorski L: Comparison between classic-differential and automatic shunt functioning on the basis of infusion tests. *Acta Neurochir (Wien)* 106:1-8, 1990
23. Czosnyka M, Czosnyka Z, Whitehouse H, Pickard JD: Hydrodynamic properties of hydrocephalus shunts: United Kingdom Shunt Evaluation Laboratory. *J Neurol Neurosurg Psychiatry* 62:43-50, 1997
24. Dahlerup B, Gjerris F, Harmsen A: Severe headache as the only symptom of long-standing shunt dysfunction in hydrocephalic children with normal or slit ventricles revealed by computed tomography. *Child's Nerv Syst* 1:49-52, 1985
25. Davidoff LE: Treatment of hydrocephalus. *Arch Surg* 18:1737-1762, 1929
26. Decq P, Blanquet A, Yépez C: Percutaneous jugular placement of ventriculo-atrial shunts using a split sheath. Technical note. *Acta Neurochir* 136:92-4, 1995
27. Di Rocco C: Is the slit ventricle syndrome always a slit ventricle syndrome? *Child's Nerv Syst* 10:49-58, 1994
28. Drake JM, Sainte-Rose C: The shunt book. Blackwell Scientific, New York, 1995
29. Drake JM, da Silva MC, Rutka JT: Functional obstruction of an antisiphon device by raised tissue capsule pressure. *Neurosurgery* 32:137-139, 1993
30. Drake JM, Tenti G, Sivaloganathan S: Computer modeling of siphoning for CSF shunt design evaluation. *Pediatr Neurosurg* 21:6-15, 1994
31. Drake JM, Kestle J: Rationale and methodology of the multicenter pediatric cerebrospinal fluid shunt design trial. Pediatric Hydrocephalus Treatment Evaluation Group. *Child's Nerv Syst* 12:434-447, 1996
32. Drake JM, Kestle J: Determining the best cerebrospinal fluid shunt valve design: the pediatric valve design trial. *Neurosurgery* 38:604-607, 1996
33. Drake JM, Kestle J, Milner R, et al: Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery* 43:294-305, 1998
34. Epstein F, Lapras C, Wisoff JH: 'Slit-ventricle syndrome': etiology and treatment. *Pediatr Neurosci* 14:5-10, 1988
35. Foltz EL, Blanks J: Symptomatic low intracranial pressure in shunted hydrocephalus. *J Neurosurg* 68:401-408, 1988
36. Fox JL, McCullough DC, Green RC: Effect of cerebrospinal fluid shunts on intracranial pressure and on cerebrospinal fluid dynamics. 2. A new technique of pressure measurements: results and concepts. 3. A concept of hydrocephalus. *J Neurol Neurosurg Psychiatry* 36:302-312, 1973
37. Fox JL, Portnoy HD, Shulte RR: Cerebrospinal fluid shunts: an experimental evaluation of flow rates and pressure values in the anti-siphon valve. *Surg Neurol* 1:299-302, 1973
38. Fuse T, Takagi T, Fukushima T, et al: [Problems encountered with a programmable pressure valve (SOPHY) positioned in the chest wall]. *No Shinkei Geka* 24:41-5, 1996
39. Ginsberg HJ, Drake J, Cobbold RSC: Ventriculoperitoneal shunt flow dependency on the number of patent holes in a ventricular catheter. *Pediatr Neurosurg* 33:7-11, 2000
40. Gruber R, Jenny P, Herzog B: Experiences with the anti-siphon device (ASD) in shunt therapy of pediatric hydrocephalus. *J Neurosurg* 61:156-162, 1984
41. Guinane JE: An equivalent circuit analysis of cerebrospinal fluid hydrodynamics. *Am J Physiol* 223:425-430, 1972
42. Haase J, Weeth R: Multiflanged ventricular catheter for hydrocephalic shunts. *Acta Neurochir (Wien)* 33:213-218, 1976
43. Hakim S: Flow through CSF shunts. *J Neurosurg* 39:127-128, 1973
44. Hakim S: Hydraulic and mechanical mis-matching of valve shunts in the treatment of hydrocephalus. The need for a servo-valve shunt. *Dev Med Child Neurol* 15:646-653, 1973
45. Hakim S, Venegas JG, Burton JD: The physics of the cranial cavity, hydrocephalus and normal pressure hydrocephalus: mechanical interpretation and mathematical model. *Surg Neurol* 5:187-210, 1976
46. Hakim S, Hakim C: A biomechanical model of hydrocephalus and its relationship to treatment. In: Shapiro K, Marmarou A, Portnoy HD (eds) *Hydrocephalus*. Raven, New York, 1984
47. Hoffman HJ: Technical problems in shunts. *Monogr Neural Sci* 8:158-169, 1982
48. Holness RO, Hoffman HJ, Hendrick EB: Subtemporal decompression for the slit-ventricle syndrome after shunting in hydrocephalic children. *Child's Brain* 5:137-144, 1979
49. Hoppe-Hirsch E, Laroussinie F, Brunet L, et al: Late outcome of the surgical treatment of hydrocephalus. *Child's Nerv Syst* 14:97-99, 1998
50. Horgan MA, Piatt JH Jr: Shaving of the scalp may increase the rate of infection in CSF shunt surgery. *Pediatr Neurosurg* 26:180-184, 1997
51. Hudgins RJ, Boydston WR: Shunt revision by coagulation with retention of the ventricular catheter. *Pediatr Neurosurg* 29:57-59, 1998
52. Hyde-Rowan MD, Rekate H, Nulsen FE: Reexpansion of previously collapsed ventricles: the slit ventricle syndrome. *J Neurosurg* 56:536-539, 1982
53. James HE, Nowak TP: Clinical course and diagnosis of migraine headaches in hydrocephalic children. *Pediatr Neurosurg* 17:310-316, 1991
54. Kadawaki C, Hara M, Numoto M, et al: Factors affecting cerebrospinal fluid flow in a shunt. *Br J Neurosurg* 1:467-475, 1987
55. Kadawaki C, Hara M, Numoto M, et al: CSF shunt physics: factors influencing shunt CSF flow. *Child's Nerv Syst* 11:203-206, 1995
56. Kaufman B, Weiss MH, Young HF, et al: Effects of prolonged cerebrospinal fluid shunting on the skull and brain. *J Neurosurg* 38:288-297, 1973
57. Kausch W: Die Behandlung des Hydrocephalus der kleinen Kinder. *Arch Klin Chir* 87:709-796, 1908
58. Kellie G: An account ... with some reflections on the pathology of the brain. *Edin Med Chir Soc Trans* 1:84-169, 1824

59. Kremer P, Aschoff A, Kunze S: Therapeutic risks of anti-siphon devices. *Eur J Pediatr Surg* 1 Suppl 1:47-48, 1991
60. Lam CH, Villemure JG: Comparison between ventriculoatrial and ventriculoperitoneal shunting in the adult population. *Br J Neurosurgery* 11:43-48, 1997
61. Langley JM, LeBlanc JC, Drake J, et al: Efficacy of antimicrobial prophylaxis in placement of cerebrospinal fluid shunts: meta-analysis. *Clin Infect Dis* 17:98-103, 1993
62. Loop JE, Foltz EL: Craniostenosis and diploic lamination following operation for hydrocephalus. *Acta Radiol [Diagn]* 13:8-13, 1972
63. Lumenta CB, Roosen N, Dietrich U: Clinical experience with a pressure-adjustable valve SOPHY in the management of hydrocephalus. *Child's Nerv Syst* 6:270-274, 1990
64. Lundar T, Langmoen IA, Hovind KH: Fatal cardiopulmonary complications in children treated with ventriculoatrial shunts. *Child's Nerv Syst* 7:215-217, 1991
65. Marmarou A, Shulman K, Rosende RM: A nonlinear analysis of the cerebrospinal fluid system and intracranial pressure dynamics. *J Neurosurg* 48:332-344, 1978
66. Martins AN: Resistance to drainage of cerebrospinal fluid: clinical measurement and significance. *J Neuro* 36:313-318, 1973
67. McCullough DC, Fox JL: Negative intracranial pressure hydrocephalus in adults with shunts and its relationship to the production of subdural hematoma. *J Neurosurg* 40:372-375, 1974
68. McCullough DC: Symptomatic progressive ventriculomegaly in hydrocephalics with patent shunts and anti-siphon devices. *Neurosurgery* 19:617-621, 1986
69. McGrail KM, Muzzi DA, Losasso TJ, et al: Ventriculoatrial shunt distal catheter placement using transesophageal echocardiography: technical note [see comments]. *Neurosurgery* 30:747-749, 1992
70. Miyake H, Ohta T, Kajimoto Y, et al: A new ventriculoperitoneal shunt with a telemetric intracranial pressure sensor: clinical experience in 94 patients with hydrocephalus. *Neurosurgery* 40:931-935, 1997
71. Munro A: Observations on the structure and functions of the nervous system. Edinburgh, 1783
72. Nagashima T, Tanaki N, Matsumoto S, et al: Biomechanics of hydrocephalus. *Neurosurgery* 21:898-904, 1987
73. Nulsen FE, Spitz EB: Treatment of hydrocephalus by direct shunt from ventricle to jugular vein. *Surg Forum* 2:399-403, 1952
74. Ortler M, Kostron H, Felber S: Transcutaneous pressure-adjustable valves and magnetic resonance imaging: an ex vivo examination of the Codman-Medos programmable valve and the Sophy adjustable pressure valve. *Neurosurgery* 40:1050-1057, 1997
75. Pattisapu JV, Trumble ER, Taylor KR, et al: Percutaneous endoscopic recanalization of catheter: a new technique of proximal shunt revision. *Neurosurgery* 45:1361-1366, 1999
76. Pena A, Bolton MD, Whitehouse H, et al: Effects of brain ventricular shape on periventricular biomechanics: a finite-element analysis. *Neurosurgery* 45:107-116, 1999
77. Piatt JH, Jr.: Pumping the shunt revisited. A longitudinal study. *Pediatr Neurosurg* 25:73-76, 1996
78. Pollack IF, Albright AL, Adelson PD, et al: A randomized, controlled study of a programmable shunt valve versus a conventional valve for patients with hydrocephalus. *Neurosurgery* 45:1388-1408, 1999
79. Portnoy HD, Schulte RR, Fox JL, et al: Anti-siphon and reversible occlusion valves for shunting in hydrocephalus and preventing post-shunt subdural hematomas. *J Neurosurg* 38:729-738, 1973
80. Portnoy HD, Tripp L, Croissant PD: Hydrodynamics of shunt valves. *Child's Brain* 2:242-256, 1976
81. Portnoy HD, Croissant PD: A practical method for measuring hydrodynamics of cerebrospinal fluid. *Surg Neurol* 5:273-277, 1976
82. Portnoy HD: Hydrodynamics of shunts. *Monogr Neural Sci* 8:179-183, 1982
83. Portnoy HD, Amirjamshidi A, Hoffman HJ, et al: Shunts: which one, and why? *Surg Neurol* 49:8-13, 1998
84. Post EM: Currently available shunt systems: a review. *Neurosurgery* 16:257-260, 1985
85. Pudenz RH: The surgical treatment of hydrocephalus – an historical review. *Surg Neurol* 15:15-26, 1981
86. Pudenz RH, Foltz EL: Hydrocephalus: overdrainage by ventricular shunts. A review and recommendations. *Surg Neurol* 35:200-212, 1991
87. Rayport M, Reiss J: Hydrodynamic properties of certain shunt assemblies for the treatment of hydrocephalus. 1. Report of a case of communicating hydrocephalus with increased cerebrospinal fluid production treated by duplication of shunting device. 2. Pressure-flow characteristics of the Spitz-Holter, Pudenz-Heyer, and Cordis-Hakim shunt systems. *J Neurosurg* 30:455-467, 1969
88. Reinprecht A, Dietrich W, Bertalanffy A, et al: The Medos Hakim programmable valve in the treatment of pediatric hydrocephalus. *Child's Nerv Syst* 13:588-593, 1997
89. Reinprecht A, Dietrich W, Bertalanffy A, et al: The Medos Hakim programmable valve in the treatment of pediatric hydrocephalus. *Child's Nervous System* 13:588-593; discussion 593-594, 1997
90. Sainte-Rose C, Hooven MD, Hirsch JF: A new approach to the treatment of hydrocephalus. *J Neurosurg* 66:213-226, 1987
91. Sainte-Rose C, Hoffman HJ, Hirsch JF: Shunt failure. *Concepts Pediatr Neurosurg* 9:7-20, 1989
92. Sainte-Rose C, Piatt JH, Renier D, et al: Mechanical complications in shunts. *Pediatr Neurosurg* 17:2-9, 1991
93. Sainte-Rose C: Shunt obstruction: a preventable complication? *Pediatr Neurosurg* 19:156-164, 1993
94. Sanders DY, Summers R, DeRouen L: Symptomatic pleural collection of cerebrospinal fluid caused by a ventriculopleural shunt. *South Med J* 90:345-346, 1997
95. Sgouros S, Malluci C, Walsh AR, et al: Long-term complications of hydrocephalus. *Pediatr Neurosurg* 23:127-132, 1995
96. Shapiro K, Marmarou A, Shulman K: Characterization of clinical CSF dynamics and neural axis compliance using the pressure-volume index: I. The normal pressure-volume index. *Ann Neurol* 7:508-514, 1979
97. Shapiro K, Marmarou A: Clinical applications of the pressure-volume index in treatment of pediatric head injuries. *J Neurosurg* 56:819-825, 1982
98. Shapiro K, Fried A: The theoretical requirements of shunt design as determined by biomechanical testing in pediatric hydrocephalus. *Child's Nerv Syst* 4:348-353, 1998
99. Shulman K, Marmarou A: Pressure-volume considerations in infantile hydrocephalus. *Dev Med Child Neurol* 13(Suppl 25):90-95, 1971
100. Spertell RB: The response of brain to transient elevations in intraventricular pressure. *J Neurol Sci* 48:343-352, 1980

101. Steinbok P, Cochrane DD: Shunt removal by choroid plexus coagulation [letter; comment]. *J Neurosurg* 85:981; discussion 982-983, 1996
102. Stellman-Ward GR, Bannister CM, Lewis MA, et al: The incidence of chronic headache in children with shunted hydrocephalus. *Eur J Pediatr Surg* 7:12-14, 1997
103. Szczerbicki MR, Michalak M: Echocardiographic placement of cardiac tube in ventriculoatrial shunt. Technical note. *J Neurosurg* 85:723-4, 1996
104. Tenti G, Sivaloganathan S, Drake J: Brain biomechanics: steady-state consolidation theory of hydrocephalus. *Can Appl Mathem Q* 94:243-266, 1998
105. Tokoro K, Chiba Y: Optimum position for an anti-siphon device in a cerebrospinal fluid shunt system. *Neurosurgery* 29:519-525, 1991
106. Trost HA, Heissler HE, Claussen G, et al: Testing the hydrocephalus shunt valve: long-term bench test results of various new and explanted valves. The need for model for testing valves under physiological conditions. *Eur J Pediatr Surg* 1:38-40, 1991
107. Tuli S, O'Hayon B, Drake JM, et al: Change in ventricular size and effect of ventricular catheter placement in pediatric shunted hydrocephalus. *Neurosurgery* 45:1329-1333, 1999
108. Ventureyra EC, Higgins MJ: A new ventricular catheter for the prevention and treatment of proximal obstruction in cerebrospinal fluid shunts. *Neurosurgery* 34:924-926, 1994
109. Walker ML, Fried A, Petronio J: Diagnosis and treatment of the slit ventricle syndrome. *Neurosurg Clin North Am* 4:707-714, 1993
110. Watts C, Keith HD: Testing the hydrocephalus shunt valve. *Child's Brain* 10:217-228, 1983
111. Will BE, Moller-Korbsch U, Bucholz R: Experience with the programmable Sophy SU-8 valve. *Child's Nerv Syst* 10:476, 1994
112. Yamada S: Dynamic changes of cerebral spinal fluid in upright and recumbent shunted experimental animals. *Child's Brain* 1:187-192, 1975

Abdominal Complications of Peritoneal Shunts

MATTHIEU VINCHON, PATRICK DHELEMME

Introduction

The prognosis of hydrocephalus changed dramatically when shunts were introduced during the second half of the last century. Following the experience with atrial shunts, the peritoneum has become the most popular site for distal catheter implantation. Comparing these two main sites, some authors noticed that, although peritoneal shunts did not have fewer complications than atrial shunts, these complications were less severe and carried a decidedly lower mortality [37]. The risk of sudden death due to pulmonary embolism, in particular, makes the atrial catheter a less attractive option than the peritoneal catheter [6]. Also, the length of the catheter is limited in atrial shunts, whereas it is not in peritoneal shunts; in children, the number of elective revisions required to lengthen atrial catheters is forbidding [60].

Although the peritoneum has definite advantages over the atrium, it is not immune to specific complications. Peritoneal insertion of the catheter brings the silicon – which is a “no-go” zone for the immune system – into contact with the bowels, which harbor potentially aggressive flora. The absorptive capacities of the peritoneum can be limited in premature infants or in patients with liver or heart disease. Furthermore, neurosurgeons do not have a monopoly in entering the abdominal space. A significant part of the population, including shunted patients, require some form of abdominal surgery at some time in their lives, the most common being appendicitis, and, in women of child-

bearing age, cesarean section. In addition, hydrocephalus is often part of a more complex problem, such as spina bifida, cerebral palsy, or other causes of severe infantile brain damage, and these patients may require abdominal surgery more often than the rest of the population.

It is increasingly recognized that abdominal problems represent a sizable number of complications specifically associated with peritoneal shunts and require special attention from clinicians dealing with shunted patients [16, 55]. Some of these complications, including appendicitis or gynecological disorders, relate to the influence of abdominal conditions on the shunt. Another group of abdominal complications, such as hernias, hydroceles, peritoneal pseudocysts, lost distal catheters, or bowel perforations, result from abdominal disturbances provoked by the presence of the shunt. Finally, some complications like ascites result from the incompatibility between abdominal problems and CSF shunting. As we shall see, only the latter condition is an absolute and generally definitive contraindication to peritoneal shunting.

In this chapter, we shall review present knowledge concerning the different types of abdominal complication and try to define guidelines for their diagnosis and treatment. This review is based on data from the literature and on a personal database of 1564 pediatric patients harboring a shunt with a peritoneal catheter who were followed at our institution for a mean period of 10.7 years. The main abdominal complications encountered in our series are summarized in Table 1.

Table 1. Summary of the main abdominal complications and operations in patients with a peritoneal shunt in the authors' experience

Diagnosis	Number of cases	Age (years) (95% CI)	Cause	Clinical presentation	External drainage	Atrial shunt	Peritoneum reused	Mortality (cause)
Ascites	13	3.4 (1.6)	Infection 2, tumor 4, overproduction 2	Abdominal 9, raised ICP 1, infection 3	4/13	13/13	2/12	2 (tumor)
Pseudocyst	36	12.2 (1.9)	Infection 15, aseptic 21	Abdominal 21, raised ICP 12, infection 6	17/36	11/36	25/36	1 (chicken pox)
Bowel perforation	13	9.1 (4.7)	Peroperative 1, late ulceration 12	Abdominal 3, raised ICP 1, infection 8, nephritis 1	12/13	1/13	12/13	2 (shunt infection)
Appendicitis	47	9.9 (1.5)	Appendicitis 33, raised ICP 4*	Appendicitis 34, peritonitis 13	15/47	6/47	36/46	2 (shunt infection)
Hernias and hydroceles	3	23.1 (1.7)	Hydrocele 12, inguinal hernia 22, umbilical 2, crural 1	Requiring surgery: 24/32	0	1/32	31/32	1 (sudden death)

* Four patients had intracranial hypertension due to shunt failure, initially mistaken for appendicitis, and underwent unnecessary appendectomy

Epidemiology

The incidence of shunt-related abdominal complications (SRAC) is variously estimated. Some authors have reported an incidence of 13% in 300 consecutive patients, who were followed for an unspecified period of time [55]. However, since SRAC can occur many

years after shunt insertion, only actuarial data can be reliable. In our experience, 228 abdominal complications occurred during 16 689 years of follow-up, representing an annual incidence of 1.37%. The actuarial incidence of SRAC is represented in Fig. 1. This figure also shows that these complications may occur very late after shunt insertion and should be considered a permanent threat to shunted patients. Many of these abdominal complications are infectious and may cause death if diagnosis and treatment are delayed, especially in debilitated children. In our series, four patients died as a result of SRAC, representing 1.6% of overall mortality, and 2.7% of non-tumor-related mortality in our patients.

The age distribution shows two peaks, one in infants, who have a high incidence of ascites or abdominal hernias, and one in older children, who are more vulnerable to appendicitis (Fig. 2). However, these complications could occur at any age, and it is possible that the lower incidence in the older patients reflects lacunae in our data on grown-up children.

All types of hydrocephalus can cause SRAC, and the cause of hydrocephalus often does not bear a relation to the incidence of SRAC (Fig. 3). In our experience, the incidence of SRAC was significantly lower in tumoral hydrocephalus and significantly higher in postinfectious and communicating hydrocephalus, probably because these patients undergo shunting earlier and have a longer life expectancy. Surprisingly, the incidence of SRAC was lower (but not significantly) in the spina bifida group, in spite of the great number of urinary infections and abdominal surgeries in this group.

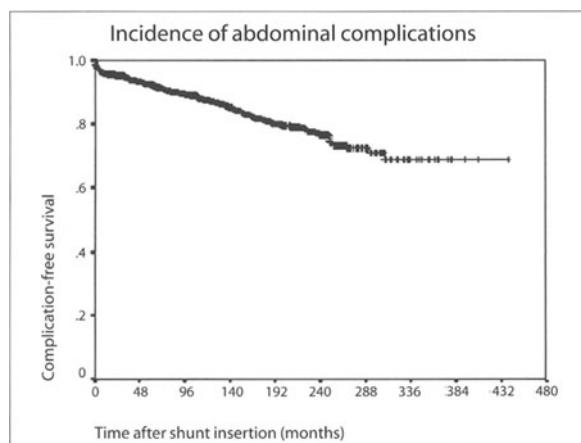


Fig. 1. Cumulated incidence of abdominal complications in the shunted population. We found the incidence of new cases to be 1.37% per year. In this retrospective study, survival analysis may overestimate the real incidence, because many patients who were lost to follow-up attended again because of the abdominal problem. The figure shows that abdominal complications may occur more than 20 years after shunt insertion, which means that shunted patients are at risk throughout their life

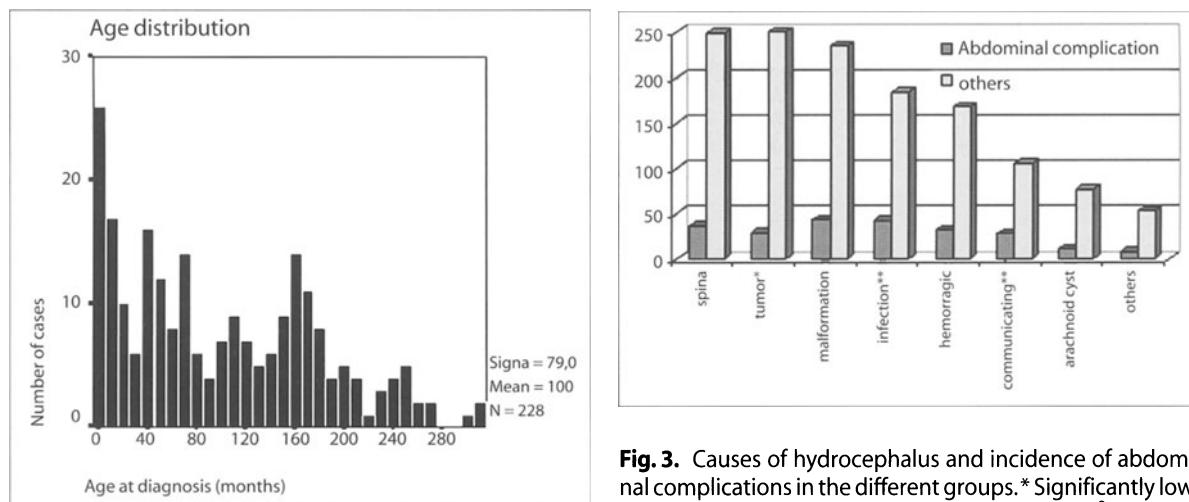


Fig. 3. Causes of hydrocephalus and incidence of abdominal complications in the different groups.* Significantly lower incidence; ** significantly higher incidence (χ^2 test). The lower incidence of abdominal complications in tumoral hydrocephalus may relate to the older age of these patients, and a shorter life expectancy in this group, which accounts for the highest mortality in hydrocephalus. The higher incidence in the communicating and postinfectious groups may relate to these same factors in the opposite direction

Surgical Management of Abdominal Complications in Shunted Patients

We present in Fig. 4 a schematic approach toward abdominal problems in shunted patients. The em-

phasis is on the interrelation between abdominal and neurological diagnoses and treatments. The first step is to decide whether a given patient with a peritoneal shunt has symptoms relating to intracranial hypertension, an abdominal problem, or requires expertise from both sides. The subsequent

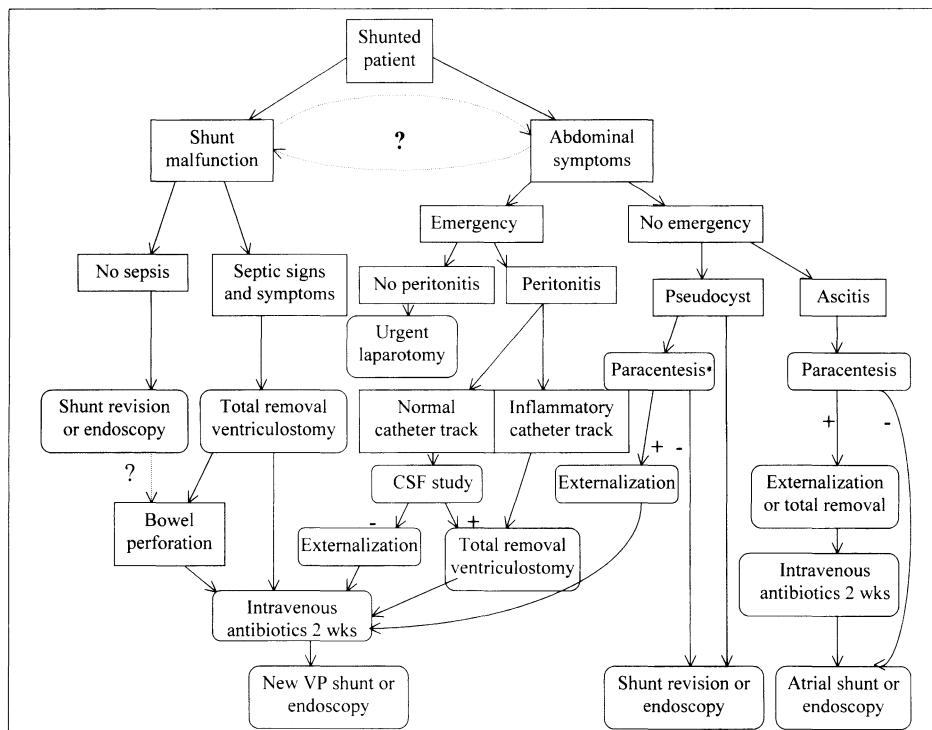


Fig. 4. Algorithm for diagnosis (square boxes) and investigation and treatment (rounded boxes) in shunted patients. The conclusion of any episode is a new shunt or an endoscopic procedure, with the exception of an acute abdomen without peritonitis, which does not require modification of the shunt system

steps depend on the clinical severity, the presence of infectious signs and symptoms, and the radiological and biological findings. The treatment should be adapted in accordance with the most frequently observed clinical pictures, which are discussed below.

Appendicitis

Appendicitis is a very common disease in the pediatric population and does generally not have any consequence for the peritoneal catheter unless complicated by peritonitis. The rate of appendiceal perforation is higher in young children and in the elderly; some authors have reported that perforation complicated as many as 40% of cases of appendicitis in children under the age of five [1] and 67% under the age of four [30]. In our experience, appendicitis was complicated by peritonitis in 13/47 cases (28%). In case of ruptured appendicitis with peritonitis, the catheter is contaminated, but the cerebrospinal fluid (CSF) is often not [25, 50]; the treatment of infection therefore does not require antibiotics that pass through the blood-brain barrier. However, shunt infection cannot be cured if the contaminated material is not removed, and treatment will require withdrawal of the peritoneal catheter and temporary external drainage [49].

The annual incidence of appendicitis in the general population varies between 1.84‰ and 1.04‰, and is reported to be decreasing for unclear reasons, possibly involving rising food and hygiene standards, and higher accuracy of medical diagnosis [46, 63]. The incidence is higher in children than in adults [1]. Some authors have reported a prevalence of 0.67% of shunted patients presenting with appendicitis [55]. In our experience, among 1564 shunted patients, 47 (3.0%) had appendicitis during a mean 10.7-year follow-up, giving an annual incidence of 2.8‰, which is in agreement with other series in the literature [46].

The diagnosis of appendicitis is difficult and fraught with error, all the more in children, and many surgeons resort to overoperating in order not to miss this benign condition with potentially life-threatening complications. In shunted patients, with shunt-aware parents, an additional risk is that abdominal symptoms are mistaken for shunt obstruction, leading to delays in the diagnosis of acute appendicitis and a higher risk of ruptured appendicitis [49]. Conversely, small children with intracranial hypertension often complain of abdominal pain, and if vomiting is associated, may be mistakenly operated on for appendicitis. In addition, peritoneal reaction around the catheter may present as an inflammatory mass and mimic ap-

pendicitis [34]. Four such patients have been referred to us for shunt failure having undergone unnecessary appendectomy. These possible diagnostic errors must be well known both by pediatric surgeons and by neurosurgeons. From the neurosurgeon's standpoint, the preponderance of vomiting over neurological symptoms, abdominal tenderness, and elevated polymorphonuclear leukocytes should prompt one to seek advice from visceral colleagues in emergency.

Uncomplicated appendicitis generally does not cause shunt infection, and we do not advise referring shunted patients for neurosurgery for simple appendicitis. Occasionally, the abdominal surgeon will see the catheter in the operating field: even in this case, we do not recommend externalization of the catheter. It is important, however, to advise abdominal surgeons that shunted children should be followed closely after uncomplicated appendicitis, because vague abdominal symptoms following appendectomy may herald slow-burning peritoneal infection, as occurred in two of our cases.

By contrast, in the case of ruptured appendicitis, shunt removal is mandatory. We consider that peritonitis can only be cured with catheter externalization, external drainage, and intravenous antibiotics for 2 weeks, followed by total shunt removal and new shunt insertion. The availability of the peritoneum for new shunt insertion immediately after peritonitis depends on the presence of abdominal drains, unhealed wounds, and the digestive transit. In five of our cases, an atrial shunt was preferred; in two of these, the shunt could be returned to the peritoneum after a subsequent episode of shunt failure (Fig. 5).

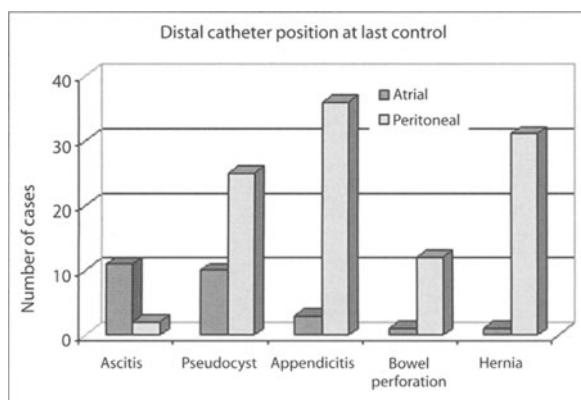


Fig. 5. Distal catheter position at last follow-up after the various abdominal complications. Many patients had a temporary atrial shunt, changed back to peritoneal during a subsequent shunt revision. The peritoneum was reusable after the majority of abdominal complications, but not after ascites, which appeared to reflect definitive peritoneal incompetence

Three shunted patients presenting with appendiceal peritonitis were not referred to us immediately: two were cured without shunt removal, but the third developed late shunt infection several years after apparent cure with the shunt left in place. These cases underline the need to provide abdominal surgeons with information on these interconnected diseases.

Appendiceal peritonitis is a serious condition, which when it occurs in debilitated patients can be devastating. In shunted children, death from appendicitis has been reported [25], and in our series, too, two patients died of recurrent shunt infection after appendiceal peritonitis. The consensus however is that prophylactic appendectomy is not justified [1], and we think that the presence of the shunt is an additional reason to avoid unnecessary abdominal surgery. Another reason to leave a healthy appendix in place is its potential usefulness for reconstructive cystostomy in patients with myelomeningocele [49].

Peritoneal Pseudocyst

Peritoneal pseudocysts (PPC) are wall-less peritoneal collections accumulating when the bowels are matted together in reaction to inflammatory or infectious processes [39, 43]. Histologically, the cyst is sealed by fibrosis and not by a mesothelial membrane [35, 57]. It may form because of aseptic inflammation related to repeated shunt revisions and abdominal surgery [26], although the latter might as

well be interpreted as the cause of germ inoculation. The resulting inflammatory reaction coats the catheter and may cause distal obstruction and raised intracranial pressure [65]. Many PPCs are infected, from the beginning or when they recur [33]; some authors even consider that all PPCs are infected [18], because cultures can remain negative in the case of a slow-growing or demanding germ. In infected PPCs, the cultures generally grow *Staphylococcus epidermidis* or diphtheroids, suggesting intraoperative contamination [2, 5, 18]. Aseptic PPCs do exist, however, as attested by many PPCs in our experience enduringly cured by simple repositioning of the peritoneal catheter. In aseptic cases, the formation of a PPC has been attributed to inflammatory reactions to surgical material or talc [52]. To complicate this issue further, in a few cases secondary infection of an aseptic collection has been documented [22]. In one of our cases, a small collection was left untouched for several years until acute infection broke out. Similar findings have been reported before [16], and could be an incentive to treat asymptomatic PPCs.

In a previous study, we estimated the incidence of PPC at 1% of shunted patients [35]. Our updated data show a more precise figure of 2.3% of the shunted patients, with an annual incidence of 2.2%. Some authors consider that premature infants are particularly at risk of developing a PPC [43], but this was not apparent in our study (Table 2).

Abdominal collections should be searched for during systematic outpatient follow-up visits, especially when the patient complains of vague abdominal pain. In most series, patients with a PPC are admitted pre-

Table 2. Avoidance and treatment of the different abdominal complications associated with peritoneal catheters

Complication	Avoidance	Treatment
Appendicitis Peritonitis	None Early diagnosis and appendectomy	Appendectomy External drainage and shunt replacement
Aseptic pseudocyst Infected pseudocyst	None Treatment of asymptomatic cysts	Catheter repositioning External drainage and shunt replacement
Ascites	Endoscopy for tumoral hydrocephalus	Atrial shunt
Operative perforation	Visual control of peritoneal opening	Laparotomy, external drainage and shunt replacement
Late perforation	Nonmetallic catheters, removal of unnecessary catheters	External drainage and shunt replacement
Hernia	None	Elective surgery; emergency surgery when ovary or catheter in the hernia
Lost catheter	Avoid connectors. Place enough catheter to allow full growth. Use striped catheters	Removal when revision is indicated. Do not lengthen catheter: change the whole system

dominantly because of abdominal signs and symptoms [3, 26], isolated or in association with symptoms of raised intracranial pressure [20]. Occasionally, hepatic enzymes will be elevated [33]. The diagnosis is especially difficult in patients with cerebral palsy, because symptoms are degraded [28]. PPCs are often asymptomatic, and in a number of cases of shunt malfunction, systematic abdominal ultrasonography may disclose an asymptomatic PPC [57]. The diagnosis is easily made on inspection, palpation, and percussion, and confirmed by plain X-rays (Fig. 6), abdominal ultrasonography, and CT (Fig. 7). Typically, the gaseous radiolucencies are pushed to the periphery by a dense rounded mass [65]; the catheter is found coiled inside the cyst and shows no mobility on seriated X-rays.

The next step of the diagnosis is to decide whether the cyst is infected or not. In our experience, 77% of aseptic PPCs presented with abdominal symptoms, and one-third of the patients had raised intracranial pressure; by contrast, in infected PPCs, only one-third had abdominal symptoms, another third had raised intracranial pressure, but only 40% had symptoms of local or general infection. According to Roitberg et al., in cases of PPC, an age below 4 years or shunt or abdominal surgery during the previous year were good



Fig. 6. Plain X-ray, anteroposterior view, showing a hyperdense mass in the left hypochondriac region, with mass effect on the colic gaseous radiolucencies. This pseudocyst occurred 2 years after a previous shunt revision and was aseptic. The distal catheter was simply repositioned in another peritoneal location. The shunt was revised again 4 years later, but has not posed any problem for 4 years

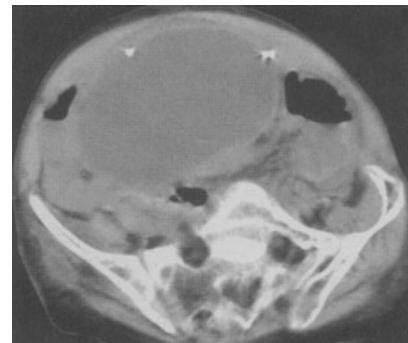


Fig. 7. A 17-year-old female with Aicardi syndrome, bedridden and requiring feeding with a jejunostomy. A few months after local suppuration of the wound around the feeding catheter, she presented with low-grade fever, abdominal swelling, altered general status, and raised intracranial pressure. The abdominal CT scan shows a prominent peritoneal pseudocyst. She underwent emergent laparotomy and catheter externalization. The fluid grew *Staphylococcus aureus*. After 2 weeks of intravenous antibiotics and shunt removal, a new shunt was inserted, with the distal catheter in the atrium because of multiple abdominal scarring and unhealed abdominal wounds

predictors of infection [52]. In our series, too, the interval since last shunt surgery was significantly longer in the case of aseptic PPC (42.2 months) than infected PPC (12.1 months), suggesting that bacterial inoculation occurred during surgery. The patient's age and a history of abdominal surgery did not appear to have any predictive value in our experience.

It is most important to ascertain whether the cyst is aseptic or not, because the treatment for each is radically different. If the cyst is aseptic, simple repositioning of the peritoneal catheter and siphoning of the collection is enough to cure it [20, 33], whereas an infected PPC requires externalization, a course of intravenous antibiotics, total shunt removal, and insertion of a new shunt. Earlier authors recommended avoiding peritoneal drainage after treatment for pseudocyst [5, 14]. In our experience, it was possible to place the distal catheter in another peritoneal site without difficulty in most cases. In our experience, treatment was inadequate because of unrecognized infection in six patients, leading to recurrent infection. Overall, the cysts recurred in seven patients (up to three times), all of these eventually requiring atrial shunting. We therefore advise close follow-up in the outpatient clinic and repeated abdominal ultrasonography after treatment of PPC.

Ascites

Ascites is the accumulation of freely circulating fluid in the peritoneal cavity, and should be distinguished

from the more common pseudocyst [65]; this distinction is not always clear in the literature. Ascites is the consequence of failure of the peritoneum to absorb CSF at a rate equivalent to its production [14]. The developed surface of the peritoneum is considered as roughly equivalent to the body surface, independently of age. Once in the abdominal cavity, the CSF is absorbed through the peritoneum by suprahepatic lymphatic vessels and returned to the venous circulation [19]. In premature infants, the available surface is smaller, but so is the amount of fluid to be absorbed, evaluated at 23 ml a day on average, in linear correlation with body weight [11]. Under normal conditions, the absorptive capacities of the peritoneum are sufficient to cope with the production of CSF. CSF absorption can fall short of this only in the exceptional cases of CSF overproduction (choroid plexus tumors or villous hypertrophy) [4] or diminished absorptive capacities. Absorption may be impaired because of the protein content of the CSF, in tumoral hydrocephalus, especially in the case of pilocytic astrocytoma [62], because of peritoneal scarring [15, 19] or elevated pressure in the venous system. In the shunted population, elevated pressure in the inferior vena cava can result from cor pulmonale associated with scoliosis, notably in patients with myelomeningocele. Ascites related to brain tumor may be associated with metastatic dissemination or may not. This complication can be treated and cured with chemotherapy [51]. In a number of cases, ascites can be infected, either primarily, or secondarily, due to colonization by a blood-borne pathogen or a germ inoculated at surgery [65]. According to Gaskill and Marlin, these represent as many as 15% of cases of CSF ascites; the germs are mainly *Staphylococcus*, *Pneumococcus*, *Haemophilus*, and *Pseudomonas*, suggesting blood-borne contamination [22].

Ascites is a rare complication of peritoneal shunt, and it has almost disappeared from our practice since endoscopic procedures became the first choice for the treatment of tumoral hydrocephalus and chemotherapy gained widespread indications for pilocytic tumors. In our experience, the age at diagnosis was significantly lower for ascites than for other abdominal complications. This may not be related to limited absorptive capacity in infants, but rather to the prevalence of optic chiasm-hypothalamic glioma in young age.

It is important to differentiate ascites and pseudocyst, which are often described together [22, 43, 55], because in ascites the peritoneum itself is incompetent, and the treatment for each differs radically. In some cases, ascites builds up rapidly after shunt insertion, and the patient can present with raised intracranial pressure [62]. In general, the diagnosis of ascites is made when the patient presents

with an increased abdominal girth and the signs and symptoms of shunt failure are absent, as is fever in the case of infected ascites [43]. Clinically, the enlargement of the abdomen is often obvious (Fig. 8). On plain X-rays, hyperdensity scatters the gaseous radiolucencies in the lower abdominal regions. Abdominal ultrasonography and CT are key for the diagnosis, showing fluid circulating freely between the bowels. In the case of ascites, more detailed studies of the liver and portal system are necessary to eliminate a local cause such as portal hypertension. The next step is to differentiate aseptic from infected ascites. In infected ascites, the child is often very sick, with infectious signs, and biological studies are revealing. Paracentesis is easily performed; if the peritoneal fluid is infected, study of CSF harvested from the shunt reservoir or lumbar tap is required.

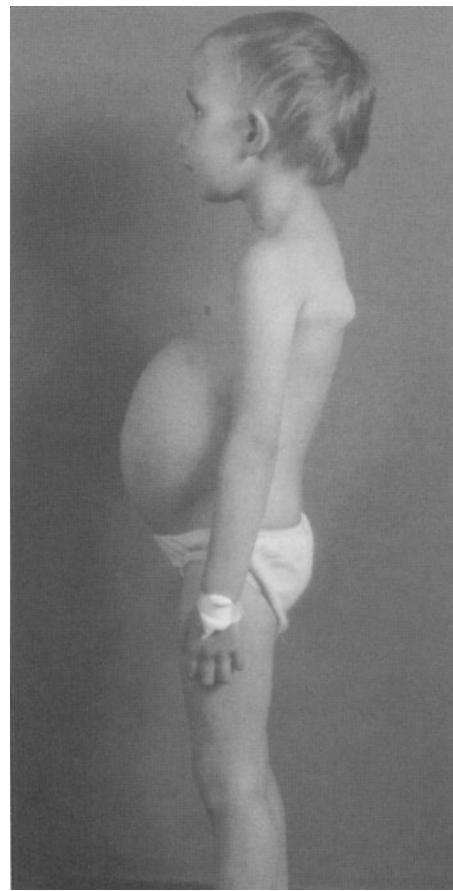


Fig. 8. Typical appearance of a child with abdominal mass, in this case related to ascites in a child shunted 6 months earlier for hydrocephalus due to a thalamic pilocytic astrocytoma. Plain X-rays showed uniform attenuation scattering the intestinal gases. The distal catheter was repositioned in the atrium and required just one more revision during the following 17 years of follow-up

Because in patients with ascites the peritoneum is incompetent, the treatment must rely on alternative shunting, the chief of which is the atrial route [4, 7, 15, 19]. In infected ascites, treatment of the shunt infection requires shunt externalization and a course of intravenous antibiotics, followed by total shunt replacement in an atrial position. Peritoneal incompetence should be considered definitive, although in rare exceptional cases the peritoneum was able to be used again after the atrial shunt had failed, several years after the initial episode.

Bowel Perforation

Bowel perforation by peritoneal catheters has generated a large number of clinical reports showing an amazing variety of perforations, involving the jejunum [54], the stomach [13, 24, 42], the hepatic duct [59], the colon [23, 55], or the vagina [44]. The majority of these perforations related to spring-loaded catheters [13, 24, 42, 55], and these have become less common since most surgeons have abandoned such materials. In our experience, we had 13 cases of bowel perforation, none of which was related to a spring-loaded catheter.

Bowel perforation can occur intraoperatively, as a complication of catheter introduction. Although promoters of the trochar method for introduction of the peritoneal catheter consider it safe [38], many authors prefer a peritoneal approach under direct vision, for fear of visceral injury [17]. The latter technique, however, is not immune to visceral complications: in scarred abdomens, identification of the peritoneal cavity can be very difficult, and surgical exploration can also result in bowel perforation.

Most cases of visceral perforation occur with some delay after surgery and appear to result from a chronic inflammatory process. Bowel perforation may obviously be the cause of shunt infection, but can itself be the result of chronic inflammation due to occult infection [16]. In our experience, four patients with bowel perforation had a history of central nervous system infection, with possible occult catheter contamination. Occasionally, abdominal perforation has been related to previous bowel surgery such as gastrostomy [24]. Severely handicapped patients appear especially at risk of developing bowel perforation: 3 of our 13 patients with bowel perforation had a myelomeningocele, and 5 had spastic tetraparesis or were bedridden. How an altered neurological status could favor bowel perforation is unclear, but it could involve weakness of the abdominal wall and deregulation of the intestinal transit. Perforation does not usually cause peritonitis, because it is preceded by

chronic ulceration, and inflammatory tissues surround the visceral perforation [54]. Operative reports of bowel or omentum agglutinating around the perforation [13] show that the immune system tends to limit the spread of infection and expel the infected foreign body. Although the catheter is contaminated, CSF remains sterile for long periods of time. The pathogens are mainly gram-negative bacilli, but gram-positive cocci such as *Staphylococcus aureus* [54] or *Staphylococcus epidermidis* [42] can also be found. These latter findings may be interpreted in favor of intraoperative contamination and secondary bowel perforation due to chronic inflammation. In most cases, however, the multiplicity of germs, including anaerobes and intestinal flora, is the signature of visceral perforation [54].

Bowel perforation may occur early after surgery as well as several years later [16, 58]. Typically, visceral perforation leads to few abdominal symptoms, so that the diagnosis can be delayed, especially in debilitated children. Anal extrusion in particular is generally an isolated finding [23], perplexing general practitioners unfamiliar with silicon catheters (Fig. 9). In many cases, the patient presents with fever, CSF shows pleocytosis, and its culture grows multiple intestinal bacteria [58]. In other cases, the infected shunt is rejected through chronic skin ulceration, without abdominal, neurological, or systemic signs [16]. In the absence of local signs, fever, and abdominal symptoms, the patient may present with symptoms mimicking shunt failure, and the diagnosis is made at surgery: the withdrawn peritoneal catheter is stained with biliary or fecal pigments, and cultures are positive. We treated 13 patients with bowel perforation.



Fig. 9. Posthemorrhagic hydrocephalus shunted when the child was 6 weeks old. Five months after insertion of a non-metallic peritoneal catheter, the child presented with catheter extrusion through the anus, without any symptoms of infection or shunt malfunction. The catheter grew both intestinal flora and *Staphylococcus aureus*. After external drainage and 2 weeks of antibiotics, a new peritoneal shunt was inserted, with favorable outcome

ration. In three cases, the diagnosis was obvious: in two, the catheter was extruded through the anus, and in the third, acute peritonitis developed a few days after shunt insertion. Among the ten others, abdominal signs were present in only two; two others had symptoms of raised intracranial pressure, and six had isolated fever. Visceral perforation should be considered in all cases of unexplained fever in a patient with a peritoneal shunt. The usually long delay between shunt surgery and infection underlines the importance of long-term follow-up. Undiagnosed cases may be treated with antibiotics, which do not cure the infection but can lead to negative CSF cultures, resulting in recurrent lymphocytic, purportedly aseptic, meningitis. In our experience, a patient with so-called "lymphocytic meningitis" was given anti-tuberculous drugs for several months, the multiple intestinal bacteria grown from the lumbar CSF being interpreted as contaminants; he eventually presented with symptoms suggesting shunt failure, was finally referred to neurosurgery, and the diagnosis was made at surgery.

In any case, the treatment relies on externalization of the catheter, external drainage, and intravenous antibiotics, then total shunt removal (including all nonabsorbable sutures) and insertion of a totally new system. Some authors have reported having inserted a new shunt on the same day as the contaminated one was removed [13, 23]. We think that the apparent lack of complications experienced by these authors should not tempt us to the same gamble. If intraoperative perforation occurs, the risk of acute abdominal complication is maximal, and the aid of an abdominal surgeon should be sought. If late perforation occurs, the visceral perforation as a rule does not pose any problem, since it is surrounded by inflammatory tissues and seals itself rapidly after catheter withdrawal [16]. Oral feeding can generally be resumed within a few days.

The peritoneum remains the preferred site for distal catheter implantation after bowel perforation; in our series, it could be used again in all but one patient. Two patients in our series could not be cured and died of recurrent shunt infection; both of these children were profoundly debilitated prior to shunt infection and were in a very poor condition when operated on.

Prevention of late bowel perforation is based on avoidance of metallic catheters, as advised by McComb (commenting on Griffith) as early as 1987, and removal of any unnecessary catheter [24]. In a previous study on subduroperitoneal drainage, we have shown that the incidence of delayed complication was a strong incentive systematically to remove these catheters [61]. Prevention of intraoper-

ative bowel perforation depends on surgical training. In general, we prefer approaching the peritoneum under direct vision, but we consider that it is mainly a question of practice and preference. In difficult cases, such as in obese patients or patients with multiple abdominal scars, the aid of an abdominal surgeon and the use of endoscopic guidance may be of help [53].

Hernias and Hydroceles

Hernias and hydroceles represent together the most common SRAC, predominantly affecting infants [55], especially males. The incidence is maximal among premature infants [41]. Abdominal hernias are very common in the general infantile population (1.2%); however, shunted infants appear to be at higher risk of developing a hernia or hydrocele [16]. A recent study estimated that inguinal hernias were found in 15% of shunted children, and hydrocele in an additional 6% of males; hernias were more often bilateral in boys than in girls [9]. In our experience, 32 children were known to have presented a hernia and/or hydrocele, representing 1.5% of shunted patients. We may assume that the real figure was higher, however, because many hernias tend to heal spontaneously. Among these 32 patients, 15 (45%) were premature and 25 (76%) were male.

The occurrence of hernias and hydroceles in shunted children is related to the persistence of a patent peritoneovaginal canal in 30% of premature infants and neonates; this canal is reported to be still patent in 10% of infants after 1 year [9]. Additional factors are low birth weight and hypotonia, which might explain a particularly high incidence among achondroplastic children. Some authors have found glial cells in the peritoneal membranes during surgical treatment of hernias in shunted patients, and have suggested that these may play a role in the persistence of a patent peritoneovaginal canal [36]. When the communication is too narrow to allow herniation of the bowels or omentum, a hydrocele may appear. The collection may be tense, suggesting the existence of a slit-valve mechanism inside the peritoneovaginal canal. Rarely, the distal end of the catheter may stray into the scrotum through the peritoneovaginal canal, putting the patient at risk of developing skin ulceration and catheter extrusion [31].

In many cases, hernias and hydroceles tend to heal spontaneously or after simple measures. Surgery is indicated if the herniated mass grows, and may represent an emergency. In particular, when the catheter

tip has herniated into the scrotum, the patient presents with a rapidly growing hydrocele, which requires rapid surgical correction with repositioning of the catheter. In girls, herniated ovary as the differential diagnosis should be ruled out as an emergency, because delayed treatment may compromise future fertility. Umbilical hernias are less common than inguinal hernias, but can lead to CSF fistula, as reported by Pompili and Cianfriglia [48], and occurred in one of our patients, who required catheter externalization, but was eventually successfully weaned off her shunt.

Lost Peritoneal Catheters

The peritoneal migration of a broken distal catheter, or in some cases of the whole system, is a common situation, and the attitude to take toward these lost catheters is much debated. This complication results from catheter degradation with time, induced by inflammatory reaction directed against the material, but may also complicate surgical practices such as systematic lengthening of the peritoneal catheter during growth. The formation of scar tissue around the catheter is induced by macrophages that produce free radicals able to oxidize the silicone polymer and transform it into silica, which is nondegradable and acts as a permanent irritant, initiating inflammatory reaction [27]. Barium-dyed catheters degrade faster because the barium is released into the surrounding tissues, leaving cracks in the catheter that give a foothold to an inflammatory reaction. These reactions hinder the progressive unreeling of the peritoneal catheter during growth, resulting in either rupture or disconnection of the catheter [10]. The introduction of striped catheters a few years ago was aimed at avoiding this complication. Another factor associated with rupture of the peritoneal tubing is the use of connectors for lengthening the peritoneal catheter. The introduction of a connector into the tubing acts as a peg during subsequent growth, and creates a weak point on the catheter [10]. Rupture of the peritoneal catheter is often associated with migration into the abdominal cavity, because its pressure is negative and sucks the catheter in (Fig. 10). Occasionally, the whole unruptured shunt may migrate into the abdomen, especially in infants, who have resilient soft tissues and grow quickly.

Langmoen found that 3.1% of peritoneal shunts were complicated by migration of a ruptured distal catheter [32]. In our experience, we collected 33 cases, although this figure underestimates the real incidence, because retrieval of lost catheter is part of our routine and is not always noted on operative charts.



Fig. 10. Four-year old boy with malformational hydrocephalus, presenting with raised intracranial pressure related to shunt failure. Systematic X-rays show that the peritoneal catheter is ruptured under the valve and has migrated *in toto* into the peritoneal cavity. During shunt replacement, the lost catheter was removed through a microlaparotomy

Piatt has noted that this complication occurred mainly in children under the age of 2, and within 8 months after shunt insertion [45]. In our experience, only 3 of our 33 cases were aged less than 2. The majority occurred after the age of 10, the median age being 11.0 years, possibly related to the pubertal growth spurt.

Although lost catheters can be well tolerated for many years, the rationale for their retrieval is based on the risk of late complications and on facilitating the interpretation of further X-rays as well as any further abdominal surgery. When the remaining catheter stump is long enough and the shunt is functioning, we do not advise systematic surgery for that purpose alone. However, if surgery is warranted because of shunt failure, catheter retrieval through finger exploration of the abdomen is simple and noninvasive, and does not significantly lengthen the procedure [47]. This complication can be prevented by the use of striped catheters and avoidance of connectors. The peritoneal catheter should never need lengthening, since the whole length required for full growth can be introduced without difficulty at the first operation, even in premature infants.

Abdominal Surgery in the Shunted Patient

The shunted population is growing in size, and the risk of a shunted patient requiring abdominal surgery for an unrelated disease is increasing. In addition, many shunted patients have an underlying condition that exposes them to undergoing abdominal surgery, such as percutaneous gastrostomy or enterocystoplasty. The risk of bacterial contamination during abdominal surgery in shunted patients is variously estimated. The peritoneum, however, appears to have amazing immune properties. In our experience, unless these operations were complicated by infection, the risk of shunt contamination was negligible. When the catheter is apparent in the operating field, it should be pushed aside, and no attempt at pulling it to remove it should be made [3]. Another concern is the growing number of laparoscopic procedures: during such operations, the abdomen is insufflated with gas, impairing CSF flow, and Pomeranz et al. pointed out the risk of intracranial hypertension related to this procedure [47]; this can be avoided clamping the peritoneal catheter during abdominal insufflation, and desufflating the abdomen while releasing CSF flow at regular intervals [21].

A shunted patient presenting in emergency with an acute abdomen is a common situation. The most common situation is the diagnosis of appendicitis [25]; as pointed out above, the diagnosis is prone to error. It is mandatory to differentiate shunt malfunction mimicking abdominal disease from a primary abdominal emergency [49]. Abdominal ultrasonography and CT scan, CSF examination, shunt X-ray, and head CT can usually differentiate the two conditions. In any case, solving this problem in emergency situations is greatly helped by systematic preventive introduction of a reservoir into the shunt tubing and performing a systematic reference CT. In many cases, the problem of an acute abdomen requires consultation between the neurosurgeon and the abdominal surgeon. In cases of doubt, surgical exploration of the abdomen may be indicated; when the situation is less tense, it may be useful to externalize the drain and observe the patient for a few hours before taking the decision [25, 50].

Pregnancy in the Shunted Patient

With the improving outcome of hydrocephalus, and clinical follow-up of shunted children extending into adulthood, pregnancy in shunted women has become

a growing concern for neurosurgeons. Data on pregnancy in shunted women are scarce [64]. In our series, we had information on 14 pregnancies in 11 women shunted during childhood.

A recent study with serial MRI before, during, and after pregnancy in normal and preeclamptic women has shown that CSF volume normally increases during pregnancy, being maximal at term; these changes were more pronounced in women with preeclampsia than during normal pregnancy [40]. In shunted women, fluid imbalance associated with pregnancy may account for symptoms of raised intracranial pressure [56]. The increased volume of the uterus might be responsible for raised pressure in the abdomen and impaired CSF drainage [12]. Wisoff et al. reported a high incidence of intracranial hypertension during pregnancy, affecting as many as 59% of shunted women [64].

Since symptoms suggesting shunt malfunction are common during normal pregnancy, a conservative attitude is warranted after control CT has eliminated a shunt malfunction [56]. Regarding delivery, although intra-abdominal pressure increases tremendously during labor, the elevation is intermittent and does not significantly impair CSF drainage, and the general consensus is that vaginal delivery is not contraindicated by the presence of a peritoneal shunt [12]. When indicated, cesarean section does not pose a problem in shunted women either. In our experience with 14 pregnancies in 11 women, no shunt complications occurred during pregnancy, one patient required shunt revision 6 months after delivery. The use of peridural anesthesia is controversial: some authors consider it should be avoided in shunted women [56], but we do not regard it as contraindicated. Some authors also advise the use of prophylactic antibiotics during labor, because of occult bacteremia and potential contamination of the shunt [56], but this attitude is not supported by the literature data [12] and we do not advise the use of prophylactic antibiotics during labor.

General Considerations

In our experience, abdominal complications could be an opportunity to achieve shunt independence. Jones et al. have initially proposed endoscopic procedures as a last resort for the treatment of recurrent shunt infections [29]. More recently, endoscopic third ventriculostomy was proposed in cases of shunt failure, with or without infection, and documented aqueductal stenosis [8], and is discussed in detail in Chap. 26. Although the best prevention of shunt complication

is no shunt at all, a large number of patients with hydrocephalus are not eligible for neuroendoscopic procedures. For these patients who still require a shunt, the peritoneum is the most easily accessible site to place a distal catheter. A number of shunt complications are specific to peritoneal catheters, but these are manageable and cause minimal mortality compared with atrial catheters. Most interestingly for these patients, who are often destined to undergo multiple reoperations, the peritoneum is reusable, and, unlike in the jugular veins, repeated operations and multiple approaches can be performed. The incidence of these complications can be reduced by simple measures. We still need to accumulate more information on these rare complications, and refine our surgical indications and techniques, to offer optimal safety for the steady number of patients who will still need a shunt.

References

1. Addiss DG, Shaffer N, Fowler BS, et al: The epidemiology of appendicitis and appendectomy in the United States. *Am J Epidemiol* 132:910-925, 1990
2. Baird C, O'Connor D, Pittman T: Late shunt infections. *Pediatr Neurosurg* 31:269-273, 1999
3. Besson R, Hladky JP, Dhellemmes P, et al: Peritoneal pseudocyst: peritoneal shunt complications. *Eur J Surg* 5:195-197, 1995
4. Britz GW, Kim K, Loeser JD: Hydrocephalus secondary to diffuse villous hyperplasia of the choroid plexus. *J Neurosurg* 85:689-691, 1996
5. Burchianti M, Cantini R: Peritoneal cerebrospinal fluid pseudocysts: a complication of ventriculoperitoneal shunts. *Child's Nerv Syst* 4:286-290, 1988
6. Byard RW: Mechanisms of sudden death and autopsy findings in patients with Arnold-Chiari malformation and ventriculoatrial catheters. *Am J Forensic Med Pathol* 17:260-263, 1996
7. Casey KF, Vries JK: Cerebrospinal fluid overproduction in the absence of tumor or villous hypertrophy of the choroid plexus. *Child's Nerv Syst* 5:332-334, 1989
8. Cinalli G, Salazar C, Mallucci C, et al: The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43:1323-1329, 1998
9. Clarnette TD, Lam SK, Hutson JM: Ventriculo-peritoneal shunts in children reveal the natural history of closure of the processus vaginalis. *Pediatr Surg* 33:413-416, 1998
10. Clyde BL, Albright AL: Evidence of a patent fibrous tract in fractured, outgrown, or disconnected ventriculoperitoneal shunts. *Pediatr Neurosurg* 23:20-25, 1995
11. Cornips E, Van Calenbergh F, Plets C, et al: Use of external drainage for posthemorrhagic hydrocephalus in very low birth weight premature infants. *Child's Nerv Syst* 13:369-374, 1997
12. Cusimano MD, Meffe FM, Gentili F, et al: Management of pregnant women with cerebrospinal fluid shunts. *Pediatr Neurosurg* 17:10-13, 1991
13. Danismend N, Kuday C: Unusual complication of ventriculoperitoneal shunt. *Neurosurgery* 22:798, 1988
14. Davidson RI, Lingley JF: Intraperitoneal pseudocyst: treatment by aspiration. *Surg Neurol* 4:33-36, 1975
15. Dean DF, Keller IB: Cerebrospinal fluid ascites: a complication of a ventriculoperitoneal shunt. *J Neurol Neurosurg Psychiatr* 35:474-476, 1972
16. Di Rocco C: The treatment of infantile hydrocephalus. CRC Press, Boca Raton, 1987
17. Di Rocco C, Marchese E, Velardi F: A survey of the first complication of newly implanted CSF devices for the treatment of nontumoral hydrocephalus. *Child's Nerv Syst* 10:321-327, 1994
18. Egelhoff J, Babcock DS, McLaurin R: Cerebrospinal fluid pseudocysts: sonographic appearance and clinical management. *Pediatr Neurosci* 12:80-86, 1985
19. Faillace WJ, Garrison RD: Hydrothorax after ventriculoperitoneal shunt placement in a premature infant: an iatrogenic postoperative complication. *J Neurosurg* 88:594-597, 1998
20. Fischer EG, Shillito J: Large abdominal cysts: a complication of peritoneal shunts. *J Neurosurg* 31:441-444, 1969
21. Gaskill SJ, Cossman RM, Hiskman MS, et al: Laparoscopic surgery in a patient with a ventriculoperitoneal shunt: a new technique. *Pediatr Neurosurg* 28:106-107, 1998
22. Gaskill SJ, Marlin AE: Spontaneous bacterial peritonitis in patients with ventriculoperitoneal shunts. *Pediatr Neurosurg* 26:115-119, 1997
23. Gonzalez MG: Extrusion of peritoneal catheter through the anus. *Child's Nerv Syst* 3:183-184, 1987
24. Griffith JA, De Feo D: Peroral extrusion of a ventriculoperitoneal shunt catheter. *Neurosurgery* 21:259-261, 1987
25. Hadani M, Findler G, Muggia-Sullam M, et al: Acute appendicitis in children with a ventriculoperitoneal shunt. *Surg Neurol* 18:69-71, 1982
26. Hahn YS, Engelhard H, McLone DG: Abdominal CSF pseudocysts: clinical features and surgical management. *Pediatr Neurosci* 12:75-79, 1985
27. Heggers JP, Kossovsky N, Parsons RW, et al: Biocompatibility of silicone implants. *Ann Plast Surg* 11:38-45, 1983
28. Horikawa M, Yamada T, Tominaga K, et al: Abdominal cerebrospinal pseudocyst in a severely handicapped patient with hydrocephalus. *J Child Neurol* 14:329-331, 1999
29. Jones RFC, Stening WA, Kwok BCT, Sands TM (1993) Third ventriculostomy for shunt infections in children. *Neurosurgery* 32:855-860
30. Körner H, Söndenaa K, Söreide JA, et al: Incidence of acute nonperforated and perforated appendicitis: age-specific and sex-specific analysis. *World J Surg* 21:313-317, 1997
31. Kwok CK, Yue CP, Wen HL: Bilateral scrotal migration of abdominal catheters: a rare complication of ventriculoperitoneal shunts. *Surg Neurol* 31:330-331, 1989
32. Langmoen IA, Lundar T, Vatne K, et al: Occurrence and management of fractured peripheral catheters in CSF shunts. *Child's Nerv Syst* 8:222-225, 1992
33. Latchaw JP, Hahn JF: Intraperitoneal pseudocysts: mimicking liver disease. *Monogr Neural Sci* 8:55-56, 1982
34. Leibrock L, Baker R, Uematsu S: Simulated acute appendicitis secondary to ventriculoperitoneal shunt. *Surg Neurol* 4:481-482, 1975
35. Lejeune JP, Sion P, Combelles G, et al: Pseudo-kistes péritonéaux de L.C.R.: complication rare des dérivations ventriculo-péritonéales. *Neurochirurgie* 30:235-223, 1983
36. Magee JF, Barker NE, Blair GK, et al: Inguinal herniation with glial implants: possible complication of ventricu-

- loperitoneal shunting. *Pediatr Pathol Lab Med* 16:591-596, 1996
37. Mazza C, Pasqualin A, Da Pian R: Results of treatment with ventriculoatrial and ventriculoperitoneal shunt in infantile nontumoral hydrocephalus. *Child's Brain* 7:1-14, 1980
38. Moss SD, Pattisapu JV, Walker ML: Use of the peritoneal trocar in pediatric shunt procedures. *Concepts Pediatr Neurosurg* 8:23-28, 1988
39. Nakagaki H, Matsunaga M, Maeyama R, et al: Intraperitoneal pseudocyst after ventriculoperitoneal shunt. *Surg Neurol* 11:447-450, 1979
40. Oatridge A, Holdcroft A, Saeed N, et al: Change in brain size during and after pregnancy: study in healthy women and women with preeclampsia. *Am J Neuroradiol* 23:19-26, 2002
41. Oi S, Matsumoto S: Hydrocephalus in premature infants. Characteristics and therapeutic problems. *Child's Nerv Syst* 5:76-82, 1989
42. Oi S, Shose Y, Oshio T, et al: Intragastric migration of a ventriculoperitoneal shunt catheter. *Neurosurgery* 21:255-257, 1987
43. Parry SW, Schuhmacher JF, Llewellyn RC: Abdominal pseudocysts and ascites formation after ventriculoperitoneal shunt procedures: report of four cases. *J Neurosurg* 43:476-480, 1975
44. Patel CD, Matloub H: Vaginal perforation as a complication of ventriculoperitoneal shunts. *J Neurosurg* 38:761-762, 1973
45. Piatt JH: Cerebrospinal fluid shunt failure: late is different from early. *Pediatr Neurosurg* 23:133-139, 1995
46. Pieper R, Kager L: The incidence of acute appendicitis and appendectomy. An epidemiological study of 971 cases. *Acta Chir Scand* 148:45-49, 1982
47. Pomeranz S, Rapaport HZ, Umansky F, et al: Technical note: the removal of free peritoneal catheters in the revision of ventriculoperitoneal shunts. *Neurosurgery* 22:436-438, 1988
48. Pompili A, Cianfriglia F: Umbilical fistula as a complication of ventriculoperitoneal shunt. *Surg Neurol* 12:129-130, 1979
49. Pumberger W, Löbl M, Geissler W: Appendicitis in children with a ventriculoperitoneal shunt. *Pediatr Neurosurg* 28:21-26, 1998
50. Rekate HL, Yonas H, White RJ, et al: The acute abdomen in patients with ventriculoperitoneal shunts. *Surg Neurol* 11:442-445, 1979
51. Rickert CH: Abdominal metastases of pediatric brain tumors via ventriculo-peritoneal shunts. *Child's Nerv Syst* 14:10-14, 1998
52. Roitberg BZ, Tomita T, McLone DG: Abdominal cerebrospinal fluid pseudocysts: a complication of ventriculoperitoneal shunt in children. *Pediatr Neurosurg* 29:267-273, 1998
53. Roth JS, Park AE, Gewirtz R: Minilaparoscopically assisted placement of ventriculoperitoneal shunts. *Surg Endosc* 14:461-463, 2000
54. Rubin RC, Ghatak NR, Visudhipan P: Asymptomatic perforated viscus and gram-negative ventriculitis as a complication of valve-regulated ventriculoperitoneal shunts. *J Neurosurg* 37:616-618, 1972
55. Rush DS, Walsh JW: Abdominal complications of CSF-peritoneal shunts. *Monogr Neural Sci* 8:52-54, 1982
56. Ryken TC: Idiopathic intracranial hypertension (pseudotumor cerebri), hydrocephalus, and ventriculoperitoneal shunts in pregnancy. In: Loftus CM (ed) *Neurosurgical aspects of pregnancy*. American Association of Neurological Surgeons, Park Ridge, Illinois, pp 165-176, 1996
57. Salomao JF, Leibinger RD: Abdominal pseudocysts complicating CSF shunting in infants and children. *Pediatr Neurosurg* 31:274-278, 1999
58. Stamos JK, Kaufman BA, Yogeve R: Ventriculoperitoneal shunt infections with gram-negative bacteria. *Neurosurgery* 33:858-862, 1993
59. Touho H, Nakauchi M, Tasawa T, et al: Intrahepatic migration of a peritoneal catheter: case report. *Neurosurgery* 21:258-259, 1987
60. Vernet O, Campiche R, de Tribolet N: Long-term results after ventriculo-atrial shunting in children. *Child's Nerv Syst* 11:176-179, 1995
61. Vinchon M, Noulé N, Soto-Ares G, et al: Subduroperitoneal drainage for traumatic subdural hematoma in infants: results with 244 cases. *J Neurosurg* 95:248-254, 2001
62. West GA, Berger MS, Geyer J: Childhood optic pathway tumors associated with ascites following ventriculoperitoneal shunt placement. *Pediatr Neurosurg* 21:254-259, 1994
63. Williams NMA, Everson NW, Jackson D, et al: Is the incidence of acute appendicitis really falling? *Ann R Coll Surg Engl* 80:122-124, 1998
64. Wisoff JH, Kratzert KJ, Hanwerker SM, et al: Pregnancy in patients with cerebrospinal fluid shunts: report of a series and review of the literature. *Neurosurgery* 29:827-831, 1991
65. Yount RA, Glazier MC, Mealey J, et al: Cerebrospinal fluid ascites complicating ventriculoperitoneal shunting. *J Neurosurg* 61:180-183, 1984

Patterns of Shunt Failure According to the Hydrodynamic Features of the Valve: Lessons from the Shunt Design Trial

JOHN R. W. KESTLE¹, JAMES M. DRAKE²

Introduction

In the early 1990s, two new valves came on the market for the management of hydrocephalus. They were designed to limit the tendency to overdrainage and to provide a more physiologic management of hydrocephalus. They were widely used based on reports of reduced shunt failure in uncontrolled series [3, 9, 10]. The Shunt Design Trial was initiated to compare the function of these valves with that of the differential pressure valves that had been on the market for many years previously. Surgeons from ten pediatric neurosurgery centers in Canada, the United States, and Europe participated in the trial and accrued patients from 1993 to 1995. A total of 344 children less than 18 years old were identified and randomized. All of them had hydrocephalus requiring a single ventriculoperitoneal shunt. Patients were only enrolled in the trial if they were undergoing their first shunt insertion; candidates for shunt revision were not included. The patients were randomized to receive the Orbis-Sigma valve (which at the time was produced by Cordis Corporation), the Delta valve, or a differential pressure valve of the surgeons' choice ("standard" group). They were followed until the end of the study period or until they had a shunt failure. The participating centers completed data forms, which were sent to the study coordinating center, but they also copied clinical notes, laboratory data, and imaging studies to the study coordinating center. These documents were used by a central committee for blind review of the outcome in each patient. The primary outcome for the study was shunt failure, which was divided into four categories: obstruction, overdrainage, infection, and loculation, each of which had a detailed definition (see Appendix in [1]).

After the accrual period of 2 years and 1 month, plus a minimum follow-up of 1 year, the data were analyzed and the primary results were published [2]. The shunt survival curves are shown in Fig. 1. There was no statistically significant difference among the three valves in

time to first shunt failure. Furthermore, when the five largest centers were compared, there was no consistent pattern suggesting that one shunt was superior to the others. The primary conclusion of the study was that no valve resulted in a clinically and statistically significant reduction in the time to first shunt failure.

The patients whose shunts were still functioning at the end of the initial study underwent continued follow-up and were reported on again in 2000 [5]. At this stage, 177 patients had shunt failure (Fig. 2). The com-

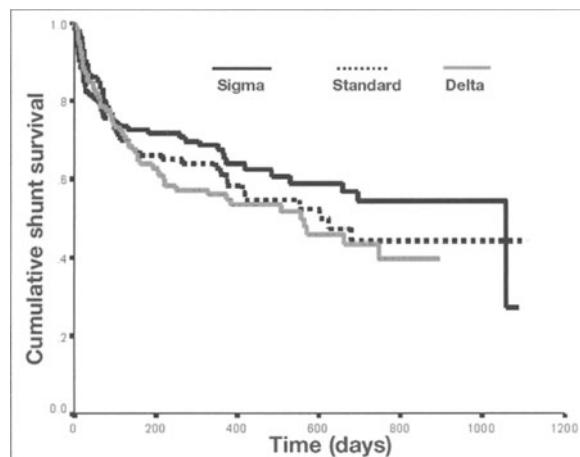


Fig. 1. Primary results

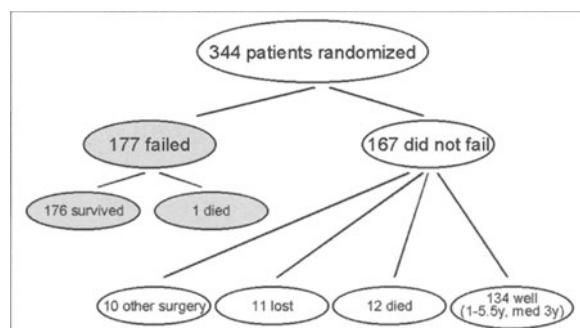


Fig. 2. Patient status at last follow-up

¹Division of Pediatric Neurosurgery, Primary Children's Medical Center, University of Utah, Salt Lake City, Utah, USA;

²Division of Neurosurgery, Hospital for Sick Children, University of Toronto, Canada

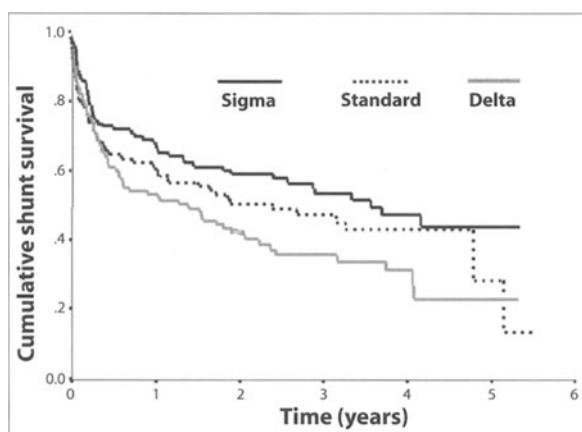


Fig. 3. Long-term shunt survival

parison of the three valves (Fig. 3) again did not suggest that any particular valve conferred a clear advantage compared to the others.

Although the primary conclusion was that the study did not identify a valve that was clearly the best, some other interesting data did come out of the study. The types of failure for the different valves are presented in Fig. 4. The most striking finding is that overdrainage was most common with the Delta valve and did not occur at all with the Sigma valve. The numbers are very small and statistical analysis of these subcategories was not appropriate. On the other hand, obstruction at the valve was most common in the Sigma group (Table 1). This apparently led to the design of the Sigma 2, which increased the size of the orifice through which the CSF has to flow, but this was apparently done without changing the flow rate through the valve.

Table 1. Location of obstruction

	Delta (n=47)	Standard (n=45)	Sigma (n=39)
Ventricular catheter	19	21	6
Valve	2	5	9
Peritoneal catheter	5	2	3
Distal	2	1	6
Migration, disconnection, fracture	9	9	7
Unknown	10	7	8

The ventricle size was measured by a modified Evans ratio [11]. This indicated that the ventricle size became smaller by 3 months after shunt insertion, but that it decreased further in size by 12 months of age. The implications for practice are that a 3-month study is not sufficient to use as a baseline for follow-up: a repeat scan should also be done at 1 year. When the three valves were compared, the decrease in size was a little slower with the Orbis-Sigma valve, but by 1 year all three valves resulted in ventricles that were about the same size.

The long-term follow-up revealed some interesting information about the timing of failure. Although infection is usually thought of as an early event, there were two infections that occurred well beyond a year after the shunt insertion (Fig. 5). In addition, there were four cases of overdrainage after 1 year or more of apparently good shunt function. Three of these four cases were due to subdural hematoma and one was due to slit ventricle syndrome (Table 2). All of the other cases of overdrainage (n=9) were due to subdural hematoma.

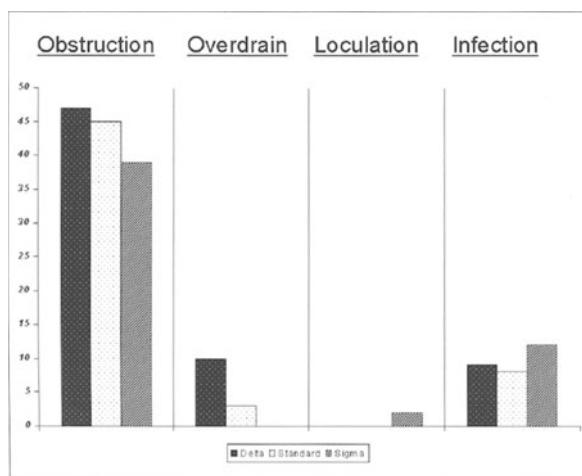


Fig. 4. Type of failure

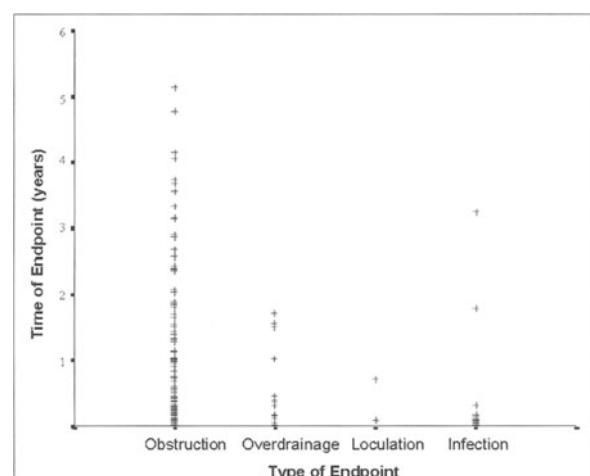


Fig. 5. Timing of endpoints

Table 2. Cases of late overdrainage

Etiology, age shunt placed	Presentation	Shunt	Presentation at failure
Myelomeningocele, 11 days	Bulging fontanelle, HC 39 cm	Delta valve 1.0 Occipital entry site Ventricular catheter in occipital horn	Subdural hematoma
Myelomeningocele, 6 days	HC 39 cm	Delta valve 1.0 Occipital entry site Ventricular catheter in occipital horn	Headache, vomiting, irritability, slit-like ventricles, ICP 40 mmHg on overnight monitoring
Intraventricular hemorrhage, 17 months	Premature (34 weeks), developmental delay, large head (60 cm)	Delta valve 1.0 Occipital entry site Ventricular catheter in occipital horn	Subdural hematoma
Unknown, 15 months	Term, developmental delay, hemiparesis large head (49 cm)	Delta valve 1.0 Occipital entry site Ventricular catheter in occipital horn	Subdural hematoma

HC, head circumference; ICP, intracranial pressure

The study design was carefully considered and published prior to the study results [1]. This was done so that clinicians, industry and other interested parties would have the opportunity to comment on the study design before the results were available. No such comments were received by the investigators. Since the study results have been announced, a number of questions have been asked and these are addressed below.

Rationale for Doing the Study

The underlying basis for doing the study was the increased cost of the new valves compared to differential pressure valves. This was in the face of uncontrolled evidence about their efficacy. The study was therefore designed as a rigorous assessment of the decreased shunt malfunction rates that were observed in the uncontrolled studies. It was felt that randomization was the only fair way to compare the valves, as this is the best study design to assess treatment efficacy [4,8].

Choice of Valves

The valves in the study were determined by randomization. When patients were randomized to the standard valve group, the surgeon implanted a differential pressure valve and was allowed to choose the opening pressure level. The rationale for doing this was that although bench testing showed different flow rates through the various levels of differential pressure

valves, the clinical experience with differential pressure valves did not reveal significant differences in shunt survival at different opening pressures. That being the case, if surgeons felt that a low or medium pressure valve was more appropriate in a particular patient, they were allowed to use it.

Entry Criteria

The study allowed only first-time shunts. It was felt that the effects of chronic shunting on hydrocephalus created quite a different situation and that it would be next to impossible to control for all of the factors that would be encountered if revision patients were included. This resulted in a very young population for the study, with a median age of 74 days. Surgeons were allowed to participate if they worked at a center which had experience with at least five insertions of each type of valve. This was done because the flow characteristics of the Delta valve and the Sigma valve after insertion result in a very different appearance when the distal end is inspected. The drip rate is much slower and it was felt that it might be more difficult to be certain that the shunt was in the correct place. It was therefore felt that people should have some experience with the new equipment because starting randomization.

Sample Size

Any prospective multicenter study requires a calculation of sample size before starting [9]. Calculating

the sample size requires a number of assumptions. The study was designed to have an 80% power using a two-sided α of 0.05. Both of these parameters are quite standard in clinical trials research. The investigators also had to determine the size of a difference that they wanted to detect with the study. On the basis of the literature, it was assumed that the differential pressure group would have a 1-year reoperation rate of about 40%. In order to calculate a sample size, we had to say how low we wanted the 1-year reoperation rate to be in the experimental valves in order to have a positive study. In other words, if the one of the new valves reduced the failure rate to 39% at 1 year, this might be interesting but it might not justify the excessive cost of the new valves. It was decided that the study would be set up to detect a reduction in the 1-year failure rate from 40% in the differential pressure group to 20% in either the Sigma or the Delta valve group. This was based on the uncontrolled literature that had been published on the new valves. This meant that the study had a power of 80% to detect such a difference. If the new valves reduced the failure rate to a lesser degree, the study power would be reduced.

Outcome Assessment

The initial idea was that the primary outcome for the study would be reoperation. However, there was a concern that the indications for reoperation might be biased. This would occur if a patient came back for follow-up with minimal symptoms and minimal change in ventricle size. The surgeon evaluating the patient would know which valve was in place. If they liked that valve, they might leave it in place and wait for a while to see if the patient's symptoms settled down. On the other hand, in the same clinical scenario, a surgeon who did not like that valve might remove it. This is observer bias [9]. The knowledge of the type of valve in place affects the decision to reoperate. Because of this potential observer bias, an adjudication process was used as the primary outcome measure. Based on the data forms, clinical notes, and imaging studies that were sent to the coordinating center, a review committee looked at every patient's data. All of the information was blinded so that the committee could not determine which valve was in place. Using the blinded information, the committee determined whether the patient's shunt had failed or not. This was the primary outcome for the study. A subsequent analysis [6] compared the outcome of the study with and without the committee evaluation. There wasn't enough discrepancy between the committee and the surgeons to alter the primary conclu-

sions of the trial, but this is impossible to know prior to the start of a study, and the potential for observer bias still exists in future hydrocephalus trials.

The investigators were also asked about the inclusion of infection or shunt misplacement as part of the primary outcome. It seems unlikely that infection rates would be unbalanced among the three valves. In addition, it was suggested that shunts that were not placed in the correct position originally should not be included in the final analysis. The decision to include all failures was based on the patient perspective. Although one would not expect infection to vary among the three valves, infection still requires a reoperation, and that is what is most important to the patient. If it is not different among the three valves, it will not affect the comparison, but it is safer to keep it in the primary outcome. The inclusion of "misplaced" shunts is necessary for a valid comparison. Because of the different flow rates, it may be more difficult to determine in the operating room that the Orbis-Sigma or Delta valve is in the correct place. If it turns out that one of the valves is in fact more difficult to use, and therefore it has a higher malfunction rate because it is more commonly "misplaced", that is important information. This is why misplacements were also included in the primary outcome.

Why Was the Study Negative?

We investigated the possibility that the study was negative because of a surgical learning curve [7]. We postulated that the surgeons might have been inexperienced with the new valves and that they might have still been learning how to put them in during the trial. The corollary is that if we had waited until there was more experience with correct placement of the new shunts, the study might have been positive. In order to investigate that possibility, we compared shunt survival results for patients early in the accrual period versus late in the accrual period (Table 3). This was done to test the hypothesis that added experience gained during the course of the trial improved the results. This was shown not to be the case. In addition, when the high-volume and low-volume centers were

Table 3. Shunt survival in early and late accrual periods

Valve	First 6 months (n=90)	Last 6 months (n=93)
Delta	0.66 (± 0.20)	0.54 (± 0.20)
Standard	0.75 (± 0.20)	0.70 (± 0.17)
Sigma	0.76 (± 0.18)	0.66 (± 0.16)

compared, overall shunt survival was the same. We therefore could not find evidence that there was learning going on during the trial, and surgeon inexperience therefore could not be used to explain the negative result.

It is possible that the valve is not the answer or that the effects of valve design on shunt survival are not of sufficient magnitude to have an effect on overall shunt failure rate. If that is the case, then perhaps all of the concentration of our efforts on valve design is misguided and at the expense of other possible improvements in hydrocephalus treatment.

Why Was the Infection Rate 8.4%?

The infection rate of 8.4% was felt to be high by some observers. The literature has infection rates which range from close to zero to 20% or 30%. The problems with comparing infection rates from study to study is that the definition of infection varies and that many of the infection rates are based on retrospective data, which may contain inaccuracies or missing information and which are subject to observer bias. The infection rate of 8.4% from this study is based on prospective, accurate data with documentation of culture results and is based on a blinded review by the adjudication committee. It is also representative of a large number of patients from ten international centers. It is therefore probably a reasonable number that we can use as a basis for further comparison. Studies with different definitions of infection, and without a blinded review process, may report different infection rates.

What Is the Take-Home Message?

The study failed to identify one valve that was clearly the best as the first shunt for children with hydrocephalus. Clearly, the study does not apply to patients

who are presenting for shunt revision. In addition, the study does not have the power to detect small differences in shunt survival rates. We are simply able to say that none of the valves cut the 1-year failure rate in half. In addition, the study demonstrated the ability of the pediatric neurosurgery community to cooperate in a scientific way and to answer a clinically relevant question. This type of cooperative effort will be important in the future assessment of hydrocephalus treatments.

References

1. Drake J, Kestle J, Group PHT: Determining the best CSF shunt valve design – the pediatric valve design trial. *Neurosurgery* 38:604-606, 1996
2. Drake JM, Kestle JR, Milner R, et al: Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery* 43:294-303; discussion 303-305, 1998
3. Horton D, Pollay M: Fluid flow performance of a new siphon-control device for ventricular shunts. *J Neurosurg* 72:926-932, 1990
4. Kestle J: Clinical trials. *World J Surg* 23:1205-1209, 1999
5. Kestle J, Drake J, Milner R, et al: Long-term follow-up data from the Shunt Design Trial. *Pediatr Neurosurg* 33:230-236, 2000
6. Kestle J, Milner R, Drake D: An assessment of observer bias in the shunt design trial. *Pediatr Neurosurg* 30:57-61, 1999
7. Kestle J, Milner R, Drake J: The shunt design trial: variation in surgical experience did not influence shunt survival. *Pediatr Neurosurg* 30:283-287, 1999
8. Sackett D, Haynes R, Guyatt G, et al: Clinical epidemiology. A basic science for clinical medicine, 2nd edn. Little, Brown and Company, Boston, 1991
9. Sainte-Rose C: Shunt obstruction: A preventable complication? *Pediatr Neurosurg* 19:156-164, 1993
10. Sainte-Rose C, Hooven M, Hirsch J-F: A new approach in the treatment of hydrocephalus. *J Neurosurg* 66:213-226, 1987
11. Tuli S, O'Hayon B, Drake J, et al: Change in ventricular size and effect of ventricular catheter placement in pediatric patients with shunted hydrocephalus. *Neurosurg* 45:1329-1335, 1999

Slit Ventricle Syndrome or Syndromes: Diagnosis and Management

HAROLD L. REKATE

The term “slit ventricle syndrome” (SVS) is widely used to describe a condition of severe, usually intermittent, headaches suffered by patients with long-standing ventricular shunting for hydrocephalus [15, 16, 20]. It is important to differentiate this condition from the smaller than normal, even almost nonexistent ventricles seen in some patients on routine imaging studies. The finding of radiographic slit ventricles occurs in at least 85% of children who are shunted and has been said to be a “goal” of shunting (M.L. Walker, personal communication, 1986). Most of these patients are asymptomatic and require no intervention. Only when patients begin to suffer from a severe headache disorder that interferes with their normal lives does the presence of radiographic slit ventricles lead to the diagnosis of the SVS.

The incidence of the syndrome is difficult to discern from the literature and arguments about whether it even exists are common. The quoted incidence ranges from 1-2% to as high as 15-20%, depending on the series. The lower numbers likely reflect centers that deal primarily with small children and that care for fewer adolescents and young adults. In my personal series, which is heavily weighted to a chronically shunted population of older children, adolescents, and young adults, the incidence of this syndrome is at least 15%. In a nonscientific poll of families taken at a recent Hydrocephalus Association Convention held in Phoenix in May 2000, a large proportion of adolescents with shunts complained of having lost some work or schooling due to headaches.

In an early article on the treatment of SVS, the condition was defined as “severe intermittent headaches lasting 10 to 90 minutes associated with smaller than normal ventricles on imaging studies and slow refill on valve pumping devices” [20]. This statement defines the syndrome in all but a small percentage of cases whose pathophysiology differs as discussed below.

Regulation of Ventricular Volume

Obstruction to the outflow of cerebrospinal fluid (CSF) usually leads to an increase in size of the lateral ventricles. Drainage of CSF at faster than normal rates or lower than normal pressures leads to smaller than normal ventricles. Therefore, the volume of the cerebral ventricles is under the dynamic control of physical forces that tend to increase or decrease the size of these spaces [39]. The force that tends to distend the ventricles is the internal hydrostatic force created by the formation of CSF, which occurs almost exclusively within the cerebral ventricles and the central canal of the spinal cord.

CSF is produced by two mechanisms [29]. In the first, CSF is produced by an active energy-requiring process at the level of the choroid plexuses. The CSF produced by these specialized organs is chemically distinct from serum and depends on the enzyme carbonic anhydrase. The carbonic anhydrase inhibitor Diamox (acetazolamide) dramatically decreases or stops the choroidal production of CSF and can decrease the total production of CSF by 50-80%.

CSF is also a byproduct of cerebral metabolism. CSF is in communication with and indistinguishable from brain and spinal cord extracerebral fluid (ECF). ECF flows passively by bulk flow into the cerebral ventricles and the central canal of the spinal cord where it mixes with choroidal CSF and flows through the intraventricular and extraventricular pathways to be absorbed, primarily through specialized absorptive organs, the arachnoid granulations, into the sagittal sinuses. Within a wide physiologic range of intracranial pressure (ICP), the production of CSF is constant at a rate of about 0.3 ml/min or 20 ml/h [6, 28, 29].

Why the ventricles enlarge at the time of occlusion or blockage of the CSF pathways on a microscopic level is controversial because the ependymal surface seems to be quite porous at the microscopic and electron microscopic level [5]. At the macroscopic level, however, the ependymal surface seems to function as a one-way

membrane that allows the free flow of CSF into the ventricle but distends the ventricular system if the flow of CSF is interrupted [34,39]. If the membrane function of the ependymal surface is bypassed, the CSF may be forced back into the brain ECF instead of leading to dilatation of the ventricular system [34]. If the ventricles are drained artificially, the distending hydrostatic force of the intraventricular CSF is lost, and the ventricles become smaller than normal or collapse completely.

The volume of the cerebral ventricles is under a dynamic equilibrium that can be defined by a hydrostatic analog of Ohm's law of electrical circuits. Briefly, the volume of the cerebral ventricle is determined by the volume of the CSF that enters that ventricle minus the flow from that ventricle. The latter is determined by the pressure differential across the exit foramina of the ventricle divided by the resistance created by the anatomy of the orifice and the condition or stiffness of the underlying brain [39]. Attempts to measure pressure changes from one CSF compartment to another have largely been unsuccessful except for some nonphysiologic experimental paradigms [36,42]. Several potential reasons may underlie this inability to record pressure differences within various intracranial compartments. The first reason relates to the insensitivity of the monitoring devices used. Most ICP monitoring transducers are only accurate to ± 1 mmHg. Given that the rate of flow within the ventricular system is only 0.3 ml/min, the pressure differentials are likely to be significantly lower than can be recorded by these devices. The second explanation relates to the intrinsic viscoelasticity of the living brain. The brain has an overall shape but is distensible and compressible. As fluid builds up in one compartment, the brain shifts to compensate and thus prevents the creation of measurable pressure differentials within the ventricular system.

In one situation pressure differentials may be measured within the ventricular system and that situation can significantly affect subsequent analyses of the symptoms and objective findings of SVS. This situation involves the resolution of the previously enigmatic condition of "postshunt ventricular asymmetries" [27, 42]. On pneumoventriculography some chronically shunted children will have a smaller than normal ventricle on the side of the shunt and a normal or larger than normal ventricle on the contralateral side. As first described by Kaufman et al. [25], laboratory experiments suggested that the pathophysiology of this condition was related to damping of the pulse wave by the shunt itself. My studies of this condition have pointed to another mechanism entirely. Experiments in my laboratory have documented the anatomic relationships between the septum pellucidum and the head of the caudate nucleus. If the size of ventricles is normal and therefore the anatomy of the foramen of Monro is reasonably normal, drainage

of CSF from one lateral ventricle leads to a distortion of the septum pellucidum: it is drawn to the side of the drainage. This distortion creates a valve effect as the septum pellucidum rests on the head of the caudate. Fluid continues to drain from the ipsilateral ventricle until that ventricle is empty.

In this situation in experimental animals, pressure differentials of as much as 3 mmHg may be recorded between the two lateral ventricles. Fluid will not flow from the contralateral ventricle to the drained ventricle until the ipsilateral ventricle collapses on the ventricular catheter, causing its obstruction. At this point ICP increases until the valve opens and flow begins again (Fig. 1a) [42]. Radiographically, the septum pellucidum is distorted, shifting midline structures (Fig. 1b). Intermittent proximal obstruction

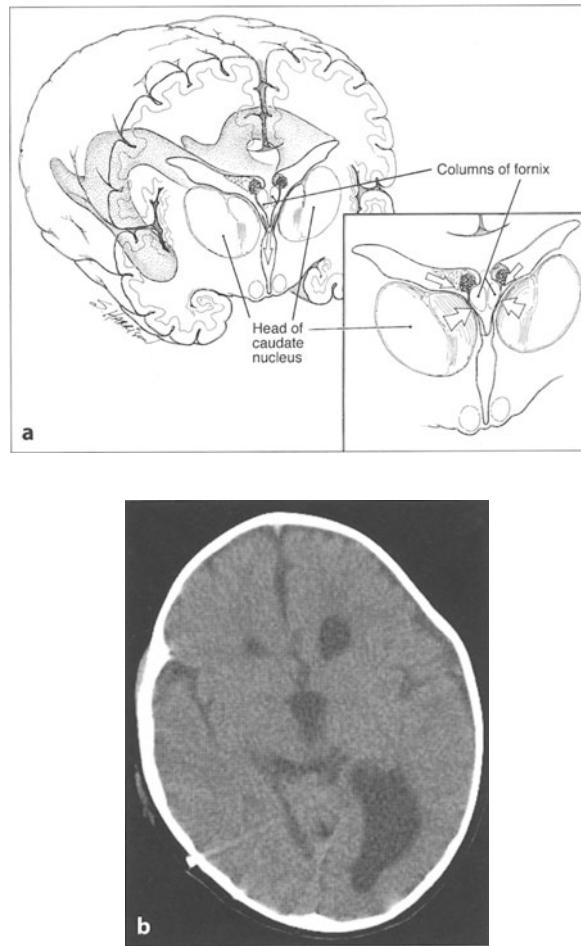


Fig. 1. **a** Artist's conception of the distortion of the septum pellucidum touching the head of the caudate nucleus and leading to postshunt ventricular asymmetries. **b** CT scan of shunted patient demonstrating the common finding that the ventricle containing the shunt has become significantly smaller than the contralateral ventricle. (Reproduced with permission from Barrow Neurological Institute)

with an intact septum pellucidum is the most overt pathophysiology among the presentations of SVS. When asymmetric ventricles are associated with a shunt-containing ventricle that is smaller than normal, the shunt is likely working. If the patient has severe intermittent headaches, the collapse of the ventricular wall around the ventricular catheter is the cause. Symptoms can be relieved by one of three strategies: upgrading the valve mechanism with a device to retard siphoning (DRS, described below), placing a second ventricular catheter in the contralateral ventricle, or performing an endoscopic septum pellucidotomy.

Recall that attempts to measure differential pressures within the CSF pathways have been unsuccessful. The only place that differential pressures are observed is in the absorption of CSF. Even in the presence of high ICP and almost complete occlusion of the aqueduct of Sylvius, the pressure in the lateral ventricles and cortical subarachnoid spaces is identical [40]. Regardless of ICP, a pressure differential of 5-7 mmHg can always be recorded between the cortical subarachnoid spaces and the superior sagittal sinus (SSS) [30, 44]. The work of Cutler and colleagues [6] defining the control mechanisms of ICP essentially shows the same findings. The production of CSF is constant over a wide range of ICP. No CSF is absorbed below the valve pressure described here as 5-7 mmHg or 68-91 mmH₂O. Above that opening pressure the absorption of CSF, which is a passive process at the arachnoid granulations, depends on ICP. In general there is a balance of ICP at about 10 mmHg or 140 mmH₂O.

The control of ventricular volume is not a purely passive process. If it were that simple, the enigmatic conditions of normal pressure hydrocephalus, pseudotumor cerebri, nonresponsive ventricles, or volume loss with CSF obstruction after radiation therapy, head injury, or cerebral infarction could not be explained. Given this discussion, the actual viscoelastic properties of the brain must play a role in regulating ventricular volume. Our initial thoughts about the role of the viscoelastic properties of the brain were oversimplified. At first, we modeled the viscoelastic properties of the brain, which we call brain "turgor", as being a constant function of each living brain. Brain "turgor", however, is not only variable within a single individual but may be a rapidly changing variable. Anything that increases the amount of fluid (water or blood) within the confines of the brain increases the brain's turgor. For most patients and in most situations, brain turgor is a product of the venous volume of the brain and relies on the unimpeded drainage of venous blood from the brain to function normally. ICP dynamics can be manipulated to increase brain

turgor quickly by impeding venous drainage from the brain by applying a gentle tourniquet around the neck. This technique decreases intracranial volume in patients whose ventricles remain enlarged after a shunt revision despite the fact that their shunt is working well [36]. Based on the regulation of ventricular volume described here, all cases of pseudotumor cerebri might be accounted for by increases in sagittal sinus pressure, whatever the cause. Pressure within the SSS was measured in patients with pseudotumor cerebri, and all patients with high ICP that can be managed with a lumboperitoneal shunt have had high sagittal sinus pressure [24]. In the obese patients in this group, high pressure in the SSS was due to high right atrial pressure (right heart failure). In contrast, thin patients with this condition had pressure differentials in the intracranial venous system. In this model of pseudotumor cerebri, it was assumed that either the point of obstruction to the flow of CSF was between the cortical subarachnoid space and the sagittal sinus, that the stiffness (turgor) of the brain itself had increased, or that pressure in the SSS was higher than normal and produced the same results [39]. In each case, the expected result of normal or smaller than normal ventricles with very high ICP was generated by the computer model. The important observation that both the volume of the spinal subarachnoid space and the cortical subarachnoid space increased was noted but not considered crucial. Radioisotope studies of pseudotumor cerebri had previously demonstrated that the cortical subarachnoid spaces were open and contained significant amounts of CSF. The critical importance of the volume of the cortical subarachnoid space is discussed in terms of "normal volume hydrocephalus," the problem of increased ICP with no distension of the cerebral ventricles at the time of shunt failure [13].

Pathophysiology of SVS Based on ICP Monitoring

Our original definition of SVS is still useful in that it describes most patients treated with the diagnosis of SVS [20]. These patients have severe intermittent headaches characteristically lasting 10-90 min, small ventricles on imaging studies, and slowly refilling valve mechanisms. In this group of patients, which represents 15-20% of adolescents and young adults seen in an active shunt practice, there is no urgency to initiate treatment. Consequently, I have rather arbitrarily decided on a threshold for action

in these patients: a child must need to leave school or lie down in the nursing station at least several times a month before pursuing intervention. Treating these patients by upgrading the valve mechanism, incorporating a DRS in the system, or both has been so successful that ICP monitoring has not been used. We assume that the underlying mechanism is that the presence of a ventricular catheter in very small ventricles leads to the eventual occlusion of all of the holes in the catheter. As ICP increases, one hole becomes uncovered and the shunt again begins to work. Although this assumption has not been tested scientifically, the symptom complex fits the presumed pathophysiologic mechanism well and the response to the treatment designed to address this pathophysiology supports the assumption.

Once the problem of severe headaches in patients with small ventricles on imaging studies varies from the above discussion, the pathophysiologic mechanism and treatment become much less obvious. These patients, who represent less than 5% of all shunted patients, need further evaluation, including chronic monitoring of ICP. These patients have resulted in the classification of SVS presented here [37]. All patients studied in this context had undergone a valve upgrade, the placement of a DRS, or both with either transient or no improvement in their symptoms or the symptom complex, or their clinical condition suggested the possible need for more complicated forms of treatment. The various forms of SVS are outlined below.

Intracranial Hypotension

Patients with shunts that do not incorporate a DRS may suffer from profound negative ICP. Patients become symptomatic at different levels of negative ICP, and most shunted patients tolerate significantly negative ICP without suffering symptoms. With the exception of patients with symptomatic hydrocephalus without a working shunt, all normal individuals and properly shunted individuals develop ICP negative relative to atmospheric pressure. In normal individuals the jugular veins are valveless structures that allow the intracranial venous blood to drain from the intracranial compartment and CSF to drain into the lumbar theca, causing it to distend. The jugular veins are collapsible tubes. When the pressure inside the jugular vein falls below atmospheric pressure, the jugular veins collapse and prevent normal ICP from falling significantly below -5 mmHg (Fig. 2) [19].

With standard differential pressure valve systems (Fig. 2), the tube draining the brain is not collapsible

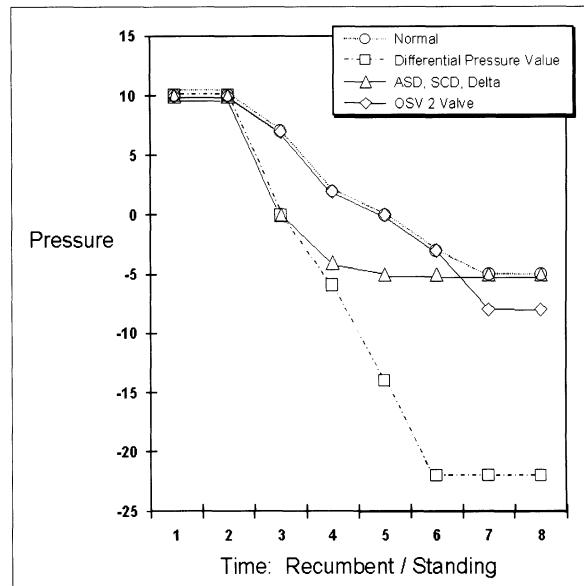


Fig. 2. Illustration of the effect of assuming an upright position in patients with various types of valve systems. Normal patients equilibrate slowly to -5 mmHg. Antisiphon (ASD)-type devices quickly equilibrate to the same level. OSV2 valves equilibrate slowly to levels slightly lower than normal. (Reproduced with permission from Barrow Neurological Institute)

and drains into the abdominal cavity. Patients with differential pressure valves who have undergone ICP monitoring show extremely negative ICP: -25 mmHg is relatively common [37]. These patients become symptomatic with headaches indistinguishable from "spinal headaches". These headaches never awaken the patient from sleep, begin after the patients have been upright for a period of time, and resolve within 30-60 min of recumbency. Magnetic resonance (MR) imaging often shows diffusely enhancing meninges. This type of headache always responds to the incorporation of a DRS into the shunt system.

In patients with Siphon Control Devices (SCD) and Delta Valves (both Medtronic PS Medical, Minneapolis, Minn.) and the Original Anti-Siphon Device (ASD, Heyer-Schulte Corp., Chicago, Ill.) developed by Portnoy, ICP rapidly falls to equilibrate at a negative level, much as occurs in normal individuals. In contrast, flow control valves (Orbis Sigma; NMT Corp., Duluth, Ga.; Siphonguard; Codman Corp., Raynham, Ma.) equilibrate more slowly but allow the final ICP to fall to a slightly more negative number but above the threshold for symptoms. These systems are considered to incorporate DRS devices. They should prevent the extremely subatmospheric ICP that leads to incapacitating low-pressure headaches. All differential pressure valves in older children with distal flow into the peritoneum result

in severely subnormal ICP even though only a small percentage of patients with this system becomes symptomatic. Differential pressure valves flowing into the jugular vein tend to equilibrate at higher levels of ICP than are measured in peritoneal shunts. If the distal terminus is the jugular vein against the direction of flow or in the transverse or sagittal sinus, siphoning will not occur and the system may be able to reconstruct the natural CSF dynamics [12].

Intermittent or Permanent Occlusion of Ventricular Catheter in Patients Whose Ventricle Do not Expand

About 20% of older children or adults who have been shunted for hydrocephalus in infancy will continue to have ventricles that are normal or smaller than normal at the time of shunt failure. Engel et al. have termed this condition "normal-volume hydrocephalus" [13]. Management of these patients is quite difficult. The ventricular catheter occlusions usually are transient. These patients typically report having been seen in emergency rooms and discharged because their ventricles had not grown. They have either been reassured and given pain medicines or been judged as exhibiting drug-seeking behavior. Although often transient, these blockages sometimes can be permanent or persist for many hours. I have recorded ICP as high as 55 mmHg in these patients with no increase in the size of their ventricles. The pathophysiology of this condition is not completely understood. When asked about what initially caused their hydrocephalus, most patients do not know and their early history is difficult to interpret.

Normal-volume hydrocephalus occurs in about 10% of patients with hydrocephalus related to the Chiari II malformation. These patients begin with hydrocephalus but have a form of pseudotumor cerebri at shunt failure. Pseudotumor cerebri is due to increased intracranial venous pressure [24]. Presumably, the initial cause of the CSF absorptive difficulty relates in some way to intracranial venous hypertension. When the fontanel and sutures are open and the intracranial contents are in communication with atmospheric pressure, ICP cannot increase sufficiently to gain the 7 mmHg pressure differential above sagittal sinus pressure that is required to lead to absorption of CSF. Instead, the head circumference increases, as does the volume of the ventricles and the cortical subarachnoid spaces [17, 31, 43, 45]. The volume of the brain remains the same. Shunting the ventricles allows the sutures and fontanelles to close. At the time of subsequent shunt failure, ICP is free to increase sufficiently to overcome the pressure

within the SSS with little or no increase in the volume within the ventricles.

Based on the mathematical modeling of ICP dynamics, intracranial venous hypertension is known to have two effects on intracranial dynamics. It causes venous blood to back up into the cerebral parenchyma, leading to an increase in cerebral blood volume and the intrinsic stiffness or turgor of the brain itself [36, 39]. The brain becomes intrinsically less compressible, and the energy of added intracranial volume results in increased ICP rather than distortion of the ventricular system. Pseudotumor cerebri also increases the absolute volume of the spinal and cortical subarachnoid spaces. In this situation, ventricular shunts have significant disadvantages. As the size of the ventricles decreases, all of the CSF that needs to be absorbed must pass through the shunt, because the shunt closing pressure will always be lower than the opening pressure of the valvular mechanism of the arachnoid granulations. At some point the retrograde passage of CSF from the subarachnoid space through the passages within the ventricles is impeded. Either the aqueduct of Sylvius becomes small enough to act as a significant resistance element or the valve mechanism described at the level of the foramen of Monro prevents the drainage of CSF from the third to the drained lateral ventricle. Because CSF cannot pass uphill through the arachnoid granulations, it accumulates in the cortical subarachnoid space under pressure and compresses the brain inward. The ventricles then collapse around the ventricular catheter.

Normal-volume hydrocephalus has been documented in the case of the Chiari II malformation when the torcular herophili reaches the level of the foramen magnum, where it is compressed by the hindbrain herniation. It also occurs in the context of achondroplasia and several craniofacial syndromes, including Crouzon's and Pfeiffer's syndrome, in which stenosis of the jugular foramina and abnormalities of intracranial venous blood can be documented [31, 43, 45]. It also occurs in patients with congenital heart disease and increased pressure in the superior vena cava.

High ICP with Small Ventricle and a Working Shunt: Cephalocranial Disproportion

The smallest number of patients with shunts, intractable headaches, and small ventricles suffer from cephalocranial disproportion. In this situation, the volume of the brain and the smaller than normal ventricles cannot be maintained within the intracranial compartment without markedly increasing ICP. To diag-

nose this condition, both aspects of the condition must be investigated. ICP must be monitored independent of CSF flow from the shunt, and shunt patency must be documented with a shunt flow study, usually with radioisotopes. There is a real possibility of recording a lower level of ICP than actually exists if ICP is monitored through the shunt reservoir and the ventricular catheter is not fully open within a ventricle containing a reservoir of CSF. In this situation the waveform usually is damped or flattened, and CSF drains slowly.

The incidence of this syndrome is a matter of some debate. Chronic shunting of children with large ventricles leads to major changes in the thickness of the skull [25]. The cause of this thickening is related to the failure of the intracranial capsule to expand and the subsequent remodeling of the inner aspect of the skull with the normal growth of the brain. Once the skull is thickened, it is difficult to demonstrate whether it is later distensible with subsequent growth of the brain. In and of itself, this thickening of the skull is not likely to be the entire cause of the SVS with this pathophysiology. When the foramen magnum is fully open, cephalocranial disproportion can cause or be associated with significant hindbrain herniation, as occurs in severe cases of pseudotumor cerebri related to intracranial venous pathology.

Most patients with this condition develop symptoms and signs of difficulty early in life and clearly are at risk of multiple complications including severe hindbrain herniation. Syndromes leading to these complications include Pfeiffer's syndrome, Crouzon's syndrome, and many unnamed, genetically determined conditions related to fibroblast growth factors and fibroblast growth factor receptors. The intracranial hypertension is due to restriction of skull and brain growth from multiple sutural closures as well as to venous hypertension caused by constriction of the venous drainage of the brain through the jugular foramina.

Patients with hydrocephalus-associated cephalocranial disproportion often become symptomatic as toddlers with irritability and have chronic papilledema. Shunt flow studies may show that the shunt is working or that the shunt has failed from obstruction of the ventricular catheter. These patients respond only transiently to a valve upgrade with placement of a DRS, or they may not respond at all [1].

Cephalocranial disproportion definitely exists in the context of multiple sutural closure, as seen in Crouzon's and Pfeiffer's syndrome, where it is associated with both hydrocephalus and chronic tonsillar herniation [17]. Patients with severe ventriculomegaly at the time of shunting may develop extreme thickening of the skull and sutural closure that is histopathologically identical to that associated with craniosynostosis.

Migraine in Patients with Shunts

Shunted patients are not immune from common maladies that affect a significant percentage of the population. Headaches are one of the most common complaints of the human race. In children, the most common cause of chronic headaches relates to seasonal or respiratory-triggered allergies. Migraine headaches are likewise extremely common, and there is a significant overlap between common migraines and headaches related to seasonal allergies. Headaches related to SVS also may be related to arterial vascular dilatation and therefore may respond to antimigraine therapy [10]. This finding was greeted with significant enthusiasm for referring patients with shunt-related headaches to a child neurologist to manage the headaches with antimigraine therapy. After several years, it became obvious that a small percentage of these patients significantly benefited from this form of treatment, and the patients eventually returned for neurosurgical management.

Based on the results of ICP monitoring, some chronically shunted patients with incapacitating headaches have other reasons underlying their headaches. The headaches related to migraine fall into two categories: "classic" and "common". The classic form is characterized by headaches preceded by a warning such as transient neurological deficits or visual symptoms such as "scintillating scotomas". Headaches in migraine patients are often triggered, stereotypic, and associated with nausea, vomiting, and photophobia. The headaches often resolve if patients sleep. Most patients with migraine headaches have a strong family history of migraines.

Initial Treatment of SVS

At a recent convention of the Hydrocephalus Association, adolescents and young adults were asked whether they suffered from intermittent headaches. Although this poll was not scientific, the results indicated that almost all chronically shunted patients experience frequent headaches that interfere with their activities of daily living. How much should headaches interfere with the daily life of shunted patients before a surgical procedure is reasonable to help ameliorate the condition? In my opinion, patients should make their own decision regarding the threshold for intervention. However, if patients need to leave school or work or need to lie down in the nurse's office at least twice a month, I recommend surgical treatment with its inherent risks.

The first and usually only step taken at this point is to replace the valve system with one that contains

a higher opening pressure and incorporates a DRS. This procedure is done with a 1-day admission. Patients can usually return to school in 2-3 days. I typically give patients a small bottle of chlorhexidine solution with which to shower and shampoo the night before and the morning of surgery. The valve is spliced into the existing system where the ventricular catheter is tested and retained. The distal tubing is retained if the distal runoff is brisk. This is my first step even before medication unless a compelling historical reason suggests that the problem is familial migraine. This procedure leads to complete or almost complete resolution of signs and symptoms in more than 90% of the cases. These are my own experiences, but about two-thirds of the patients were referred from other practices in other regions of the world.

Figure 3 is a previously published algorithm for managing severe headaches in shunted children [37]. In patients with profoundly low ICP, the implication is that the DRS is not functioning in that capacity. This failure can be seen in two contexts. Antisiphon de-

vices may become encased in scar tissue that prevents the membrane from sensing the atmospheric pressure transcutaneously [9]. To my knowledge, this particular complication has not been reported with the Delta chamber of the Delta™ valve. Improper placement of these diaphragm-related devices, including ASD, SCD, and Delta valves, can also lead to these problems. They must be on the scalp and, by the manufacturers' recommendations, above the ventricular system. They also need to be placed under freely moving skin and so may malfunction if placed under previous scars.

Profound intracranial hypotension has occurred late (>3 years) in the course of treatment of patients with symptomatic slit ventricles who had Orbis Sigma™ valves. On several occasions while monitoring ICP in patients with this valve, arising from recumbency has led to a rapid decrease in ICP to very high negative values. In one case, the valve was returned to the manufacturer who found that the valve was stuck in the fully opened position by a piece of debris that had passed through the valve. We have seen no such failures with the redesigned OSV2™.

Several other classes of valves have been used successfully to manage SVS in general and profound low pressure states in particular. The Gravity Compensating Device™ (NMT Corp., Duluth, Ga.) is a valve mechanism related to the HV™ (horizontal-vertical; NMT Corp., Duluth, Ga.) valve, which is manufactured specifically for use in lumboperitoneal shunts. It has two settings dependent on the orientation of the valve relative to gravity. The Phoenix™ valve has a dual chamber with two different channels to prevent overdrainage.

The newer programmable valves are rarely able to resolve this problem because they do not incorporate DRS devices. Recently, the Hakim Programmable Valve™ (Codman Corp., Waltham, Mass.) has become available with Siphon Guard™ (Codman Corp., Waltham, Mass.), which has a dual flow chamber to resist "dumping" of CSF. This device has not been available long enough in the United States to make a definitive statement about its usefulness but it appears promising. Clinical trials are now underway for the Strata™ Valve from Medtronic Corporation, which uses the Delta chamber with a programmable valve in series.

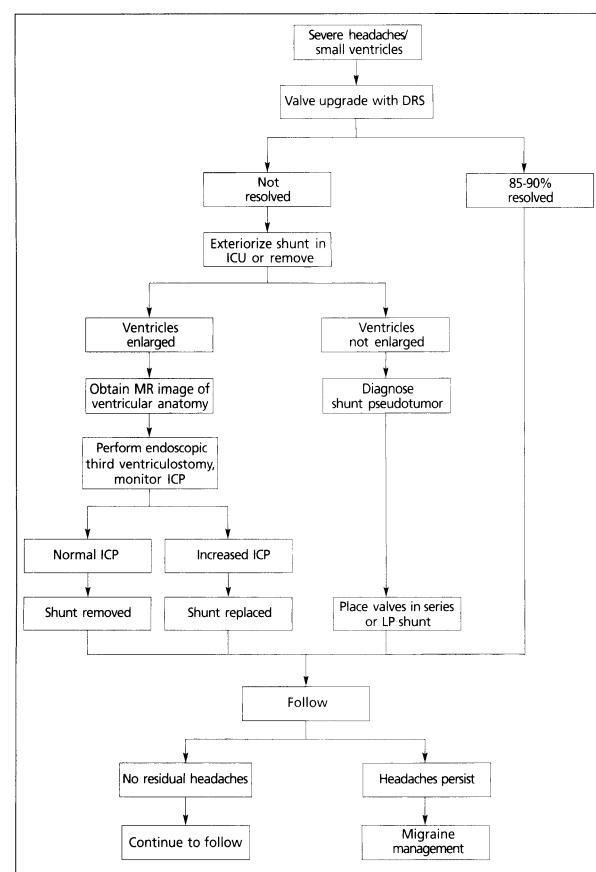


Fig.3. Algorithm for the management of severe headaches in patients with small ventricles. (Reproduced with permission from Barrow Neurological Institute)

Treatment of Refractory SVS Guided by ICP Monitoring

Since the creation of the algorithm shown in Fig. 3, we have had significant experience using it, which has led

to its modification. Some of the modifications are the result of a more thorough understanding of the pathophysiology of these conditions, and some have resulted from the development of new shunting technologies, particularly the use of more than one valve in series when no one manufactured valve is sufficient to prevent overdrainage at the source of most of these syndromes.

Intracranial Hypotension

As stated, all my patients with SVS initially have been managed by incorporating a DRS in the valve system with an upgraded valve. The finding of severe intracranial hypotension when monitoring ICP in these patients implies that the DRS has failed for mechanical reasons. The treatment of this condition is straightforward and involves replacing the valve system with another. Usually, replacement with a valve system of the same type suffices to solve the problem. In the case of diaphragm-related valves that must sense atmospheric pressure, it is probably wise to create a new pathway for the valve so that it is under freely moving skin that has not previously contained a valve mechanism.

Intermittent Ventricular Catheter Obstruction in Patients Whose Ventricles Do not Expand

Valve upgrades by incorporating DRS mechanisms may be insufficient to prevent the ventricle from collapsing around the ventricular catheter. If the valve closing pressure or resistance could be made high enough so that the CSF within the cortical subarachnoid space would drain through the arachnoid villi, there would be no tendency for the brain to collapse around the ventricular catheter. The empty cortical subarachnoid space would maintain CSF within the ventricles, preventing them from collapsing around the ventricular catheter. If high-pressure valves with DRS devices are insufficient in preventing the collapse of the ventricular system, valves in series have proved useful in the management of this condition. I have used multiple valve combinations with success. Differential pressure valves of all types have been used in combination with OSV2™ valves and with Level II and Level III Delta™ valves. Recently I combined OSV2™ valves with Hakim Programmable™ valves with excellent results. Other valve combinations have been used by other surgeons with equal success.

Recognizing the importance of the cortical subarachnoid space in the pathophysiology of normal-volume hydrocephalus has resulted in specific strategies for the management of this condition that specifically access the cortical subarachnoid space.

All patients with normal-volume hydrocephalus have an increased resistance to CSF outflow from the cortical subarachnoid space. My first approach is to determine whether the blockage to CSF outflow from the cortical subarachnoid space is the only point of obstruction. In these patients iohexol is injected into the ventricle through the reservoir, and computed tomography (CT) is performed about 30 min later. The CT scan is carried further caudad than usual CT scans of the brain so that the cervical spinal subarachnoid space is imaged. This study has been performed in 28 patients with normal-volume hydrocephalus. In 25 patients the ventricular CSF communicated briskly with the spinal subarachnoid space and the cortical subarachnoid space. The course of treatment in the three patients with no communication had been complicated by severe ventriculitis after the initial treatment of their hydrocephalus. Communicating hydrocephalus had been complicated by scarring of the ependyma, which led to multiple sites of obstruction to the flow of CSF. The clinical situation in two of these three patients was improved after a lumboperitoneal shunt was placed in addition to a functioning ventriculoperitoneal shunt. In the other 25 patients the ventricular shunt was removed except for the reservoir, and shunt systems that accessed the subarachnoid spaces were employed. In a significant number of patients, this treatment not only improved symptoms but also increased the size of the lateral ventricles toward normal.

Lumboperitoneal shunting has become unpopular since the development of hindbrain herniation was reported as a result of performing the procedure in small children [3, 4]. The ages of the patients and the types of shunts used in these studies are difficult to discern. However, it is assumed that most of the patients were infants at the time their original shunts were placed, and that the shunts were placed without additional valves being added to the systems. Because of the risk of hindbrain herniation, Johnston and coworkers [21, 22] have recommended shunting from the cisterna magna, whether created or extant, to the peritoneum for patients with pseudotumor cerebri and communicating forms of hydrocephalus.

I now prefer to use lumboperitoneal shunts to manage patients with documented normal-volume hydrocephalus who fail to respond to routine valve

manipulation as described above. The lumbar theca has a permanent reservoir of CSF. The walls of the thecal sac cannot collapse around the proximal catheter. The shunt accesses the CSF in the ventricle and in the cortical subarachnoid space in a balanced way. The use of high-pressure valves in these shunts does not seem to lead to significant hindbrain herniation when used in children as young as preschoolers. Treating children and young adults with pseudotumor cerebri and communicating hydrocephalus with standard, off-the-shelf, lumboperitoneal shunt systems that do not incorporate valves results in severe postural headaches and probably eventually in hindbrain herniation. High-pressure valve systems of various designs, including Spetzler™ In-line Valves (Heyer-Schulte Neurocare, Pleasant Prairie, Wis.), HV™ valves (NMT Neurosciences, Duluth, Ga.), and Codman-Hakim Programmable™ valves (Codman/Johnson & Johnson, Raynham, Mass.) with or without Siphon-guard™ (Codman, Raynham, Mass.), have been used to prevent overdrainage in these systems. DRS systems involving diaphragms cannot be applied to lumbar shunting because of the distance between the position of the valve on the flank or back and the intracranial compartment. As of this writing, I have had the largest experience with a combination of HV™ and Hakim Programmable™ valves. This combination has allowed the fine tuning of pressure to prevent the late afternoon headaches often associated with simpler systems.

In patients who are not candidates for lumboperitoneal shunts, I have been performing a posterior fossa craniotomy to increase the size of the cisterna magna followed by shunting the newly created cistern to the peritoneum with a high-resistance valve system (Fig. 4). The foramen magnum is opened, and the bone from the craniotomy is rotated to increase the size of the posterior fossa. The dura is opened as in the decompression of a Chiari I malformation, and a graft is sewn in place with bovine pericardium. Finally, a central tack-up stitch to the craniotomy is used to make the new cisterna magna significantly larger than it was originally. A ventricular catheter is placed within the new cisterna magna and connected to a shunt system to the pleura or peritoneum with a high-pressure valve system that incorporates a DRS.

Patients who require shunts from the newly created cisterna magna to the peritoneum or pleural cavity are those who are not candidates for lumboperitoneal shunts. This group includes patients with achondroplasia caused by the constriction of the foramen magnum. Within the remainder of the spine, spinal stenosis is so severe that the continuing flow of CSF to the lumbar theca cannot be as-

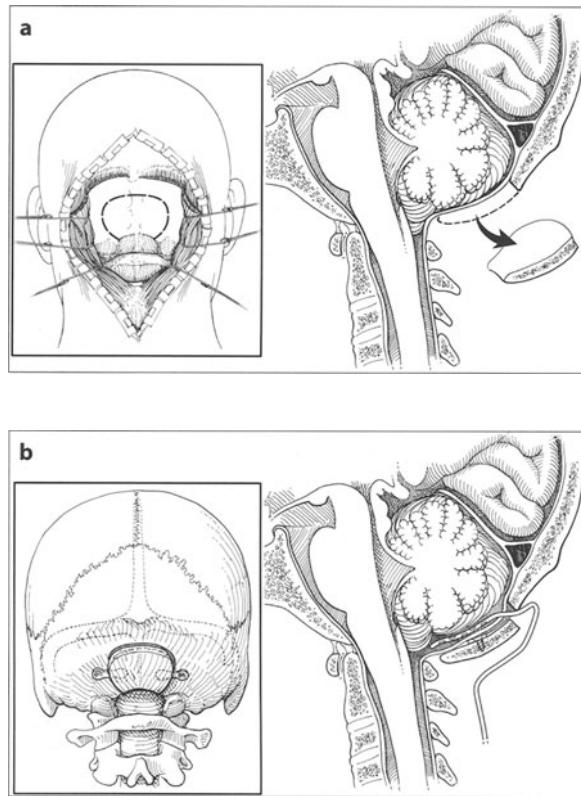


Fig. 4. **a** Artists' rendering of severe Chiari I malformation seen in sagittal and posterior (*insert*) views in a patient with concurrent pseudotumor cerebri. **b** Midsagittal and posterior (*insert*) view of patient after cranial expansion and creation of new, enlarged cisterna magna. (Reproduced with permission from Barrow Neurological Institute)

sumed. Patients whose hydrocephalus is already complicated by hindbrain herniations are seldom candidates for lumboperitoneal shunts, which may worsen the degree of cerebellar descent. This is particularly true of patients with hindbrain herniation in the context of craniofacial syndromes or Chiari II malformations as found in spina bifida patients.

I have had only one significant complication from primary shunting of the subarachnoid space. A 13-year-old patient was treated with a cistern-to-pleural shunt for severe pseudotumor cerebri coexistent with a Chiari I malformation. Six months after the decompression and shunt placement, the patient developed weakness in her lower extremities and was found to have further herniation of her cerebellar tonsils and a holocord syringomyelia (Fig. 5). Subsequently, she was treated with a ventricle-to-cistern-to-pleural shunt that successfully reversed the condition.



Fig. 5. Sagittal magnetic resonance image of patient treated with a cistern-to-peritoneal shunt complicated by the development of syringomyelia and further tonsillar descent

Cephalocranial Disproportion

Subtemporal decompression was an early form of therapy for SVS. The craniectomy improved the compliance of the brain and the ability to keep the ventricular catheter working [14, 15, 16]. It was later recognized that chronically shunted individuals often were left with secondary microcephaly, and various cranial expansion operations were used to manage SVS in patients with long-standing overgrowth of the skull [1, 15]. This approach to managing SVS has been supported by the documentation of closure of cranial sutures as a result of chronic overdrainage [1].

My own experiences with cranial expansion operations for the treatment of SVS in a highly select group of patients in whom other forms of treatment failed has been less successful. Nine operations were performed in six patients. Three patients required a second procedure 18–24 months later. Three patients had a Chiari II malformation with spina bifida, one patient had Pfeiffer's syndrome with a hindbrain herniation, and two patients had hydrocephalus related to posthemorrhagic hydrocephalus of the premature newborn whose course was complicated by severe ventriculitis in the perinatal period and severe secondary microcephaly. The severe headaches with documented increases in ICP were relieved immediately in all six patients in all nine episodes. Symptoms recurred in all patients within 2 years of the procedure. Two patients with severe brain stem dysfunction did not tolerate significant increases in valve pressures. These patients were managed with

bilateral subtemporal craniectomies. The other four patients finally responded to placement of the valves in series.

Headaches Unrelated to ICP

On the recommendation of the Division of Child Neurology at our institution, patients with normal or relatively normal ICP profiles who have shunts and severe headaches are treated with a trial of cyproheptadine. If this therapy is unsuccessful, the patients are referred to specialists in headache management. Except in the context of typical symptoms of migraine and ICP monitoring showing that the shunt is working optimally, one should assume that shunt manipulation is needed.

Shunt Removal: The Ultimate Treatment of the SVS

All hydrocephalus is ultimately obstructive hydrocephalus; we begin to treat hydrocephalus based on the point of obstruction. Frustration with the management of shunt complications and an idea first proposed by Walker et al. [47] led to the possibility that these complications could be treated definitively by a third ventriculostomy to remove shunts and to reestablish reasonably normal CSF dynamics. Others have tried this approach with excellent outcomes [33]. My initial results with this procedure have also been encouraging [2]. Patients with normal volume hydrocephalus are never candidates for endoscopic third ventriculostomy (ETV) for two reasons. First, the ventricles cannot be made large enough to navigate the endoscope safely within the normal or smaller than normal ventricles. Second, the failure of the ventricles to enlarge means that the hydrocephalus is caused by obstruction to CSF outflow from the cortical subarachnoid space and the bypass is proximal to the obstruction.

At this point, only patients with normal-volume hydrocephalus are definitely not candidates for ETV. In other words, if the ventricles expand at the time of shunt occlusion, a patient should be considered for ETV. The obstruction to the CSF flow in these patients is between the third and lateral ventricles and the cortical subarachnoid space. The potential exception to this premise is patients with spina bifida, all of whom harbor the Chiari II malformation. Other authors have had considerable success with ETV in this context [23, 46], but none of my spina bifida patients who have undergone this protocol are shunt-free, for two possible reasons. The first is the markedly distorted

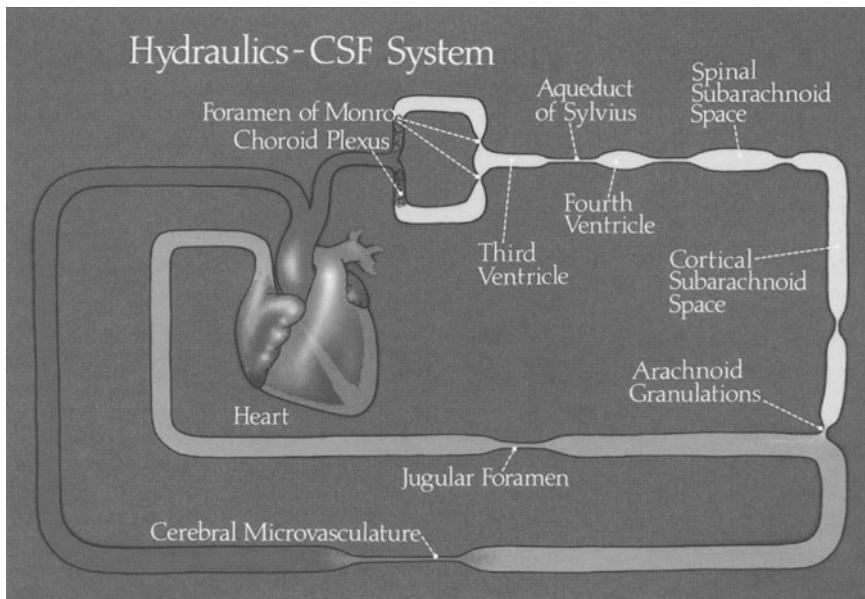


Fig. 6. Circuit diagram of the potential points of obstruction to the flow of CSF. (Reproduced from [38], with permission)

anatomy of the third ventricle in this situation, and the second reflects the four potential sites of obstruction in these patients [35].

The traditional Dandy classification of hydrocephalus as communicating or noncommunicating cannot help determine who is and who is not a candidate for ETV [7, 8]. In 1960, Ransohoff et al. [32] emphasized the obstructive nature of hydrocephalus and suggested changing the name of “communicating hydrocephalus” to “extraventricular obstructive hydrocephalus” and “noncommunicating hydrocephalus” to “intraventricular hydrocephalus”. A circuit diagram of the CSF pathway based on the actual point of obstruction (Fig. 6) [38] leads to a classification scheme that helps individualize the treatment of hydrocephalus and its complications. Contemporary imaging techniques pinpoint the actual site of obstruction, especially at the time of shunt failure. Consequently, treatment strategies can be individualized to each patient’s specific needs.

ETV is a bypass between the third ventricle and the cortical subarachnoid space. I have always assumed that patients with an obstruction of the aqueduct of Sylvius (between the third and fourth ventricles) were ideal candidates for ETV. Based on this discussion, patients with an obstruction within or at the outflow of the fourth ventricle and between the spinal subarachnoid space and cortical subarachnoid space would also be candidates for the procedure. Numerous pathophysiolgies cause obstructions between the spinal subarachnoid space and cortical subarachnoid space, including Chiari I and II malformations and subarachnoid hemorrhage. Acute hemorrhage from

aneurysms, arteriovenous malformations, trauma, and intraventricular hemorrhage of the premature newborn initially leads to filtration of the blood products through the arachnoid granulations (i.e., blockage between the cortical subarachnoid space and the SSS). Weeks later in the course of these diseases, the hemorrhage leads to thickening of the arachnoid around the base of the skull surrounding the cerebellar tonsils. In autopsy series, patients who objectively have responded to shunting for normal-pressure hydrocephalus show severe thickening of the arachnoid at the basal cisterns at the foramen magnum [11]. Theoretically, patients with normal-pressure hydrocephalus may be candidates for ETV. Several small series of patients with normal-pressure hydrocephalus have been treated with ETV, and the results have been encouraging [26].

Figure 7 is my algorithm for the treatment of patients with SVS who have not responded to valve upgrade with the placement of a DRS device. Depending on the ability to plan treatment, patients either underwent exteriorization of the shunt along the tract, or the shunt was removed and replaced with an external ventricular drain. The latter is preferred because the EVD allows ICP to be measured as the ventricles attempt to expand. Postoperatively, patients are monitored carefully in the intensive care unit. The next morning, CT or MR imaging is performed to determine whether the ventricular system has dilated sufficiently to allow a third ventriculostomy to be performed. In a minority of patients, the ventricles dilate only slightly and they will be asymptomatic. This group of patients has been de-

fined previously [41]. Except in the context of the Chiari II malformation, patients with only moderate ventricular dilatation and no increase in ventricular size may have the ventricular drain removed. These patients have become “shunt-independent” and need no further intervention. We tend to observe these patients for 3–4 days to ascertain that it is safe to remove the shunt. Patients with spina bifida whose hydrocephalus is related to the Chiari II malformation are a special case. Uniquely, these patients have a propensity to deteriorate insidiously and may return as long as 5 years after shunt removal with sudden death or severe respiratory compromise. The diagnosis of shunt-independent arrest of hydrocephalus must be made with extreme caution in individuals with spina bifida. These patients must be followed as closely as shunted individuals for subtle signs of deterioration [35, 41].

If the ventricles have enlarged significantly, patients undergo ETV. Several key technical points should be remembered when performing ETV in this context. ETV should probably not be the first third ventriculostomy performed by the surgeon because it may be more challenging than other endoscopic third ventriculostomies. When performing ETV in chronically shunted individuals, the

surgeon must assume that a new entry burr hole will need to be drilled. Accessing the frontal horn of the lateral ventricle in small children with large ventricles is quite simple, and the point of entry may not be vitally important. Safe performance of ETV in this context depends to a great extent on surgical planning. Many burr holes for ventricular catheter placement are either too far forward or too lateral to perform an ETV safely. If the burr hole is drilled about 2 cm lateral to the sagittal suture and just on or just anterior to the coronal suture, the trajectory into the third ventricle is almost always ideal. If the burr hole is placed too far anteriorly, the trajectory will be toward the cerebral peduncle. After the endoscope is in the third ventricle, it will need to be directed anteriorly with the high likelihood of damaging at least the ipsilateral column of the fornix (Fig. 8).

Patients with chronically distended ventricles have a clear membrane at the floor of third ventricle that allows clear visualization of the mamillary bodies and the underlying basilar artery. In patients undergoing this protocol, the floor of the third ventricle is thin enough that it can be seen to fall away with gentle irrigation. However, it is not so thin as to be transparent. Therefore, it is important to make the perforation under direct vision and as far forward as is practical. The trajectory from the level of the coronal suture allows the red-orange structure of the infundibular recess to be visualized. The safest place to make the hole is in the midline just behind the infundibular recess. Personally, I like to use a blunt grabbing instrument to make the original hole and to dilate the hole with small balloons.

To maximize safety for patients, an external ventricular drain is left behind at the time of ETV. It allows residual blood to be flushed and ICP to be monitored. In patients who do not tolerate ETV, it allows the drainage of CSF before definitive shunting. In patients who are suspected of showing chronic drug-seeking behavior, a ventricular reservoir can be left behind so that ICP can be measured easily if the patient later returns with recurrent headaches. One group of neurosurgeons has recommended managing post-ETV patients with a reservoir incorporating a Telesensor™ so that ICP can be measured noninvasively [18].

It is difficult to predict who will and who will not respond to ETV based on the origin of the hydrocephalus. Apart from hydrocephalus in the context of spina bifida, I am unable to define candidates based on the original etiology of their hydrocephalus. I have had successes and failures in patients with congenital hydrocephalus, hydrocephalus related to subarachnoid hemorrhage or infection, and hydrocephalus that persists late after

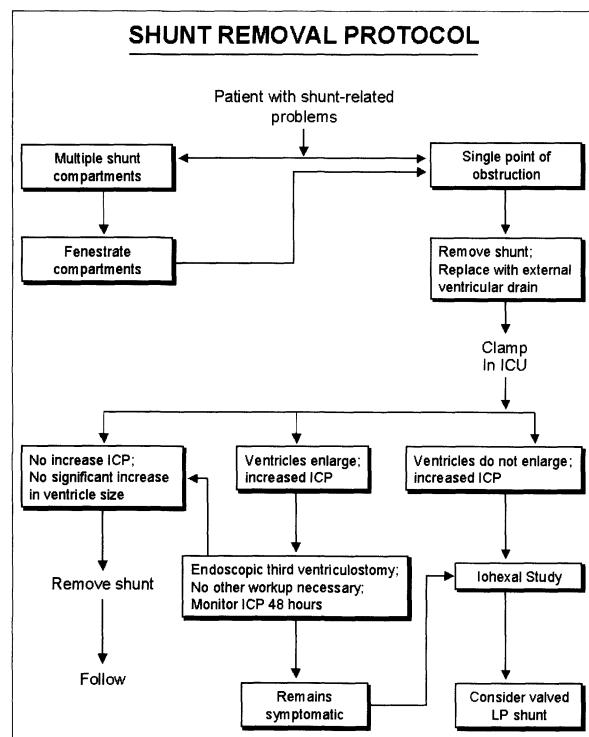


Fig. 7. Algorithm for the programmed removal of shunts in patients with recurrent shunt difficulties. (Reproduced with permission from Barrow Neurological Institute)

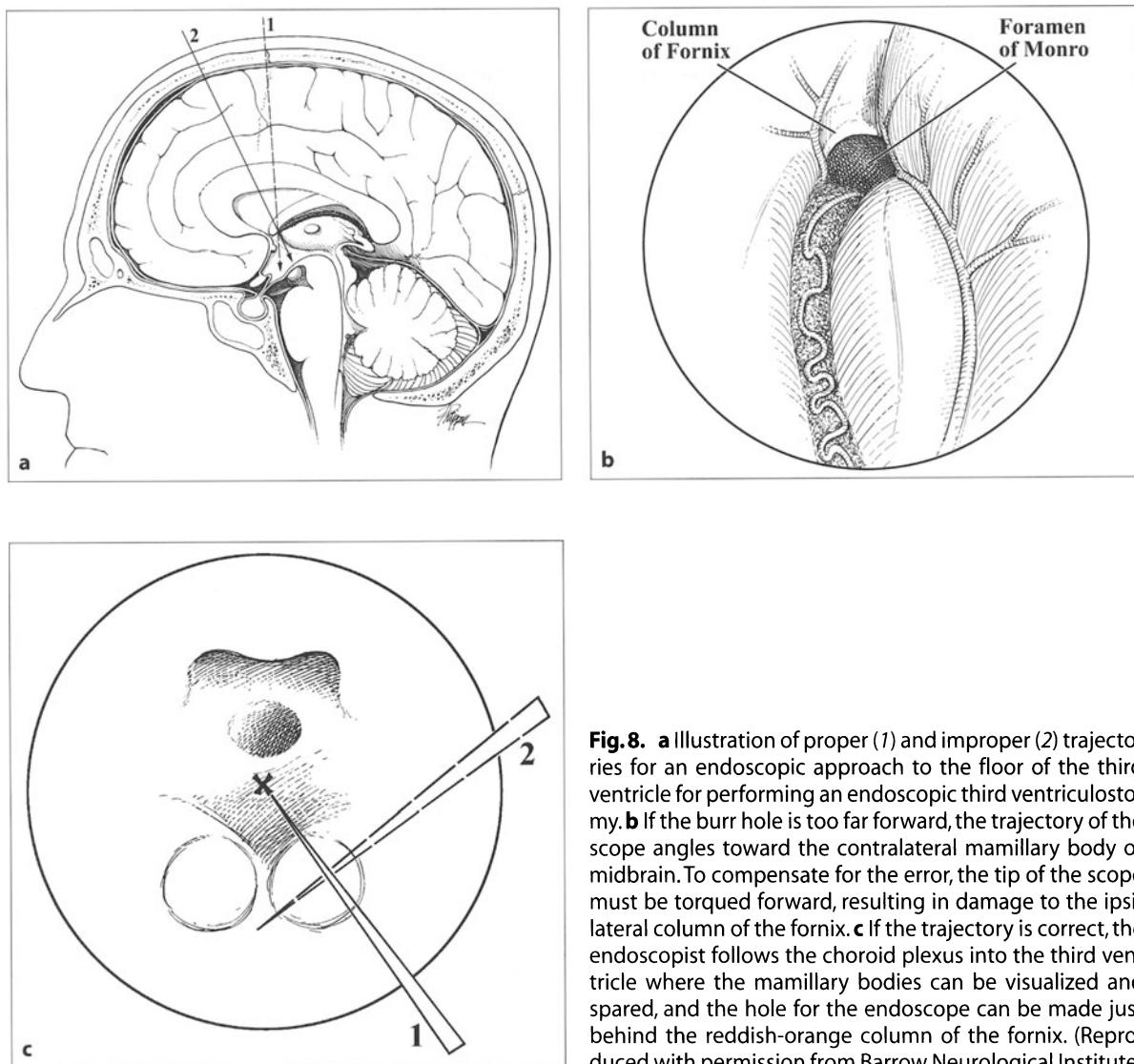


Fig. 8. **a** Illustration of proper (1) and improper (2) trajectories for an endoscopic approach to the floor of the third ventricle for performing an endoscopic third ventriculostomy. **b** If the burr hole is too far forward, the trajectory of the scope angles toward the contralateral mamillary body or midbrain. To compensate for the error, the tip of the scope must be torqued forward, resulting in damage to the ipsilateral column of the fornix. **c** If the trajectory is correct, the endoscopist follows the choroid plexus into the third ventricle where the mamillary bodies can be visualized and spared, and the hole for the endoscope can be made just behind the reddish-orange column of the fornix. (Reproduced with permission from Barrow Neurological Institute)

tumor resection [2]. I have attempted ETV in five patients with spina bifida, all of whom have had to have their ventriculoperitoneal shunts replaced. In contrast, Teo and Jones have been successful in more than 50% of their cases [46].

My experience with late deterioration in the spina bifida population has led me to be quite conservative about the diagnosis of “shunt-independent arrest” in this context. The third ventricular anatomy in patients with Chiari II malformation is very challenging. Despite massive dilatation of the lateral ventricles, the foramen of Monro is usually quite small, as is the third ventricle. This geometry is related to the large size of the massa intermedia in this condition. Finally, the third ventricle almost has a vertical orientation and the floor is almost always opaque. These conditions make it difficult to deter-

mine where it is safe to make the hole. Finally, patients with the Chiari II malformation have as many as four potential sites of obstruction to the flow of CSF, and a significant number of these patients have high sagittal sinus pressure.

Patients without spina bifida who remain symptomatic despite ETV undergo ventriculography with iohexol several days after ETV. Patients undergo a CT scan of the head about 1 h after iohexol (3–8 ml) is injected. This protocol allows the neurosurgeon to determine the cause of the failure. If the hole in the floor of the third ventricle is closed, the surgeon may decide that the technical problems in performing the ETV were such that a second attempt should be made. However, in most cases, dye will rapidly flow into the spinal subarachnoid space if the surgeon has succeeded in creating the hole in the floor of the third ventricle.

cle. I prefer to treat these patients with lumboperitoneal shunts as the definitive treatment for SVS. Usually, imaging of the brain after a lumboperitoneal shunt has been placed reveals a slight degree of dilatation of the ventricular system because the shunt now accesses both the ventricular CSF and the CSF within the cortical subarachnoid space. Patients also can be treated by shunting the cisterna magna where the CSF of the spinal and cortical subarachnoid space mixes. Very high-pressure valves or valves in series should be used in these situations.

Finally, patients who are symptomatic with high ICP despite having no change in ventricular volume have normal-volume hydrocephalus and are treated with lumboperitoneal shunts or cisterna magna shunting as described above. When a lumboperitoneal shunt is selected for patients with normal-volume hydrocephalus, I replace the EVD with a ventricular reservoir to measure ICP if the patient later becomes symptomatic. It is easier to measure ICP from a subcutaneous cranial reservoir than to perform a lumbar puncture for pressure measurements in a struggling child. I have termed this combination of a ventricular reservoir with a lumboperitoneal shunt the "Caleb procedure" in honor of a patient with achondroplasia from whom I learned some of these experiences.

Conclusion

The lack of accepted definitions has led to considerable misunderstanding among clinicians and researchers. What one pediatric neurosurgeon means by the term "slit ventricle syndrome" is not the same as the meaning intended by another pediatric neurosurgeon. I believe that all of the potential definitions of SVS have been incorporated into this discussion. Personally, I would like to see the term "slit ventricle syndrome" reserved for our most common group of patients – those with either intermittent proximal obstruction or intermittent low-pressure states. This relatively straightforward problem confronts all pediatric neurosurgeons and all neurosurgeons who have a population of children and young adults in their practices. The condition responds well to intervention, and most shunt manufacturers have hardware that addresses the problem.

There are more precise terminologies for the other syndromes associated with shunts, incapacitating headaches, and small ventricles. Patients should be referred to as having shunt failure without ventricular enlargement, for which the term "normal-volume hydrocephalus" has been used. However, "shunt-associated pseudotumor" might be a more appropriate

term. Patients with working shunts but high ICP have cephalocranial disproportion. Finally, patients with normal ICP dynamics, severe intermittent headaches typical of migraines, and a strong family history of migraine should probably be referred to as having shunt-related migraines. The use of these terms will demystify this straightforward problem in biophysics. Each term suggests a specific, individual strategy for management which is likely to bring relief to the patient and peace to the neurosurgeon.

References

1. Albright AL, Tyler-Kabara E: Slit-ventricle syndrome secondary to shunt-induced suture ossification. *Neurosurgery* 48:764-770, 2001
2. Baskin JJ, Manwaring KH, Rekate HL: Ventricular shunt removal: the ultimate treatment of the slit ventricle syndrome. *J Neurosurg* 88:478-484, 1998
3. Chumas PD, Armstrong DC, Drake JM, et al: Tonsillar herniation: the rule rather than the exception after lumboperitoneal shunting in the pediatric population. *J Neurosurg* 78:568-573, 1993
4. Chumas PD, Kulkarni AV, Drake JM, et al: Lumboperitoneal shunting: a retrospective study in the pediatric population. *Neurosurgery* 32:376-383, 1993
5. Cserr HF: Relationship between cerebrospinal fluid and interstitial fluid of brain. *Fed Proc* 33:2075-2078, 1974
6. Cutler R, Page L, Galicich J, et al: Formation and absorption of cerebrospinal fluid in man. *Brain* 91:707-720, 1968
7. Dandy W, Blackfan K: An experimental and clinical study of internal hydrocephalus. *JAMA* 61:2216-2217, 1913
8. Dandy W, Blackfan K: Internal hydrocephalus. An experimental, clinical and pathological study. *Am J Dis Child* 8:406-482, 1914
9. da Silva MC, Drake JM: Effect of subcutaneous implantation of anti-siphon devices on CSF shunt function. *Pediatr Neurosurg* 16:197-202, 1991-1992
10. DeLand FH, James AEJ, Ladd DJ, et al: Normal pressure hydrocephalus: a histologic study. *Am J Clin Pathol* 58:58-63, 1972
11. Di Rocco C, Di Trapani G, Maira G, et al: Anatomical-clinical correlations in normotensive hydrocephalus. Reports on three cases. *J Neurol Sci* 33:437-452, 1977
12. el Shafei I, Hafez MA: Ventriculojugular shunt against the direction of blood flow. IV. Technical modifications and policy for treatment. *Childs Nerv Syst* 7:197-204, 1991
13. Engel M, Carmel PW, Tutoring AM: Increased intraventricular pressure without ventriculomegaly in children with shunts: "normal volume" hydrocephalus. *Neurosurgery* 5:549-552, 1979
14. Epstein FJ, Fleischer AS, Hochwald GM, et al: Subtemporal craniectomy for recurrent shunt obstruction secondary to small ventricles. *J Neurosurg* 41:29-31, 1974
15. Epstein F, Lapras C, Wisoff JH: 'Slit-ventricle syndrome': etiology and treatment. *Pediatr Neurosci* 14:5-10, 1988
16. Epstein F, Marlin AE, Wald A: Chronic headache in the shunt-dependent adolescent with nearly normal ventricular volume: diagnosis and treatment. *Neurosurgery* 3:351-355, 1978

17. Francis PM, Beals S, Rekate HL, et al: Chronic tonsillar herniation and Crouzon's syndrome. *Pediatr Neurosurg* 18:202-206, 1992
18. Frim DM, Goumnerova LC: Telemetric intraventricular pressure measurements after third ventriculocisternostomy in a patient with noncommunicating hydrocephalus. *Neurosurgery* 41:1425-1430, 1997
19. Hakim CA (ed): The physics and physiopathology of the hydraulic complex of the central nervous system. Massachusetts Institute of Technology, Boston, 1985
20. Hyde-Rowan MD, Rekate HL, Nulsen FE: Reexpansion of previously collapsed ventricles: the slit ventricle syndrome. *J Neurosurg* 56:536-539, 1982
21. Johnston I, Jacobson E, Besser M: The acquired Chiari malformation and syringomyelia following spinal CSF drainage: a study of incidence and management. *Acta Neurochir (Wien)* 140:417-428, 1998
22. Johnston IH, Sheridan MM: CSF shunting from the cisterna magna: a report of 16 cases. *Br J Neurosurg* 7:39-43, 1993
23. Jones RF, Kwok BC, Stening WA, et al: Third ventriculostomy for hydrocephalus associated with spinal dysraphism: indications and contraindications. *Eur J Pediatr Surg* 1(6 Suppl):5-6, 1996
24. Karahalios DG, Rekate HL, Khayata MH, et al: Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. *Neurology* 46:198-202, 1996
25. Kaufman B, Weiss MH, Young HF, et al: Effects of prolonged cerebrospinal fluid shunting on the skull and brain. *J Neurosurg* 38:288-297, 1973
26. Larsson A, Stephensen H, Wikkelso C: Adult patients with "asymptomatic" and "compensated" hydrocephalus benefit from surgery. *Acta Neurol Scand* 99:81-90, 1999
27. Linder M, Diel JT, Sklar FH: Significance of postshunt ventricular asymmetries. *J Neurosurg* 55:183-186, 1981
28. Lorenzo A, Page L, Watters G: Relationship between cerebrospinal fluid formation, absorption and pressure in human hydrocephalus. *Brain* 93:679-692, 1970
29. Milhorat T, Hammock M, Fenstermacher J, et al: Cerebrospinal fluid production by the choroid plexus and brain. *Science* 173:330-332, 1971
30. Olivero WC, Rekate HL, Chizeck HJ, et al: Relationship between intracranial and sagittal sinus pressure in normal and hydrocephalic dogs. *Pediatr Neurosci* 14:196-201, 1988
31. Pierre-Kahn A, Hirsch JF, Renier D, et al: Hydrocephalus and achondroplasia. A study of 25 observations. *Childs Brain* 7:205-219, 1980
32. Ransohoff J, Shulman K, Fishman R: Hydrocephalus. *J Pediatr* 56:399-411, 1960
33. Reddy K, Fewer HD, West M, et al: Slit ventricle syndrome with aqueduct stenosis: third ventriculostomy as definitive treatment. *Neurosurgery* 23:756-759, 1988
34. Rekate HL: Parenchymal cerebrospinal fluid extravasation as a complication of computerized tomography. Case report. *J Neurosurg* 52:113-115, 1980
35. Rekate HL: Management of hydrocephalus and the erroneous concept of shunt independence in spina bifida patients. *BNI Quarterly* 4:17-20, 1988
36. Rekate HL: Brain turgor (K_b): intrinsic property of the brain to resist distortion. *Pediatr Neurosurg* 18:257-262, 1992
37. Rekate HL: Classification of slit-ventricle syndromes using intracranial pressure monitoring. *Pediatr Neurosurg* 19:15-20, 1993
38. Rekate HL: Circuit diagram of the circulation of cerebrospinal fluid. 1989. *Pediatr Neurosurg* 21:248-252, 1994
39. Rekate HL, Brodkey JA, Chizeck HJ, et al: Ventricular volume regulation: a mathematical model and computer simulation. *Pediatr Neurosci* 14:77-84, 1988
40. Rekate HL: McCormick JM: Failure to demonstrate a brain transmissibility factor. In: Marlin A (ed) Concepts in pediatric neurosurgery. Karger, Zurich, pp 235-242, 1990
41. Rekate HL, Nulsen FE, Mack HL, et al: Establishing the diagnosis of shunt independence. In: Choux M (ed) Shunts and problems with shunts. Karger, Basel, pp 223-226, 1982
42. Rekate HL, Williams FCJ, Brodkey JA, et al: Resistance of the foramen of Monro. *Pediatr Neurosci* 14:85-89, 1988
43. Sainte-Rose C, LaCombe J, Pierre-Kahn A, et al: Intracranial venous sinus hypertension: cause or consequence of hydrocephalus in infants? *J Neurosurg* 60:727-736, 1984
44. Shulman K, Ransohoff J: Sagittal sinus venous pressure in hydrocephalus. *J Neurosurg* 23:169-173, 1965
45. Steinbok P, Hall J, Flodmark O: Hydrocephalus in achondroplasia: the possible role of intracranial venous hypertension. *J Neurosurg* 71:42-48, 1989
46. Teo C, Jones R: Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25:57-63, 1996
47. Walker ML, Fried A, Petronio J: Diagnosis and treatment of the slit ventricle syndrome. *Neurosurg Clin N Am* 4:707-714, 1993

Endoscopic Anatomy of the Ventrices

PHILIPPE DECQ

Introduction

Dilated ventricular cavities are particularly suitable for neurosurgical endoscopy. Although purely diagnostic endoscopy is no longer particularly useful due to progress in medical imaging, especially MRI, this technique is still very useful for certain precise procedures optimally and most safely performed under visual control [1]. The main indication for neurosurgical endoscopy remains ventriculocisternostomy for the treatment of obstructive hydrocephalus. The other indications are much more limited due to the small number of cases to be treated, but include colloid cysts of the third ventricle or rare cases of biopsy of intraventricular lesions poorly accessible to stereotactic biopsy procedures. Intraventricular endoscopic navigation is facilitated by accurate guidance; in other words, the operator must always know where he is. It is therefore essential to have perfect knowledge of the intraventricular anatomy, in order at all times to recognize the part of the ventricular system in which the endoscope is situated and clearly identify the anatomical structures and outlines encountered [6].

Materials and Method

Technical Considerations

Intracranial endoscopy in man is performed in France with rigid endoscopes, as the modalities of sterilization of flexible endoscopes are not compatible with current legislation in this country. Due to the fear of contamination by prions, all surgical instruments must be sterilized by a combination of two procedures: decontamination in alkaline medium and sterilization for 20 min at 134 °C. Flexible systems cannot be sterilized by such procedures and therefore

cannot be used apart from disposable systems, which remain expensive.

Rigid systems offer a quality of vision which remains incomparable to that provided by flexible systems. They also offer the theoretical possibility of an angle of view of 0° to 120° according to the objective lens used. The most commonly used in practice is a 30° objective, for two main reasons:

1. As instruments are introduced via an operating channel parallel to the objective, their extremities converge towards the center of the image directed at 30° and are therefore perfectly visualized, while, with a 0° objective, the instruments remain in the periphery of the image and are consequently less effectively controlled.
2. A 30° objective, by simple rotation, provides an angle of view with a surface area twice as large as that obtained with a 0° objective (Fig. 1).

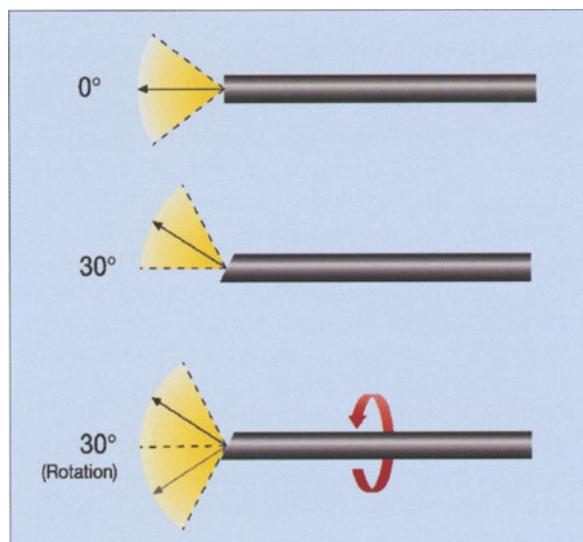


Fig. 1. Field of view of a 0° objective compared to a 30° objective. Simple rotation of the 30° objective provides a very large field of view

On the other hand, manipulation of a 30° objective is more difficult and requires a learning curve that is actually rapidly acquired by practice.

The endoscopic images presented in this paper were obtained with a Storz 2.9-mm-diameter objective with a 30° angle of view (Karl Storz GmbH & Co. Kg, Tuttlingen, Germany). The objective is introduced into an endoscope sheath maintained in place by an articulated arm, which is used to immobilize the endoscope as required, allowing sufficient time to easily recognize the various structures observed while avoiding the risk of excessive manipulation of the cerebral parenchyma crossed by the endoscope, as can occur when the endoscope is guided and held by hand. The endoscope is equipped with a miniature camera connected to a digital image acquisition system (DKR® Sony, Sony, Paris, France) and then to a video monitor.

Method

Ventricular endoscopy can only be performed after considerable dilatation of the ventricular cavities. It must therefore be kept in mind that the anatomy observed corresponds to that of dilated ventricular cavities in which the structures have been displaced and separated from each other. Endoscopic navigation cannot be performed in normal ventricles, which are too small and would be damaged by passage of the endoscope.

Ventricular cavities can theoretically be approached from a number of angles depending on the aim of treatment [3]. In practice, the vast majority of operations are performed through the third ventricle via the interventricular foramen of Monro, using an immediately precoronal frontal burr hole. This burr hole is classically placed just anterior to the coronal suture, 2–3 cm from the midline, on the mid-pupillary line [3]. The images obtained initially visualize the periphery of the interventricular foramen of Monro and its variations: the anterior part of the frontal horn is visualized by directing the 30° objective anteriorly; the objective is then rotated medially to visualize the region of the interventricular septum and then enters the body of the lateral ventricle; finally, the end of the rotation visualizes the lateral wall of the lateral ventricle. The structures adherent to these walls, essentially veins and choroid plexuses, are clearly and easily identified.

Introduction of the endoscope into the cavity of the dilated third ventricle visualizes all of its walls and constituent elements and structures by progressive rotation of the objective.

Results

Orifice of the Third Ventricle: The Interventricular Foramen of Monro

The interventricular foramen of Monro, corresponding to the inlet orifice of the third ventricle situated in the floor of the lateral ventricle, is identified by the endoscope introduced into the lateral ventricle. The first identifiable anatomical structures are the choroid plexuses running over the floor of the lateral ventricle. The foramen is identified by following the choroid plexuses anteriorly, as the choroid plexuses constitute the posterior wall of the foramen (Fig. 2). The choroid plexuses are reflected posteriorly at the posterior wall of the foramen and contribute to formation of the roof of the third ventricle. Choroid plexuses are therefore never observed anterior to the interventricular foramen of Monro. The anterior horn of the lateral ventricle is totally devoid of choroid plexus (Fig. 3).

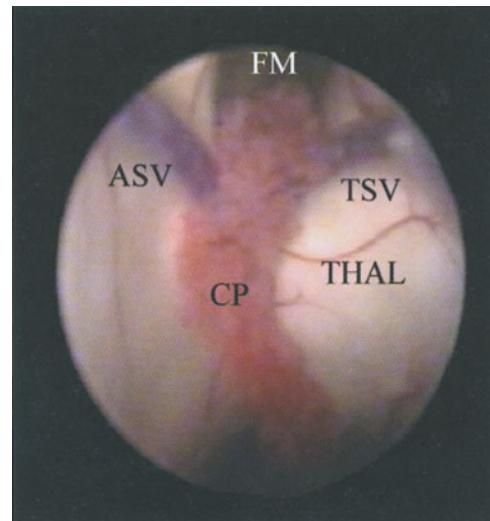


Fig. 2. Endoscopic view of the right lateral ventricle. The choroid plexus (CP) is easily identified at the medial border of the outline of the thalamus (THAL). The interventricular foramen of Monro (FM) with the venous angle formed by anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV) can be identified by following the choroid plexus anteriorly

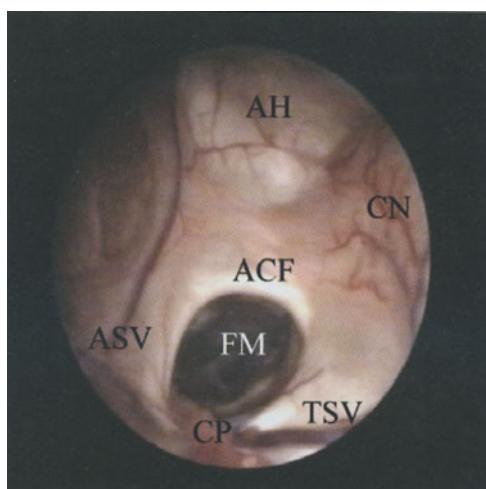
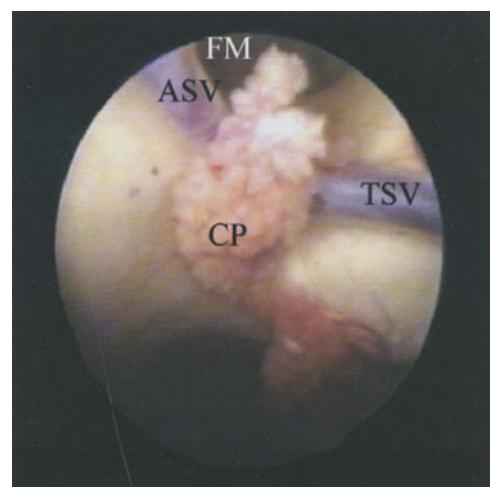


Fig. 3. Endoscopic view of the anterior horn (AH) of the right lateral ventricle. The posterior margin of the interventricular foramen of Monro (FM) corresponds to the anterior extremity of the choroid plexus (CP) with the venous angle formed by anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV). The anterior margin of the foramen is composed of the anterior column of the fornix (ACF). The outline of the head of the caudate nucleus (CN) can be seen in the lateral part of the anterior horn

sential landmark of the foramen, as the choroid plexus is the most easily identifiable structure of the lateral ventricle. Once this structure has been identified, it can be simply followed progressively anteriorly until the interventricular foramen of Monro is visualized (Fig. 2). The choroid plexus travels over the superior surface of the thalamus, either in a straight line (Fig. 2) or with a sinuous course (Fig. 4). The posterior horn of the lateral ventricle, whose walls are covered by fine vessels, especially medial atrial veins [4], can sometimes be seen posteriorly (Fig. 5). The cau-



Anterior Margin of the Foramen

The totally avascular anterior margin is composed of the anterior column of the fornix. This structure, 2–3 mm in diameter, arises from the mamillary bodies, elements of gray matter protruding into the floor of the third ventricle. The anterior column of the fornix travels from the mamillary bodies towards the lamina terminalis, crosses over the anterior commissure posteriorly, and travels superiorly and medially, describing an anterior concave curve to form the anterior and then the medial margins of the interventricular foramen. The anterior column merges anteriorly, with no visible margin, with the floor of the anterior horn of the lateral ventricle, containing small vessels, but never any choroid plexus (Fig. 3). The protruding head of the caudate nucleus may be seen in the lateral part of the anterior horn.

Posterior Margin of the Foramen

The posterior margin of the foramen is essentially composed of the angle of reflection of the choroid plexus, as it corresponds to the most anterior projection in the lumen of the lateral ventricle before it turns inferiorly and then posteriorly to become part of the choroid plexus of the third ventricle. It is the es-

Fig. 4. Endoscopic view of the right lateral ventricle. The choroid plexus (CP) may have a sinuous course. The interventricular foramen of Monro (FM) with the venous angle formed by anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV) can be identified by following the choroid plexus anteriorly

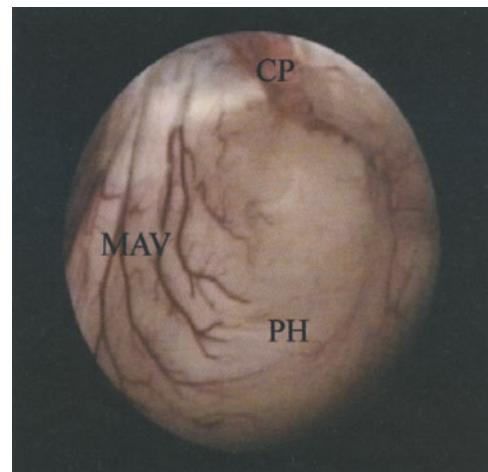


Fig. 5. Endoscopic view of the posterior horn (PH) of the right lateral ventricle. The choroid plexus (CP) is easily identified and indicates the floor of the lateral ventricle. The group of medial atrial veins (MAV) run over the medial wall

date nucleus can be seen at the lateral edge of the floor of the body of the lateral ventricle (Fig. 6).

The posterior and medial margin is also composed of the angle of anastomosis of anterior septal veins, choroidal veins (rarely visible within the choroid plexus), and thalamostriatal veins. The angle of this anteriorly facing Y is usually about 80–90° (Fig. 7). This angle can be much more acute (Fig. 8) or, on the contrary, completely open to 180° (Fig. 4). The veins usual-

ly have the same caliber (Fig. 7), but one of the veins, either the thalamostriatal vein (Fig. 8) or the anterior septal vein [4], may be much larger (Fig. 9). In some cases, no vein can be clearly identified at the edge of the interventricular foramen (Fig. 10). Finally, in some cases of hydrocephalus, the lateral ventricle opens widely into the third ventricle, with loss of the posterior margin. In this case, the choroid plexus remains adherent laterally to the outline of the thalamus (Fig. 11).

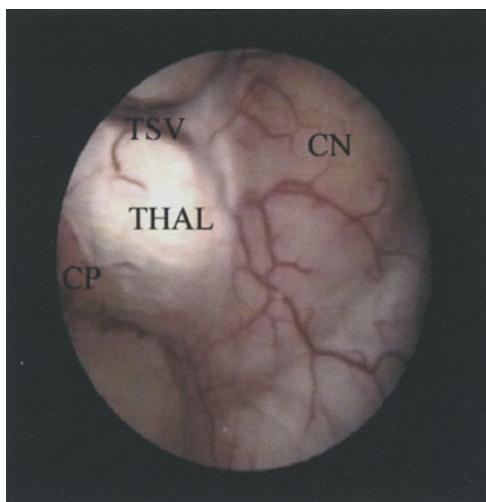


Fig. 6. Endoscopic view of the right lateral ventricle. The choroid plexus (CP) is easily identified at the medial edge of the outline of the thalamus (THAL). The body of the caudate nucleus (CN), drained anteriorly by the thalamostriatal vein (TSV), can be seen at the lateral edge of the body of the ventricle

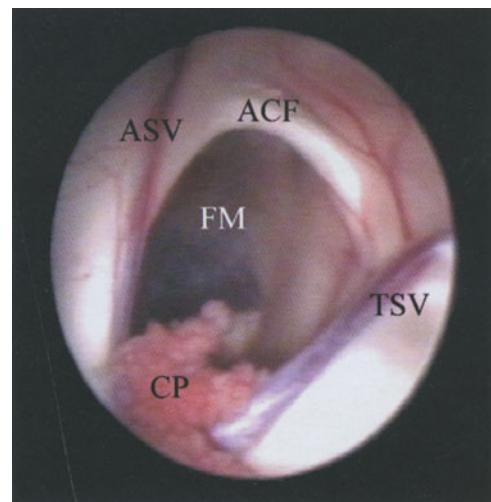


Fig. 8. Endoscopic view of the right interventricular foramen of Monro (FM). The anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV) forms an acute angle. The ASV has a smaller caliber than the TSV. The anterior column of the fornix (ACF) constitutes its anterior limit

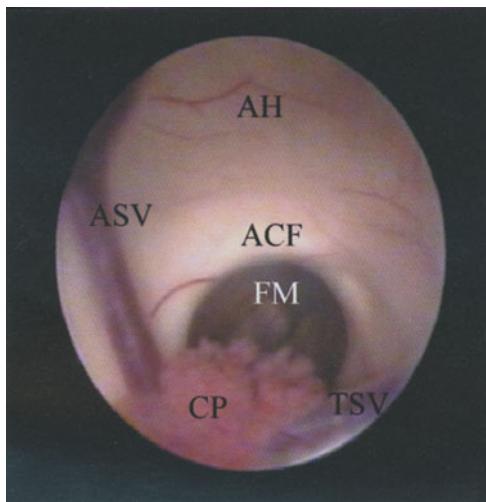


Fig. 7. Endoscopic view of the right interventricular foramen of Monro (FM). The anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV) forms an angle of 90°. The anterior column of the fornix (ACF) constitutes the anterior limit prolonged by the floor of the anterior horn (AH)

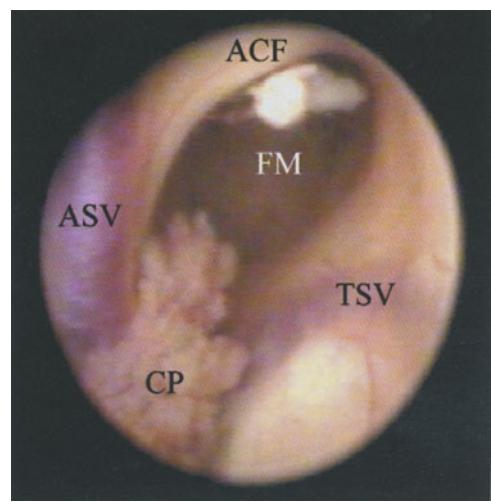


Fig. 9. Endoscopic view of the right interventricular foramen of Monro (FM). The anastomosis of the anterior septal vein (ASV) and thalamostriatal vein (TSV) forms an acute angle. The ASV has a larger caliber than the TSV. The anterior column of the fornix (ACF) constitutes its anterior limit

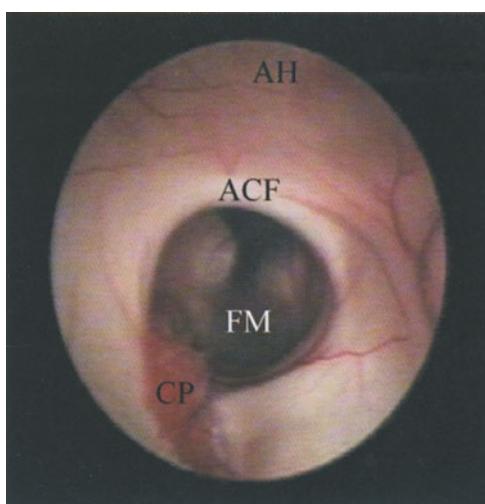


Fig. 10. Endoscopic view of the right interventricular foramen of Monro (FM). No vein is visible at its periphery. The anterior column of the fornix (ACF) constitutes its anterior limit prolonged by the floor of the anterior horn (AH)

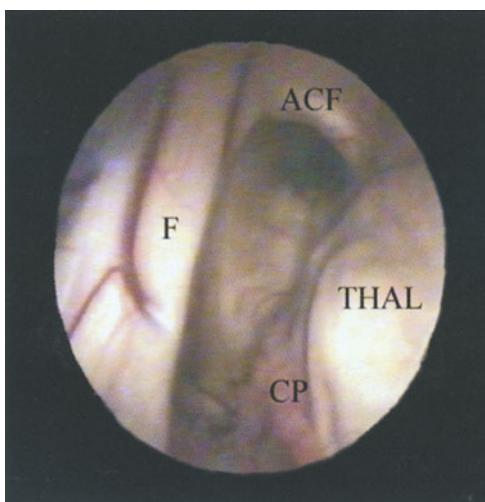


Fig. 11. Endoscopic view of the right interventricular foramen of Monro. It is completely open posteriorly, allowing free communication between the lateral ventricle and the third ventricle. The choroid plexus (CP) remains adherent laterally to the thalamus (THAL). The anterior column of the fornix (ACF) constitutes its anterior limit. F, fornix

vein. It is not unusual, in longstanding hydrocephalus, for the septum to be dehiscent, with a spiderweb appearance, and the interventricular foramen or the contralateral choroid plexus may be seen through the spaces of this network (Fig. 12). All of the posterior part of the two lateral ventricles can be seen more posteriorly (Fig. 13).

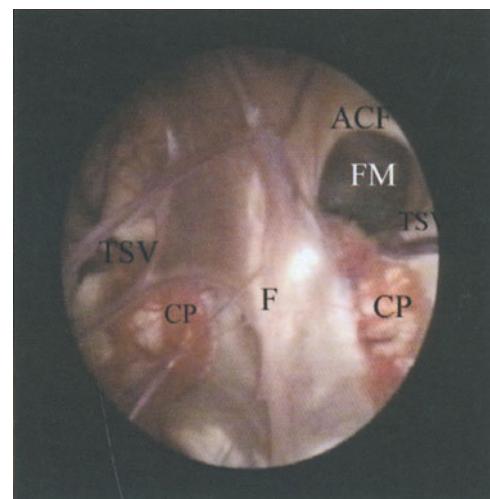


Fig. 12. Endoscopic view of the two lateral ventricles seen from the right side. The choroid plexus (CP) is easily identified in the two ventricles, together with the two thalamostriate veins (TSV) through the dehiscent septum, the inferior part of which contains the body of the fornix (F)

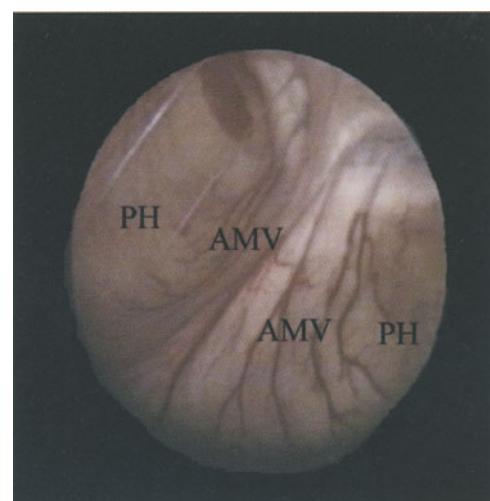


Fig. 13. Endoscopic view of the posterior part of the two lateral ventricles seen from the right side. The two groups of medial atrial veins (AMV) are easily identified on the two medial walls of the posterior horns (PH) through the dehiscent septum

Medial Margin of the Foramen

The medial margin of the foramen is composed of the anterior column of the fornix, which fuses with the contralateral column to form the body of the fornix. It continues, with no apparent distinction, with the interventricular septum, containing the anterior septal

Lateral Margin of the Foramen

The lateral margin of the foramen is marked by the anterior outline of the thalamus, in front of which the thalamostriatal vein is often observed. More laterally, this vein arises from the junction of several branches draining the anterior part of the caudate nucleus (striatum), hence its name (Fig. 14).

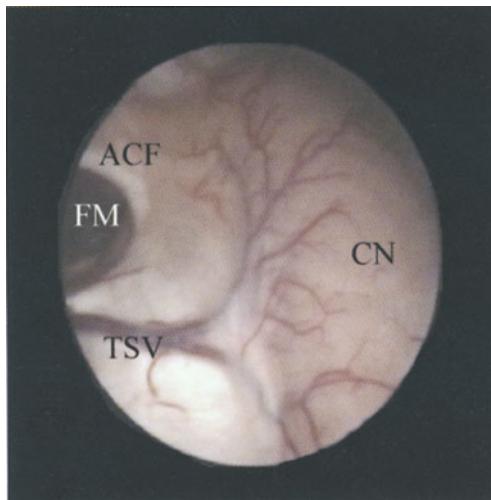


Fig. 14. Endoscopic view of the lateral edge of the right foramen of Monro (FM) prolonged anteriorly by the anterior column of the fornix (ACF). The outline of the caudate nucleus (CN), drained by the thalamostriatal vein (TSV), can be seen laterally

cinereum and the mamillary bodies. The orifice of the ventriculocisternostomy should be performed in the anterior part of the premamillary recess, immediately posterior to the outline of the dorsum sellae that may sometimes be observed. The premamillary recess is sometimes very small (Fig. 16) or, on the contrary, may be very large (Fig. 17), or even deep (Fig. 18). The mamillary bodies are sometimes widely separated from each other with less marked relief (Fig. 17).

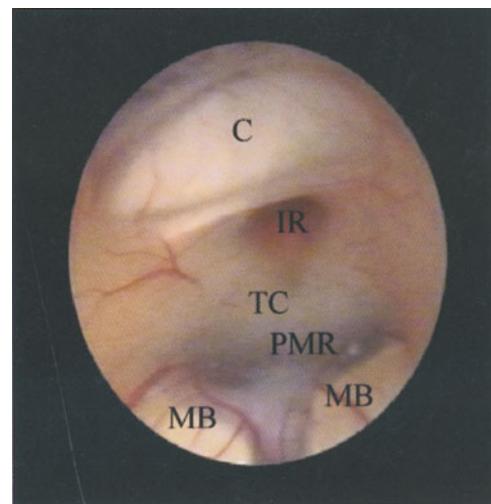


Fig. 15. Endoscopic view of the anterior part of the third ventricle. The anterior wall is formed, from superior to inferior, by the outline of the optic chiasm (C). The anterior part of the floor of the third ventricle is composed, from anterior to posterior, of the infundibular recess (IR), tuber cinereum (TC), premamillary recess (PMR), and the prominence of the two mamillary bodies (MB)

Anterior Part of the Third Ventricle

Once the interventricular foramen of Monro has been clearly identified, it is easy to enter the third ventricle. After passing through the foramen, it becomes of course no longer visible. It is then essential to avoid any traumatic movements that can damage the margins of the foramen, which may be forgotten as they are no longer visible. Advancement of the scope may deform the anterior column of the fornix, and retraction may damage the venous angle, possibly causing bleeding that may be difficult to control.

When advanced anteriorly at an angle of 30°, the endoscope visualizes all of the anterior wall and the anterior part of the floor of the third ventricle (Fig. 15). From superior to inferior, the following structures can be identified: anterior commissure, outline of the optic chiasm, then the pink orifice of the infundibular recess. A zone of whitish matter, the tuber cinereum, lies just posteriorly to the infundibular recess. A premamillary recess can be seen between the tuber

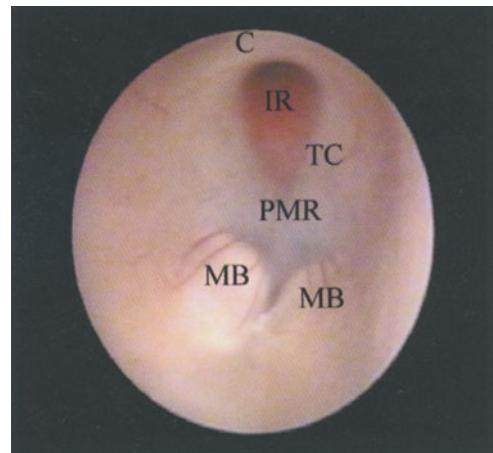


Fig. 16. Endoscopic view of the anterior part of the floor of the third ventricle, composed, from anterior to posterior, of the optic chiasm (C), infundibular recess (IR), tuber cinereum (TC), premamillary recess (PMR) (fairly narrow in this case), and the prominence of the two mamillary bodies (MB)

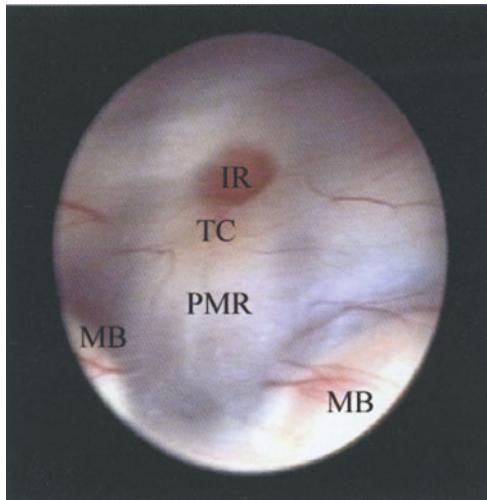


Fig. 17. Endoscopic view of the anterior part of the floor of the third ventricle, composed, from anterior to posterior, of the infundibular recess (*IR*), tuber cinereum (*TC*) almost invisible, premamillary recess (*PMR*) (very large in this case), and the prominence of the two mamillary bodies (*MB*)

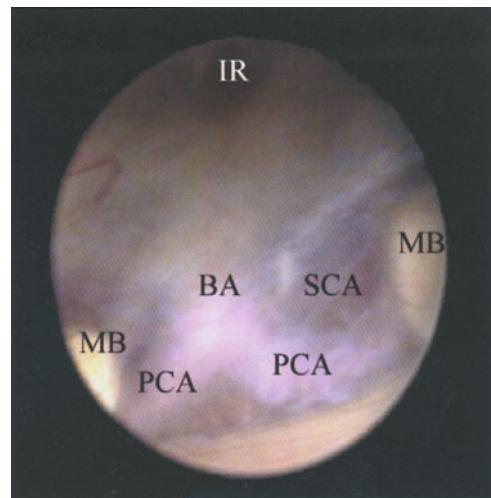


Fig. 19. Endoscopic view of the anterior part of the floor of the third ventricle, composed anteriorly of the infundibular recess (*IR*) and posteriorly by the prominence of the two mamillary bodies (*MB*). The termination of the basilar artery (*BA*), giving rise to the two posterior cerebral arteries (*PCA*) and the right superior cerebellar artery (*SCA*), can be seen in the premamillary recess

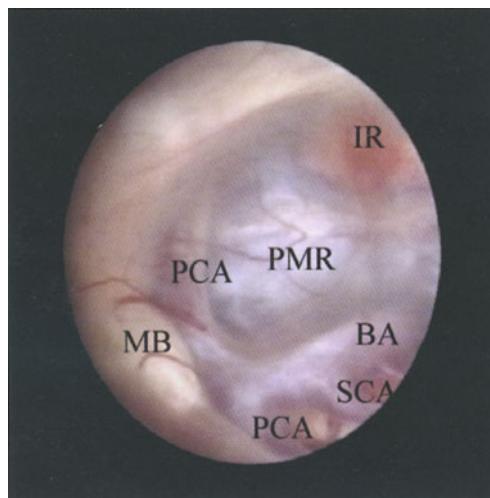


Fig. 18. Endoscopic view of the anterior part of the floor of the third ventricle, composed, from anterior to posterior, of the infundibular recess (*IR*), premamillary recess (*PMR*) (which is large and deep in this case) and the prominence of the two mamillary bodies (*MB*). The premamillary recess contains the termination of the basilar artery (*BA*) giving rise to the two posterior cerebral arteries (*PCA*) and the right superior cerebellar artery (*SCA*)

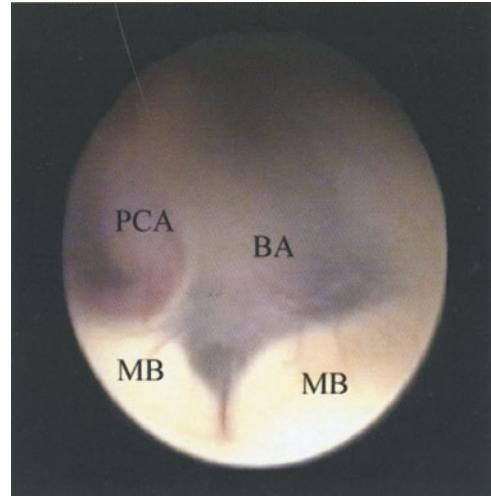


Fig. 20. Endoscopic view of the termination of the basilar artery (*BA*) and origin of the posterior cerebral artery (*PCA*), observed by transparency in the recess lying anteriorly to the two mamillary bodies (*MB*)

The termination of the basilar artery and its branches, posterior cerebral artery, or even the superior cerebellar artery, may be visible through the premamillary recess, which is often translucent in the case of advanced hydrocephalus (Figs. 18-20).

Posterior Part of the Third Ventricle

When the 30° objective is turned backwards, the interthalamic adhesion is immediately observed blocking vision of the third ventricle (Fig. 21). This adhesion

is sometimes very large (Fig. 22) or else, in 25% of cases [2], it may be absent (Fig. 23). By passing underneath this adhesion, the posterior wall of the third ventricle is revealed with the orifice of the cerebral aqueduct and the posterior commissure (Fig. 24). The posterior commissure is sometimes distended when it is pushed anteriorly by a pineal tumor (Fig. 25). In other

cases, the cause of obstruction of the aqueduct may be observed (Fig. 26). In the absence of an interthalamic adhesion, the pineal recess, habenular commissure, and choroidal network can be seen forming the roof of the third ventricle (Fig. 27). Although these structures may be visible, they are not always accessible, especially with a rigid endoscope introduced via a

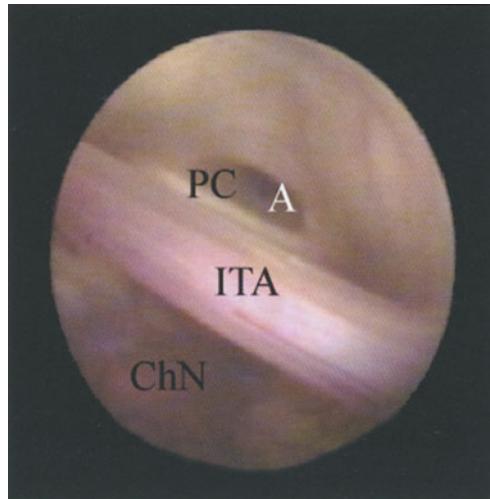


Fig. 21. Endoscopic view of the posterior part of the third ventricle, composed, from superior to inferior, of the choroidal network (ChN), the interthalamic adhesion (ITA), posterior commissure (PC) and orifice of the cerebral aqueduct (A)

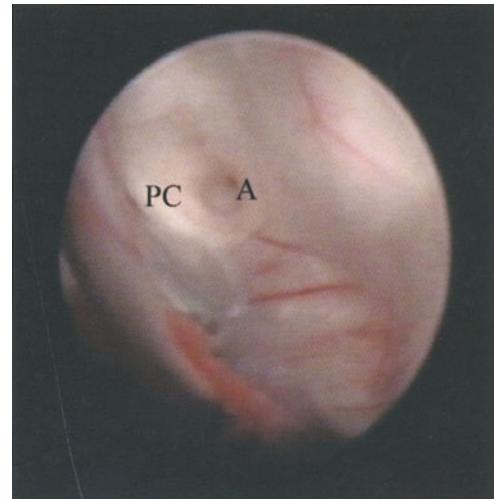


Fig. 23. Endoscopic view of the posterior part of the third ventricle. There is no interthalamic adhesion. The posterior commissure (PC) and the orifice of the cerebral aqueduct (A) are clearly visible

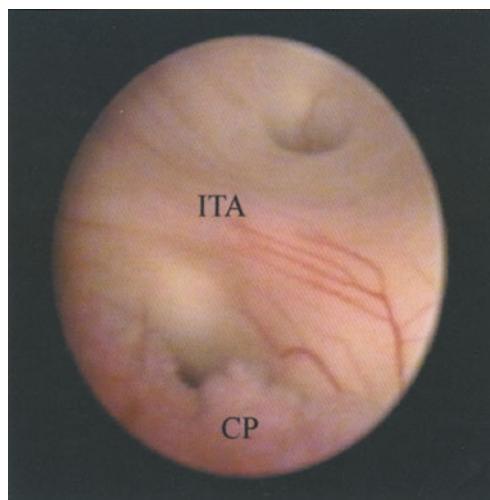


Fig. 22. Endoscopic view of the posterior part of the third ventricle. The interthalamic adhesion (ITA) is very large in this case, masking the posterior part of the third ventricle

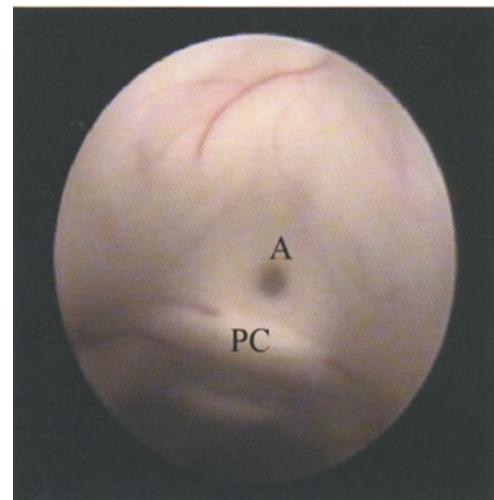


Fig. 24. Endoscopic view of the posterior part of the third ventricle passing underneath the interthalamic adhesion (ITA): the posterior commissure (PC) and the orifice of the cerebral aqueduct (A) are clearly visible

coronal burr hole. Although a flexible endoscope appears to be easier to use in order to reach this region, introduction of the endoscope into the posterior part of the third ventricle and especially in the region of the aqueduct or even the fourth ventricle carries a considerable risk of damage to the interthalamic adhesion and the margins of the foramen of Monro [5].

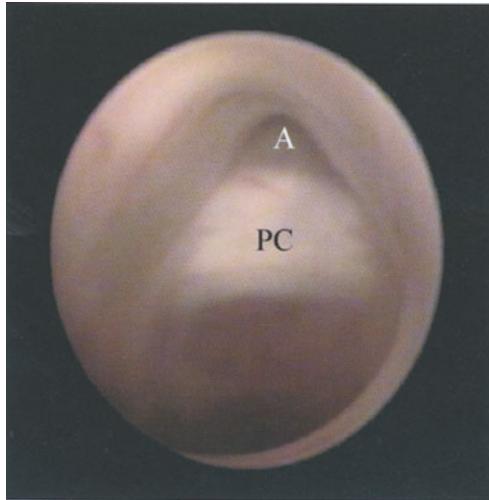


Fig. 25. Endoscopic view of the posterior part of the third ventricle. The posterior commissure (PC) is stretched and displaced anteriorly by a tumor of the extraventricular pineal region, compressing the orifice of the cerebral aqueduct (A)

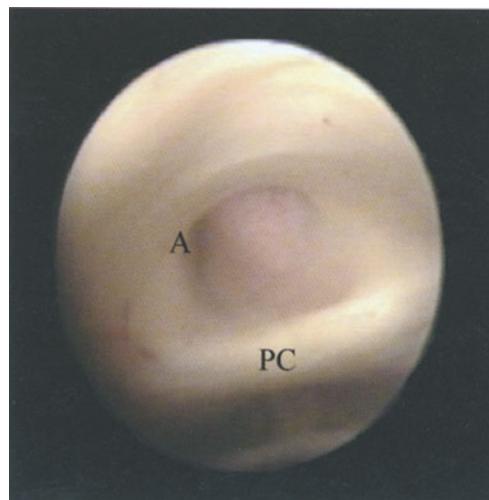


Fig. 26. Endoscopic view of the posterior part of the third ventricle. The orifice of the cerebral aqueduct (A), below the posterior commissure (PC), is obstructed by a tumor (in this case a metastasis from a lung cancer)

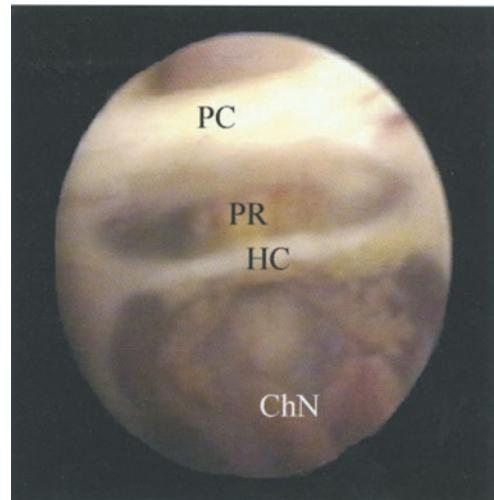


Fig. 27. Endoscopic view of the posterior part of the third ventricle, composed, from superior to inferior, of the choroidal network (ChN), habenular commissure (HC), pineal recess (PR), and posterior commissure (PC)

Conclusion

There has been considerable progress in the field of neurosurgical endoscopy over recent years with, in particular, a renewed interest in endoscopic ventriculocisternostomy as a simple, reliable, and effective technique for the treatment of obstructive hydrocephalus. However, this operation requires a good knowledge of the anatomy of dilated ventricular cavities, including the main landmarks and the main variants.

References

1. Decq P, Yépez C, Anno Y, Djindjian M, Nguyen JP, Kéravel Y: L'endoscopie neurochirurgicale. Indications diagnostiques et thérapeutiques. Neurochirurgie 14: 313-321, 1994
2. Lang J: Topographic anatomy of preformed intracranial spaces. In: Bauer BL, Hellwig D, (eds) Minimally invasive neurosurgery. Acta Neurochir (Wien) [suppl] 54:1-10, 1992
3. Mapstone TB, Ratcheson RA: Techniques of ventricular puncture. In: Wilkins RH, Rengachary SS (eds) Neurosurgery, McGraw-Hill, New York, pp 151-152, 1985
4. Passaglia JG, Gay E, Chirossel JP: Réseau veineux des ventricules latéraux. Neurochirurgie, 44, no 5, I-IV, 1998
5. Riegel T, Hellwig D, Bauer BL, Mennel HD: Endoscopic anatomy of the third ventricle. Acta Neurochir [suppl] 61:54-56, 1994
6. Segal S: Endoscopic anatomy of the ventricular system. In: King W, Frazee J, De Salles A (eds) Endoscopy of the central and peripheral nervous system. Thieme, Stuttgart, pp 37-57, 1998

Endoscopic Third Ventriculostomy

GIUSEPPE CINALLI

Nothing more than a hole.

Anonymous Neurosurgeon, 20th Century A.C.

Something more than a hole.

Anonymous Neurosurgeon, 20th Century A.C.

History

Attempts to surgically bypass the aqueductal obstruction in noncommunicating hydrocephalus began in the 1920s. In the modern era, Dandy was the first to create a direct communication between the third ventricle and chiasmatic cistern by opening the lamina terminalis using a subfrontal approach [43], or between the third ventricle and the interpeduncular cistern through the floor of the third ventricle using a subtemporal approach [44, 45]. His early subfrontal approach was rapidly abandoned, and only Voris reported some experience using the subtemporal approach [192]. Stookey and Scarff [177] modified the subfrontal approach, opening the lamina terminalis, entering the third ventricle, and then perforating the floor of the third ventricle into the interpeduncular cistern [130, 144]. Others proposed limiting the procedure to the opening of the lamina terminalis, and obtained comparable results [196].

Cannulation of the aqueduct as an alternative to third ventriculostomy was first described by Dandy in 1920 [42] and was reported by several authors [54, 110] with variants of aqueductal reconstruction [7, 111]. Interventriculostomy between the lateral ventricle and the cisterna magna was proposed by Torkildsen [185] and became quite a popular and widespread procedure [142], modified by Matson in the simpler ventriculocervical shunt [120]. Other forms of ventriculocisternal shunt by means of silicon catheters implanted between the third ventricle and the subarachnoid spaces were described but failed to achieve widespread favor [16, 144].

In 1947 McNickle proposed a ventriculocisternostomy using a needle with percutaneous technique under X-ray control during ventriculography [122]. The technique was modified by several authors, who introduced the use of a leukotome to enlarge the stoma [72, 91, 146, 166] and in some cases implanted a catheter through the stoma [59]. Stereotactic con-

trol was combined with ventriculographic control by Poblete and Zamboni [147] and used as the sole control method by several other authors [86, 104, 105, 204].

During the first half of the twentieth century, neuroendoscopy began slowly to develop from the first pioneering attempts of Lespinasse in 1910 [46] and Dandy [41, 43], who used it mainly for choroid plexus fulguration and avulsion. The first to use neuroendoscopic control to perform a third ventriculostomy was Mixter. In 1923 he used a urethroscope to enter the third ventricle through the foramen of Monro. The opening into the interpeduncular cistern was performed by puncturing the floor of the third ventricle with a sound [126]. After that first experience, the idea of endoscopic control for third ventriculostomy was abandoned, essentially because of the poor quality of illumination and magnification offered by the endoscopes and because of the advent of shunt surgery in the 1950s [135]. Only a few authors continued to report on neuroendoscopic avulsion of the choroid plexus [149] or neuroendoscopic third ventriculostomy [167-169]. With the evolution of technology, improvement of optical systems, and growing awareness of the problems related to shunt implantation, neuroendoscopy was reintroduced in the 1970s by Fukushima [67], Griffith [69], and Vries [193], but the endoscopic technique of third ventriculostomy was really introduced by pioneering work of some authors only at the beginning of the 1990s [50, 94-96, 163, 179], and began to be widely accepted during the second half of the decade with the publication of the results in large series of patients [17, 34, 68, 87, 180, 181].

Endoscopic third ventriculostomy offers significant advantages over other methods: it combines a minimally invasive approach with brilliant visual control of manipulation, the risk of vascular and neural damage is reduced under direct vision, and the avoidance of intraoperative radiopaque dyes reduces the risk of later closure of the ventriculostomy due to development of arachnoiditis [94].

Indications

Any form of hydrocephalus that is purely obstructive in nature, with one or multiple sites of obstruction located between the mid third of the third ventricle and the peripontine cistern, can be cured by endoscopic third ventriculostomy. The main etiological groups are analyzed below.

Aqueductal Stenosis

Historically, the ideal candidate for endoscopic third ventriculostomy is the patient with primitive aqueductal stenosis. In this form of hydrocephalus, whatever the pathological process responsible for the stenosis (aqueductal forking, membrane, periaqueductal gliosis, tectal dysplasia, mesencephalic hamartoma, etc.) the obstruction to CSF circulation is well delimited to the Sylvian aqueduct. The CSF pathways downstream are free, the foramina of Luschka and Magendie are open, the basal cistern has never been invaded by blood of intraventricular or subarachnoid origin or involved in a meningitic process and therefore they have not been obliterated by the fibrous reaction that follows such events. A positive diagnosis of primitive aqueductal stenosis is usually not difficult to obtain, the clinical and radiological features of this entity being described in Chap. 19. In summary, the signs of intracranial hypertension are usually insidious and often associated with pyramidal, extrapyramidal, and ocular signs. The MRI study must include at least a sagittal T₂-weighted slice on the midline. This can usually show the site of the stenosis as an interruption of the hyperintensity of the CSF through the aqueduct. This may be related to membranes, sometimes visible on the MRI (Fig. 1), or to anatomical deformities of the tectal plate (Fig. 2) or of the whole mesencephalic region associated with an MRI suggestive of aqueductal stenosis. Other radiological signs are often evident on MRI; they are secondary to the transtentorial pressure gradient induced by the obstructive triventricular hydrocephalus and may be regarded as good reinforcing signs for the surgical indication. Downward bulging of the third ventricular floor into the prepontine cistern, dilatation of the suprapineal recess into the quadrigeminal cistern, flattening of the mesencephalon, funneling of the upper part of the aqueduct, and normal or even small size of the fourth ventricle are all frequently associated with aqueductal stenosis and rarely found in other forms of communicating hydrocephalus.



Fig. 1. Aqueductal stenosis due to a small membrane in the lower third of the aqueduct in a 11-week-old boy. Note the significant enlargement of the third ventricle and the deformation of the floor

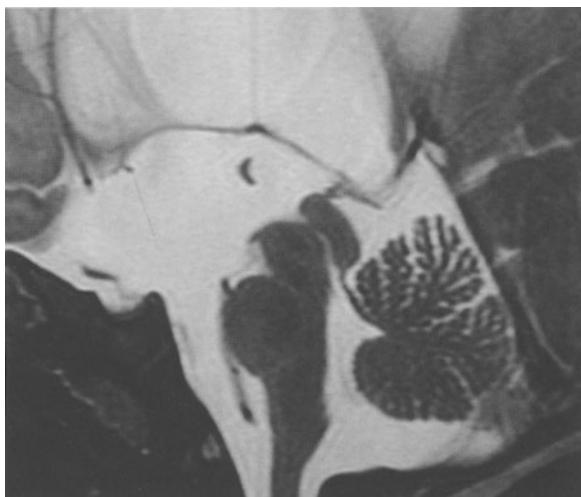


Fig. 2. Aqueductal stenosis in an 11-month-old boy. Note the thickening of the tectal plate, the focal obstruction in the upper third of the aqueduct, the dilatation of the third ventricle, and the deformation of the floor, which is pushed downward into the prepontine cistern

Tumoral Hydrocephalus

Many tumors can be responsible for obstructive hydrocephalus. Tumors arising within or around the sylvian aqueduct are responsible for the onset of secondary obstruction of the aqueduct. Usually tectal gliomas or hamartomas induce hydrocephalus even when they are very small, whereas pineal re-

gion tumors, inducing distortion of the whole mesencephalon from outside, are usually much larger by the time hydrocephalus is diagnosed. Third ventriculostomy has been shown to be effective in treating this form of hydrocephalus in large series of patients [57, 116, 127, 137, 138, 141, 148, 156, 159]. In the case of pineal region tumors, Oi et al. have proposed that third ventriculostomy should be part of a therapeutic protocol. Six patients presenting with hydrocephalus and negative serum levels of α -fetoprotein and human chorionic gonadotropin were considered candidates for endoscopic tumor biopsy, endoscopic inspection of the ventricular cavities in order to detect gross intraventricular metastatic nodules, and, finally, third ventriculostomy and cisternal inspection. In five of them third ventriculostomy allowed resolution of hydrocephalus with normalization of intracranial pressure (ICP). Only one presented increasing ICP after the procedure and had to have a shunt placed because of an ipsilateral subdural fluid collection [137]. Other authors have reported resolution of the hydrocephalus following third ventriculostomy in 17 out of 18 cases of pineal tumors [148] and in all out of seven cases [156]. These results and other series show that hydrocephalus induced by pineal region tumors [119] and tectal plate gliomas [195] is an excellent indication for endoscopic third ventriculostomy. Moreover, this procedure allows generous tissue sampling with the possibility to control bleeding, diagnose intraventricular metastases not visible on imaging studies, and sample CSF for markers. Endoscopic biopsy exposes the patient to the risk of tumor dissemination along the endoscopy track; this complication has been the subject of sporadic reports [76], but could become more frequent with the widespread adoption of endoscopic management of hydrocephalus in cases of pineal tumor.

Posterior fossa tumors are frequently responsible for obstructive hydrocephalus, especially when they arise in the fourth ventricle. In this case they tend to fill the fourth ventricular cavity and infiltrate the CSF pathways, invading the contiguous CSF spaces and filling the cisterna magna through the foramen of Magendie posteriorly and the perimedullary cisterns through the foramina of Luschka anteriorly and laterally. When the tumor arises in the cerebellar hemispheres the CSF pathways are progressively occluded by the anatomical distortion induced by the tumor. In both cases the obstruction is clearly located in the fourth ventricular cavity or at the level of its outlets.

In malignant brainstem gliomas, progressive occlusion of the aqueduct and of the fourth ventricular cavity by the progressive growth of the tumor is observed [3]. The metastatic nodules observed in the subarachnoid spaces in many cases of medulloblas-

toma and primitive neuroectodermal tumor are usually small and scattered at presentation, and rarely contribute to the pathophysiology of hydrocephalus. Several authors have reported good results with third ventriculostomy [3, 87, 94, 96, 104] in sporadic cases. In a series of 149 patients presenting with posterior fossa tumors and hydrocephalus, Sainte-Rose et al. [165] performed third ventriculostomy prior to tumor removal in 67 cases, obtaining a significant reduction of the postoperative hydrocephalus (4/67) compared to the patients treated with external ventricular drainage or emergency tumor removal (22/82), thus demonstrating the effectiveness and feasibility of third ventriculostomy in the preoperative management of posterior fossa tumors. Concerns were raised by the authors about the dangers of this procedure given the significant anatomical distortions of the brainstem induced by the tumor (Fig. 3), but this was not a problem in the end, and all the procedures were performed without complications. This is probably due to the fact that after ventricular tapping, the floor of the third ventricle is no longer pushed downward behind the clivus, thus recreating the basal cistern space and allowing perforation of the floor.

Moreover, in eight cases where hydrocephalus arose after the removal of the posterior fossa tumor, this was successfully managed by third ventriculostomy, reinforcing the evidence that in most cases postoperative hydrocephalus is obstructive in nature, is probably related to scarring at the level of the posteri-

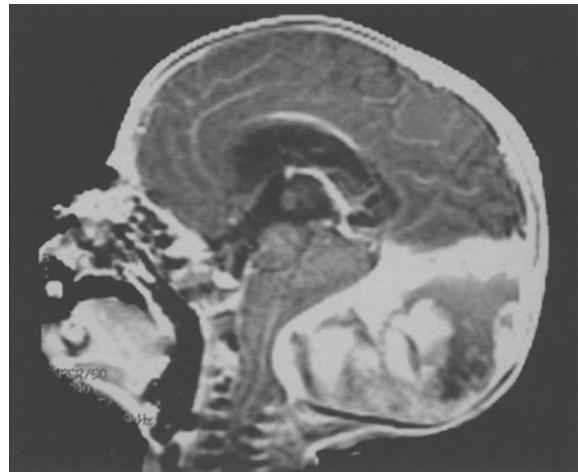


Fig. 3. Hydrocephalus in a 4-month-old baby girl due to a dural sarcoma of the posterior fossa. Note the significant upward displacement of the brainstem with disappearance of the CSF spaces of the posterior fossa. Third ventriculostomy was uneventfully performed before tumor biopsy and chemotherapy and cured the hydrocephalus. Complete removal of the tumor was performed 11 months later

or fossa cisterns, and can be successfully cured by third ventriculostomy.

Third ventriculostomy before tumor removal probably cannot be proposed as a routine procedure, because it exposes as many as 75% of the patients to unnecessary operations [13]. However, in all cases where immediate control of intracranial hypertension is required, endoscopic third ventriculostomy should be preferred to preoperative external ventricular drainage [108] or preoperative ventriculoperitoneal shunt, both of which are associated with risks of infection and overdrainage complications.

Shunt Malfunction

In all cases of shunt malfunction, third ventriculostomy should always be considered as an alternative to shunt revision (Fig. 4). Whatever the etiology

of the hydrocephalus, there is a 50%-80% probability of curing the hydrocephalus and removing the shunt following third ventriculostomy [8, 14, 24, 35, 36, 64, 95, 103, 104, 166, 176, 180, 181] (see Chap. 26).

Slit Ventricle Syndrome

Microsurgical third ventriculostomy has been proposed to treat slit ventricle syndrome in patients shunted for hydrocephalus due to aqueductal stenosis [150]. Baskin et al. reintroduced the concept using a neuroendoscopic technique and proposing an algorithm of treatment for all patients presenting with slit ventricle syndrome [8]. Externalization of the shunt is necessary to obtain slow dilatation of the ventricles in order to perform third ventriculostomy [21] (see Chap. 23).

Dandy-Walker Malformation

Good results were reported in the pre-endoscopic era in hydrocephalus associated with this rare malformation both by Pierre-Kahn and Hoffmann [86, 146]. The hydrocephalus is probably of an obstructive nature and related to the lack of communication between the fourth ventricle and the subarachnoid spaces of the posterior fossa. Several authors proposed a direct approach to the posterior fossa to create surgical fenestrations in the cyst wall, allowing CSF to circulate from the cystic fourth ventricle to the subarachnoid spaces. The results were not always good because of the high complication rate in the premicrosurgical era and because Dandy-Walker malformation is frequently associated with other central nervous system (CNS) malformations (agenesis of the corpus callosum, schizencephaly, encephaloceles, glial heterotopias) that can be responsible for further obstructions to the CSF circulation. Endoscopic third ventriculostomy is much less invasive than direct surgical approach and can lead to the same result. We had good results when endoscopic third ventriculostomy was performed in cases not associated with other CNS malformations visible on MRI. Because of the severe anatomical distortions induced by the posterior fossa cyst, endoscopic third ventriculostomy in Dandy-Walker malformation should be considered as an extremely difficult procedure and should be performed only by experienced endoscopists (Fig. 5). The pons is extremely high and pushes up the basilar tip, which can bulge into the third ventricle through the attenuated

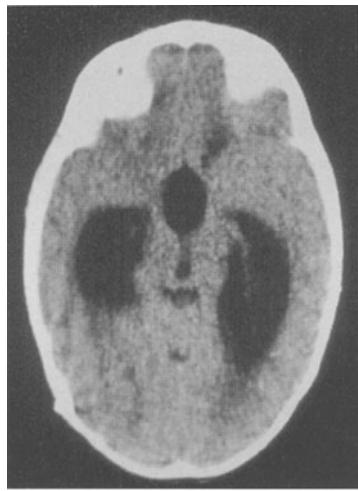


Fig. 4. Shunt malfunction in a 4-year-old boy shunted at 3 months of age for aqueductal stenosis. Because of the significant triventricular dilatation the patient was considered a good candidate for third ventriculostomy. After endoscopic third ventriculostomy, the shunt was definitively removed

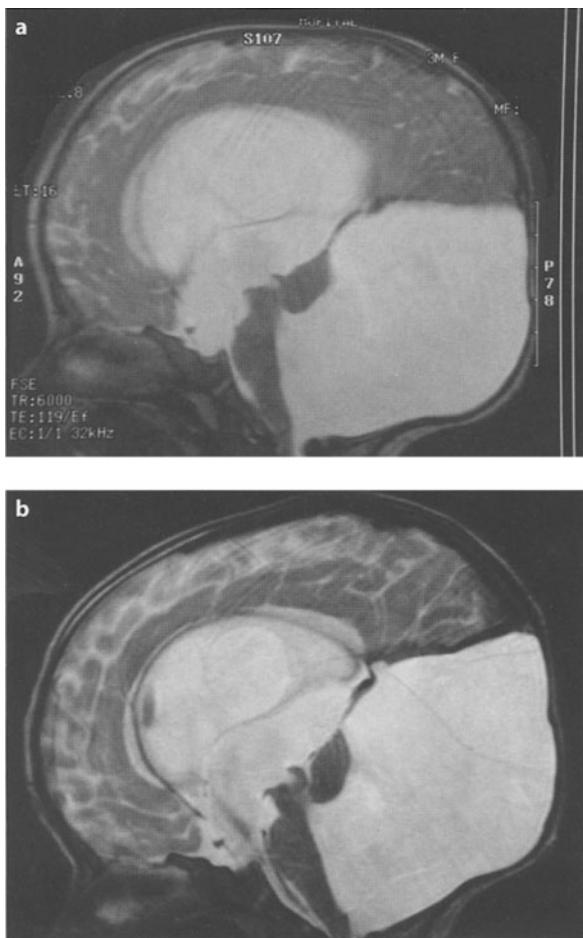


Fig. 5. **a** Dandy-Walker malformation with significant hydrocephalus and upward brainstem displacement. **b** Same patient as in **a** after endoscopic third ventriculostomy. Flow void artifact is visible through the floor of the third ventricle. The wall of the fourth ventricular cyst is well visible, floating below the tentorium

floor [33]. The floor of the third ventricle is usually deformed and verticalized, and can be almost parallel to the trajectory of the endoscope. Because of the large volume of the cyst and of the anatomical deformation, the interpeduncular cistern is virtual. For these reasons, endoscopic third ventriculostomy would seem impossible on the basis of the pre-operative MRI. Nevertheless, the feasibility of the procedure should always be evaluated at surgery, because of the dynamic changes that occur after ventricular tapping: the intraventricular pressure decreases, the volume of the cystic fourth ventricle slowly decreases, the pons goes down, and the interpeduncular cistern becomes visible, thus allowing perforation of the floor.

Neonatal Hydrocephalus

Historically, bad results have been reported by several authors for endoscopic third ventriculostomy in neonates. In the pre-endoscopy and pre-CT scan era, using Guiot's technique, Pierre-Kahn reported a lower success rate (60%) for children under 2 years of life than in older children (83%) [146]. Other authors, describing sporadic cases in larger, non-pediatric series, have reported a lower success rate in this age group. Jones reported on five children aged less than 1 year in a series of 24 patients, where the procedure was successful in three cases (60%) [94]. Hopf et al., describing a series of 100 consecutive endoscopic third ventriculostomies, reported four cases in neonates (<1 year), with four failures. On this basis they concluded that endoscopic third ventriculostomy was contraindicated in neonates; but one of these patients suffered from meningitis, in another the procedure was not completed because of venous hemorrhage, and a third presented with associated CNS malformations [70, 87]. Buxton et al. described a series of 27 endoscopic third ventriculostomies in children aged below 1 year with hydrocephalus from a wide variety of etiologies, mainly posthemorrhagic. The overall success rate was extremely low (23%), but rose to 57% when only the obstructive cases were considered [22]. Goumnerova and Frim reported the same concept in describing a series of 23 patients of whom 5 were in the first year of life, and 3 of the procedures failed. In this report all etiologies were grouped together [68].

The analysis of these papers clearly shows that the main problem in this age group is the indication for endoscopic third ventriculostomy. The analysis of a series of patients affected by hemorrhage, meningitis, myelomeningocele, and aqueductal stenosis will necessarily give misleading indications if the patients are not stratified by etiology. In a homogeneous population of patients affected by obstructive triventricular hydrocephalus, the results of endoscopic third ventriculostomy do not differ from older children or adolescents [10, 34, 61, 92]. The selection criteria for surgical candidates must be based on the following points: no history of pre-neonatal intraventricular hemorrhage or meningitis, no myelomeningocele, no other CNS malformations (corpus callosum agenesis, schizencephaly, holoprosencephaly, etc.), presence of triventricular hydrocephalus, and a positive diagnosis of aqueductal stenosis on median T2-weighted thin-slice sagittal MRI (Fig. 6). The surgical technique differs from that for adults in several points (see "Surgical Technique" below).

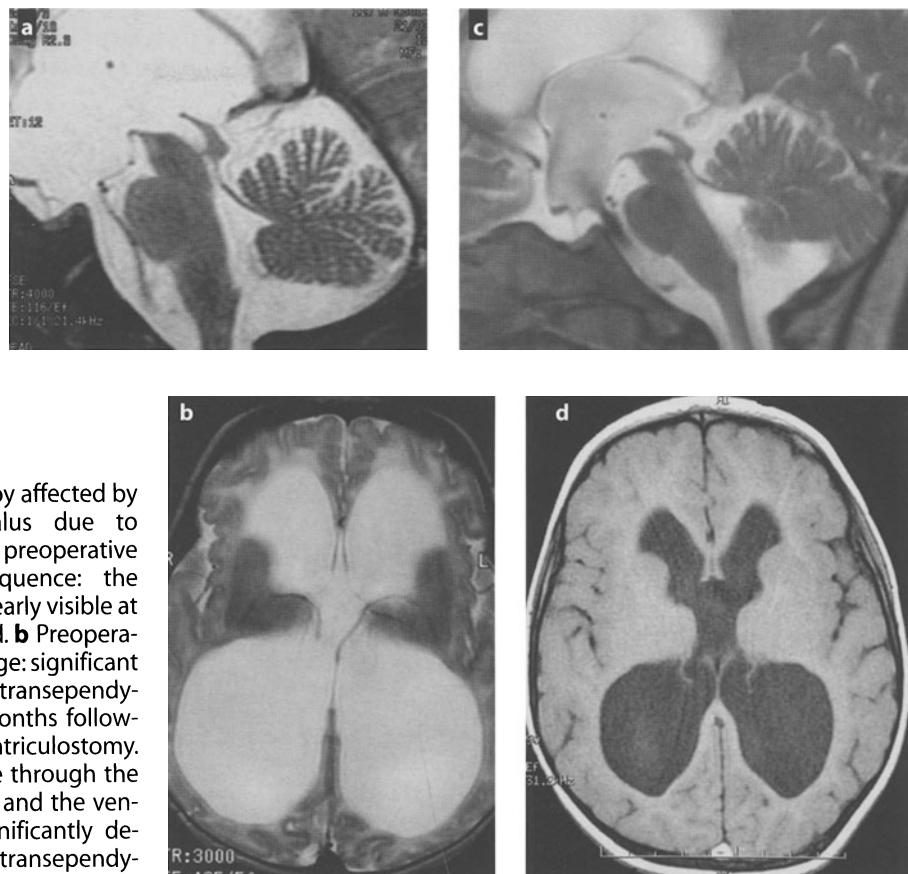


Fig. 6a-d. One-year-old boy affected by triventricular hydrocephalus due to aqueductal stenosis. **a** MRI, preoperative sagittal T2-weighted sequence: the aqueduct obstruction is clearly visible at the level of the lower third. **b** Preoperative axial T2-weighted image: significant ventricular dilatation with transependymal resorption. **c** Three months following endoscopic third ventriculostomy. Flow void artifact is visible through the floor of the third ventricle and the ventricular dilatation has significantly decreased with resolution of transependymal resorption (**d**)

Vein of Galen Malformation

Although hydrocephalus in patients with vein of Galen malformation has a multifactorial etiology, two obstructive components can be observed. The first and more frequent is compression of the tectal plate; the second, not always present, is tonsillar herniation. Tonsillar herniation usually resolves rapidly following successful complete embolization, whereas the decrease in size of the vascular malformation can take several months. Thus, the persistence of hydrocephalus after endovascular treatment is mainly related to the residual volume of the malformation, and the patient may require treatment in the meanwhile. Third ventriculostomy is indicated in these cases for two main reasons: the pathophysiological factor of hydrocephalus related to the venous hypertension is eliminated by the endovascular treatment, and the hydrocephalus is transformed in a purely obstructive type; shunt implant should be avoided in these patients whenever possible, for several hemodynamic and hydrodynamic reasons [203]. The MRI studies should be carefully analyzed in order to detect possible vascular abnormalities at the level of the interpeduncular cistern, which are not rare and could contraindicate the procedure.

Obstructive Tetraventricular Hydrocephalus

Obstruction of the foramina of Luschka and Magendie is a condition that was considered to be rare in the pre-MRI era [28, 75, 89, 100, 128]. It can be often associated with chronic tonsillar herniation and possibly syringomyelia [48]. It can be easily differentiated from aqueductal stenosis because of the excellent visibility of the aqueduct, which is significantly widened along its whole length, can be funnel-shaped, and presents increased CSF flow with a higher flow rate and no measurable flow in the foramina of Magendie and Luschka [28]. The fourth ventricle is extremely enlarged, with mass effect on the brain stem and distortion of the cerebellum (Fig. 7), and flattening and downward displacement of the cerebellar tonsils, which can herniate into the cervical spinal canal, possibly inducing syringomyelia [26, 38, 123, 133, 178]. In these cases chronic tonsillar herniation is the result of the chronic intracranial hypertension, and of the enlargement of the fourth ventricle. In this rare form of obstructive hydrocephalus, third ventriculostomy allows resolution of the hydrocephalus in virtually all cases and disimpaction of the cerebellar tonsils with resolution of the associated syringomyelia. Rare cases



Fig. 7. Obstructive tetraventricular hydrocephalus. The patient had no previous history of intracranial hemorrhage or meningitis. The aqueduct is patent and enlarged (a), the obstruction is located at the level of the foramina of Luschka (b) and Magendie. The brainstem is displaced anteriorly, the cerebellum significantly compressed

of tetraventricular hydrocephalus with open communication with the cisterna magna and a downward bulging floor of the third ventricle have been reported to respond to third ventriculostomy, probably because of mechanical obstruction to the CSF flow located in the basal cistern, between the foramen of Magendie and the interpeduncular cistern [101].

Postinfectious Hydrocephalus

Some forms of CNS infection can be complicated by obstructive hydrocephalus that can be successfully



Fig. 8. Obstructive triventricular hydrocephalus following prenatal toxoplasmosis in a 3-month old boy. The aqueduct is occluded in the lower third. The patient was successfully treated by endoscopic third ventriculostomy

treated by third ventriculostomy. Triventricular hydrocephalus complicating congenital toxoplasmosis (Fig. 8) has been considered a good indication for third ventriculostomy since the technique was first introduced [146], and long-term results confirmed a 60% success rate in a series of 22 patients at 9-year follow-up [34]. Mumps virus encephalitis is the CNS viral disease that is most frequently complicated by aqueductal stenosis and triventricular hydrocephalus [93, 136, 187]. Hydrocephalus can arise very early, during the acute inflammatory phase, or many years following the episode of CNS infection, and can be successfully treated even in the acute phase of the disease or in the presence of radiological signs of diffuse encephalitis [187]. Repeated obstruction of the stoma has been reported in case of long-term persistence of CNS infection, probably related to the chronic inflammatory reaction [187]. Other forms of postinfectious hydrocephalus can be occasionally considered for third ventriculostomy [1, 176], even in the case of hydrocephalus following tuberculous meningitis [58], although further evidence is needed before the procedure can be considered as a first-option treatment in primary forms of postmeningitic hydrocephalus, especially in infants [176].

Hardware

It is beyond the purpose of this chapter to discuss in detail the characteristics of all types of endoscopes available. Briefly, the endoscopes specifically designed for neuroendoscopy can be classified into four types:

- Flexible fiberscopes
- Steerable fiberscopes
- Rigid fiberscopes
- Rigid rod lens endoscopes

Flexible Fiberscopes

Flexible fiberscopes have a very small diameter (<2 mm), which allows them to be used inside the lumen of ventricular catheters for optimal ventricular catheter positioning during ventriculoperitoneal shunting. Their main limitations are poor quality of vision and the absence of a working channel.

Steerable Fiberscopes

The last 4 cm of a steerable fiberscope can be oriented 100° upward and 160° downward. The diameter of the working channel is usually around 1 mm, allowing the introduction of 3-French instruments. In fact, when an instrument is introduced into the working channel, the steering properties are decreased, sometimes significantly, according to the stiffness of the instrument introduced. This is the only system that makes looking and working around a corner possible. The steerable scope modifies the orientation of the optical fibers but also of the working channel, allowing the instruments to reach all the structures visualized. This option is almost irreplaceable when performing complex endoscopic surgery such as for pineal tumors with hydrocephalus, which requires tumor biopsy and third ventriculostomy for hydrocephalus during the same procedure (Fig. 9). A holder is necessary to maintain the rigid part of the scope. The distance from the target should be carefully and precisely evaluated. Being too close to the target obliges the surgeon to work with a curved endoscope, while being too far obliges the surgeon to release the holder, with possible rough movements in the proximi-

ty of potentially delicate anatomical structures. Finally, when the endoscope is in the position of maximum flexion, the flexible instruments can have some problems in progressing through the working channel.

Rigid Fiberscopes

These fiberscopes are formed by a main rigid body of variable length (13-27 cm) with a diameter of 4 mm. This contains the end of the optic fiber tract, a large working channel (2 mm), and the irrigation-aspiration channel. The instrument is extremely light and short, and can be handled like a pencil. This is made possible by the fiberoptic technology, which allows remote placement of the camera and the light source – they can be placed 40 cm away on the operating table. One single soft, light cable is the only link to the fiberscope itself. The absence of a rigid rod lens system allows a very wide working channel and a wide irrigating channel, making it possible to use virtually all endoscopically designed surgical instruments, of any length. Vision is superior to that with the steerable fiberscopes because the number of optic fibers can be higher since there is no need for tip orientation. Nevertheless, the quality of vision cannot be compared to that offered by rigid rod lens endoscopes.

Rigid Endoscopes

The quality of vision is the main advantage that makes the rigid rod lens scope an indispensable item in the armamentarium of any neuroendoscopist. The quality of the camera and of the monitor are also important in determining the final result and should not be underestimated. The rod lens system requires the presence of the camera and of the fiberoptic cable for the cold light attached to the proximal extremity of the endoscope. The whole system requires good surgical training to be manipulated freehand during navigation and throughout the whole surgical procedure. The holder may be needed during longer procedures such as tumor biopsy, colloid cyst removal, or tumor removal, but is not mandatory in shorter, straightforward procedures like uncomplicated third ventriculostomies. Holders with pneumatic or electromagnetic brakes offer a significant improvement over the traditional screwing systems, combining the advantages of freehand movements with the possibility of very secure and firm positioning, and are certainly the gold standard for both beginners and expert surgeons. The rigid lens system only allows targets to be reached that are located on a straight line from the burr hole. Further technical details are discussed in Chap. 13.

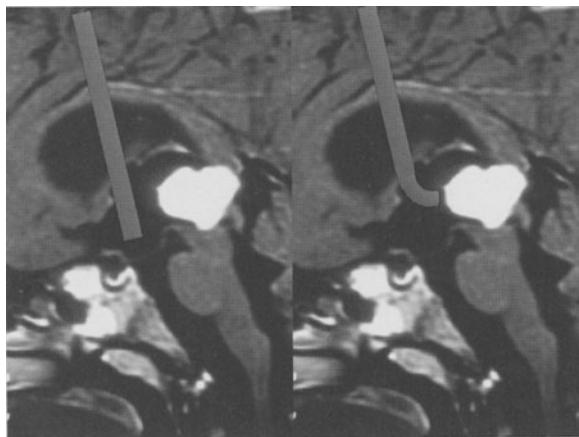


Fig. 9. In cases of triventricular hydrocephalus, a steerable endoscope allows third ventriculostomy in the straight position and tumor biopsy when directed backward

Preoperative Management

There is no ancillary test that can preoperatively predict the probability of success in the individual candidate. Lumbar and ventricular infusion tests have been proposed as possible preoperative predictors of reabsorption capacity. Some authors have proposed that a significant difference of the increased outflow resistance (R_{out}) between lumbar and ventricular infusion tests observed in cases of obstructive hydrocephalus [40] could be routinely used as a preoperative test to be performed under general anesthesia immediately before the surgical procedure planned for hydrocephalus, thus predicting a successful outcome for third ventriculostomy [9, 117, 118]. Further studies have proved that the preoperative values of intraventricular outflow resistance (IV- R_{out}) and subarachnoid space outflow resistance (SAS- R_{out}), and the difference between them, are not predictive of outcome following third ventriculostomy. Preoperative elastance, on the other hand, correlates strongly with a good outcome and with reduction of ventricular size [184]. Although interesting as an approach, this method has the inconvenience of being invasive, especially in small children, and requiring lumbar tapping in cases of noncommunicating hydrocephalus, where this should be contraindicated.

The most important criterion with the highest predictive value of good outcome remains the clinical history and preoperative MRI studies showing morphological obstruction of the aqueduct on the T1- and T2-weighted sagittal midline sequences and little or no flow in the aqueduct in the cine PC sequences [33, 35, 77]. Preoperative MRI is mandatory, not only to assess the indication for the procedure, but also for the surgical planning. Sagittal sequences are extremely helpful in defining the anatomy and predicting anatomical abnormalities [131] that will be found at surgery. Constructive interference in steady-state (CISS) MRI sequences are of invaluable help in the preoperative planning because of the excellent definition of arachnoid membranes, fibrous septations, and CSF-filled arachnoid pouches [2, 109, 115] (see Chap. 28).

Virtual neuroendoscopy is a very useful tool in preoperative planning, allowing 3D reconstructions of the anatomical structures as they will be encountered during the procedure on the basis of MRI images [6, 20, 154, 162].

Surgical Technique

Preparation

No specific preparation is required. For routine procedures, a first shampooing with foamy povidone io-

dine solution on the evening before the procedure and a second one in the morning are the standard procedure if shaving is not required. For emergency surgery, careful brushing of the hair with foamy povidone iodine solution in the operating room and generous rinsing is sufficient.

Patient Positioning

The patient lies supine with slight flexion (15°) of the head, which should be securely fixed. A horseshoe headframe is sufficient unless a stereotactic or neuronavigation procedure is required, in which case the dedicated stereotactic frame or three-point Mayfield headframe is needed. On a routine basis, it is widely accepted that a straightforward third ventriculostomy with mild ventricular dilatation can easily be performed without neuronavigation or stereotactic guidance and with a freehand technique, since the anatomical landmarks are easy to recognize. If a neuronavigation system is used, a three-point Mayfield headframe could be necessary, depending on the system used for navigation. In any case, secure fixation of the head should be ensured. The monitor should be placed in front of the surgeon to allow him to operate with his head in a neutral position.

Skin Incision

A 5-cm skin incision is usually sufficient. It is always preferable to clip the hair along a thin strip of 5 cm–1 cm on the parasagittal line crossing the mid-pupillary point. The incision should be planned 2 cm behind and 3 cm ahead of the coronal suture, which can usually be palpated, depending on the burr hole location. Although not mandatory, clipping or shaving this small surface is certainly preferable because it makes it easier to manage any postoperative CSF leaks. If postoperative external drainage or ICP monitoring is required (e.g., following shunt removal), an additional 2 cm–2 cm shaving or clipping should be done to ensure secure fixation of the device and a watertight suture around it to avoid CSF leak.

In neonates, the skin incision should be more posterior, on the lateral corner of the bregmatic fontanel, half in front of and half behind the coronal suture. It is usually preferable to do a longer incision, since in neonates a very important factor is the watertight suture of the dura following removal of the endoscope, and a larger bone opening is necessary to allow this.

Burr Hole

The burr hole should be placed 0.5 cm in front of the coronal suture, which should always be identified after skin incision. Kanner et al. performed a retrospective evaluation of the ideal burr hole placement on the basis of stereotactic coordinates in 17 patients [99]. They found that the most frequent placement of the burr hole was less than 3 cm lateral to the midline (median 28 mm, mean 26.5 mm) and less than 1 cm anterior to the coronal suture (median 8 mm, mean 6.5 mm). Some degree of variation is always possible, in accordance with the individual variability of the cephalocranial components. In any case, the burr hole should be placed within a square area with a side of 2 cm, where the posterior side is the coronal suture and the medial side is 2 cm distant from the midline. Too posterior a burr hole could lead to damage of the pyramidal tract, while too anterior a one could lead to a wrong trajectory with excessive anteroposterior inclination through the foramen of Monro. Any attempt to correct this trajectory after entering the foramen of Monro could lead to anatomical damage of the anterior column of the fornix. The burr hole should be large enough to allow entry and easy manipulation of the endoscope. It is al-

ways preferable to rongeur some bone from the inner table with a small Kerrison or, better, with a bone curet, in order to allow small adjustments of the trajectory of the endoscope without being limited by the thickness of the bone. After coagulation of the dura, bipolar coagulation of arachnoid and pia should be performed so as to enter the white matter without resistance and avoid exerting excessive pressure on the cortical surface. Entering the cortical surface at the level of a sulcus should be avoided, in order to avoid injuries to blood vessels in the depth of the sulcus. This could lead to unrecognized bleeding around the endoscope during the procedure or after withdrawal of the endoscope, and accounts for the rare cases of intraparenchymal hematomas observed along the track of the endoscope, which can require surgical evacuation.

In neonates the burr hole is usually not necessary, because hydrocephalic neonates usually have large fontanelles and the entry point can be precisely located at the outer angle of the bregmatic fontanel or just medial to it. Nevertheless, since all care should be taken to perform watertight closure of the dura after the procedure in order to avoid CSF leaks, some degree of bone rongeuring is often necessary to allow a linear, parasagittal incision of the dura at least 3 cm long, extended behind and in front of the coronal suture (Fig. 10).

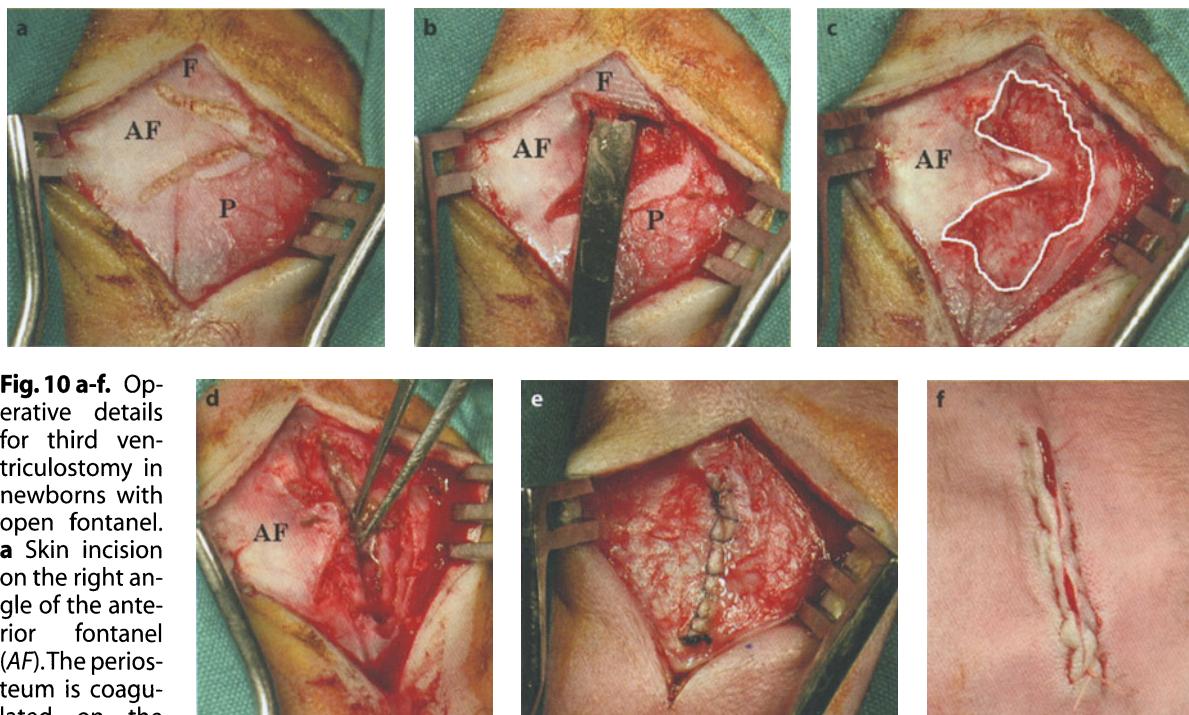


Fig. 10 a-f. Operative details for third ventriculostomy in newborns with open fontanel. **a** Skin incision on the right angle of the anterior fontanel (AF). The periosteum is coagulated on the edge of the frontal bone (F) and the parietal bone (P). **b** The dura is dissected by inserting a smooth instrument below the frontal bone (F) and the parietal bone (P). **c** Small areas of frontal and parietal bone (dotted line) are rongeured in order to allow a rectilinear, parasagittal dural incision. **d** After rectilinear incision of the dura, arachnoid and pia are coagulated. **e** After removal of the endoscope, the dura is sutured with a 5/0 resorbable suture in a watertight fashion. **f** Running mattress suture of the skin after careful subcutaneous closure

Ventricular Entry and Navigation

Many authors advocate ventricular tapping with a thin brain needle to identify the ventricle and create a small hole in the ependyma that would facilitate the ependymal penetration of the endoscope trocar (see Chaps. 26–29). This procedure is certainly wise in the case of small ventricles, for example, following shunt malfunction. In primary procedures in children, the ventricles are usually very large and are not difficult to find with a specifically designed peel-away sheath. In more than 300 neuroendoscopic procedures performed by the present author in pediatric patients, no significant bleeding was ever observed at the time of ventricular entry with a blunt-ended peel-away sheath. The ventricle can be entered following the same direction as for ventricular tapping, directing the trocar or the peel-away sheath perpendicularly to the imaginary plane tangential to the skull at the level of the entry point. The ependymal layer of the frontal horn is usually found at 5 cm depth, less in cases of significant ventricular dilatation. This is confirmed by the CSF coming out of the central channel of the peel-away sheath. After the stylet is removed from the sheath, a significant amount of CSF comes out under pressure through the wide channel of the sheath. The CSF should be sampled, but care should be taken to prevent significant CSF loss, which can cause cortical collapse and subdural hemorrhage. This can be avoided by asking the assistant to remove the stylet and introducing the endoscope into the sheath as soon as the stylet is removed. After entering the ventricle and identifying the anatomical structures of the frontal horn, the lights in the operating room should be switched off as well as any light source (light box, doors, windows) behind the screen, in order to concentrate the surgeon's attention and enhance the visibility of the screen, as in any surgical procedure performed under video control.

Within the ventricle, precise identification of the anatomical structures is mandatory before further introduction of the ventriculoscope. If the burr hole position was correct as well as the trajectory of ventricular entry, the foramen of Monro is immediately visible in the surgical field (see Figs. 7–10 in Chap. 24). If the trajectory is too far anterior, only the ependyma of the frontal horn will be visible, without choroid plexus and small ependymal veins (see Fig. 3 in Chap. 24). If the trajectory is too far posterior, the choroid plexus will be immediately visible on the floor of the lateral ventricle (see Figs. 2–4 in Chap. 24). In this case the choroid plexus should be followed anteriorly until the foramen of Monro comes into vision. This can be easily identified by the convergence of the choroid

plexus, the thalamostriate vein (or veins) and the septal vein (see Fig. 8 in Chap. 24).

The foramen of Monro should be entered cautiously, with care being taken to advance the endoscope keeping the geometric center of the foramen always in the middle of the video image. In this way, the outer edges of the tip of the endoscope will always remain equidistant from the anatomical structures that delimit the foramen of Monro. This reduces the risk of injury of the thalamostriate veins (for a too far posterior trajectory) or of the column of the fornix (for a too far anterior trajectory). If the trajectory is correct and the foramen of Monro is mildly dilated because of the hydrocephalus, the floor of the third ventricle should be already visible through the foramen immediately after entering the lateral ventricle. If the burr hole is too far anterior or if the foramen of Monro is not dilated, the floor of the third ventricle can become clearly visible only after the third ventricle is entered and after slight anterior adjustment of the trajectory.

Stereotactic guidance was used well before the advent of neuroendoscopy [86, 104, 132, 147, 204], and was used in association with neuroendoscopy by several authors at the beginning of their experience [71, 79, 80–82, 87, 173]. In fact, stereotactic guidance can be of some value only in choosing the correct entry point and entering the lateral ventricle in a small-sized ventricular system. Once the frontal horn is entered, all movements of the endoscope should be directed by the visual control that is obtained through the endoscope. A good alternative to traditional stereotactic frames can be the combination with frameless neuronavigation, which can offer invaluable help in the identification of anatomical structures in cases of brain malformation or of complex hydrocephalus [18, 88, 154, 155, 160], and should be considered superior to frame-based stereotactic guidance [27].

The use of ultrasound to guide entry into the lateral ventricle and intraventricular navigation has been proposed, but it requires an additional bone flap for the ultrasound probe and does not offer any real advantage in straightforward cases [157, 158].

Irrigation

After insertion of the endoscope, if the ventricular tapping was technically perfect, no bleeding should be visible in the intraventricular CSF. However, it is not rare to see a little venous bleeding coming from behind the light source, frequently originating within the endoscope track and falling into the ventricle around the trocar, or from some small ependymal vein on the ventricular roof broken by the endoscope

during ventricular entry. If bleeding occurs, intra-ventricular irrigation is required to stop it before visibility decreases significantly – possibly before entering the third ventricle. Ringer's lactate is the fluid most frequently used at body temperature (36°C), but 0.9% saline solution can also be used at the same temperature. As a precaution, it is advisable to have at least 2 l of suitable fluid at body temperature ready to use, although in more than 95% of procedures no more than 100 ml is used. Transcranial Doppler (TCD) monitoring coupled with intraendoscopic pressure monitoring during irrigation for neuroendoscopic procedures has shown that high pressure peaks (30-100 mmHg) are recorded in more than 50% of patients during irrigation. These peaks induce significant changes in the TCD wave profile, consistent with “near intracranial circulatory arrest-like” wave, with a significant drop in cerebral perfusion pressure. This phenomenon disappears as soon as the rinsing fluid is allowed to escape from the intracranial cavity. These peaks of increased ICP ($>30 \text{ mmHg}$) seem to be significantly associated with postoperative complications, such as delayed awakening from anesthesia [55, 56]. For this reason it is of the utmost importance to start irrigation only when really indispensable, and before starting the irrigation, one should be sure that adequate drainage for the irrigation fluid is available and open, to avoid a significant increase in ICP. In our experience, the easiest awakening from anesthesia and the most uneventful immediately postoperative periods occur when the procedure is performed without the need for irrigation.

After entering the third ventricle, one should be aware that the endoscope can easily occlude the foramen of Monro, and this situation is the most dangerous if adequate drainage is not provided for irrigation. In fact, sudden and significant increases of third ventricle pressure with potentially hazardous consequences (e.g., severe bradycardia) can be observed if irrigation is started within the third ventricle before the third ventricular floor is opened [52, 53, 74, 145].

Floor Perforation

Microanatomical Basis

The floor of the third ventricle extends from the optic chiasm anteriorly to the inlet of the aqueduct of Sylvius posteriorly. The anterior half is formed by diencephalic structures, the posterior half by the roof of the mesencephalon. The furthest anterior structure is the optic chiasm, which appears on endoscop-

ic view as a thick white bundle of horizontal fibers covered by ependyma (see Fig. 15 in Chap. 24). Behind the optic chiasm is the infundibulum, from where the pituitary stalk takes its origin, leading inferiorly to the sella turcica. On the endoscopic view from inside the third ventricle, the origin of the infundibulum is clearly demarcated by the infundibular recess, a conical depression of the ependyma that is always clearly identified as a rounded dark red or brown spot, due to the origin of the hypothalamo-hypophyseal vascular system (see Figs. 16-19 in Chap. 24). This is probably the most important landmark for the surgeon, since the infundibular recess is always extremely well visible; it is always on the midline, and can always be observed whatever the anatomical modifications of the floor. Behind the infundibular recess, the floor of the third ventricle becomes progressively thinner and is formed only by ependyma on the upper side and arachnoid on the lower side. In most cases of hydrocephalus this part is also partially transparent and allows visualization of the main neurovascular structures of the interpeduncular cistern and of the dorsum sellae (see Figs. 17-20 in Chap. 24). Posteriorly, this part of the floor is delimited by the mamillary bodies, two symmetrical round structures that are part of the limbic system and bulge inferiorly into the interpeduncular cistern. On the endoscopic view they are usually well visible as two round white symmetrical structures 6-8 mm in diameter. Below the anterior part of the floor of the third ventricle lies the interpeduncular cistern.

This is a conically shaped subarachnoid cavity located between the cerebral peduncles and Liliequist's membrane [190]. It is delimited posteriorly by the posterior perforate substance, a triangular area behind the mamillary bodies penetrated by multiple perforating vessels branches of the posterior cerebral arteries. Laterally it communicates with the oculomotor, crural and ambiguus cistern. It is divided in two parts by an arachnoidal membrane arising from the posterior edge of Liliequist's membrane. The posterior part contains the perforating vessels, the anterior part contains the basilar artery and its bifurcation.

Techniques of Perforation

Once the third ventricle is entered with the endoscope, careful identification of the anatomy should be performed before any attempt to perforate the floor. The first structure that can be recognized is the mamillary bodies; the second is the infundibular recess. Between these two structures lies the floor of the third ventricle, usually visible as a translucent mem-

brane with the gross shape of an irregular rhomboid, where the smaller triangle is included between the two mamillary bodies with the apex posterior and the larger triangle with the apex anterior at the level of the dark spot identifying the infundibular recess. The perforation should be performed at the midpoint of the height of the second triangle (Fig. 11). Because of the extreme variability of the anatomy, this rule must of course be adapted to the anatomical modifications encountered. The perforation should never be performed behind the mamillary bodies: this would result in entering the posterior perforated substance, with severe risk of injury to the basilar artery or to the perforating vessels coursing to the ventral aspect of the mesencephalon; even if the perforation itself is uneventful in this area, inflating the balloon for the dilation of the stoma would tear these perforating vessels, with catastrophic consequences.

The most frequently observed variations are in the thickness of the floor and in its position. In cases of acute ventricular dilatation, e.g., in hydrocephalus induced by posterior fossa tumor or following shunt malfunction, the floor may be undistended and extremely thick, without any transparency and with the mamillary bodies hardly recognizable [35, 155, 161]. By contrast, in cases of long-standing ventriculomegaly due to chronic hydrocephalus, such as can be observed in some cases of aqueductal stenosis, the floor of the third ventricle can be extremely distended and bulge downward into the interpeduncular cistern because of the pressure gradient between the third ventricle and the subarachnoid space [131].

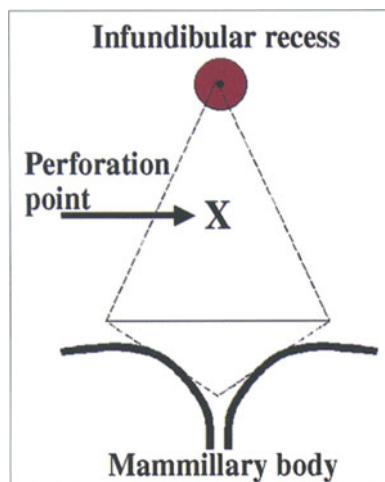


Fig. 11. Schematic drawing of the floor of the third ventricle. Ideally, the perforation point is located at the midpoint of the height of the triangle formed by the base of the mamillary bodies and the apex of the infundibular recess

This feature was even considered as an anatomical prerequisite for third ventriculostomy when the patients were studied ventriculographically and the floor was perforated under ventriculographic control [146]. Significant variations can be observed in cases of hydrocephalus associated with other CNS anomalies like myelomeningocele [33, 180], Dandy-Walker malformation [31, 33], or septo-optic dysplasia [31]. Overall, variations in the anatomy of the third ventricle may be encountered in as many as 36% of cases and may be responsible for a longer operating time and additional surgical manipulation of the third ventricular floor. This can result in transient postoperative hyperthermia [161, 163] or more serious complications such as transient diabetes insipidus [161], hyponatremia [188], and neuropsychological problems [12].

The perforation should be performed very carefully, with the clear awareness that this is the most “traumatic” and potentially hazardous moment of the whole procedure. For this reason, several techniques have been described. Some authors have described perforation with the endoscope itself (“blunt” perforation), gently pushed through the floor behind the clivus, stretching the fibers of the floor progressively until complete perforation is achieved and entry into the subarachnoid spaces is ensured by the sudden, direct visualization of the anatomical structures of the interpeduncular cistern [52, 53, 181]. This technique has several inconveniences: the traction on the floor can be significant and it is directly transmitted to the hypothalamic structures situated above. Until perforation is achieved this is a blind procedure, with no visual control of the depth reached by the endoscope or of the space remaining behind the membrane to be perforated. Moreover, at the moment of the perforation, manual control of the instrument is lost because all the fibers resisting progress have been torn. This induces a short but sudden acceleration that could lead the tip of the endoscope to injure some neurovascular structure in the interpeduncular cistern. Moreover, significant bradycardia occurs in more than 40% of the patients during pressure on the third ventricular floor with the endoscope, obliging the surgeon to withdraw the instrument from the floor [5, 53]. This phenomenon is almost never observed during floor perforation with less traumatic techniques, and is certainly related to the severe distortion of the brainstem anatomy induced by the procedure, which cannot be seen by the surgeon because vision is obscured during the pressure on the third ventricular floor.

A less traumatic variant of the “blunt” technique has been described using a 1.2-mm semirigid stylet neuroendoscope in the lumen of a ventricular

catheter [194]. After perforation with the fiberscope, the ventricular catheter is gently pushed along the stylet so as further to dilate the opening. Although very simple, the technique remains a “blunt” procedure, with loss of vision during perforation; moreover, the largest diameter that can be obtained is no larger than the outer diameter of the ventricular catheter, and enlarging the stoma requires further holes or lateral movements of the catheter that ought to be avoided.

The perforation of the floor can be achieved more safely using bipolar or monopolar coagulation [83, 164]. The advantages of this technique are evident. The point at which to perforate can be precisely chosen: if the floor is translucent, the tip of the coagulating wire can be positioned where the interpeduncular cistern is wider, as far as possible from the basilar bifurcation. This ideal condition can be observed 1-2 mm away from the midline, where the basilar artery reduces the axial diameter of the interpeduncular cistern (Fig. 12). Moreover, the straight trajectory of the endoscope between the burr hole and the foramen of Monro presents an approximately 15°-20° inclination compared to the sagittal plane on the midline. In patients with mild to moderate ventricular dilatation, this naturally leads the tip of the endoscope to be oriented toward the contralateral half of the third ventricular floor (Fig. 13). For the same reason, the instruments will be oriented more perpendicularly to the floor membrane in this region, where the tip will naturally tend to slide, allowing easier and safer surgical manipulations [205]. Both monopolar and bipolar coagulation should be used at the lowest effective energy to bring about coagulation of the floor. In

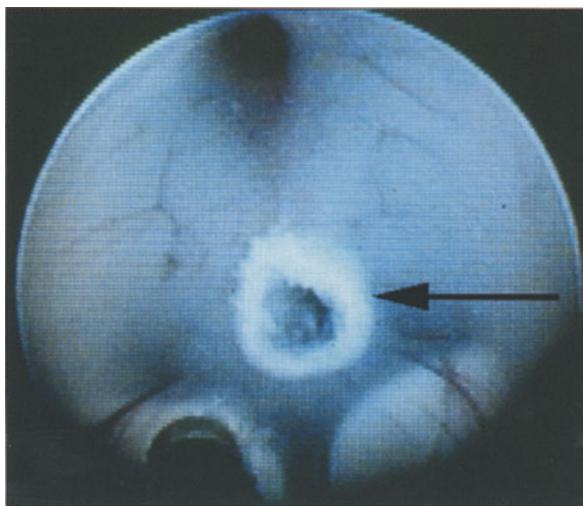


Fig. 12. Floor of the third ventricle immediately after monopolar coagulation (arrow)

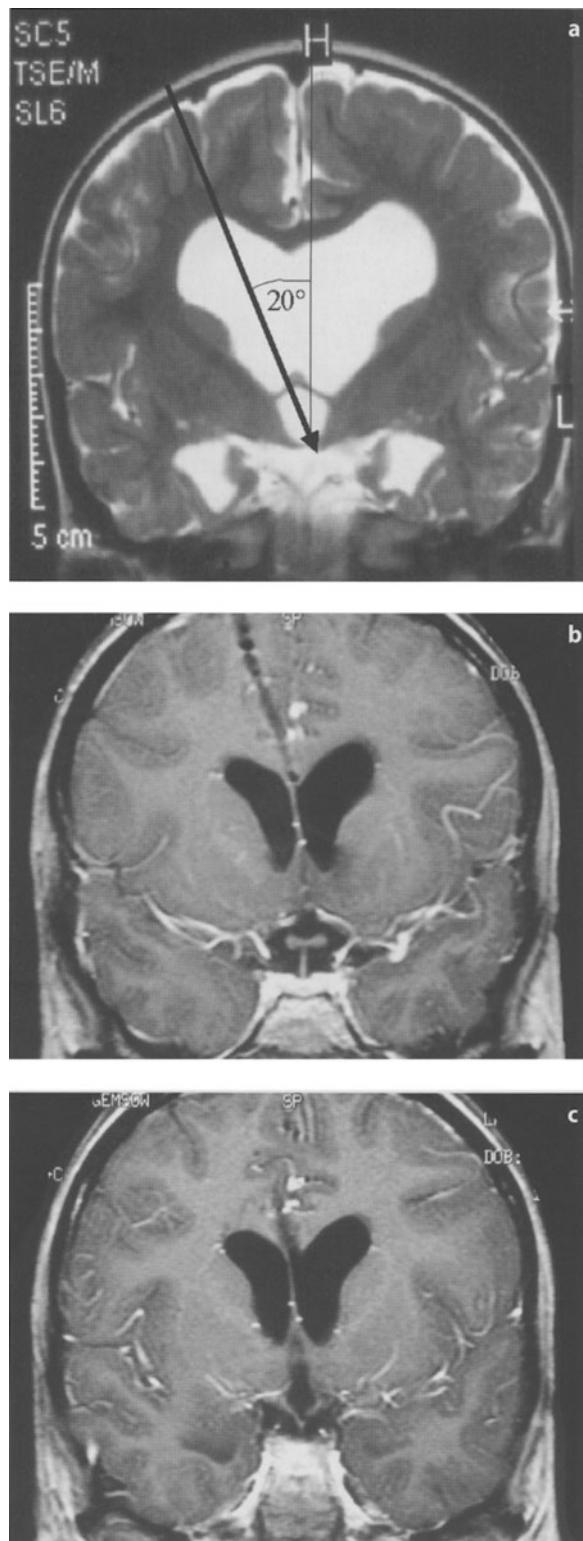


Fig. 13. **a** Ideal trajectory for third ventriculostomy. **b** Wrong trajectory for third ventriculostomy. The burr hole was too close to the midline and the angle of progression too wide in relation to the burr hole. The endoscope crossed the corpus callosum and entered the contralateral ventricle (**c**). The procedure was nevertheless carried out uneventfully

most cases it is not necessary to maintain the coagulation until the perforation is achieved. A very short coagulation (<1 s) is usually sufficient to weaken the floor enough to allow perforation easily and atraumatically with the inactive probe, avoiding the risk of entering the interpeduncular cistern with an electric device on.

Free laser light cannot be used because it would be rapidly absorbed by the CSF with scattering and possible thermal injury to the surrounding structures [189]. Some authors have proposed the use of contact tipped neodymium-yttrium aluminum garnet (Nd-YAG) laser (1064 nm) [124, 139, 201], although this only offers a partial solution to the problem [189]. Vandertop et al. propose the use of specially designed laser probes with atraumatic ball-shaped fiber tips coated with a layer of carbon particles [189]. This allows 90% absorption of the laser light that is converted into heat [199], allowing both the amount of laser light used and the length of exposure to be reduced. This would result in more concentrated and superficial damage to the target and allow safer perforation of the third ventricular floor by progressive vaporization of the layers encountered [189], without the need for mechanical strength to complete the perforation. Other authors [19] have proposed combined pulsed holmium(Ho)-Nd-YAG laser and claim that it is superior to mechanical cutting of the tissues, both for third ventriculostomy and for cyst fenestration.

Perforation of the floor can also be obtained with a suction-cutting device (Synergetics™, Inc. St. Charles, USA). This is composed of a thin suction cannula that can be introduced through an operative channel at least 2 mm in diameter. The outer surface and the edges of the inlet of the cannula are smooth, whereas small blades are inserted into the lumen of the cannula. When the tip of the cannula comes into contact with the floor of the third ventricle, the suction hole on the handle is closed and the membrane is sucked into the lumen of the cannula. Rotation of the cannula allows section of only the tissue aspirated into the lumen, limiting the risk of accidental injury to vascular structures.

A useful tool for detecting the basilar artery behind a thick, nontranslucent floor could be a Doppler ultrasound probe inserted into the working channel of the endoscope and applied to the floor of the third ventricle. This device could atraumatically identify a silent point of the floor safe for perforation [29]. Surgical tools specifically designed for safe perforation of a resistant and/or thick floor have a semisharp, slightly angulated tip that, directed anteriorly and pushed inferiorly along the clivus, would allow safe perforation minimizing the risk of injury of the basilar artery [102].

Ultrasound microprobe have been specifically designed for use through the working channel of the endoscope (6 French) or paraendoscopically (8 French).

These probes offer the major advantage of direct visualization of the anatomical structures of the interpeduncular and prepontine cisterns and can be used for blunt perforation of the floor. This allows safer perforation under the double control of the floor of the third ventricle (endoscopic) and of the anatomical and vascular structures hidden behind the floor membrane (ultrasonographic) [143, 151-153].

Dilatation of the Stoma

After perforation of the floor, the hole obtained is usually no larger than the outer diameter of the instrument used (<2 mm). If left like this, it is bound to close rapidly because of the inflammatory reaction induced by the thermal or mechanical injury inflicted for perforation and the consequent formation of glial scar tissue. Dilatation can be achieved by introducing a grasping or biopsy forceps into the hole closed, then carefully opening it. This technique is usually relatively safe, but has several drawbacks. The dorsal surface of the forceps is smooth, so that the edges of the hole slip on this surface during opening: this necessitates several maneuvers of opening and closing the forceps to obtain a satisfactory result, especially in the case of a thick, nontranslucent floor. These repeated maneuvers can result in accidental grasping of a perforating vessel in the interpeduncular cistern. Dilatation with a Fogarty balloon (usually 3 or 4 French) is much safer, since both the tip of the catheter and the surface of the balloon are smooth (Fig. 14). For the same reason, the edges of the stoma slip very easily on this surface, requiring repeated inflations before the stoma is dilated to the largest diameter allowed by the balloon (4-

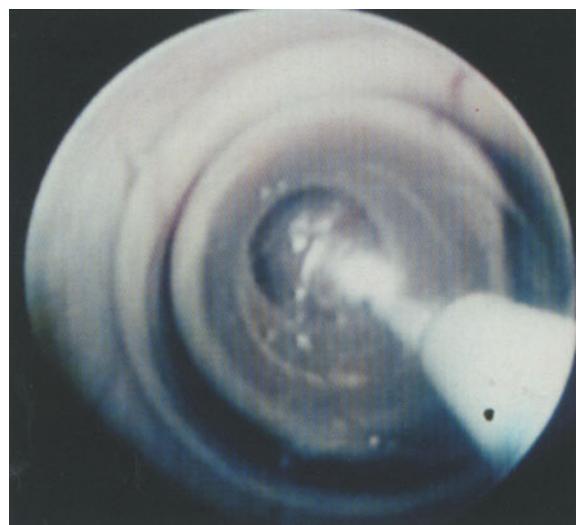


Fig. 14. Fogarty balloon inflated for dilatation of the stoma

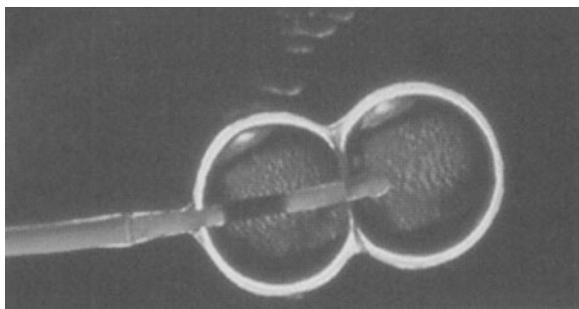


Fig. 15. Balloon specifically designed for dilatation of a third ventriculostomy. Note the dumbbell shape that avoids displacement of the floor membrane on the smooth surface of the balloon during inflation, allowing large dilatations with one single maneuver. (Lighttouch balloon, Integra Neuroscience, Biot, France)



Fig. 16. Dilatation of a third ventriculostomy using the forceps (Karl Storz GmbH & Co, Tuttlingen, Germany) described by Decq (see [47]). (With the kind permission of Dr. Philippe Decq, Hôpital Henri Mondor, Créteil, France)

5 mm). A balloon specifically designed for third ventriculostomy (Lighttouch balloon, Integra Neuroscience, Biot, France) offers the ideal solution since the inflatable part is a dumbbell-shaped silicone membrane (Fig. 15). The narrowest part is marked with a black dot when the balloon is deflated. The catheter is introduced deflated into the stoma and advanced until the black dot is at the level of the floor. The distal part inflates first, then the proximal one. The floor membrane remains trapped between the two balloons and the stoma is gently dilated with further air inflation to the largest extent allowed with one single maneuver. This technique remains by far the simplest, safest, and fastest and should be recommended.

A variant of the balloon technique has been proposed using instruments designed for stone extraction in urological endoscopic surgery [200]. The device is composed by a four-flat-wire basket tip that has a 1-mm outer diameter when closed. When opened it has a basket-like shape that enlarges the stoma by tearing the edges. The risk of catching a small vessel within the wires of the basket during closure reduces the advantages of this device compared to a Fogarty balloon.

Another useful device designed for both floor perforation and membrane fenestration has been recently proposed by Decq et al. [47]. It is a sterilizable forceps with a thin tip to allow easy perforation of the floor by the application of gentle pressure. The inner surface of the forceps is smooth whereas the outer surface presents indentations: this avoids accidental catching of vessels during closure and slipping of the edges of the stoma during opening, allowing easy dilatation with one single movement and avoiding the repeated maneuvers that are often necessary to enlarge the first opening and that are potentially hazardous (Fig. 16).

Opening of Liliequist's Membrane

After perforation of the floor and dilatation of the stoma, the floor membrane begins to move in a pulsatile way synchronous with the heartbeat. The subarachnoid space should now be entered with the endoscope in order to ascertain the existence of a communication between the third ventricle and the subarachnoid space. The anatomical structures of the interpeduncular or prepontine cistern (i.e., basilar artery and/or its branches, ventral surface of the brainstem, third cranial nerve, dura of the clivus) should be clearly visualized. In a significant number of cases visualization of these structures is impossible because of the presence of Liliequist's membrane. This arachnoid membrane originates laterally at the junction between the caudal oculomotor membrane and the mesencephalic membrane. From this point the membrane spreads between the two oculomotor nerves and extends caudally to the arachnoid that covers the dorsum sellae. Superiorly the membrane extends to the ventral surface of the brain between the mamillary bodies and the infundibulum [15, 113, 114, 191]. The insertion of the posterior edge of the membrane is variable: some authors describe an attachment in the premamillary area [15, 114, 202]; others [121, 191] also describe the possibility of a more posterior attachment in the retromamillary region. The variability of the posterior insertion and of the precise location of perforation of the floor during third ventriculostomy explains the variability of anatomical findings at endoscopic exploration of the subarachnoid spaces. In fact, in most cases the perforation of the floor and dilatation of the stoma allow direct access to the prepontine cistern with good visualization of the basilar

artery and its branches: this could be explained by greater frequency of an anterior attachment in the premamillary region. When the insertion of the membrane is more posterior, it appears after the insertion of the endoscope into the third ventriculostomy stoma. Sometimes it can be very close to the floor and can be inadvertently opened during the surgical maneuvers to dilate the stoma, but in most cases it appears as a thick, whitish membrane that prevents visualization of the anatomy of the prepontine cistern. In such cases it must be opened, since its presence could exclude or reduce CSF circulation between the ventricular cavity and the subarachnoid spaces of the posterior fossa and of the spinal subarachnoid spaces, impairing or reducing CSF pulsatile flow and possibly leading to early closure of the stoma. The opening of Liliequist's membrane requires delicate surgical manipulation, since it can be more difficult to perforate than the floor of the third ventricle itself. Bipolar coagulation should be preferred; monopolar coagulation should be avoided because of the proximity of the basilar artery. In any case, only smooth instruments should be used at this level and the grasping forceps should also be avoided. It is common experience that after the opening of Liliequist's membrane, the pulsatile movements synchronous with the heartbeat of the third ventricular floor dramatically increase, as if the communication with the caudal subarachnoid spaces was the most important event of the whole procedure.

Closure

After obtaining good communication between the third ventricle and the subarachnoid spaces with a large opening (at least 4 mm), the endoscope can be slowly withdrawn from the ventricular cavity. The small-scale bleeding that usually occurs at the level of the edges of the stoma can be easily controlled by irrigation with Ringer's lactate at body temperature or by inflating the balloon within the stoma and leaving it inflated for 40-50 s. The endoscope should be withdrawn very slowly through the track in the white matter, in order to ensure the absence of intraparenchymal bleeding, which can be the origin of the rarely occurring intraparenchymal hematoma along the track of the endoscope [171, 172]. If a lesion biopsy has been performed, it is recommended to remove the endoscope before removing the peel-away sheath, to minimize the risk of dissemination of the biopsied lesion along the endoscope track [76]. After removal of the endoscope, care should be taken to avoid excessive CSF loss or the entrance of air and blood from the burr hole site. For this reason, a small cylinder of

oxymethyl cellulose should be inserted into the small leukotomy. Fibrin glue can be used and bone dust should be replaced into the burr hole. It is important to replace the bone dust in the burr hole only after refilling the endoscope track with oxymethyl cellulose and glue, since bone cookies can migrate into the ventricle, graft onto the ventricular wall, and evolve into growing intraventricular calcifications [182]. In neonates where the dural incision was linear at the level of the lateral angle of the fontanel, the dura should be closed in a watertight fashion with a continuous suture (see Fig. 10e). The skin should be closed in two layers, using continuous mattress sutures in order to minimize the risk of CSF leaks postoperatively (see Fig. 10f). Intracranial pressure monitoring can be inserted into the ventricle through the same endoscope track, depending on the preoperative evaluation and the surgeon's preference. When the procedure is performed in a patient operated on for shunt malfunction, whose shunt has been removed during the same procedure, implantation of a transducer for continuous ICP monitoring and a safety external ventricular drainage that can be left closed in the postoperative period is mandatory. If the third ventriculostomy performed is not sufficient to restore normal CSF flow, these patients are at significant risk of clinical degradation in the first few postoperative hours, and having an external drainage in place that can be opened if necessary can be life-saving and avoids additional emergency procedures.

Postoperative Period

Awakening from anesthesia is usually prompt after an uneventful procedure [4, 55]. Transient bradycardia can be observed at the time of reversal of the neuromuscular block [5]. A phase of agitation may be observed, especially in cases of intraoperative bleeding and subsequent irrigation with Ringer's lactate [55, 56].

If, in cases of aqueductal stenosis or acute shunt malfunction in obstructive triventricular hydrocephalus, Parinaud's sign was present in the preoperative period, it should have disappeared completely, from the earliest postoperative moment; persistence of this sign should be taken as a potential predictor that the procedure has failed [36]. If other elements of sylvian aqueduct syndrome or dorsal global midbrain dysfunction were present in the preoperative period, these usually disappear or improve later and more slowly than Parinaud's sign [36].

Significant hyperthermia (39-40 °C) is frequently observed during the first 48-72 h, especially follow-

ing a troublesome procedure requiring repeated manipulations of the floor of the third ventricle. This is probably related to transient dysfunction of hypothalamic thermoregulation [161,163] and should not be considered as a sign of CSF infection in the absence of other clinical or positive ancillary tests. Persistence of significant hyperthermia after 72 h should prompt CSF sample by lumbar tapping followed by antibiotic therapy. Transient mild hyperkalemia has been described in the 4-5 days following the procedure, the suggested mechanism being distortion of the posterior hypothalamus during floor perforation [5].

An early CT scan should be obtained in the first 24-48 h in order to assess the degree of ventricular dilatation immediately after the procedure. ICP monitoring in the earliest postoperative hours usually reveals very low values as a consequence of CSF loss during the procedure. After 6-8 h, ICP values begin to rise, reaching abnormally high values within the first 12 postoperative hours [11, 37, 60, 87, 103, 104, 163] (Fig. 17). This has been interpreted as a consequence of higher CSF outflow resistance to the increased amount of CSF entering the subarachnoid spaces. In fact, in cases of obstructive triventricular hydrocephalus, only the CSF produced at the level of the choroid plexus of the fourth ventricle (<10% of the whole choroid plexus volume) circulates through the natural CSF pathways, the rest being absorbed through alternative pathways or drained through a pre-existing shunt. After the opening of the third ventriculostomy, the increased amount of circulating CSF may require a so-called "adaptation period" [11, 87]. This phenomenon has been very well known since the time of Matson, who described the post-operative period of ventriculocervical subarachnoid shunt implanted to bypass aqueductal stenosis. He reported that "occasionally, the shunt does not seem to be working for several

days and then suddenly, or usually more gradually over the next few days, free communication between the ventricle and the lumbar subarachnoid space becomes established" [120]. The origin of this phenomenon still remains under debate: possible hypotheses are the progressive reopening of the subarachnoid spaces of the convexity, a slow increase in permeability of the pacchionian granulations, and possible effusion of the CSF into the spinal subdural space [30]. The ICP elevation after the procedure is not observed in all cases. After more than 40 ICP recordings following endoscopic third ventriculostomy, we have observed that the highest levels of postoperative ICP were recorded in the patients who presented the most serious clinical picture preoperatively, as if a direct relationship existed between preoperative and postoperative ICP levels. In these first 2-4 days high ICP can become symptomatic with headache and possibly vomiting, especially in patients who carried ventriculoperitoneal shunts before the procedure [103]. The symptoms can be so impressive that a diagnosis of failure may be made [103]. Analysis of the amount of CSF drained through an external drainage positioned at 30 cm height in 15 patients treated with endoscopic third ventriculostomy for shunt malfunction showed that adaptation can be roughly summarized into two patterns. In the first, the amount of CSF drained is insignificant (<20 ml/day) and rapidly decreases within 2 days. In the second, the amount of CSF drained is larger (150-250 ml/day) and decreases more slowly over several days [134]. These two patterns of CSF resorption may account for the variability of ICP values observed after endoscopic third ventriculostomy [37].

Subcutaneous swelling is frequently observed at the site of the burr hole and CSF leaks can occur, especially in small babies or when two-layer closure with mattress skin stitches has not been performed.

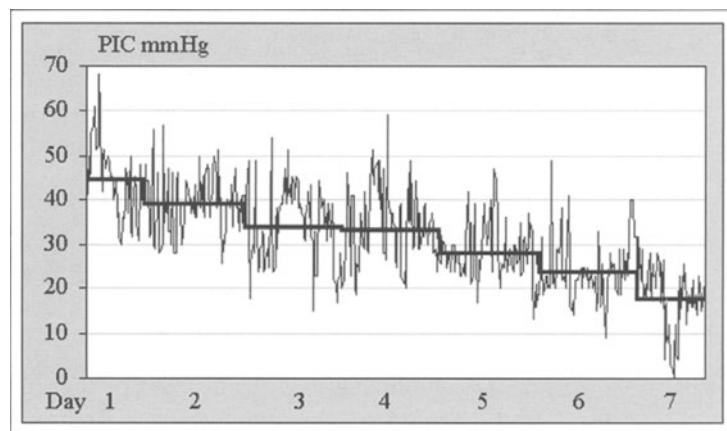


Fig. 17. Postoperative ICP monitoring in an 11-year-old boy with aqueductal stenosis and hydrocephalus treated by third ventriculostomy. The ICP levels remained very high during the immediately postoperative days, but showed slowly progressive normalization during the first week following third ventriculostomy

Occasionally, a CT scan performed in this period may show increasing dilatation of the ventricular system, adding further evidence of failure, and the patient may be reoperated for shunt implantation. To avoid this misinterpretation of the clinical course, some authors have proposed leaving an external ventricular drainage in place during the procedure, to allow intermittent CSF drainage during the periods of pathological ICP elevation [11]. According to the authors, this would allow transient drop in intraventricular pressure, allowing re-expansion of the intracranial subarachnoid spaces and facilitating CSF circulation toward the convexity. We have seen that the same result can be obtained by performing lumbar tap under ICP monitoring, withdrawing the amount of CSF necessary to restore a normal ICP [37], as already suggested and reported by Matson [120]. In some cases lumbar tapping can be repeated 24–48 h later; a third tap is rarely necessary (Fig. 18). The positive effects on the ICP last longer than can be explained by simple subtraction of the small CSF volume, which is usually 5–10 ml. One possible explanation is the increased compliance of the spinal subarachnoid spaces (SAS) and the increased pressure gradient between third ventricle and posterior fossa SAS (SAS pressure < intraventricular pressure) following CSF subtraction. The effect would be prolonged in time because of the CSF leak in the peridural space and in the muscles through the dural hole opened by the spinal needle. This would facilitate CSF flow through the third ventriculostomy, reducing ventricular volume and allowing re-expansion of the intracranial subarachnoid spaces. This maneuver is probably to be preferred to the intermittent opening of the external ventricular drainage, which acts by the same mechanism but with the pressure gradient inverted (SAS pressure > intraventricular pressure) and with the beneficial effect limited to the time when the drainage is open.

Usually after 7–10 days the ICP values become normal and the external drainage and ICP transducer can be removed. MRI should be performed early, before or immediately after discharge, with cine phase-contrast (cine PC) MRI (see Chap. 27) to prove the permeability of the stoma. This early MRI is mandatory, especially in children, because of the risk of early closure of the stoma, which can be easily managed by repeating the third ventriculostomy [34, 106, 175].

Both fast spin-echo T2-weighted MRI sequences and cine PC MRI are highly reliable in assessing the patency of third ventriculostomy; the latter should be preferred in the case of doubtful findings [39, 62, 90, 112, 125, 198]. Cine PC MRI can show patterns of obstruction of the stoma even in cases where surgical exploration reveals small residual perforations. In doubtful cases, promising results are also offered by MR ventriculography [97]. In the follow-up period, an MRI scan is advised at 3 months; after that, every 6 months for the first 2 years and every 12 months up until 6 years postoperatively is the protocol we use. After 6 years, the risk of closure of the stoma is considered extremely low [34], and further investigation should be performed only on the basis of clinical features.

Results

The reported success rates in the literature range from 22.2% [22] to 94.1% [158], with a mean of 68% in 20 series of the literature [8, 17, 22–24, 32, 34, 49, 51, 61, 63, 70, 72, 87, 92, 96, 104, 158, 179, 181, 186]. This wide range of success rates is due to the publication of series of pediatric patients including those with posthemorrhagic hydrocephalus of prematurity and postmeningitic hydrocephalus [22, 23] or several affected

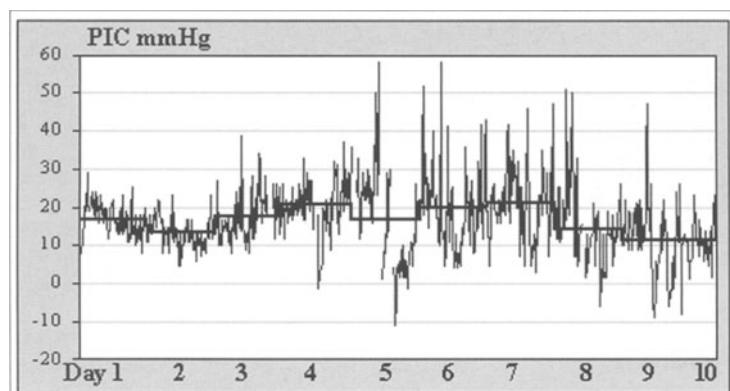


Fig. 18. Postoperative ICP monitoring in a 12-year-old girl affected by aqueductal stenosis and hydrocephalus treated by ventriculoperitoneal shunt at the age of 3 months. She presented with shunt malfunction and was treated by third ventriculostomy and shunt removal. The ICP values remained stable during the first 3 days, then began to raise from day 4 with recurrence of symptoms of increased ICP. Two lumbar punctures on day 4 and day 5 allowed resolution of the symptoms and slow, progressive normalization of the ICP values

by myelomeningocele [17], where third ventriculostomy, although rather contraindicated, was performed as a primary treatment at a very early age. When only patients affected by obstructive triventricular hydrocephalus are considered, the success rate is actually quite homogeneous and stable, being above 60% at any age [34, 61, 92]. Only Tuli et al. [186] reported a 44% failure rate in a group of pediatric patients affected by obstructive triventricular hydrocephalus. The variability of results may also depend on the pre-operative indication criteria for the procedure and the postoperative criteria for evaluation of its success. Compared to shunt surgery, the most important difference is the radiological outcome. Ventricular size usually decreases rapidly and significantly following shunt implantation due to the siphoning effect induced by the orthostatic pressure in the upright position. The volume decrease is much slower and smaller in scale after third ventriculostomy, for several reasons: the transient “adaptation period” [11, 87] in which the CSF “finds its way” through the subarachnoid spaces; the lack of communication with a lower-pressure cavity (e.g., right atrium, peritoneal cavity); and the nature of hydrocephalus related to aqueductal stenosis, which often evolves over several years before becoming symptomatic. The ventricular dilatation observed in these cases is often severe, with long-standing compression of the periventricular white matter and macrocrania easily associated [65].

The radiological criteria that must be fulfilled for success are as follows:

1. Reduction in ventricular size ranging from 10% to 50% must be observed from the first week [174], even if the ventricles remain large (see Fig. 6b-d).
2. Periventricular lucency, if present before operation, must disappear (see Fig. 6b-d).

3. CSF flow artifact must be visible on sagittal median T2-weighted fast spin-echo MRI sequences [66, 107] (see Chap. 27) (Figs. 5b, 6c, 19b, 20b,c, 21b-d). CSF flow has been described in newborns with color Doppler ultrasonography [197].
4. The floor of the third ventricle, if bulging downward in the preoperative images, must be straight on postoperative images (Fig. 19).
5. Atrial diverticula and pseudocystic dilatation of the suprapineal recess, if present preoperatively, must disappear or decrease significantly (Fig. 20).
6. Pericerebral sulci, if not visible before operation, must reappear or increase in size.

When considering different neuroradiological indices, it has been shown that the width of the third ventricle is the quickest to decrease and remains stationary in size 3 months later. The downward deviation and flattening of the brainstem reverts within 1 year, whereas the width and height of the lateral ventricles continue to decrease steadily for 2 years [140]. A more than 15% decrease in size of the third ventricle within 1 month is considered the most reliable indicator of favorable outcome following third ventriculostomy [25, 173, 174]. The more significant decrease of both the third ventricle (30%-40%) and the lateral ventricles (30%-32%) is already visible from the first postoperative week. The extent of ventricular volume decrease is in inverse correlation with the preoperative duration and magnitude of clinical symptoms. A decrease in volume of less than 10% may be observed in patients with long-standing chronic symptoms [174]. In some pathologies, such as vein of Galen malformation and cysts of the quadrigeminal cisterns, repermeabilization of the aqueduct can be observed if embolization of the malformation and cystocisternostomy are performed (Figs. 21, 22).

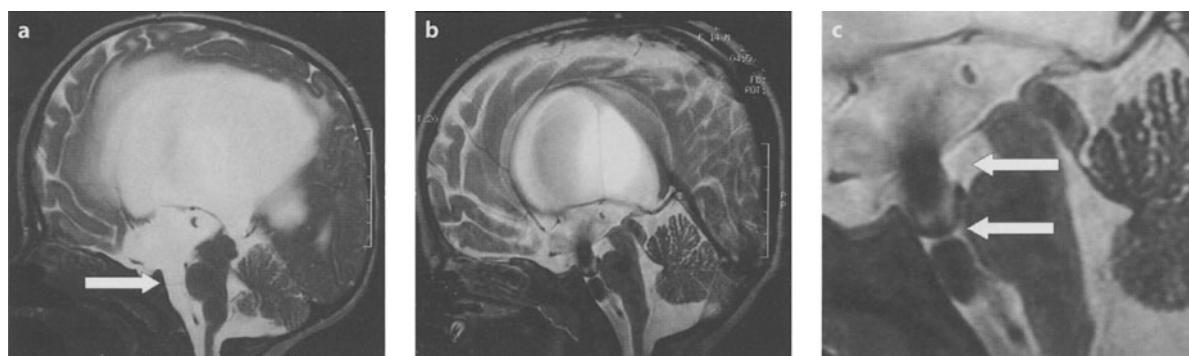


Fig. 19. **a** Aqueductal stenosis in a 12-month-old baby girl. Note the position of the floor of the third ventricle, bulging almost 1 cm below the level of the posterior clinoid (arrow). **b** Postoperative MRI. The perforated floor is now in its normal position, well above the level of the posterior clinoid. Flow artifact is clearly visible through the third ventriculostomy and through Liliequist's membrane, visible in the detail shown in **c** as a thin membrane dividing the prepontine cistern into two compartments. The anterior edge is attached on the posterior aspect of the clivus; the membrane can be followed through the prepontine cistern to the anterior margin of the pons (lower arrow) and then upward into the interpeduncular cistern (upper arrow)



Fig. 20. **a** Aqueductal stenosis in a 3-month-old boy. The quadrigeminal cistern is invaded by an atrial diverticulum formed by the ependyma of the left lateral ventricle herniated through the pacchionian foramen. **b** Postoperative MRI 1 week following third ventriculostomy, showing significant reduction of the volume of the diverticulum and of the third ventricle. **c** Two years after third ventriculostomy, the atrial diverticulum has almost completely disappeared, the ependyma of the lateral ventricle being visible at the level of the tentorial edge (*upper arrow*), leaving a large, dilated quadrigeminal cistern (*lower arrow*)

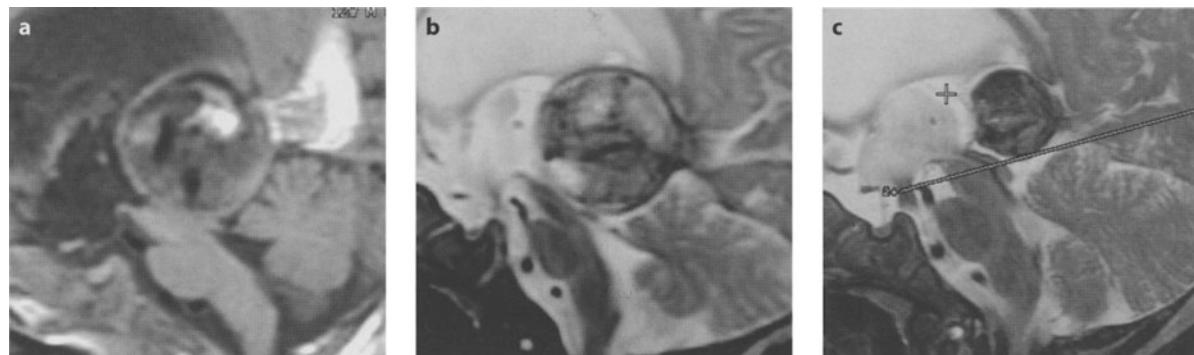


Fig. 21. Twelve-week-old boy presenting with vein of Galen malformation diagnosed prenatally and embolized at the age of 11 weeks, admitted with symptoms and signs of intracranial hypertension. **a** MRI performed 5 days following embolization, showing aqueductal stenosis due to the vascular malformation and triventricular hydrocephalus. The hydrocephalus was treated the same day with third ventriculostomy. **b** Three weeks following endoscopic third ventriculostomy and complete resolution of the symptoms. Flow void is visible through the third ventriculostomy, the aqueduct is still compressed. **c** MRI performed 4 months after third ventriculostomy, showing significant decrease of the malformation and patency of the aqueduct and third ventriculostomy with CSF flow void well visible through them

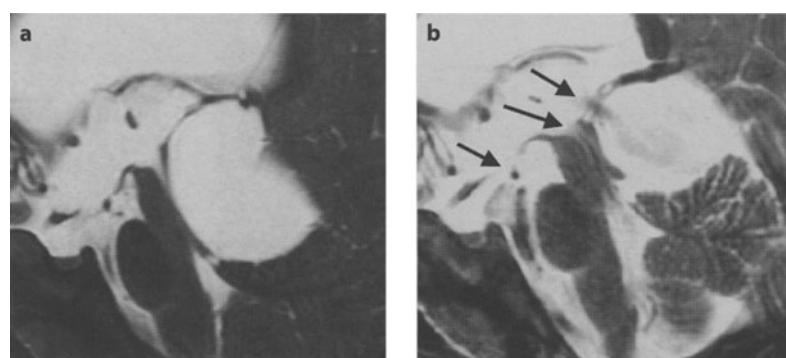


Fig. 22. **a** Eleven-month-old boy with an arachnoid cyst of the quadrigeminal cistern causing aqueductal stenosis and obstructive triventricular hydrocephalus. **b** 10 weeks following endoscopic third ventriculocisternostomy and third ventriculocystostomy. Note the CSF flow void through the ventriculocystostomy (*upper arrow*), through the aqueduct and the superior part of the fourth ventricle (*middle arrow*), and through the third ventriculostomy (*lower arrow*)

Clinical criteria of success are as follows:

1. Parinaud's sign, if present preoperatively, must disappear at the awakening from anesthesia [36, 170].
2. Papilledema must disappear within 2-3 weeks.
3. Other signs and symptoms of intracranial hypertension must resolve spontaneously or after two lumbar punctures performed according to the criteria described in the first 2 weeks.

ICP must return to normal values within 10 days after endoscopic third ventriculostomy. If ICP remains elevated with persistent symptoms of intracranial hypertension, at least two lumbar taps must be performed before the conclusion is drawn that the procedure has failed.

If any of these criteria are not fulfilled, a failure should be recognized and the patient should rapidly undergo shunting. In children, most failures are observed in the first postoperative weeks [34, 51, 85, 186] and may be explained by a multifactorial pathophysiological mechanism of hydrocephalus. If all the criteria are fulfilled and the patient is discharged, the procedure should be considered a success.

Close follow-up is mandatory in the first 5-6 years, and parents must be informed that immediate neurosurgical assessment is required if symptoms and signs of intracranial hypertension appear. These precautions are necessary because delayed failure can occur [34, 51, 78, 106, 129, 175, 186], usually due to obstruction of the stoma by the growth of gliotic ependymal scarring tissue [34, 73]. Such failures can manifest with a very acute clinical onset, and if not recognized early may have dramatic consequences [73]. If the patient is readmitted with recurrent signs of intracranial hypertension and increased ventricu-

lar dilatation on CT scan or MRI, the most likely diagnosis is obstruction or severe narrowing of the third ventriculostomy. This must be immediately confirmed by sagittal median T2-weighted fast spin-echo MRI sequences, which will show disappearance of the flow artifact and recurrence of the indirect signs of occlusion of the stoma (Fig. 23) [34, 51, 106, 175]. The treatment for obstruction can be reopening or enlargement of the stoma; this procedure carries the same success rate as the primary treatment (>65%) [51, 106, 175] and should be preferred in a first instance to shunt implantation.

If MRI at this stage shows good flow through the stoma, then a ventriculoperitoneal shunt should be inserted. In adult patients, recent reports seem to show that in the long term a greater number of patients than expected could show delayed failure of the third ventriculostomy with an open stoma at MRI [183]. This delayed "open-stoma" failure can rarely be observed also in children, especially in patients who have multiple potential etiological factors for hydrocephalus (e.g., hemorrhage, meningitis). This is the most insidious form of failure because of the difficulties in diagnosing it. Patients can present mild developmental delay that is sometimes difficult to diagnose without appropriate psychomotor testing. Radiology reveals large ventricles (stable at follow-up) and open stoma at MRI with clearly visible pericerebral CSF and no transependymal resorption. Clinically, papilledema is usually absent and only mild hyperreflexia can be observed, but progressive macrocrania in the first 2-3 years of life is almost the rule. ICP monitoring in these patients reveals abnormal baseline ICP values

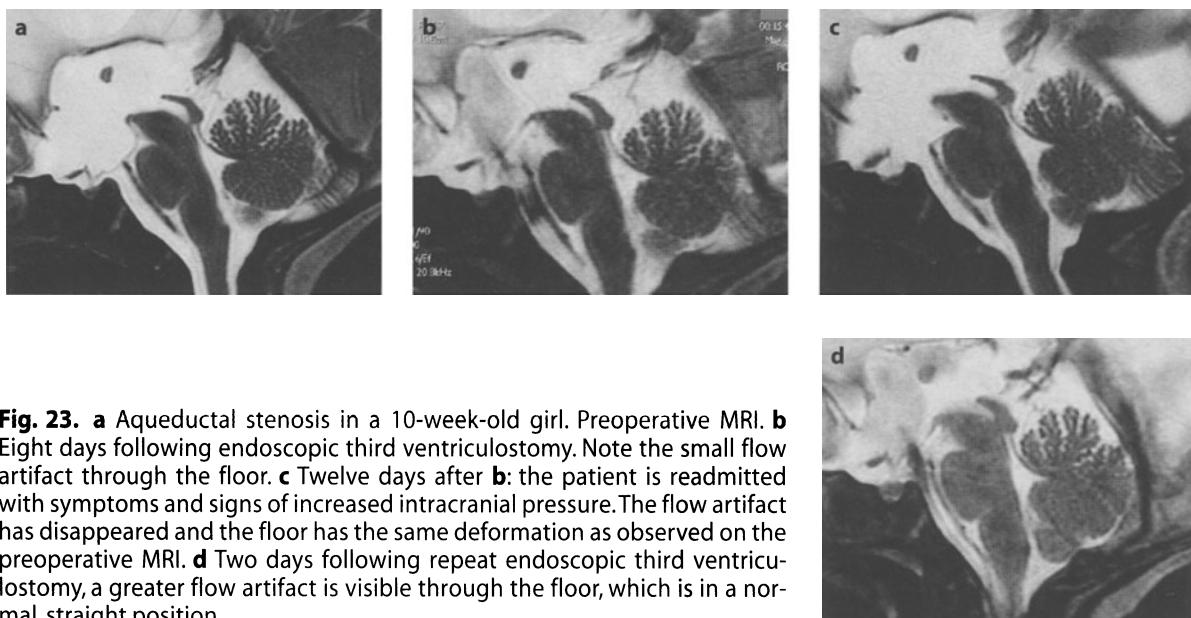


Fig. 23. **a** Aqueductal stenosis in a 10-week-old girl. Preoperative MRI. **b** Eight days following endoscopic third ventriculostomy. Note the small flow artifact through the floor. **c** Twelve days after **b**: the patient is readmitted with symptoms and signs of increased intracranial pressure. The flow artifact has disappeared and the floor has the same deformation as observed on the preoperative MRI. **d** Two days following repeat endoscopic third ventriculostomy, a greater flow artifact is visible through the floor, which is in a normal, straight position

and B waves. After ventriculoperitoneal shunting, patients usually show significant improvements in psychomotor testing.

Long-term studies of the patency and clinical effectiveness of third ventriculostomy are available [34, 51, 85, 186]. They all show that no failure is to be expected after the 5th year following the procedure. Retrospective and prospective studies comparing similar groups of patients affected by aqueductal stenosis treated by third ventriculostomy or ventriculoperitoneal shunt present discordant conclusions, some of them claiming different rates of complications in the long term [168], others reporting no significant differences in the long term [85, 163, 186]. A controlled randomized study comparing neuroendoscopic versus nonneuroendoscopic treatment of hydrocephalus in children seems to show that the outcome of the patients treated initially with a neuroendoscopic procedure is significantly better than that of the patients initially treated with a shunt, but this observation requires further investigation in multicenter studies [98].

References

1. Akdemir H, Kurtsoy A, Oktem IS, Menku A, Kemal Koç R, Tucer B: Failure of third ventriculostomy for shunt infections in infants. *Pediatr Neurosurg* 30:305-309, 1999
2. Aleman J, Jokura H, Higano S, Akabane A, Shirane R, Yoshimoto T: Value of constructive interference in steady-state, three-dimensional, Fourier transformation magnetic resonance imaging for the neuroendoscopic treatment of hydrocephalus and intracranial cysts. *Neurosurgery* 48:1291, 2001
3. Amano T, Inamura T, Nakamizo A, Inoha S, Wu CM, Ikezaki K: Case management of hydrocephalus associated with the progression of childhood brain stem gliomas. *Child's Nerv Syst* 18:599-604, 2002
4. Ambesh SP, Kumar R: Neuroendoscopic procedures: anesthetic considerations for a growing trend: a review. *J Neurosurg Anesthesiol* 12:262-270, 2000
5. Anand B, Madhusudan Reddy KR, Mohanty A, Umamaheswara Rao GS, Chandramouli BA: Intraoperative bradycardia and postoperative hyperkalemia in patients undergoing endoscopic third ventriculostomy. *Minim Invasive Neurosurg* 45:154-157, 2002
6. Auer LM, Auer DP: Virtual endoscopy for planning and simulation of minimally invasive neurosurgery. *Neurosurgery* 43:529, 1998
7. Backlund BO, Grepe A, Lunsford D: Stereotaxic reconstruction of the aqueduct of Sylvius. *J Neurosurg* 55:800-810, 1981
8. Baskin JJ, Manwaring KH, Rekate HL: Ventricular shunt removal: the ultimate treatment of the slit ventricle syndrome. *J Neurosurg* 88:478-484, 1998
9. Bech RA, Bogeskov L, Borgesen SE, Juhler M: Indications for shunt insertion or III ventriculostomy in hydrocephalic children, guided by lumbar and intraventricular infusion tests. *Child's Brain* 15:213-218, 1999
10. Beems T, Grotenhuis JA: Is the success rate of endoscopic third ventriculostomy age-dependent? An analysis of the results of endoscopic third ventriculostomy in young children. *Child's Nerv Syst* 18:605-608, 2002
11. Bellotti A, Rapana A, Iaccarino C, Schonauer: Intracranial pressure monitoring after endoscopic third ventriculostomy: an effective method to manage the 'adaptation period'. *Clin Neurol Neurosurg* 103:223-227, 2001
12. Benabarre A, Ibanez J, Boget T, Obiols J, Martinez Aran A, Vieta E: Neuropsychological and psychiatric complications in endoscopic third ventriculostomy: a clinical case report. *J Neurol Neurosurg Psychiatry* 71:268-271, 2001
13. Bognar L, Borgulya G, Benke P, Madarassy G: Analysis of CSF shunting procedure requirement in children with posterior fossa tumors. *Child's Nerv Syst* 2003; epub 23 April, print 19:332-336
14. Böschert J, Hellwig D, Krauss JK: Endoscopic third ventriculostomy for shunt dysfunction in occlusive hydrocephalus: long-term follow up and review. *J Neurosurg* 98:1032-1039, 2003
15. Brasil AV, Schneider FL: Anatomy of Liliequist's membrane. *Neurosurgery* 32:956-960, 1993
16. Brocklehurst G: Trans-callosal ventriculochiasmatic cisternostomy. A new approach to hydrocephalus. *Surg Neurol* 2:109-114, 1974
17. Brockmeyer D, Abtin K, Carey L, Walker M: Endoscopic third ventriculostomy: an outcome analysis. *Pediatr Neurosurg* 28:236-240, 1998
18. Broggi G, Dones I, Feroli P, Franzini A, Servello D, Duca S: Image guided neuroendoscopy for third ventriculostomy. *Acta Neurochir* 142:893-899, 2000
19. Büki A, Doczi T, Veto F, Horvath Z, Gallyas F: Initial clinical experience with a combined pulsed holmium-neodymium-YAG laser in minimally invasive neurosurgery. *Minim Invasive Neurosurg* 42:35-40, 1999
20. Burtscher J, Dessl A, Bale R, Eisner W, Auer A, Twerdy K, Felber S: Virtual endoscopy for planning endoscopic third ventriculostomy procedure. *Pediatr Neurosurg* 32:77-82, 2000
21. Butler WE, Khan SA: The application of controlled intracranial hypertension in slit ventricle syndrome patients with obstructive hydrocephalus and shunt malfunction. *Pediatr Neurosurg* 35:305-10, 2001
22. Buxton N, Macarthur D, Mallucci C, Punt J, Vloeberghs M: Neuroendoscopy in the premature population. *Child's Nerv Syst* 14:649-652, 1998
23. Buxton N, Macarthur D, Mallucci C, Punt J, Vloeberghs M: Neuroendoscopic third ventriculostomy in patients less than 1 year old. *Pediatr Neurosurg* 29:73-76, 1998
24. Buxton N, Ho KJ, Macarthur D, Vloeberghs M, Punt J, Robertson I: Neuroendoscopic third ventriculostomy for hydrocephalus in adults: Report of a single unit's experience with 63 cases. *Surg Neurol* 55:74-78, 2001
25. Buxton N, Turner B, Ramli N, Vloeberghs M: Changes in third ventricular size with neuroendoscopic third ventriculostomy: a blinded study. *J Neurol Neurosurg Psychiatry* 72:385-387, 2002
26. Buxton N, Jaspan T, Punt J: Treatment of Chiari malformation, syringomyelia and hydrocephalus by neuroendoscopic third ventriculostomy. *Minim Invasive Neurosurg* 45:231-4, 2002
27. Caemaert J: Comment to Broggi, et al: *Acta Neurochir* 142:899, 2000

28. Carpentier A, Brunelle F, Philippon J, Clemenceau S: Obstruction of Magendie's and Luschka's foramina. Cine MRI, aetiology and pathogenesis. *Acta Neurochir* 143:517-522, 1999
29. Cartmill M, Vloeberghs M: The use of transendoscopic Doppler ultrasound as a safety-enhancing measure during neuroendoscopic third ventriculostomy. *Eur J Pediatr Surg* 9(Suppl 1):50-51, 1999
30. Cartmill M, Vloeberghs M: The fate of the cerebrospinal fluid after neuroendoscopic third ventriculostomy. *Child's Nerv Syst* 16:879-881, 2000
31. Cartmill M, Jaspan T, McConachie N, Vloeberghs M: Neuroendoscopic third ventriculostomy in dysmorphic brains. *Child's Nerv Syst* 17:391-394, 2001
32. Choi JU, Kim DS, Kim SH: Endoscopic surgery for obstructive hydrocephalus. *Yonsei Med J* 40:600-607, 1999
33. Cinalli G: Alternatives to shunting. *Child's Nerv Syst* 15:718-731, 1999
34. Cinalli G, Sainte-Rose C, Chumas P, Zerah M, Brunelle F, Lot G, Pierre-Kahn A, Renier D: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90:448-454, 1999
35. Cinalli G, Salazar C, Yada JZ, Zerah M, Brunelle F, Lot G, Pierre-Kahn A, Renier D, Sainte-Rose C: The role of third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43:1323-1329, 1998
36. Cinalli G, Sainte-Rose C, Simon I, Lot G, Sgouros S: Sylvian aqueduct syndrome and global dorsal midbrain dysfunction associated with shunt malfunction. *J Neurosurg* 90:227-236, 1999
37. Cinalli G, Ruggiero C, Aliberti F, Maggi G: ICP monitoring following endoscopic third ventriculostomy in children. *Child's Nerv Syst* 18:548, 2002
38. Cipri S, Cafarelli F: Successful endoscopic third ventriculostomy in noncommunicating thoracic syringomyelia. *Acta Neurochir (Wien)* 144:93-95, 2002
39. Connor SEJ, O'Gorman R, Summers P, Simmons A, Moore EM, Chandler C, Jarosz JM: SPAMM, cine phase-contrast imaging and fast spin-echo T2-weighted imaging in the study of intracranial cerebrospinal fluid (CSF) flow. *Clin Radiol* 56:763-772, 2001
40. Czosnyka M, Whitehouse H, Smielewski P, Simac S, Pickard JD: Testing of cerebrospinal compensatory reserve in shunted and non-shunted patients: a guide to interpretation based on an observational study. *J Neurol Neurosurg Psychiatry* 60:549-558, 1996
41. Dandy W: Extirpation of the choroid plexus of the lateral ventricle in communicating hydrocephalus. *Ann Surg* 68:569-579, 1918
42. Dandy WE: Diagnosis and treatment of hydrocephalus resulting from strictures of the aqueduct of Sylvius. *Surg Gynec Obstet* 31:340-358, 1920
43. Dandy WE: An operative approach for hydrocephalus. *Bull Johns Hopkins Hosp* 33:189-190, 1922
44. Dandy WE: Surgery of the brain. In: Lewis' practice of surgery, vol 12. Prior, Hagerstown, pp 671-688, 1932
45. Dandy WE: Diagnosis and treatment of strictures of the aqueduct of Sylvius (causing hydrocephalus). *Arch Surg* 51:1-14, 1945
46. Davis L: Neurological surgery. Lea & Febiger, Philadelphia, p 405, 1936
47. Decq P, Leguerinel C, Palfi S, Djindjian M, Keravel Y, Nguyen JP: A new device for endoscopic third ventriculostomy. *J Neurosurg* 93: 509-512, 2000
48. Decq P, Le Guérinel C, Sol JC, Brugières P, Djindjian M, Nguyen JP: Chiari I malformation: a rare cause of non-communicating hydrocephalus treated by third ventriculostomy. *J Neurosurg* 95:783-790, 2001
49. Doczi T, Veto F, Horvath Z: Clinical analysis of 89 consecutive 3rd ventriculostomies (abstract). *Minim Invasive Neurosurg* 41:112, 1998
50. Drake JM: Ventriculostomy for treatment of hydrocephalus. *Neurosurg Clin North Am* 4:657-666, 1993
51. Elbabaa SK, Steinmetz M, Ross J, Moon D, Luciano M: Endoscopic third ventriculostomy for obstructive hydrocephalus in the pediatric population: evaluation of outcome. *Eur J Pediatr Surg* 11(Suppl 1):552-554, 2001
52. El-Dawlatly AA, Murshid WR, El-Khwsky F: Endoscopic third ventriculostomy: a study of intracranial pressure vs hemodynamic changes. *Minim Invasive Neurosurg* 42:198-200, 1999
53. El-Dawlatly AA, Murshid WR, Elshamy A, Magboul MA, Samarkandi A, Takrouri MS: The incidence of bradycardia during endoscopic third ventriculostomy. *Anesth Analg* 91: 1142-1144, 2000
54. Elvidge AR: Treatment of obstructive lesions of the aqueduct of Sylvius and the fourth ventricle by interventricular shunting. *J Neurosurg* 24:11-23, 1966
55. Fabregas N, Lopez A, Valero R, Carrero E, Caral L, Ferrer E: Anesthetic management of surgical neuroendoscopies: usefulness of monitoring the pressure inside the neuroendoscope. *J Neurosurg Anesthesiol* 12:21-28, 2000
56. Fabregas N, Valero R, Carrero E, Tercero J, Caral L, Zavala E, Ferrer E: Episodic high irrigation pressure during surgical neuroendoscopy may cause intermittent intracranial circulatory insufficiency. *J Neurosurg Anesthesiol* 13:152-157, 2001
57. Ferrer E, Santamarta D, Garcia-Fructuoso G, Caral L, Rumia J: Neuroendoscopic management of pineal region tumors. *Acta Neurochir* 139:12-21, 1997
58. Figaji AA, Fiegen AG, Peter JC: Endoscopic third ventriculostomy in tuberculous meningitis. *Child's Nerv Syst* 19:217-25, 2003
59. Forjaz S, Martelli N, Latuf N: Hypothalamic ventriculostomy with catheter. Technical note. *J Neurosurg* 29: 655-659, 1966
60. Frim DM, Goumnerova L: Telemetric intraventricular pressure measurement after third ventriculostomy in a patient with noncommunicating hydrocephalus. *Neurosurgery* 41:1425-1428, 1997
61. Fritsch MJ, Mehdorn M: Endoscopic intraventricular surgery for treatment of hydrocephalus and loculated CSF space in children less than one year of age. *Pediatr Neurosurg* 36:183-188, 2002
62. Fukuhara T, Vorster SJ, Ruggieri P, Luciano MG: Third ventriculostomy patency: comparison of findings at cine phase-contrast MR imaging and at direct exploration. *AJR Am J Neuroradiol* 20:1560-1566, 1999
63. Fukuhara T, Vorster SJ, Luciano MG: Risk factors for failure of endoscopic third ventriculostomy for obstructive hydrocephalus. *Neurosurgery* 46:1100-1111, 2000
64. Fukuhara T, Vorster SJ, Luciano MG: Critical shunt-induced subdural hematoma treated with combined pressure-programmable valve implantation and endoscopic third ventriculostomy. *Pediatr Neurosurg* 33:37-42, 2000
65. Fukuhara T, Luciano MG: Clinical features of late-onset idiopathic aqueductal stenosis. *Surg Neurol* 55:132-137, 2001

66. Fukuhara T, Luciano MG, Kowalski RJ: Clinical features of third ventriculostomy failures classified by fenestration patency. *Surg Neurol* 58:102-10, 2002
67. Fukushima T, Ishijima B, Hirakawa K, et al: Ventriculofiberscope: a new technique for endoscopic diagnosis and operation. *J Neurosurg* 38:251-256, 1973
68. Goumnerova LC, Frim D: Treatment of hydrocephalus with third ventriculostomy: outcome and CSF flow patterns. *Pediatr Neurosurg* 27:149-152, 1997
69. Griffith HB: Technique of fontanelle and persutural ventriculoscopy and endoscopic ventricular surgery in infants. *Child's Brain* 1:359-363, 1975
70. Grunert P, Charalampaki P, Hopf N, Filippi R: The role of third ventriculostomy in the management of obstructive hydrocephalus. *Minim Invasive Neurosurg* 46:16-21, 2003
71. Grunert P, Perneczky A, Resch K: Endoscopic procedures through the foramen of Monro under stereotactic conditions. *Minim Invasive Neurosurg* 37:2-8, 1994
72. Guiot G: Ventriculo-cisternostomy for stenosis of the aqueduct of Sylvius. Puncture of the floor of the third ventricle with a leucotome under television control. *Acta Neurochir* 28:275-289, 1973.
73. Hader WJ, Drake J, Cochrane D, Sparrow O, Johnson ES, Kestle J: Death after late failure of third ventriculostomy in children. *J Neurosurg* 97:211-215, 2002
74. Handler MH, Abott R, Lee M: A near fatal complication of endoscopic third ventriculostomy: case report. *Neurosurgery* 35:525-527, 1994
75. Hashish H, Guenot M, Mertens P, Sindou M: Hydrocéphalie chronique de l'adulte par occlusion membranaire congénitale de l'ouverture médiane du quatrième ventricule (foramen de Magendie). *Neurochirurgie* 45: 232-236, 1999
76. Haw C, Steinbok P: Ventriculoscope tract recurrence after endoscopic biopsy of pineal germinoma. *Pediatr Neurosurg* 34:215-217, 2001
77. Hayashi N, Endo S, Hamada H, Shibata T, Fukuda O, Takaku A: Role of pre-operative midsagittal magnetic resonance imaging in endoscopic third ventriculostomy. *Minim Invasive Neurosurg* 42:79-82, 1999
78. Hayashi N, Hamada H, Hirashima Y, Kurimoto M, Takaku A, Endo S: Clinical features in patients requiring reoperation after failed endoscopic procedures for hydrocephalus. *Minim Invasive Neurosurg* 43:181-186, 2000
79. Hellwig D, Bauer BL: Endoscopic procedures in stereotactic neurosurgery. *Acta Neurochir Suppl* 52:30-32, 1991
80. Hellwig D, Bauer BL: Stereotactic-endoscopic procedures on processes of the midline. *Acta Neurochir Suppl* 53:23-32, 1991
81. Hellwig D, Riegel T, Bertalanffy H: Neuroendoscopic techniques in treatment of intracranial lesions. *Minim Invasive Ther Allied Technol* 7:123-135, 1998
82. Hellwig D, Heinemann A, Riegel T: Endoscopic third ventriculostomy in treatment of obstructive hydrocephalus caused by primary aqueductal stenosis. In Hellwig D, Bauer B (eds) *Minimally invasive techniques for neurosurgery*. Springer, Berlin, pp 65-72, 1998
83. Hellwig D, Haag R, Bartel V, Riegel T, Eggers F, Becker R, Bertalanffy H: Application of new electrosurgical devices and probes in endoscopic neurosurgery. *Neurol Res* 21:67-72, 1999
84. Hirsch JF: Percutaneous ventriculocisternostomies in non-communicating hydrocephalus. *Monogr Neurol Sci* 8:170-178, 1982
85. Hirsch JF, Hirsch E, Sainte-Rose C, Renier D, Pierre-Kahn A: Stenosis of the aqueduct of Sylvius. Etiology and treatment. *J Neurosurg Sci* 30:29-36, 1986
86. Hoffman HJ, Harwood-Nash D, Gilday DL, Craven MA: Percutaneous third ventriculostomy in the management of noncommunicating hydrocephalus. *Neurosurgery* 7: 313-321, 1980
87. Hopf NJ, Grunert P, Fries G, Resch KDM, Perneczky A: Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 44: 795-804, 1999
88. Hopf NJ, Grunert P, Darabi K, Busert C, Bettagi: Frameless neuronavigation applied to endoscopic neurosurgery. *Minim Invasive Neurosurg* 42:187-193, 1999
89. Inamura T, Morioka T, Nishio S, Ikezaki K, Nonaka H, Yoshiura T: Diverticular enlargement of the foramina of Luschka and congenital hydrocephalus. *Child's Nerv Syst* 18:652-655, 2002
90. Jack CR Jr, Kelly PJ: Stereotactic third ventriculostomy: assessment of patency with MR imaging. *AJNR Am J Roentgenol* 10:515-522, 1989
91. Jaksche H, Loew F: Burr hole third ventriculostomy: An unpopular but effective procedure for treatment of certain forms of occlusive hydrocephalus. *Acta Neurochir* 79:48-51, 1986
92. Javadpour M, Mallucci C, Brodbelt A, Golash A, May P: The impact of endoscopic third ventriculostomy on the management of newly diagnosed hydrocephalus in infants. *Pediatr Neurosurg* 35:131-135, 2001
93. Jellinger G: Anatomopathology of nontumoral aqueductal stenosis. *J Neurosurg Sci* 30:1-16 1986
94. Jones RF, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26:86-91, 1990
95. Jones RFC, Stening WA, Kwok BCT, Sands TM: Third ventriculostomy for shunt infection in children. *Neurosurgery* 32:855-860, 1993
96. Jones RFC, Kwok BCT, Stening WA: The current status of endoscopic third ventriculostomy in the management of non-communicating hydrocephalus. *Minim Invasive Neurosurg* 37:28-36, 1994
97. Joseph VB, Raghurom L, Korah IP, Chacko AG: MR Ventriculography for the Study of CSF Flow. *AJR Am J Neuroradiol* 24:373-381, 2003
98. Kamikawa S, Inui A, Kobayashi N, Kuwamura K, Kasuga M, Yamadori T, Tamaki N: Endoscopic treatment of hydrocephalus in children: a controlled study using newly developed Yamadori-type ventriculoscopes. *Minim Invasive Neurosurg* 44:25-30, 2001
99. Kanner A, Hopf NJ, Grunert P: The "optimal" burr hole position for endoscopic third ventriculostomy: results from 31 stereotactically guided procedures. *Minim Invasive Neurosurg* 43:187-189, 2000
100. Karachi C, Le Guerinel C, Brugieres P, Melon E, Decq P: Hydrocephalus due to idiopathic stenosis of the foramina of Magendie and Luschka. Report of three cases. *J Neurosurg* 98:897-902, 2003
101. Kehler U, Gliemroth J: Extraventricular intracisternal obstructive hydrocephalus - a hypothesis to explain successful 3rd ventriculostomy in communicating hydrocephalus. *Pediatr Neurosurg* 38:98-101, 2003

102. Kehler U, Gliemroth J, Knopp U, Arnold H: How to perforate safely a resistant floor of the third ventricle? Technical note. *Minim Invasive Neurosurg* 41:198-199, 1998
103. Kehler U, Gliemroth J, Knopp U, Arnold H: The role of third ventriculostomy in previously shunted hydrocephalus. In: Hellwig D, Bauer B (eds) *Minimally invasive techniques for neurosurgery*. Springer, Berlin, pp 77-80, 1998
104. Kelly PJ: Stereotactic third ventriculostomy in patients with nontumoral adolescent/adult onset aqueductal stenosis and symptomatic hydrocephalus. *J Neurosurg* 75:865-873, 1991
105. Kelly PJ: Comments. *Neurosurgery* 41:1429, 1997
106. Koch D, Grunert P, Filippi R, Hopf N: Re-ventriculostomy for treatment of obstructive hydrocephalus in cases of stoma dysfunction. *Minim Invasive Neurosurg* 45:158-63, 2002
107. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB: Imaging correlates of successful endoscopic third ventriculostomy. *J Neurosurg* 92:915-919, 2000
108. Kwiek SJ, Mandera M, Baowski P, Luszawski J, Duda I, Wolwender A, Zymon-Zagorska A, Grzybowska K: Endoscopic third ventriculostomy for hydrocephalus: early and late efficacy in relation to aetiology. *Acta Neurochir (Wien)* 145:181-184, 2003
109. Laitt RD, Mallucci CL, Jaspan T, McConachie NS, Vloeberghs M, Punt J: Constructive interference in steady-state 3D Fourier-transform MRI in the management of hydrocephalus and third ventriculostomy. *Neuroradiology* 41:117-123, 1999
110. Lapras C, Bret P, Patet JD, Huppert J, Honorato D: Hydrocephalus and aqueductal stenosis. Direct surgical treatment by interventriculostomy (Aqueduct cannulation). *J Neurosurg Sci* 30:47-53, 1986
111. Leksell L: Surgical procedure for atresia of aqueduct of Sylvius. *Acta Psychiatr Neurol* 24:559-568, 1949
112. Lev S, Bhadelia RA, Estin D, Heilman CB, Wolpert SM: Functional analysis of third ventriculostomy patency with phase-contrast MRI velocity measurements. *Neuroradiology* 39:175-179, 1997
113. Liliequist B: The anatomy of the subarachnoid cisterns. *Acta Radiol* 46:61-71, 1956
114. Liliequist B: The subarachnoid cisterns: an anatomical and roentgenologic study. *Acta Radiol [Suppl]* 185:1-108, 1959
115. MacArthur DC, Robertson IJ, Punt J: Third ventricular cysts and membranes unsuspected on conventional CT and MRI. *Br J Neurosurg* 14:455-457, 2000
116. MacArthur DC, Buxton N, Vloeberghs M, Punt J: The effectiveness of neuroendoscopic interventions in children with brain tumours. *Child's Nerv Syst* 17:589-594, 2001
117. Magnaes B: Cerebrospinal fluid hydrodynamics in adult patients with benign non-communicating hydrocephalus: one-hour test shunting and balanced cerebrospinal fluid infusion test to select patients for intracranial bypass operation. *Neurosurgery* 11:769-775, 1982
118. Magnaes B: Hydromechanical testing in non-communicating hydrocephalus to select patients for microsurgical third ventriculostomy. *Br J Neurosurg* 3:443-450, 1989
119. Mandat T, Roszkowski M, Barszcz S, Podgorski JK, Jurkiewicz E: Neuroendoscopy in the treatment of third ventricular hydrocephalus accompanying tumors of the posterior part of the third ventricle in children. *Neurol Neurochir Pol* 36:711-722, 2002
120. Matson DD: *Neurosurgery of infancy and childhood*, 2nd edn. Charles C Thomas, Springfield, Illinois, 1969
121. Matsuno H, Rhonan AL: Microsurgical anatomy of the posterior fossa cisterns. *Neurosurgery* 23:58-80, 1988
122. McNickle HF: The surgical treatment of hydrocephalus. A simple method of performing third ventriculostomy. *Br J Surg* 34:302-307, 1947
123. Metellus P, Dufour H, Levrier O, Grisoli F: Endoscopic third ventriculostomy for treatment of noncommunicating syringomyelia associated with a Chiari I malformation and hydrocephalus: case report and pathophysiological considerations. *Neurosurgery* 51:500-503, 2002
124. Miller MN: Organisation of the neuroendoscopy suite. In: Manwaring KH, Crone KR (eds) *Neuroendoscopy*, vol 1. Mary Ann Liebert, New York, pp 9-15, 1992
125. Missir O, Dormont D, Pierot L: MR visualization of CSF flow through a ventriculocisternostomy. *Neuroradiology* 31:93-94, 1989
126. Mixter WJ: Ventriculostomy and puncture of the floor of the third ventricle. Preliminary report of a case. *Boston Med Surg J* 188:277-278, 1923
127. Mizoguchi M, Inamura T, Hikita T, Cheng CL, Ohgami S: Neuroendoscopic biopsy of tectal glioma: a case report. *Minim Invasive Neurosurg* 43:53-55, 2000
128. Mohanty A, Anandh B, Sastry Kollury VR, Praharaj SS: Neuroendoscopic third ventriculostomy in the management of fourth ventricular outlet obstruction. *Minim Invasive Neurosurg* 42: 18-21, 1999
129. Mohanty A, Vasudev MK, Sampath S, Radhesh S, Sastry Kolluri VR: Failed endoscopic third ventriculostomy in children: management options. *Pediatr Neurosurg* 37:304-309, 2002
130. Morello G, Migliavacca F: Third ventriculostomy (Stookey & Scarff operation) in the treatment of benign aqueductal stenosis. *Acta Neurochir (Wien)* 7:417-424, 1959
131. Morota N, Watabe T, Inukai T, Hongo K, Nakagawa H: Anatomical variants in the floor of the third ventricle; implications for endoscopic third ventriculostomy. *J Neurol Neurosurg Psychiatry* 69:531-534, 2000
132. Musolino A, Soria V, Munari C, Devaux B, Merienne L, Constans JP, Chodkiewicz JP: Stereotaxic ventriculo-cisternostomy in the treatment of obstructive triventricular hydrocephalus. A propos of 23 cases. *Neurochirurgie* 34:361-373, 1988.
133. Nishihara T, Hara T, Suzuki I, Kirino T, Yamakawa K: Third ventriculostomy for symptomatic syringomyelia using flexible endoscope: case report. *Minim Invasive Neurosurg* 39:130-132, 1996
134. Nishiyama K, Mori H, Tanaka R: Changes in cerebrospinal fluid hydrodynamics following endoscopic third ventriculostomy for shunt-dependent noncommunicating hydrocephalus. *J Neurosurg* 98:1027-1031, 2003
135. Nulsen FE, Spitz EB: Treatment of hydrocephalus by direct shunt from ventricle to jugular vein. *Surg Forum* 2: 399-402, 1952
136. Ogata H, Oka K, Mitsudome A: Hydrocephalus due to acute aqueductal stenosis following mumps infection: report of a case and review of the literature. *Brain Dev* 14: 417-419, 1992

137. Oi S, Shibata M, Tominaga J, Honda Y, Shinoda M, Takei F, Tsugane R, Matsuzawa K, Sato O: Efficacy of neuroendoscopic procedures in minimally invasive preferential management of pineal region tumors: a prospective study. *J Neurosurg* 93:245-253, 2000
138. Oi S, Kamio M, Joki T, Abe T: Neuroendoscopic anatomy and surgery in pineal region tumors: role of neuroendoscopic procedure in the 'minimally-invasive preferential' management. *J Neurooncol* 54:277-286, 2001
139. Oka K, Tomonaga M: Instruments for flexible endoneurosurgery. In: Manwaring KH, Crone KR (eds) *Neuroendoscopy*, vol 1. Mary Ann Liebert, New York, pp 17-28, 1992
140. Oka K, Go Y, Kin Y, Utsunomiya H, Tomonaga M: The radiographic restoration of the ventricular system after third ventriculostomy. *Minim Invasive Neurosurg* 38:158-162, 1995
141. Oka K, Yoshiaki K, Yoshinori G, Yushi U, Katsuyuki H, Masamichi T, Tohru I, Susumu Y: Neuroendoscopic approach to tectal tumors: a consecutive series. *J Neurosurg* 91:964-970, 1999
142. Paine KWE, McKissok W: Aqueduct stenosis. Clinical aspects, and results of treatment by ventriculocisternostomy (Torkildsen's operation). *J Neurosurg* 12:127-145, 1955
143. Paladino J, Rotim K, Stimac D, Pirker N, Stimac A: Endoscopic third ventriculostomy with ultrasonic contact microprobe. *Minim Invasive Neurosurg* 43:132-134, 2000
144. Patterson RH Jr, Bergland RM: The selection of patients for third ventriculostomy based on experience with 33 operations. *J Neurosurg* 29:252-254, 1968
145. Perneczky A: Comment to Handler MH, et al: Neurosurgery 35:528, 1994
146. Pierre-Kahn A, Reneir D, Bombois B, Askienay S, Moreau R, Hirsch J: La place de la ventriculocisternostomie dans le traitement des hydrocephalies non communicantes de l'enfant. *Neurochirurgie* 21:557-569, 1975
147. Poblete M, Zamboni R: Stereotaxic ventriculocisternostomy. *Confin Neurol* 37:150-155, 1975
148. Pople IK, Athanasiou TC, Sandeman DR, Coakham HB: The role of endoscopic biopsy and third ventriculostomy in the management of pineal region tumours. *Br J Neurosurg* 15:305-311, 2001
149. Putnam T: Treatment of hydrocephalus by endoscopic coagulation of the choroid plexus. *N Engl J Med* 210:1373-1376, 1934
150. Reddy K, Fewer HD, West M, et al: Slit ventricle syndrome with aqueduct stenosis. Third ventriculostomy as definitive treatment. *Neurosurgery* 23:756-759, 1988
151. Resch KDM: Endo-neuro-sonography: first clinical series (52 cases). *Child's Nerv Syst* 19:137-144, 2003
152. Resch KDM, Reisch R: Endo-neuro-sonography: anatomical aspects of the ventricles. *Minim Invasive Neurosurg* 1:2-7, 1997
153. Resch KDM, Perneczky A: Endo-neuro-sonography: basics and current use. In: Hellwig D, Bauer BL (eds) *Minimally invasive techniques for neurosurgery*. Springer, Berlin Heidelberg New York, pp 21-31, 1998
154. Riegel T, Alberti O, Retsch, Shiratori V, Hellwig D, Bertalanffy H: Relationship of virtual reality neuroendoscopic simulations to actual imaging. *Minim Invasive Neurosurg* 43:176-180, 2000
155. Riegel T, Alberti O, Hellwig D, Bertalanffy H: Operative management of third ventriculostomy in cases of thickened, non translucent third ventricular floor: Technical note. *Minim Invasive Neurosurg* 44:65-69, 2001
156. Rieger A, Rainov NG, Brucke M, Marx T, Holz C: Endoscopic third ventriculostomy is the treatment of choice for obstructive hydrocephalus due to pediatric pineal tumors. *Minim Invasive Neurosurg* 43:83-86, 2000
157. Rieger A, Rainov NG, Sanchis L, Schopp G, Burkert W: Ultrasound-guided endoscopic fenestration of the third ventricular floor for non-communicating hydrocephalus. *Minim Invasive Neurosurg* 39:17-20, 1996
158. Rieger A, Rainov NG, Sanchis L, Schopp G, Burkert W: Ultrasound-guided endoscopic fenestration of the third ventricle in obstructive hydrocephalus. In: Hellwig D, Bauer B (eds) *Minimally invasive techniques for neurosurgery*. Springer, Berlin, pp 81-85, 1998
159. Robinson S, Cohen A: The role of neuroendoscopy in the treatment of pineal region tumors. *Surg Neurol* 40:360-365, 1997
160. Rohde V, Reinges MHT, Krombach GA, Gilsbach JM: The combined use of image-guided frameless stereotaxy and neuroendoscopy for the surgical management of occlusive hydrocephalus and intracranial cysts. *Br J Neurosurg* 12:531-538, 1998
161. Rohde V, Gilsbach JM: Anomalies and variants of the endoscopic anatomy for third ventriculostomy. *Minim Invasive Neurosurg* 43:111-117, 2000
162. Rohde V, Krombach GA, Struffert T, Gilsbach JM: Virtual MRI endoscopy: detection of anomalies of the ventricular anatomy and its possible role as a presurgical planning tool for endoscopic third ventriculostomy. *Acta Neurochir (Wien)* 143:1085-1091, 2001
163. Sainte-Rose C: Third ventriculostomy. In: Manwaring KH, Crone KR (eds) *Neuroendoscopy*. Mary Ann Liebert, New York, pp 47-62, 1992
164. Sainte-Rose C, Chumas P: Endoscopic third ventriculostomy. *Tech Neurosurg* 1:176-184, 1995
165. Sainte-Rose C, Cinalli G, Roux FE, Maixner W, Chumas PD, Mansour M, Carpenter A, Bourgeois M, Zerah M, Pierre-Kahn A, Renier D: Management of hydrocephalus in pediatric patients with posterior fossa tumors: the role of endoscopic third ventriculostomy. *J Neurosurg* 95:791-797, 2001
166. Sayers MP, Kosnik EJ: Percutaneous third ventriculostomy: Experience and technique. *Child's Brain* 2:24-30, 1976
167. Scarff JE: Treatment of obstructive hydrocephalus by puncture of lamina terminalis and floor of the third ventricle. *J Neurosurg* 8:204-213, 1951
168. Scarff JE: Treatment of hydrocephalus: a historical and critical review of methods and results. *J Neurol Neurosurg Psychiatry* 26:1-26, 1963.
169. Scarff JE: Evaluation of treatment of hydrocephalus. Results of third ventriculostomy and endoscopic cauterization of choroid plexus compared with mechanical shunts. *Arch Neurol*, 14: 382-391, 1966
170. Schijns OE, Beuls EA: Parinaud's syndrome as a sign of acute obstructive hydrocephalus: recovery after acute ventriculostomy. *Ned Tijdschr Geneeskd* 46:1136-1140, 2002
171. Schroeder HWS, Gaab MR: Endoscopic aqueductoplasty: technique and results. *Neurosurgery* 45:508-518, 1999
172. Schroeder HWS, Niendorf WR, Gaab MR: Complications of endoscopic third ventriculostomy. *J Neurosurg* 96:1032-1040, 2002

173. Schwartz TH, Yoon SS, Cutruzzola FW, Goodman RR: Third ventriculostomy: post-operative ventricular size and outcome. *Minim Invasive Neurosurg* 39:122-129, 1996
174. Schwartz TH, Ho B, Prestigiacomo CJ, Bruce JN, Feldstein NA, Goodman RR: Ventricular volume following third ventriculostomy. *J Neurosurg* 91:20-25, 1999
175. Siomin V, Weiner H, Wisoff J, Cinalli G, Pierre-Kahn A, Sainte-Rose C, Abbott R, Elran H, Beni-Adani L, Ouaknine G, Constantini S: Repeat endoscopic third ventriculostomy: is it worth trying? *Child's Nerv Syst* 17:551-555, 2001
176. Siomin V, Cinalli G, Grotenhuis A, Golash A, Oi S, Kothbauer K, Weiner H, Roth J, Beni-Adani L, Pierre-Kahn A, Takahashi M, Mallucci C, Abbott R, Wisoff J, Constantini S: Endoscopic third ventriculostomy for patients with cerebrospinal fluid infections and/or hemorrhage. *J Neurosurg* 97:519-524, 2002
177. Stookey B, Scarff JE: Occlusion of the aqueduct of Sylvius by neoplastic and non-neoplastic processes with rational surgical treatment for relief of resultant obstructive hydrocephalus. *Bull Neurol Inst New York* 5:348-377, 1936
178. Suehiro T, Inamura T, Natori Y, Sasaki M, Fukui M: Successful endoscopic third ventriculostomy for hydrocephalus and syringomyelia associated with fourth ventricular outlet obstruction. *J Neurosurg* 93:326-329, 2000
179. Teo C, Jones RFC, Stening WA: Neuroendoscopic third ventriculostomy. In: Matsumoto S (ed) *Hydrocephalus: pathogenesis and treatment*. Springer, New York, pp 680-691, 1991
180. Teo C, Jones R: Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25:57-63, 1996
181. Teo C: Third ventriculostomy in the treatment of hydrocephalus: Experience with more than 120 cases. In: Hellwig D, Bauer B (eds) *Minimally invasive techniques for neurosurgery*. Springer, Berlin, pp. 73-76, 1998
182. Thomson S, Tyagi AK, Chumas P: Intracranial calcification complicating neuroendoscopy. *J Neurosurg* 98:186-189, 2003
183. Tisell M, Almstrom O, Stephensen H, Tullberg M, Wikkelso C: How effective is endoscopic third ventriculostomy in treating adult hydrocephalus caused by primary aqueductal stenosis? *Neurosurgery* 46:104-110; discussion 110-111, 2000
184. Tisell M, Edsbagge M, Stephensen H, Czosnyka M, Wikkelso C: Elastance correlates with outcome after endoscopic third ventriculostomy in adults with hydrocephalus caused by primary aqueductal stenosis. *Neurosurgery* 50:70-77, 2002
185. Torkildsen A: New palliative operation in cases of inoperable occlusion of the sylvian aqueduct. *Acta Chir Scand* 82: 117-123, 1939
186. Tuli S, Alshail E, Drake JM: Third ventriculostomy versus cerebrospinal fluid shunt as a first procedure in pediatric hydrocephalus. *Pediatr Neurosurg* 30:11-15, 1999
187. Tyagi A, Chumas P, Ferrie C: Obstructive hydrocephalus following herpes simplex virus type I encephalitis treated by repeated third ventriculostomy. *Pediatr Neurosurg* 34:244-246, 2001
188. Vaicys C, Fried A: Transient hyponatremia complicated by seizures after endoscopic third ventriculostomy. *Minim Invasive Neurosurg* 43:190-191, 2000
189. Vandertop WP, Verdaasdonk RM, Van Swol CFP: Laser-assisted neuroendoscopy using a neodymium-yttrium aluminium garnet or diode contact laser with pretreated fiber tips. *J Neurosurg* 88:82-92, 1998
190. Vinas FC, Dujovny N, Dujovny M: Microanatomical basis for the third ventriculostomy. *Minim Invasive Neurosurg* 39:116-121, 1996
191. Vinas FC, Panigrahi M: Microsurgical anatomy of the Liliequist's membrane and surrounding neurovascular territories. *Minim Invasive Neurosurg* 44:104-109, 2001
192. Voris HC: Third ventriculostomy in treatment of obstructive hydrocephalus in children. *Arch Neurol Psychiatr* 65:265-271, 1951
193. Vries JK: An endoscopic technique for third ventriculostomy. *Surg Neurol* 9:165-168, 1978
194. Wellons JC, Bagley CA, George TM: A simple and safe technique for endoscopic third ventriculostomy. *Pediatr Neurosurg* 30:219-223, 1999
195. Wellons JC, Tubbs RS, Banks JT, Grabb B, Blount JP, Oakes WJ, Grabb PA: Long-term control of hydrocephalus via endoscopic third ventriculostomy in children with tectal plate gliomas. *Neurosurgery* 51:63-67, 2002
196. White JC, Michelsen JJ: Treatment of obstructive hydrocephalus in adults. *Surg Gynecol Obstetr* 74:99-109, 1942
197. Wilcock DJ, Jaspan T, Punt J: CSF flow through third ventriculostomy demonstrated with colour Doppler ultrasonography. *Clin Radiol* 51:127-129, 1996
198. Wilcock DJ, Jaspan T, Worthington BS, Punt J: Neuro-endoscopic third ventriculostomy: Evaluation with magnetic resonance imaging. *Clin Radiol* 52:50-54, 1997
199. Willems PW, Vandertop WP, Verdaasdonk RM, van Swol CF, Jansen GH: Contact laser-assisted neuroendoscopy can be performed safely by using pretreated 'black' fibre tips: experimental data. *Lasers Surg Med* 28:324-329, 2001
200. Wong TT, Lee LS: A method of enlarging the opening of the third ventricular floor for flexible endoscopic third ventriculostomy. *Child's Nerv Syst* 12:396-398, 1996
201. Yamakawa K: Instrumentation for neuroendoscopy. In: Cohen AR, Haines SJ (eds) *Minimally invasive techniques in neurosurgery*. Baltimore: Williams & Wilkins, pp 6-13, 1995
202. Yasargil MG: Subarachnoid cisterns. In: Yasargil MD (ed). *Microsurgery*, vol 1. Thieme, New York, 5-53, 1984
203. Zerah M, Garcia-Monaco R, Rodesch G, Terbrugge K, Tardieu M, de Victor D, Lasjaunias P: Hydrodynamics in vein of Galen malformations. *Child's Nerv Syst* 3:111-117, 1992
204. Zidsas de Plantes BG, Crezee P: Transfrontal perforation of the lamina terminalis. *Neuroradiology* 16:51-53, 1978
205. Zohdi A, Ibrahim I: Variations in the site and size of third ventriculostomy. *Minim Invasive Neurosurg* 41:194-197, 1998

Third Ventriculostomy in Shunt Malfunction

JONATHAN PUNT

Rationale for Third Ventriculostomy in Shunt Malfunction

The principal advantage of treating hydrocephalus primarily by third ventriculostomy whenever possible is the avoidance of a diversionary cerebrospinal fluid (CSF) shunt, thereby sparing the patient the dangers and distress of further surgery for shunt complications. Nearly 40 years ago, a study comparing 618 published cases of hydrocephalus treated by operations not requiring implanted materials with 1087 published cases treated by implanted shunts, identified that, whereas early success rates were equivalent at around 65%, the late complication rates were vastly different at 35%-100% for implants versus 3%-5% for non-prosthetic techniques [52]. The risk of shunt failure is so great that the patient with a shunt can effectively expect further surgery (see Chap. 22). The risk is cumulative over time, rising to 81% by 12 years [48] and 83% by 20 years [55]. This background combined with the renaissance of neuroendoscopic neurosurgery provides the rationale for neuroendoscopic third ventriculostomy (NTV) *ab initio* (*primary* NTV); it is an even more logical approach to the management of shunt malfunction, as an alternative to shunt revision. It is clear that the requirement for an effective alternative to hydrocephalus shunts will continue to increase whilst shunts continue to be employed. For the patient already smitten with multiple shunt complications, the possibility of NTV (*secondary* NTV) as an alternative to shunt revision can come as a positive release from misery. The list of shunt complications amenable to neuroendoscopic treatment is extensive and well documented elsewhere [32, 44].

History of Third Ventriculostomy in the Management of Shunt Malfunction

Within a decade of the introduction of implanted hydrocephalus shunts, frustrations with shunt complications led to the occasional use of TV as an alternative to shunt revision. Perlman (1968) described a single case of a baby with congenital hydrocephalus treated by a ventriculo-atrial shunt who, having experienced multiple episodes of shunt malfunction and major infection, was treated successfully by percutaneous TV. Despite some sporadic enthusiasm for treating infantile hydrocephalus by percutaneous TV [21, 22, 42], the percutaneous approach was used very little, even by its advocates, for treating shunt malfunction. Only seven children were operated upon at one leading centre: in these cases there were two technical failures and two patients suffered intraventricular haemorrhages. This makes for an interesting comparison with the 90 children treated by primary percutaneous TV at the same centre: there was a late closure rate of 16.3% requiring a second operation, either a repeat percutaneous TV or a shunt [20]. The centre concerned abandoned the percutaneous method in favour of the neuroendoscopic approach in 1987 [9]. The largest published series of percutaneous secondary TV is that of Sayers and Kosnik [51] who, encouraged by their own 70% success rate in 15 cases of open, transfrontal TV, also devised a technique for percutaneous TV. Forty-six children with shunted hydrocephalus who had accumulated a total of 163 shunt revisions were operated upon. Subsequently the entire group experienced only four revisions, and 22 children exceeded their longest previous revision-free interval. There were two procedure-re-

lated deaths and 7 transient complications. After the advent of neuroendoscopy (see Chap. 25), secondary NTV as the ideal management for shunt malfunction was reported from the United States [31] and subsequently from Sydney, Australia [29], from Nottingham, England [37, 38], and from Paris, France [9].

NTV in Shunt Malfunction

Anatomical Considerations

Anatomical abnormalities can occur at a number of points that impact on the ease or otherwise of the operative procedure.

The *skull* can be pathologically thick and abnormally vascular in the patient who has been shunted from a very young age. This can lead to unexpectedly heavy bleeding and can restrict the range of direction of approach when using a rigid neuroendoscope. The *dura* can also be pathologically thick. There may be thick, even calcific, subdural membranes, the residuum of old subdural haematoma formation. The *wall of the lateral ventricle* may be tough and thick, especially in patients shunted for perinatal post-haemorrhagic hydrocephalus or those with slit ventricle syndrome. The internal anatomy of the lateral ventricle can be bizarre. There may be synechiae related, and unrelated, to the presence of a ventricular shunt catheter. The usual landmarks leading to the interventricular foramen may not be found as the thalamo-striate vein can be obscured by scarring and the choroid plexus may have disappeared, especially in patients who have suffered intraventricular haemorrhage, or ventriculitis associated with meningitis or serious ventricular shunt infections. On occasion the lateral ventricles can be subdivided by complete or incomplete septae. The *septum pellucidum* may be spontaneously perforated or even absent to the point that the fornices appear to be dangling in space. In cases of unilateral loculation of the lateral ventricle, distortion of the septum may render the pericallosal artery vulnerable. The *interventricular foramen* may be completely obliterated by gliosis or may have assumed an abnormal configuration. Patients with myelomeningocele or occipital encephalocele frequently have oblique, elongated interventricular foramina. Alternatively, patients with very large lateral ventricles due to chronic shunt malfunction can have very large interventricular foramina that are so huge that the third ventricle is almost assimilated into the lateral ventricle. The *third ventricle* can also be very abnormal, with gliotic septae obscuring or

frankly obstructing the pathways. The cavity of the third ventricle may be narrow. The usual landmarks on the third ventricle floor of the mammillary bodies and the fine vessels that course over them like a mouse's whiskers may be quite unclear; the anterior part of the floor may be thick and opaque; fortunately, the vascular area that marks the recess of the pituitary infundibulum is usually preserved. The *mammillary bodies* can sometimes appear to be conjoined, with a bare space posterior to them that might mislead the uninitiated into attempting a ventriculostomy too posteriorly, with very great risk of damage to the basilar artery or its perforating branches. Occasionally, the *lamina terminalis* can be so thin that it can be mistaken for the floor of the third ventricle, especially if the usual landmarks of the anterior floor are indistinct. In patients with neural tube defects the *massa intermedia* may be unusually large, but, more significantly, there may be an extra commissure running in the sagittal plane above the anterior part of the floor of the third ventricle, obscuring the site of the intended ventriculostomy. There may be buckling of the floor of the third ventricle and there can be multiple basal cisternal subarachnoid adhesions [24, 25]. The *interpeduncular cistern* may be densely obliterated by subarachnoid adhesions that may in themselves conceal the basilar artery and its branches and the third and sixth cranial nerves. *Liliequist's membrane*, the "second membrane" that must be breached if NTV is to be successful, may be abnormally thick [6]. The *circle of Willis* may be in an unusual position. The two most frequent variants are an unusual application of the basilar artery to the dorsum sellae and upper clivus, usually due to subarachnoid scarring, and an abnormal tortuosity of the anterior communicating artery that may bulge into the anterior part of the third ventricle. The hindbrain will be abnormal with a varying degree of herniation in most cases of neural tube defect. There may be an associated hydrocephalus. In addition to the aforementioned anomalies, patients with intracranial tumours may have abnormalities and distortions due to the presence of tumour tissue or the effects of previous surgery and radiation therapy. Patients with major cerebral malformations may have very unusual anatomy.

Pre-operative Preparation

It is abundantly clear from the above that there are many potential anatomical variants in patients who are candidates for secondary NTV that are rarely encountered in primary NTV. Pre-operative evaluation by magnetic resonance imaging (MRI) is invaluable in assessing anatomical suitability for secondary

NTV, selecting the neuroendoscope to be employed, and evaluating the hazards that may be encountered. While secondary NTV can be undertaken on the basis of clinical need coupled with imaging by computed tomography (CT), it is best to obtain MRI if at all possible. The proprietary sequence available exclusively on some Siemens MR scanners, such as the 1.5-T Vision, known as Constructive Interference in the Steady State (CISS), is particularly useful in defining structures that have two CSF interfaces, such as the floor of the third ventricle, and is routinely employed in Nottingham for evaluation of patients for nearly all neuroendoscopic procedures, but especially secondary NTV [34].

The only absolute anatomical considerations are that one lateral ventricle and one interventricular foramen, and the third ventricle, must be wide enough to admit the endoscope with sufficient room to manoeuvre without risk of damage to the contained and adjacent structures; there should be no major anatomical abnormality of the third ventricle, especially the anterior floor; and there should be some space between the dorsum sellae and the basilar artery. Ideally there should not be any, or any marked, degree of subarachnoid membrane formation in the pre-pontine cistern. MRI with CISS is especially helpful in patients with hydrocephalus in association with neural tube defect as the third ventricle anomalies outlined above can be elegantly displayed [24, 25, 62]. The width of the third ventricle as judged on MRI is frequently narrower in patients under evaluation for secondary NTV. In one small study made in Nottingham of 13 patients aged under 16 years with hydrocephalus due to aqueduct stenosis, the mean third ventricle width was 9.4 mm in 7 children undergoing secondary NTV compared to 19.0 mm in 6 children undergoing primary NTV [59].

Operative Technique

Choice of Neuroendoscope

The choice of neuroendoscope is an important one and must take into account the ventricular size and configuration, any obstacles that might be encountered en route to the anterior third ventricle, the need for any alternative or additional manoeuvre beyond TV, and the neurosurgeon's personal experience and preferences. The usual relative advantages and disadvantages between rigid and flexible neuroendoscopes apply [45]. The author's distinct preference in this context is for a flexible neuroendoscope.

Entry Point

As for primary NTV, the ideal entry point is a burr-hole on, or just anterior to, the coronal suture in the mid-orbital line [45]. Because of the possibility of an unusually thick skull and an unusual shape to the interventricular foramen, greater precision is therefore called for in placing the burr-hole, particularly when using a rigid neuroendoscope. Consideration must be given to existing wounds and external ventricular drains, healed incisions, and the potential sites for a further shunt if NTV fails. As with shunt insertion, it is poor practice to use wounds that have not yet fully healed, because of the risk of introducing infection. If the skull is exceptionally thick it may be necessary to perform a small craniectomy or employ a high-speed air drill. If the dura is exceptionally thick or if there are old subdural membranes it is probably safer to gain slightly better access by enlarging the burr-hole.

Tapping the Ventricle

Because both the pia-arachnoid and the wall of the lateral ventricle may be thick and tough, it is advisable to diathermize the pia and cortex and make a short cortical incision with a scalpel. This prevents a firm brain from being subjected to excessive pressure when the ventricle is tapped. The lateral ventricle is then located with a standard brain cannula. The cannula may be deflected by a tough lateral ventricular wall, but it will certainly be easier to enter with minimal depression of the hemisphere than if the trocar and cannula of the neuroendoscope is passed without prior tapping. Unless the intracranial pressure is very high, or the patient is in a critical state, no CSF is vented at this stage, beyond what is needed to confirm placement in the ventricle. The cannula to be used with the neuroendoscope is then passed along the track made by the brain cannula; CSF for microbiological examination is now drained but the drainage must not be excessive. In brain tumour cases the opportunity is also taken to obtain CSF for cytology and, if relevant, for germ cell tumour markers. The neuroendoscope is now introduced.

Manoeuvres Within the Ventricular System

Immediately upon entering the lateral ventricle every effort is made to become orientated by reference to the usual landmarks. This can be hampered by their prior destruction by disease processes and also by intraventricular debris that can lead to rapid deteriora-

tion in the quality of the view, which may not clear with irrigation. Continuous irrigation with normal saline at body temperature is maintained. If the ipsilateral interventricular foramen is impassable it may be possible to cross the septum pellucidum through a spontaneous or manufactured pellucidotomy and try to enter the third ventricle via the contralateral foramen. Obviously this is a manoeuvre that can only be attempted with a flexible neuroendoscope! The third ventricle is entered and the site for the NTV is identified as rapidly as possible without wasting time on "ventricular tourism" that may aggravate any problems of visibility.

Choosing a Site for NTV

The usual point on the floor of the anterior third ventricle just posterior to the dorsum sellae is selected. The various anatomical variants described above must be recalled and negotiated, especially in dysraphic patients. Because the vascular area at the infundibular recess only rarely loses its pink colour, it is usually a reliable landmark. A Doppler ultrasound probe passed down the working channel of the neuroendoscope has been used successfully to identify the position of the basilar artery [7, 53]. Although this is not required in all cases, it may be a useful adjunct in those patients who have been identified on pre-operative MRI as having a thick third ventricle floor.

Making the NTV

The ventriculostomy is made by whatever technique the neurosurgeon habitually employs (see Chap. 25). Greater care may be needed if the floor of the third ventricle is thick and opaque. It is important to stay in the midline. As soon as possible a view should be taken through the opening created to inspect the state of the basal cisterns and to look for aberrant blood vessels. The opening is then enlarged mechanically or by diathermy. A Fogarty balloon catheter or a hourglass balloon can be used. The desired endpoint is as in primary NTV, namely a clear view into the basal cisterns.

Additional Procedures

Once the NTV has been made it may be necessary to take the opportunity of the ventriculomegaly arising as a result of shunt malfunction to perform alternative or additional neuroendoscopic procedures such as pellucidotomy and liberation of ventricular catheters. If the contralateral ventricle is much smaller, the pericallosal arteries may be at risk from the

neuroendoscopic pellucidotomy. Opinions differ widely on the need for an external ventricular drainage (EVD) as a safety measure and the author reserves it for cases of NTV of uncertain quality in patients with critically raised intracranial pressure, and likewise for postoperative invasive intracranial pressure monitoring. The author's current preference is to remove any indwelling hydrocephalus shunt material. This makes it quite clear that any control is by the NTV, provides material for microbiological examination, and may also be a factor in reducing late re-sealing of the NTV by removing any possible alternative pathway for the CSF.

Post-operative Care

When the patient is fit for discharge into the community, a secure route back to the neurosurgical ward must be established. The patient or carer must understand the need to report relevant symptoms rapidly. Follow-up imaging by MRI with CISS or similar sequence provides the best images but cine-MRI is an alternative. Further follow-up should be at the same level as for patients with shunts.

Results

Results of NTV in Shunt Malfunction

In an early landmark account of the Sydney, Australia, experience, Jones et al. [28] reported 24 patients, aged between 6 weeks and 24 years, with non-communicating hydrocephalus, who were operated upon between 1979 and 1988. Of 14 patients who had previously been shunted, secondary NTV was successful in 8 cases, as judged by relief of symptoms and the presence of flow voids on post-operative MRI. Follow-up was for an average of 68 months.

Kelly [31] reported on 16 patients aged 10 years to 39 years. Eleven of the patients were previously shunted and had undergone up to 21 previous operations in infected cases and up to 14 previous operations in non-infected cases. In a mean follow-up period of 3.5 years only one patient required a further procedure. There were no complications related to NTV, but one patient suffered transient symptoms due to intraventricular haemorrhage following shunt removal. Of note was that none of the patients undergoing primary NTV showed a return to normal ventricular size, but 9 out of 11 patients undergoing secondary NTV regained normal ventricular size. Two years later the same group [30] were able to report a series of 54 primary and sec-

ondary NTVs made in 59 patients in a mixed paediatric and adult population operated upon between 1978 and 1990. Within an overall success rate of 80% the authors noted the value in previously shunted patients, in whom it was more successful [20 out of 27 cases] than in those never previously shunted [13 out of 27 cases]. Important favourable factors were a third ventricle wider than 7 mm and normal anatomy; unfavourable was prior radiotherapy. The complication rate was 8%. A further 2 years on and the Sydney group reported 103 patients operated on between 1978 and 1994 [26] with an overall success rate of 61% and no difference between those previously shunted and those undergoing primary NTV. The first published single-institution account of a systematic attempt to treat patients with malfunctioning ventricular shunts was from Nottingham, UK [37, 38, 46], and the results can be summarized as follows: the study population was 47 patients with hydrocephalus arising in childhood and previously treated by ventricular shunting. The median age at the time of first shunt insertion was 3 months (range 1 week to 20 years). The median number of previous shunt procedures was 2, with a range of 1–18. Sixteen patients had also suffered a total number of 30 previous shunt infections, with some having up to 5 infective episodes. These 47 patients underwent 51 neuroendoscopic procedures at a median age of 118 months (range 6–339 months). Thirty of the 51 procedures were performed in emergency operating sessions. The majority of the procedures were performed with a flexible neuroendoscope and a monopolar cutting/coagulating electrode. NTV was technically possible in 47 procedures. In a median follow-up of 13 months there was durable relief of symptoms in 37 out of 47 patients (77%) and only 10 patients needed another shunt insertion. There were significant complications in three patients: one patient developed a superficial, extracranial wound infection; two patients suffered lasting palsies affecting the third and sixth cranial nerves. There was no operative mortality. There was a relationship between the underlying pathology and the outcome of secondary NTV: this ranged from 100% success rate in patients with tumoral hydrocephalus to 50% success rate in cases of post-haemorrhagic hydrocephalus and 60% in post-meningitic hydrocephalus. Patients with aqueduct stenosis or Dandy-Walker malformation had a 70% success rate. Patients with dysraphic states had an 88% success rate. This compared favourably with a series from Little Rock, Arkansas, and Sydney, Australia [57], in which secondary NTVs had been performed between July 1978 and July 1995 in 54 patients with hydrocephalus associated with myelomeningocele with a success rate of 80%; the

concomitant success rate for the overall series was 72% when primary NTVs were included. In the Nottingham experience the dysraphic patients were the only group in which the success rates for secondary NTV were not equal to, or were higher than, those for primary NTV performed by the same surgeons over the same time period. Indeed, Barlow [1] is one of the few authors to report less success with secondary NTV than with primary NTV. In a subsequent Nottingham series of 77 patients undergoing a variety of neuroendoscopic procedures in the course of brain tumour management, all 6 who underwent secondary NTV gained durable relief, while 55 of 66 (83%) having primary NTV experienced long-term remission from hydrocephalus [36]. Both patients who had received radiation therapy had successful NTVs. This contrasts with another tumour-related series [15] in which the overall success rate of NTV was only 31 out of 63 cases (49%). In a series of patients treated in Paris, France, between 1987 and 1996 [9], 23 patients underwent secondary NTV using a rigid neuroendoscope. Shunts were generally removed and an EVD was left in place for a period of 48 h. There were 5 failures requiring reinsertion of a ventricular shunt at intervals of up to 45 days post-NTV. There were two serious complications: one arterial haemorrhage which did not leave permanent sequelae, and one post-operative extradural haematoma attributed to excessive drainage from a dependent EVD. The overall success rate was 78%.

Results of NTV in Shunt Infection

In Kelly's uniformly successful series described above [31], 5 out of 11 previously shunted patients had infected shunts and had undergone between 1 and 21 previous shunt operations. Jones et al. [29] reported 4 children and 2 adults with shunted hydrocephalus and intractable or recurrent shunt infections. Secondary NTV was successful, allowing shunt removal, in all of the children and in one of the adults. Follow-up was for a mean of 33 months. One child required a second NTV at 30 months. In the Nottingham series [46], 9 out of 47 patients undergoing secondary NTV had infected shunts and a successful NTV. In the Paris series [9], secondary NTV was successful in 8 out of 13 patients with infected shunts.

Results of NTV in the Management of Slit Ventricles

The neuroendoscopic approach in slit ventricle syndrome is of utmost importance and has deserved a dedicated chapter (see Chap. 23).

Results of Alternative or Complementary Neuroendoscopic Procedures in Shunt Malfunction

Even when it is not possible to perform secondary NTV, an alternative neuroendoscopic strategy may be helpful. For example, in one series of 51 secondary NTVs [46], during the 4 procedures in which NTV was not technically feasible, it was possible to undertake an alternative neuroendoscopic procedure at the same operation that led to relief of raised intracranial pressure; this included liberation of blocked ventricular catheters and marsupialization of loculated ventricles.

Loculated Ventrices

Kleihaus et al. [33] described a single case in which a 3.5-mm rigid paediatric endoscope and biopsy forceps were employed to deloculate a lateral ventricle in a baby with shunted post-meningitic hydrocephalus. The authors speculated on the future value of a new generation of rigid and flexible endoscopes in the management of complex hydrocephalus. Lewis et al. [35] reported 34 patients aged between 10 days and 68 years who underwent neuroendoscopic procedures to treat loculated ventricles. Twelve of the patients had been previously shunted. A 4-mm fiberoptic flexible neuroendoscope was employed in conjunction with a Laserscope KTP laser. A 600- μm laser fibre at 3.5 W of power was used. Fenestrations of at least 1 cm were attempted. Intraoperative ultrasound was helpful in demonstrating communication. The shunt revision rate was reduced from 3.04 per year to 0.25 per year. Six out of the 12 previously shunted patients required a second neuroendoscopic fenestration, as did 6 out of 13 of the patients with multiloculated hydrocephalus and 3 out of 4 with post-meningitic hydrocephalus. Complications occurred in only 2 cases; CSF leak and ventriculitis. The authors concluded that neuroendoscopy was so effective that it was the treatment of choice for loculated ventricles. This represents a considerable advance as this particular complication is a great burden for the patient and represents a significant proportion of hydrocephalus practice in the continuing care of paediatric cases [4]. However, despite imaging that may look deceptively inviting, these are difficult and technically demanding operations because of difficulty with intra-operative orientation through lack of normal landmarks and the thick, often excessively vascular walls that have to be broken down [43].

Liberation of Shunt Components

As well as the retrieval of loose ventricular catheters, neuroendoscopy can be employed for freeing up catheters blocked by debris [11, 56]. The tissue blocking the holes in the catheter may be either relatively avascular glial/ependymal scars or, less frequently, choroid plexus. Application of a cutting/coagulating electrode or use of the KTP laser is very effective.

Endoscopic Shunt Placement

Vries [61] reported use of a 3.8-mm rigid Hopkins endoscope to facilitate placement of ventricular catheters in 85 children; 18 had been previously shunted and 11 of these had slit ventricles. The site and depth of catheter position was determined by endoscopic inspection of the ventricle and the catheter was then passed "blind" along the track made by the endoscope. Eighteen out of 85 patients suffered a total of 24 complications in 102 insertions: this included 9 patients with blocked ventricular catheters of whom 7 significantly had slit ventricles. Six patients experienced shunt infections within 14 days of operation. More recently, Taha and Crone [56] have favourably evaluated the benefits of endoscopically guided shunt placement.

Cyst Drainage

In patients with pre-existing paraventricular cystic lesions, such as supracerebellar arachnoid cysts, who have been previously treated by a ventricular shunt, it may well be appropriate to take the opportunity of symptomatic shunt malfunction to perform cyst marsupialization with or without secondary NTV.

Ventriculscopy

Patients with shunts in the setting of tumoral hydrocephalus may present with symptoms that mimic shunt malfunction but are actually due to diffuse meningeal spread of tumour. Ventriculscopy may reveal the truth of the situation when imaging is inconclusive [36]. A careful look for macroscopic tumour at the time of secondary NTV is therefore necessary, as is sampling of ventricular CSF for exfoliative cytology and, if relevant, for germ cell tumour markers.

Complications

As pointed out by Teo et al. [58] and again by Buxton and Punt [5] in reporting complications in their own patients, there has been some regrettable reticence in reporting the complications of NTV in general. They have, however, been catalogued [5, 46, 54, 58] in the literature and will be treated in two separate chapters (see Chaps. 29 and 30).

Conclusion

Secondary NTV is a procedure of considerable efficacy in the management of ventricular shunt malfunction. There are few absolute contraindications and not many accurate predictors of success or failure: all patients with symptomatic shunt malfunction or shunt infection should therefore at least be actively considered. The numbers of candidates will continue to increase until either primary NTV is more widely available or shunts become less troublesome. Eventually, however, the numbers should stabilize and this is beginning to be seen in centres with a dedicated NTV policy, adequate equipment, and appropriate staffing levels. The economics of repeated implanted shunts versus neuroendoscopic equipment must eventually favour the latter. The need for equipment and appropriately trained staff calls for a commitment that sadly may not always be forthcoming. This must be identified as a requirement for the modern neurosurgical service if the proper responsibility towards those afflicted with the numerous complications of implanted devices are to be met and the patients, their families, and the health care systems that support them have at some stage the opportunity of release from the misery of shunt co-morbidity.

References

1. Barlow P: Indications for endoscopic third ventriculostomy: a review of successful and failed cases. *Br J Neurosurg* 11: 456, 1997
2. Barrer SJ, Schut L, Bruce DA: Global rostral midbrain dysfunction secondary to shunt malfunction in hydrocephalus. *Neurosurgery* 7: 322-325, 1980
3. Baskin JJ, Manwaring KH, Rekate HL: Ventricular shunt removal: the ultimate treatment of the slit ventricle syndrome. *J Neurosurg* 88: 478-484, 1998
4. Brockmeyer D, Walker ML, Carey C, et al: The role of ventriculostomy in shunt avoidance, reduction or elimination in hydrocephalic children. *Child's Nerv Syst* 11: 539-40, 1995
5. Buxton N, Punt J: Subtemporal decompression in hydrocephalus related raised intracranial pressure. *Neurosurgery* 44: 513-519, 1999
6. Buxton N, Vloeberghs M, Punt J: Lilliequist's membrane in minimally invasive endoscopic neurosurgery. *Clin Anat* 11: 187-190, 1998
7. Cartmill M, Vloeberghs M: The use of transendoscopic Doppler ultrasound as a safety enhancement measure during neuroendoscopic third ventriculostomy. *Br J Neurosurg* 14: 276, 2000
8. Casey ATH, Kimmings EJ, Kleinlugtebeld AD, et al: The long-term outlook for hydrocephalus in childhood. *Pediatr Neurosurg* 27: 63-70, 1997
9. Cinalli G, Salazar C, Mallucci C, et al: The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43: 1323-1329, 1998
10. Cohen AR: Endoscopic ventricular surgery. *Pediatr Neurosurg* 19: 127-134, 1993
11. Crone KR: Endoscopic technique for removal of adherent ventricular catheters. In: Manwaring KH, Crone KR, Dante MD (eds) *Neuroendoscopy*. Liebert, New York, pp 41-46, 1992
12. Dandy WE: The diagnosis and treatment of hydrocephalus due to occlusions of the foramina of Magendie and Luschka. *Surg Gynecol Obstet* 32: 112-124, 1921
13. Drake JM, Sainte-Rose C: The Shunt Book. Blackwell Science, Cambridge, Mass, p 123-192, 1995
14. Fukushima T, Ishijima B, Hirakawa K, et al: Ventriculofiberscope: a new technique for endoscopic diagnosis and operation. *J Neurosurg* 38: 251-256, 1973
15. Goh KYC, Abbott R: Is endoscopic third ventriculostomy of benefit in tumor related aqueduct stenosis? *Child's Nerv Syst* 16: 127-128, 2000
16. Griffith HB: Technique of fontanelle and persutural ventriculostomy and endoscopic ventricular surgery in infants. *Child's Brain* 1: 359-363, 1975
17. Guiot G, Derome P, Herzog E, et al: Ventriculo-cisternostomie sous contrôle radioscopique pour hydrocéphalie obstructive. *Presse Med* 40: 1923-1926, 1968
18. Guiot G: Ventriculo-cisternostomy for stenosis of the aqueduct of Sylvius. Puncture of the floor of the third ventricle under television control. *Acta Neurochir* 28: 274-289, 1973
19. Handler MH, Abbott R, Lee M: Near-fatal complication of endoscopic third ventriculostomy: case report. *Neurosurgery* 35: 525-8, 1994
20. Hirsch JF, Hirsch E, Sainte-Rose C, et al: Stenosis of the aqueduct of Sylvius. Etiology and treatment. *J Neurosurg Sci* 30: 29-39, 1986
21. Hoffman HJ: The advantages of percutaneous third ventriculostomy over other forms of surgical treatment for infantile obstructive hydrocephalus. In: Morley TP (ed) *Current controversies in neurosurgery*. Saunders, Philadelphia, p 691-703, 1976
22. Hoffman HJ, Harwood-Nash D, Gilday DL: Percutaneous third ventriculostomy in the management of noncommunicating hydrocephalus. *Neurosurgery* 7: 313-321, 1980
23. Hoppe-Hirsch E, Laroussinie F, Brunet L, et al: Late outcome of the surgical treatment of hydrocephalus. *Child's Nerv Syst* 14: 97-99, 1998
24. Jaspan T, McConachie NS, Costigan CM, Punt JAG: New features of the Chiari II malformation shown by CISS imaging. Proceedings of the American Society of Neuroradiology 36th Annual Meeting. American Journal of Neuroradiology, Oak Brook, IL, 1998

25. Jaspan T, McConnachie NS, Punt JA: Ultra-high resolution CISS imaging of the Chiari II malformation. *Child's Nerv Syst* 14: 663, 1998
26. Jones RFC, Kwok BCT, Stening WA, et al: Neuroendoscopic third ventriculostomy. A practical alternative to extracranial shunts in non-communicating hydrocephalus. *Acta Neurochir (Suppl)* 61: 79-83, 1994
27. Jones RFC, Kwok BCT, Stening WA, et al: The current status of endoscopic third ventriculostomy in the management of non-communicating hydrocephalus. *Minim Invas Neurosurg* 37: 28-36, 1994
28. Jones RFC, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26: 86-92, 1990
29. Jones RFC, Stening WA, Kwok BC, et al: Third ventriculostomy for shunt infections in children. *Neurosurgery* 32: 855-860, 1993
30. Jones RFC, Teo C, Stening WA, et al: Neuroendoscopic third ventriculostomy. In: Manwaring KH, Crone KR, Dante MD (eds) *Neuroendoscopy*. Liebert, New York, pp 63-77, 1992
31. Kelly PJ: Stereotactic third ventriculostomy in patients with nontumoral adolescent/adult onset aqueductal stenosis and symptomatic hydrocephalus. *J Neurosurg* 75: 865-73, 1991
32. Keucher TR, Mealey J Jr: Long term results after ventriculoatrial and ventriculoperitoneal shunting for infantile hydrocephalus. *J Neurosurg* 50: 179-186, 1979
33. Kleihaus S, Germann R, Sheran M, et al: A role for endoscopy in the placement of ventriculoperitoneal shunts. *Surg Neurol* 18: 179-180, 1982
34. Laitt RD, Mallucci CL, McConachie NS, et al: Constructive interference in steady state 3D Fourier transform MRI in the management of hydrocephalus and third ventriculostomy. *Neuroradiology* 41: 324-327, 1999
35. Lewis AI, Keiper GLJ, Crone KR: Endoscopic treatment of loculated ventricles. *J Neurosurg* 82: 780-785, 1995
36. Macarthur DC, Buxton N, Punt J, et al: The role of neuroendoscopy in the management of brain tumours. *Child's Nerv Syst* 17: 589-594, 2001
37. Mallucci C, Vloeberghs M, Punt J: Should shunts be revised when neuroendoscopic third ventriculostomy is available? *Br J Neurosurg* 1: 473, 1997
38. Mallucci C, Vloeberghs M, Punt J: Neuroendoscopic third ventriculostomy: the first-line treatment for blocked ventricle-peritoneal shunts? *Child's Nerv Syst* 13: 498, 1997
39. Miller CF, White RJ, Roski RA: Spontaneous ventriculocisternostomy. *Surg Neurol* 11: 63-66, 1979
40. Mixter WJ: Ventriculostomy and puncture of the floor of the third ventricle. *Boston Med Surg J* 188: 277-278, 1923
41. Perlman BB: Percutaneous third ventriculostomy in the treatment of a hydrocephalic infant with aqueduct stenosis. *Int Surg* 49: 443, 1968
42. Pierre-Kahn A, Renier D, Bombois B, et al: Place de la ventriculo-cisternostomie dans la traitement des hydrocephalies non-communicantes. *Neurochirurgie* 21: 557-569, 1975
43. Powers SK: Fenestration of intraventricular cysts using a flexible, steerable endoscope. *Acta Neurochir (Suppl)* 54: 42-6, 1992
44. Punt J: Principles of CSF diversion and alternative treatments. In: Schurr PH, Polkey CE (eds) *Hydrocephalus*. Oxford Medical Publications, Oxford, pp 137-160, 1993
45. Punt J, Vloeberghs M, Terrett M: An introduction to neuroendoscopy. A computer based tutorial system on CD-ROM. Hypertech/2nd Messenger, Nottingham, 1996
46. Punt J, Vloeberghs M: Endoscopy in neurosurgery. *Minim Invas Ther Allied Technol* 7: 159-170, 1998
47. Reddy K, Fewer HD, West M, et al: Slit ventricle syndrome with aqueduct stenosis: third ventriculostomy as definitive treatment. *Neurosurgery* 23: 756-9, 1988
48. Sainte-Rose C, Piatt JH, Renier D, et al: Mechanical complications in shunts. *Pediatr Neurosurg* 17: 2-9, 1991
49. Sainte-Rose C: Third ventriculostomy. In: Manwaring KH, Crone KR, Dante MD (eds) *Neuroendoscopy*. Liebert, New York, pp 47-62, 1992
50. Sainte-Rose C, Chumas P: Endoscopic third ventriculostomy. *Techn Neurosurg* 1: 176-164, 1995
51. Sayers MP, Kosnik EJ: Percutaneous third ventriculostomy: experience and technique. *Child's Brain* 2: 22-30, 1976
52. Scarff JE: Treatment of hydrocephalus: an historical and critical review of methods and results. *J Neurol Neurosurg Psychiatry* 26: 1-26, 1963
53. Schmidt RH: Use of microvascular Doppler probe to avoid basilar artery injury during endoscopic third ventriculostomy. *J Neurosurg* 90: 156-158, 1999
54. Schroeder HWS, Niendorf WR, Gaab MR: Complications of endoscopic third ventriculostomy. *J Neurosurg* 96: 1032-1040, 2002
55. Sgouros S, Mallucci C, Hockley AD: Long-term complications of hydrocephalus. *Pediatr Neurosurg* 23: 127-32, 1995
56. Taha JM, Crone KR: Endoscopically guided shunt placement. *Techn Neurosurg* 1: 159-167, 1996
57. Teo C, Jones R: Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25: 57-63, 1996
58. Teo C, Rahman S, Boop FA, et al: Complications of endoscopic neurosurgery. *Child's Nerv Syst* 12: 248-253, 1996
59. Thomson S, Cartmill M, Vloeberghs M: Third ventricle width variations in patients undergoing primary and secondary neuroendoscopic third ventriculostomies. *Br J Neurosurg* 14: 291, 2000
60. Vries JK: An endoscopic technique for third ventriculostomy. *Surg Neurol* 9: 165-168, 1978
61. Vries JK: Endoscopy as an adjunct to shunting for hydrocephalus. *Surg Neurol* 13: 69-72, 1980
62. Wilcock D J, Jaspan T, Worthington BS, et al: Neuro-endoscopic third ventriculostomy: evaluation with magnetic resonance imaging. *Clin Radiol* 52: 50-54, 1997

Dynamic MRI of Cerebrospinal Fluid in Children

FRANCIS BRUNELLE

Introduction

The flow of cerebrospinal fluid (CSF) is a dynamic phenomenon, as reported in other chapters of this book. The net flow is small and is difficult to measure noninvasively. Most diseases involving the CSF are due to an anomaly in the dynamics of its flow. Until now the diagnosis of CSF pathology was based on the morphology of the CSF-containing spaces. CT and MRI can demonstrate the ventricular and subarachnoid spaces. Several indexes have been published, but subtle changes are difficult to assess. Moreover, ventricular shape and volume do not correlate with the pressure and circulation of the CSF. A fruitful comparison is with the physiology of the heart: no cardiologist today would try to assess heart function on the basis of the size of the heart as seen on a plain film of the thorax.

Technique

MRI can reliably measure flow. A specially designed sequence (flow-sensitive gradient echo sequence) can accurately measure the flow perpendicular to the plane of acquisition. The parameters of this sequence are as follows: TR: 50 ms; TE: 30 ms; scan thickness: 5 mm; spacing: 0; matrix: 256×160; 1 NEX, velocity encoding: 15 cm/s; peripheral gating. The number of cardiac phases to be encoded (usually around 10 in children) depends on the heart frequency. Two different sequences are available, a cine phase contrast (PC) sequence, in which the flow is coded on a gray scale, and cine PCF (phase contrast flow) sequence, in which the velocity is coded on a gray scale but also on a quantitative scale. Absolute velocity measurement is possible on dedicated software by means of flow analysis. The time parameter

is given by a signal synchronized on the heartbeat either through a peripheral pulse meter or a central electrocardiographic set of electrodes. To understand the basic physics of this sequence, a good comparison is with Doppler ultrasonography. The measurement involves special software that can measure the maximum velocity, the minimum velocity, and the mean velocity of the pixels included in the region of interest (ROI). Multiplying the surface of the ROI by the mean velocity will give the mean flow through the assessed structure.

Normal Findings

It is now well established that the CSF flow is driven by systolic expansion of the arteries of the brain during cardiac systole [1]. The skull is an unexpandable structure, so any increase in volume in one section must result in a decrease in the volume of another sector. The skull contains the brain, arteries, veins, and CSF. The brain cannot be compressed, being assimilated to noncompressible water. When the volume of arteries increases during systole, the only two compartments that can balance this increase are the venous compartment and the CSF. Very little is known about the adaptation of the venous bed [2]. The CSF, however, may be understood as being divided into two compartments, one peripheral and one central. The peripheral compartment is made up of subarachnoid spaces around the brain and the cisterns of the base and posterior fossa. This compartment can now be easily measured by volumetric techniques by MRI. The total volume of this compartment is about 150 ml, the subarachnoid spaces being 100 ml and the basal cisterns being 50 ml. The central compartment is the ventricular system, the total volume of which is from 15 ml in the newborn to 20 ml in children (Figs. 1, 2).

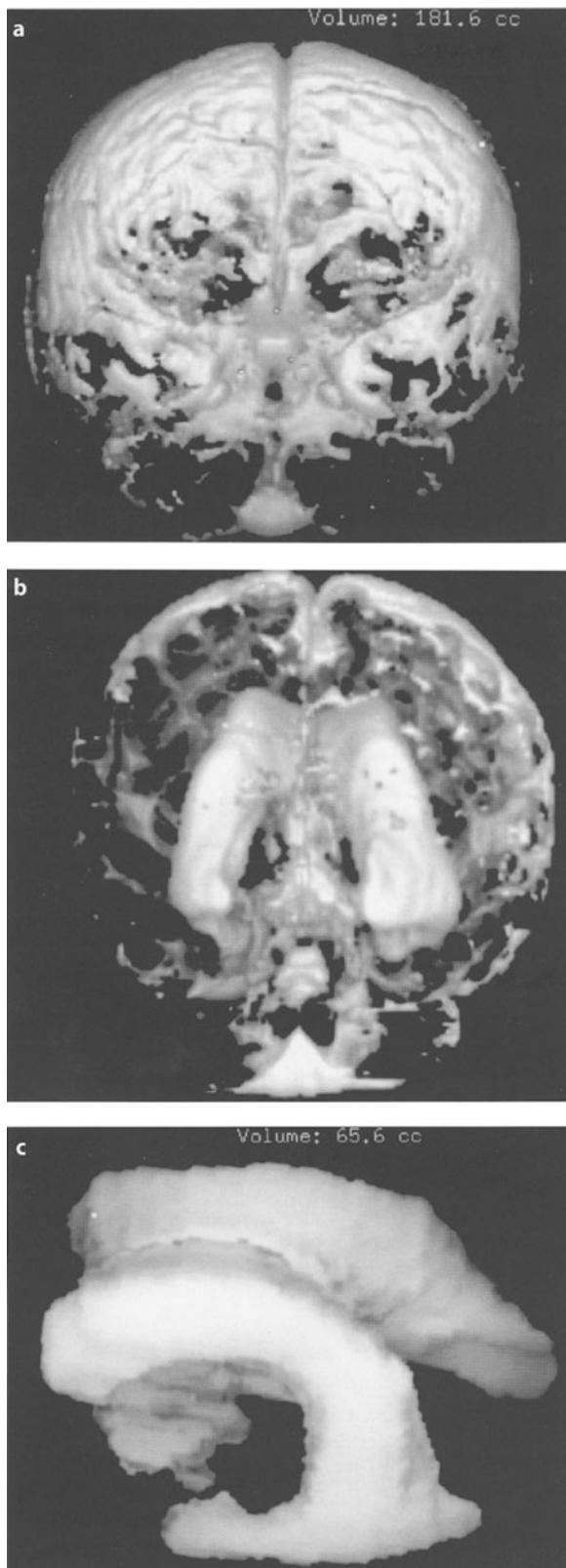


Fig. 1. **a** A 3D reconstruction of the entire CSF volume of a child with moderate dilatation of the ventricle, anterior view. The volume is measured at 181.6 ml. **b** Posterior view. **c** The ventricles are displayed after elimination of the CSF spaces. Measurement is 65.6 ml



Fig. 2. Normal ventricles of a 2-month-old baby boy. They measure 14.6 ml

Assessing the dynamic flow of CSF is very complex as it is a three-dimensional flow and the techniques available today can only assess the flow in a two-dimensional plane. When the systolic expansion of the intracranial arteries occurs, the brisk expansion of the volume leads to expulsion of the CSF from the periphery of the brain toward the basal cisterns and the foramen magnum. The compliance of the spinal canal and subarachnoid spaces is high and copes with this sudden increase. This flow of CSF can be seen not only in the foramen magnum but also down to the spinal canal to the lumbosacral level. After a short delay, the force is transmitted to the brain and the ventricles are compressed; the ventricular CSF is then expelled from the ventricles toward the foramen of Monro, the fourth ventricle, and the posterior fossa. Flow can be seen in the foramen of Monro and be measured in the aqueduct of Sylvius (Fig. 3). It must be said that the flow in the posterior fossa is not only a passive consequence of the flow in the aqueduct as flow can be seen in the vallecula and the foramen of Luschka even in cases of true aqueductal stenosis. It is probable that the systolic expansion of the arteries in the posterior fossa plays the same role independently from the net flow of CSF in the aqueduct. In other words, the presence of flow in the vallecula is not only the consequence of the flow in the aqueduct but also a result of the fourth ventricle's own dynamics. The role of choroid plexuses is probably minimal as their expansion during systole, if it occurs, cannot explain the large volume of CSF mobilized during each cycle. During diastole the phenomenon is reversed as the volume of the arterial vascular bed is decreasing. It is however not a true mirror phenomenon as the flow is passive and the diastolic pattern of the arterial flow is not nil. The role of the veins cannot be underestimated but is

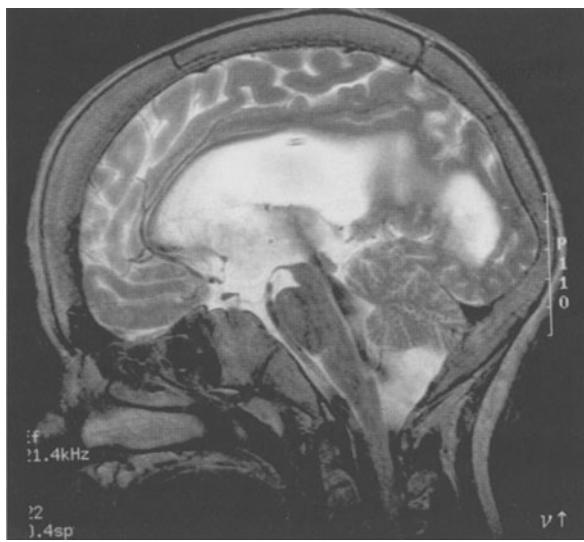


Fig. 3. A 2 year-old boy with moderate cerebral atrophy with dilated ventricles. The sagittal T2-weighted MRI scan shows the flow void phenomenon in the aqueduct, fourth ventricle, and vallecula due to increased velocity of CSF (black)

still poorly understood. A possible explanation for hydrocephalus in patients with venous obstruction, besides the classical resorption impairment theory could be lack of compliance of a dilated vascular venous bed. During diastole most of the flow is ascending in the foramen magnum refilling the subarachnoid spaces from the reservoir accumulated in the spinal canal during systole. In the aqueduct of Sylvius the flow refills the ventricles and in this instance the pattern is symmetric as the flow in the aqueduct is passive during systole and during diastole as well [3-5].

Pathological Findings

Obstructive Hydrocephalus

In obstructive hydrocephalus cine PC MRI is the first and, so far, the only technique by which to objectively assess the absence of flow in a given structure. Unilateral atresia of the foramen of Monro can be easily confirmed. Aqueductal stenosis is no longer a diagnostic problem as measurement of flow in this structure can readily differentiate between an obstructed and a patent aqueduct. The

analysis of flow is, however, more difficult in the region of the foramen magnum as this region is more complex and a true understanding of the CSF dynamics would require a three-dimensional volumetric assessment. If this physiological dynamics is understood, hydrocephalus can be seen as a consequence of any relative impairment of the normal pattern of CSF flow. Relative obstruction of the CSF flow may at any level result in dilatation of the *upstream* CSF spaces. Then, relative obstruction of the foramen magnum may be the cause of hydrocephalus, because the pressure needed to restore a normal flow pattern must be above the normal level. This is true of any pathological process that impedes normal CSF flow even if the normal pathways of CSF are not obstructed. Hydrocephalus as a consequence of a spinal canal tumor can be understood thanks to this mechanism, since the presence of a tumor in the CSF reservoir of the spinal canal leads to relative obstruction of the CSF pathways. In this instance, the presence of proteins in the CSF has also been cited [6-10].

Assessment of Ventriculocisternostomies

In several instances of obstructing hydrocephalus a ventriculocisternostomy (VCS) is performed to restore an active pathway for the CSF. Postoperative assessment of its patency is important as in this type of surgery the ventricular size slowly returns to normal. Although the clinical findings are useful they are not always reliable. Moreover, the rapid shortening of the mean length of hospital stay necessitates a reliable method of verification of the patency of these neoshunts.

Visual Assessment

On T2-weighted MRI scans, the presence of flow creates a flow void phenomenon that is visible as a black area. This is true for most of the vessels that appear black on T2-weighted images. On sagittal T2 MRI scans, the presence of CSF flow can also be seen in the foramen magnum and in the aqueduct as well as in the vallecula as a normal finding. This is true even on antenatal MRI scans in which the aqueduct and the vallecula can be seen. When a VCS is created, the flow in the region of the third ventricle becomes visible as a flow void. This flow void is seen as a funnel-shaped black region (Fig. 4).

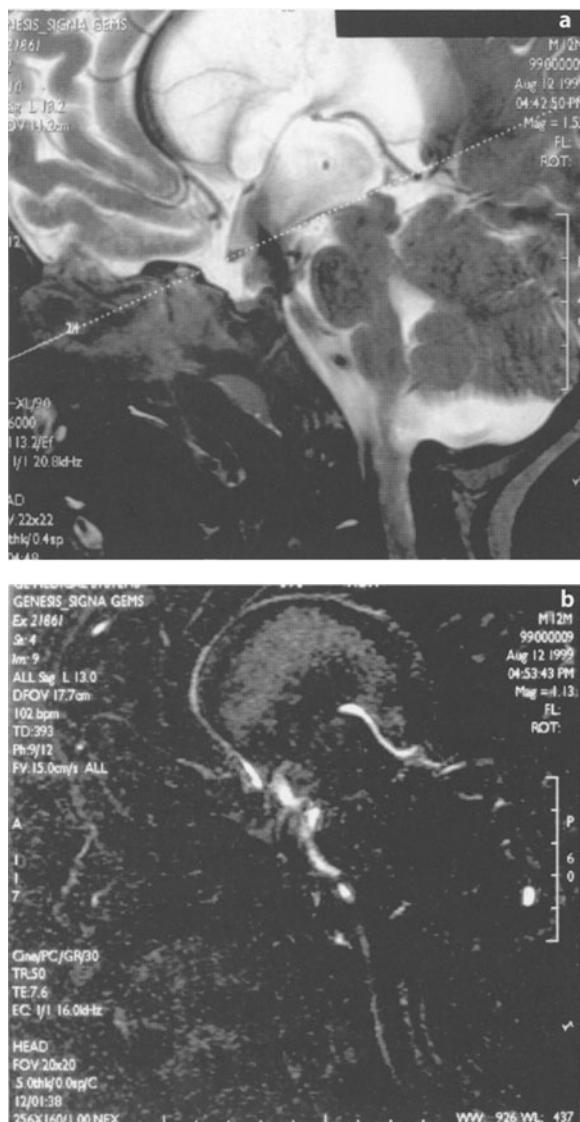


Fig. 4. **a** A 1-year-old baby girl with an aqueductal stenosis treated by ventriculocisternostomy. The flow is visible in the region of the floor of the fourth ventricle on the sagittal T2-weighted image. **b** On cine PC imaging the flow is visible as a white ribbon. It is descending during systole. The flow is also visible as well in the cervical spine

Semiquantitative Method

A semiquantitative method can be used. This method uses the fact that MRI is sensitive to flow and this later creates a phase shift that is related to the speed of flow. The sequence is described above as a cine PC sequence. On a sagittal scan the descending flow is visible as a white funnel-shaped area, and on diastole it is visible as a black region. The presence of these two signs confirms the patency of the VCS. It is easier to see the flow on a cine loop sequence displayed on the workstation.

Quantitative Method

The cine PCF (F for flow) sequence allows not only display but also measurement of the flow. After acquisition of the sequence, the flow in a given region of interest (ROI) is automatically measured by the computer (Fig. 5).

Typically, the velocity of a patent VCS is that of a normal aqueduct of Sylvius, that is to say about 10 cm/s. The net flow, that is to say the mean velocity multiplied by the area, does not mean anything, as the

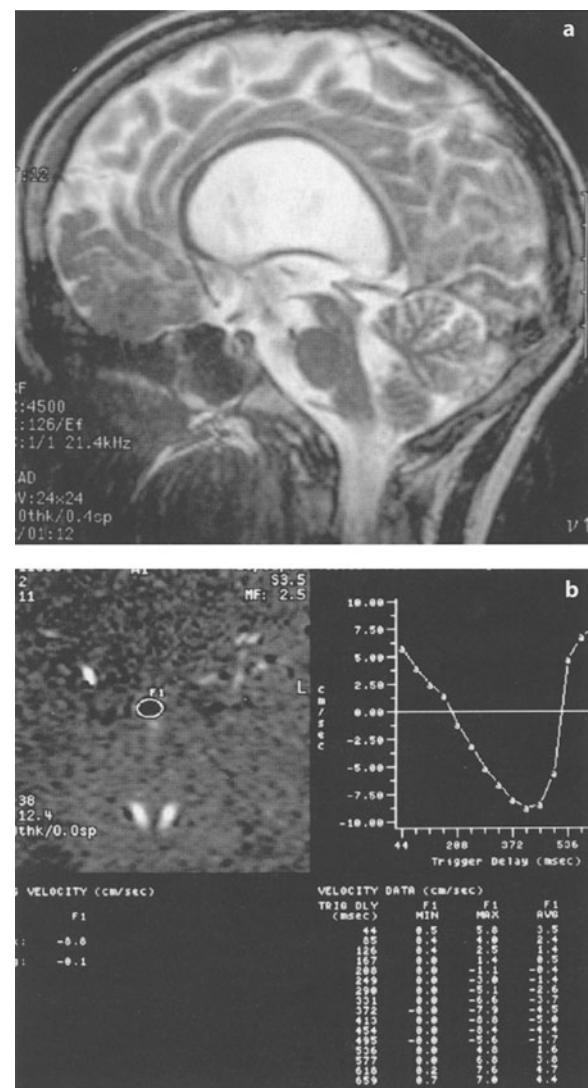


Fig. 5. **a** Aqueduct stenosis treated by ventriculocisternostomy (VCS). The flow is visible in the region of the flow of the third ventricle. **b** Cine PCF. The flow is measured in the VCS. It replicates an almost normal aqueductal flow: the maximum velocity reaches 7.5 cm/s

surface of the ROI does not necessarily correspond to the true surface of the VCS, which is usually irregular. If the VCS displays such velocities, it is declared patent. If no flow at all is seen, it is easy to declare it nonpatent. The difficulty arises when a flow is seen but with velocities inferior to 10 cm/s. One must know that CSF is moving back and forth in the prepeduncular cistern even if no VCS is created. It is then sometimes difficult to be sure that the observed flow is actually due to CSF moving through the VCS. This is even more difficult when this flow is minimal. In these situations we report that the VCS is "non- or poorly functioning."

Other Applications

Ventriculocystostomies

In some situation a communication is made between a cyst and the ventricles. Some arachnoid cysts, especially tentorial edge cysts, can be treated by creating a stoma between the cyst and the lateral ventricles (Figs. 6, 7). The even more complex supraoptic arachnoid cysts are treated with a ventriculocystostomy

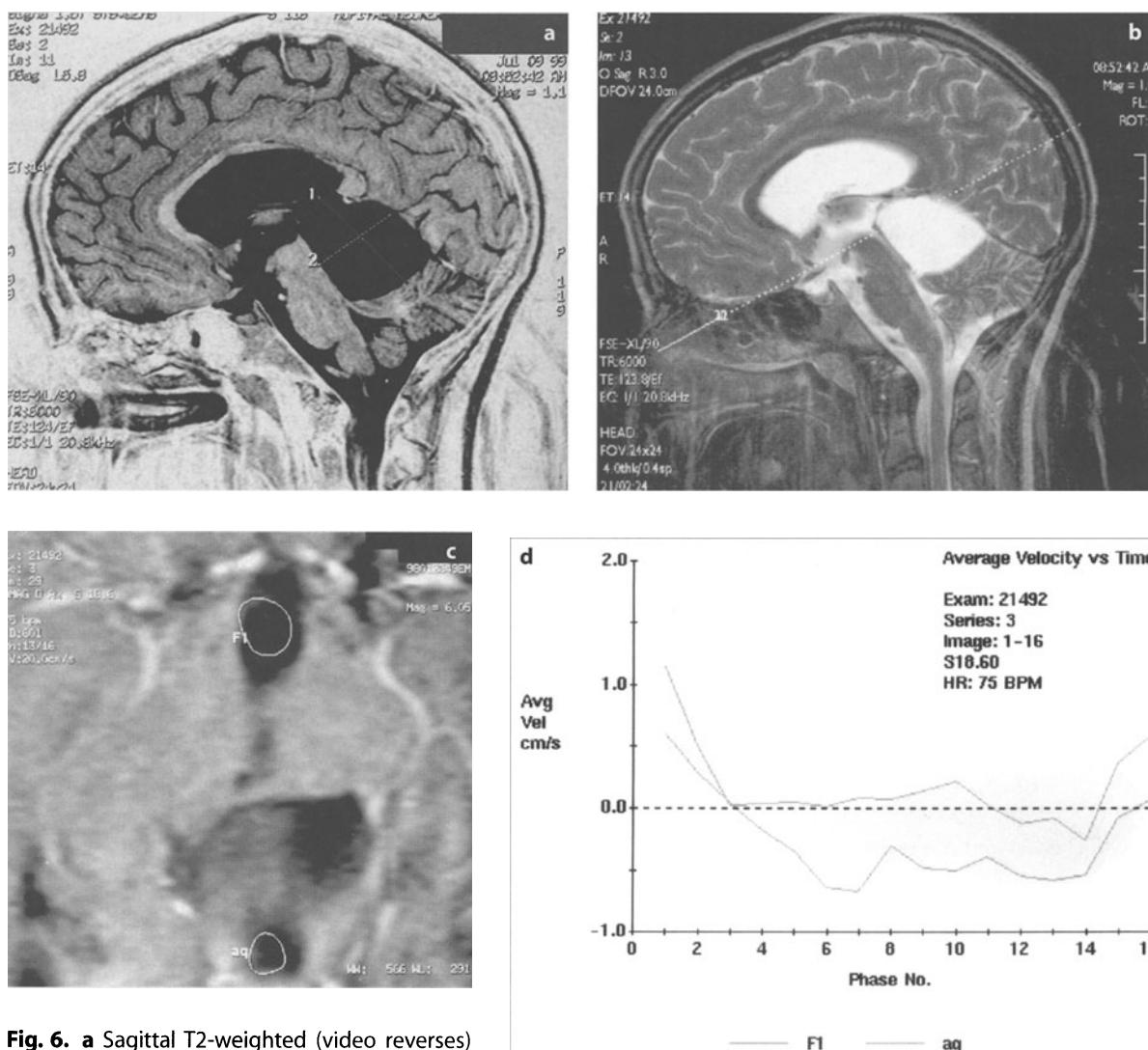
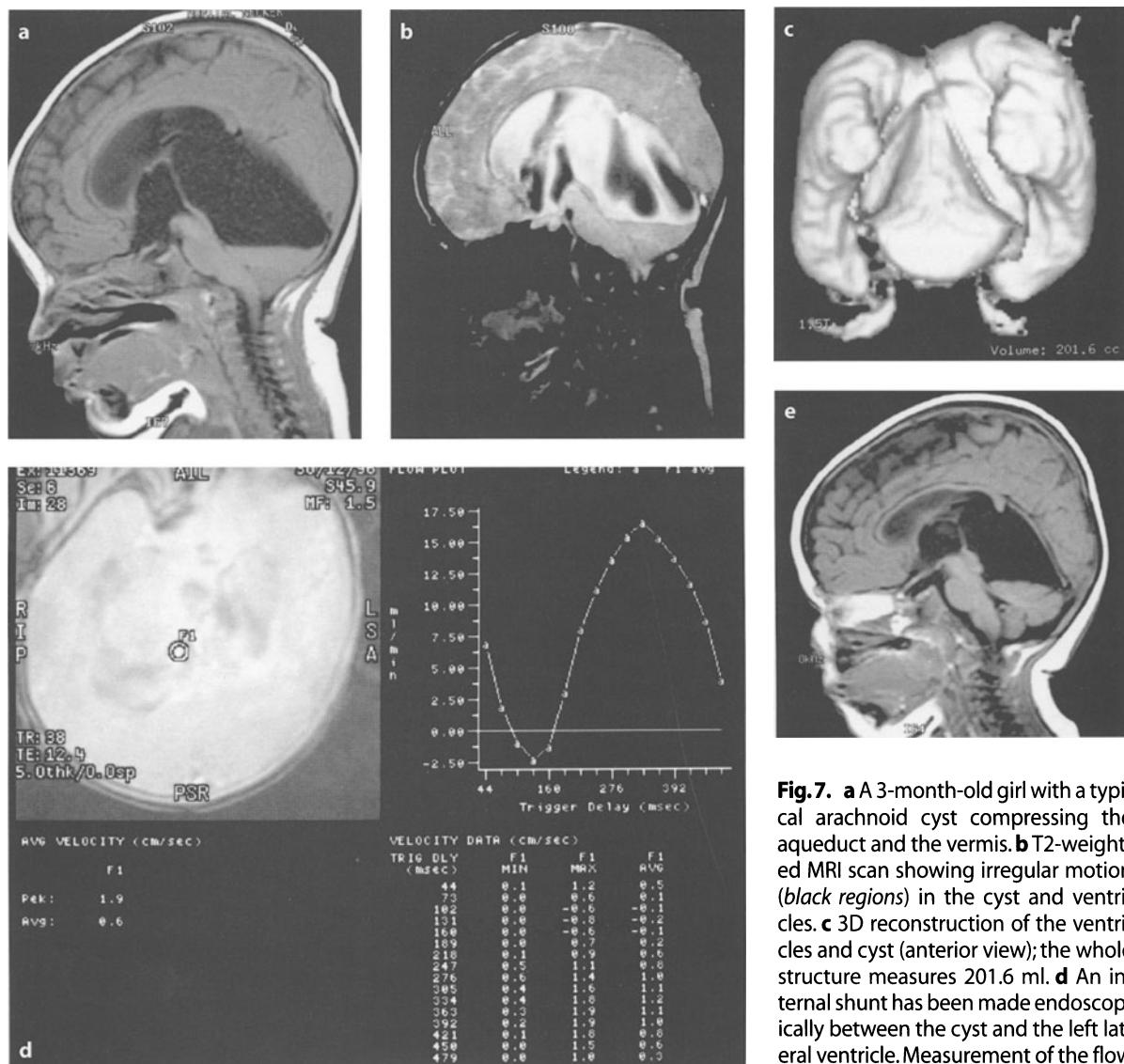


Fig. 6. **a** Sagittal T2-weighted (video reverses) MRI scan. A tentorial edge arachnoid cyst is responsible for compression of the aqueduct leading to obstructive hydrocephalus. **b** Sagittal T2-weighted MRI showing the position of the cine PCF acquisition (dotted line). **c** Axial view of the cine PCF acquisition. The ventriculocisternostomy flow is measured (*F1*), as is the flow in the aqueduct (*aq*). **d** Flow curve of the aqueduct and VCS (*F1*). The flat line represents the aqueduct flow and indicates no flow within the aqueduct. The lower curve is the flow in the VCS (*F1*), indicating patency of the internal shunt



the patency of the shunt. **e** Sagittal T1-weighted MRI showing reduction in the size of the cyst after shunting

that opens the third ventricle into the cyst and a cystoventriculostomy that opens the cyst into the prepeduncular cistern. In these instances, MRI can be difficult to use, as it is necessary to know the exact position of the communication in order to place the MRI plane of acquisition. If the plane of acquisition is slightly offset, no flow is observed.

Conclusion

Cine PC and cine PCF are now routinely used to assess the patency of VCS in children. It is noninvasive,

can be repeated, can be performed soon after surgery, and is accurate. Much work is still needed to understand some aspects of hydrocephalus in children. The role of the veins is still poorly understood.

References

1. Alperin N, Vikingstad EM, Gomez-Anson B, et al: Hemodynamically independent analysis of cerebrospinal fluid and brain motion observed with dynamic phase contrast MRI. *Magn Reson Med* 35: 741-754, 1996
2. Badhela RA, Bogdan AR, Wolpert SM: Cerebrospinal fluid flow waveforms: effect of altered cranial venous outflow. *Neuroradiology* 40: 283-292, 1998

3. Badhelia RA, Bogdan AR, Kaplan RF, et al: Cerebrospinal fluid pulsation amplitude and its quantitative relationship to cerebral blood flow pulsations a phase-contrast MR flow imaging study. *Neuroradiology* 39: 258-264, 1997
4. Feinberg DA, Mark AS: Human brain motion and cerebrospinal fluid circulation demonstrated with MR velocity imaging. *Radiology* 163: 793-799, 1987
5. Kahn T, Muller E, Lewin JS, et al: MR measurement of spinal CSF flow with the RACE technique. *J Comp Assist Tomogr* 16: 54-61, 1992
6. Lee E, Wang JZ, Mezrich R: Variation of lateral ventricular volume during the cardiac cycle observed by MR imaging. *AJNR Am J Neuroradiol* 10: 1145-1149, 1989
7. Marks MP, Pelc NJ, Ross MR, et al: Determination of cerebral blood flow with a phase-contrast cine MR imaging technique: evaluation of normal subjects and patients with arteriovenous malformations. *Radiology* 182: 467-476, 1992
8. Paakkko, E, Lopponen T, Saukkonen AL, et al: Information value of magnetic resonance imaging in shunted hydrocephalus. *Arch Dis Child* 70: 530-535, 1994
9. Pang D, Altschuler E: Low-pressure hydrocephalic state and viscoelastic alterations in the brain. *Neurosurgery* 35: 643-656, 1994
10. Van der Knaap MS, Bakker CJ, Faber JA, et al: Comparison of skull circumference and linear measurements with CSF volume MR measurements in hydrocephalus. *J Comp Assist Tomogr* 16: 737-743, 1992

The CISS Sequence in the Preoperative MRI Assessment of Neuroendoscopic Third Ventriculostomy

NORMAN S. MCCONACHIE

Role of Preoperative Imaging

Neuroendoscopic third ventriculostomy (NTV) is a well-established technique for the management of patients with hydrocephalus [6, 10, 11-13]. It is of particular value for patients in need of long-term cerebrospinal fluid (CSF) diversion who formerly often required frequent shunt revision [25]. Imaging has an important role in diagnosing the underlying cause of hydrocephalus. In addition, as the primary disease and the secondary changes from hydrocephalus and shunting can obscure the normal endoscopic intraventricular landmarks, imaging can provide anatomical information that helps to guide the surgical approach, identify potential hazards, and assist with selection of the type of neuroendoscope to be used. Moreover, those who are likely or unlikely to benefit from the procedure can be identified by, for instance, demonstrating dense basal arachnoiditis, which can compromise the success of NTV. Imaging also has an important role in the postoperative assessment of ventriculostomy patency [4, 7, 14, 16, 18].

Much useful information can be obtained using cranial ultrasonography in infants with a patent anterior fontanelle, including quantification of flow using Doppler ultrasonography [23]. However, magnetic resonance imaging (MRI) is the modality of choice in the pre- and postoperative work up of these patients [24]. Different MRI protocols have been proposed to assess these patients and have included the use of T1-weighted spin echo (SE), T2-weighted SE [7, 18] or fast/turbo SE [24], and cine phase-contrast MR techniques [4, 16, 19, 20]. Disadvantages of SE or FSE techniques are relatively poor spatial resolution, with 2-3 mm minimal slice thickness, and CSF flow effects that produce further problems in image interpretation. At our centre, three-dimensional constructive interference in the steady state (CISS) is employed as the primary imaging tool as it provides greater detail of the ventricular system and basal cisterns with excellent CSF-to-brain contrast and vastly superior spa-

tial resolution [8, 9, 14]. Our imaging protocol also includes standard T2-weighted TSE axial imaging of the brain, TR 4000/TE 90/2 NEX.

The CISS Sequence

Conventional MR sequences are sensitive to flow (of CSF or blood), with signal loss occurring secondary to dephasing and washout of moving spins [1, 21]. Cardiac-driven pulsatile CSF flow is seen as areas of signal loss (flow void). CISS uses fast imaging with steady state free precession (FISP) [3]. To minimize the loss of signal from pulsatile CSF motion, a FISP sequence is used with flow compensation applied over each TR cycle rather than conventional compensation techniques which are applied to the echo. This compensates for slow flow, thereby enhancing the cisternographic effect. However, signal loss due to phase dispersion is still seen on CISS imaging at high CSF velocities and in conditions of turbulent flow. To overcome image artefact due to patient-driven field inhomogeneities, two true FISP data sets are acquired successively with alternating and non-alternating radiofrequency pulses. The data sets are then combined to produce an image with excellent CSF-to-brain contrast. Each data set covers a volume of 32 mm to include the third ventricle and foramina of Monro. This slab is divided into 42 partitions with an effective section thickness of 0.7 mm. The other parameters are TR 12.2 ms, TE 5.9 ms, 2 NEX, 70° flip angle, 256×512 matrix size, and 20 cm field of view. The total acquisition time is 8.39 min, which gives rise to potential artefact from patient movement. However, this is seldom a problem if younger patients are routinely sedated for the procedure. The floor of the third ventricle is seen to best advantage on the source sagittal images. Reformatted images in the oblique coronal plane define the foramina of Monro (Fig. 1). The high resolution, lack of CSF flow artefacts, and excellent contrast between CSF and other structures mean that the CISS data set is also very suit-

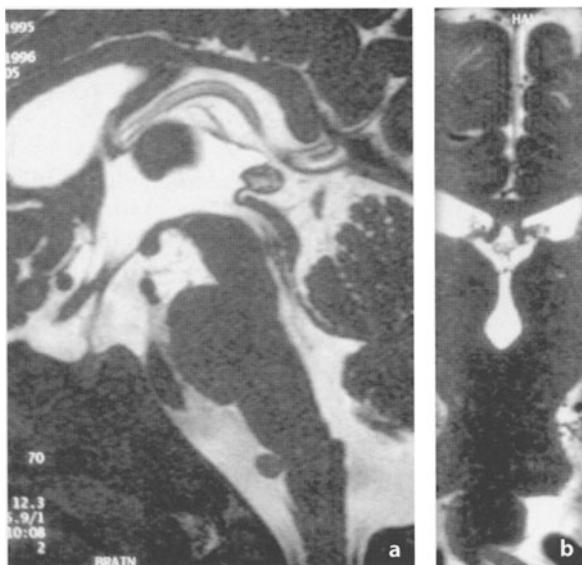


Fig. 1. **a** Mid-sagittal CISS image showing excellent contrast between CSF and other structures. Note the flow void in a normal aqueduct. **b** Coronal images, reformatted from the 3-D imaging slab, allow measurement of the diameters of the foramina of Monro

able for providing computer-simulated representations of the ventricles and cisterns for “virtual endoscopy” [22]. This can provide a surgeon’s eye view that may be helpful for training purposes or for rehearsing the approach to a difficult neuroendoscopy case.

Assessment of Anatomy

Features of Note

To provide access for NTV, the access route should be adequate for passage and for manoeuvring the endoscope. The minimum acceptable dimensions will depend on the type and diameter of the endoscope. The following imaging details should be documented: (1) sizes of the foramina of Monro, (2) third ventricular width, (3) position of basilar artery tip relative to the mamillary bodies, (4) presence or absence of membranes in the ventricles and basal cisterns, (5) presence or absence of a severe skull base anomaly.

Liliequist’s Membrane

Liliequist’s membrane was originally described as obstructing the passage of air in encephalography [17]. This normal arachnoid condensation passes from the

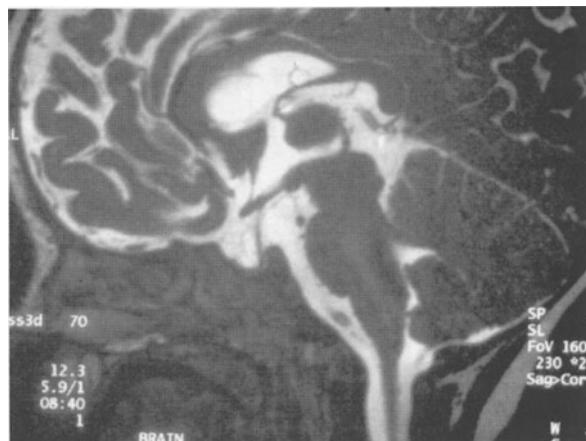


Fig. 2. Liliequist’s membrane clearly shown below the floor of the third ventricle

tip of the dorsum sellae to the anterior edge of the mamillary bodies. It is frequently seen on CISS imaging in patients scanned for unrelated pathology (Fig. 2). It can be clearly defined at endoscopy and it can cause obstruction to flow through a third ventriculostomy defect. The importance of identifying this membrane on preoperative scans is therefore obvious, as this membrane should be divided as part of the neuroendoscopic procedure [2].

Chiari II Malformation

In all cases of Chiari II malformation, it is important to emphasize the morphological anomalies of the third ventricle, which may comprise beaking of the ventricular floor anterior to the mamillary bodies and/or an anterior septum related to the lamina terminalis, lying inferior to the anterior commissure [8, 9]. It is also noteworthy that the tip of the basilar artery lies significantly further from the mamillary bodies (Fig. 3).



Fig. 3. Chiari II malformation. There is beaking of the floor of the third ventricle (arrow) and an accessory commissural band related to the lamina terminalis (arrowhead). Note the increased distance between the basilar artery tip and the mamillary bodies

Causes of Hydrocephalus

Tumour

In the preoperative work-up of large intraventricular tumours or of those causing external compression of the ventricles, the addition of a CISS sequence may better define the internal tumour structure [26]. It

may also more elegantly show the distortion of the ventricular anatomy, but it seldom adds much to the management of either the tumour or the hydrocephalus. However, small intraventricular obstructions may be difficult or impossible to define with conventional MR imaging, particularly if the lesion is a cyst or a tumour with a significant cystic component. CISS can add considerably to diagnosis and management by revealing the precise anatomical location and cyst wall, if present (Figs. 4,5).

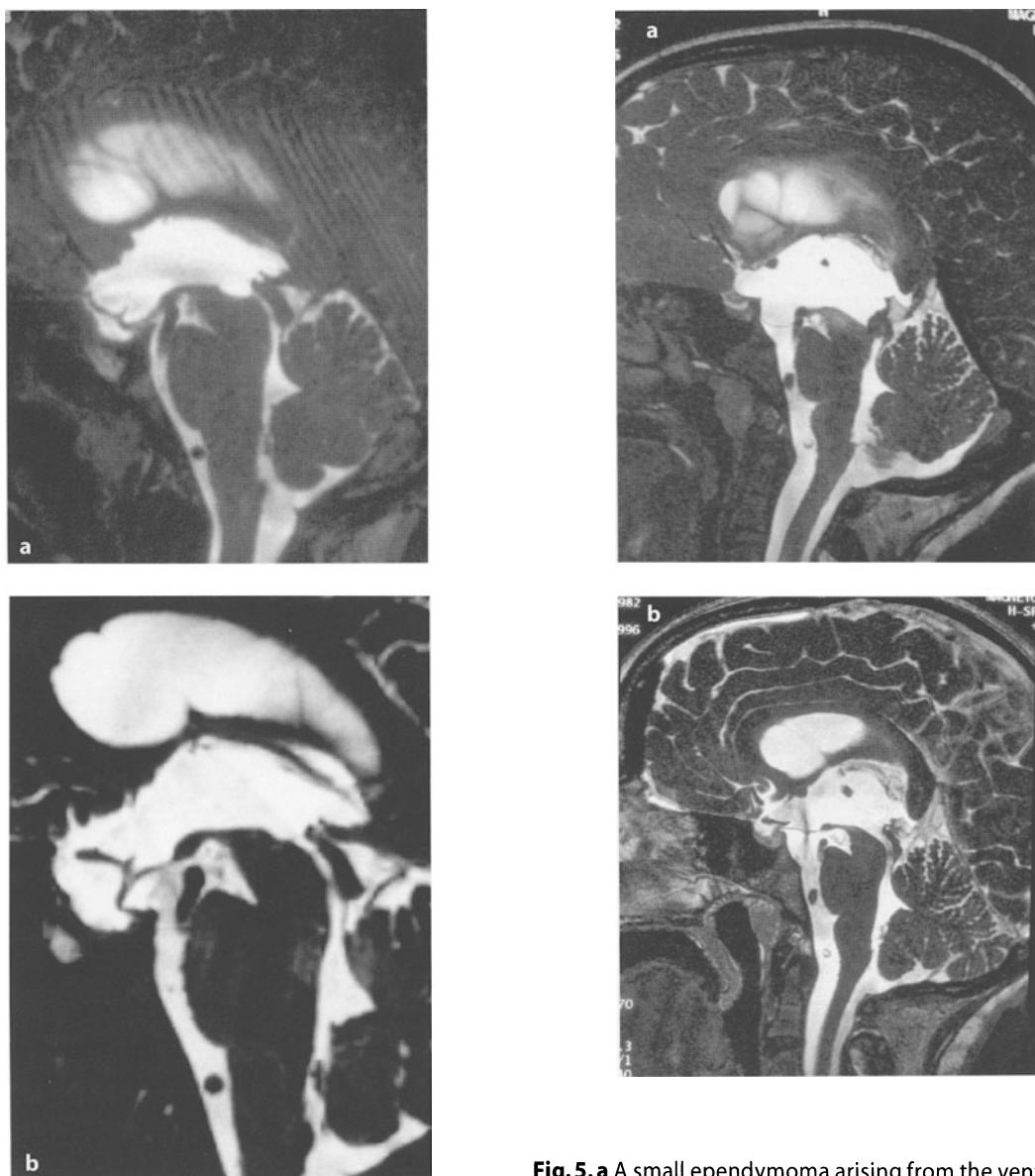


Fig. 4. **a** Intraventricular cyst obstructing the iter. This lesion was invisible on thin T2-weighted conventional FSE images. **b** The lesion has disappeared after neuroendoscopic cyst puncture. The NTV is patent

Fig. 5. **a** A small ependymoma arising from the ventral surface of the tectum obstructs the aqueduct, preventing flow. The depressed floor of the third ventricle is in contact with the tip of the basilar artery. **b** After neuroendoscopic resection, normal flow returns to the aqueduct. An NTV is patent

Aqueduct Stenosis

The submillimetric slice thickness, high resolution, and relative homogeneity of CSF signal that the CISS sequence provides enables the aqueduct to be clearly depicted in health and disease. Absence of a flow void and obstruction by membranes, webs (see Fig. 7) or hypoplasia, or by cyst or tumour, is easily identified [5, 14, 26].

Membranes

The cisternographic effect of the CISS images allows greater definition of basal cisterns and their contents, including cranial nerves, vessels, and arachnoid membranes [3, 14, 15]. Patent basal cisterns are important to allow flow from the third ventricle into the pre-pontine and perimesencephalic cisterns. In all patients investigated in our centre with post-haemorrhagic or post-meningitic hydrocephalus, complex and dense arachnoid membranes were found throughout the basal cisterns on CISS imaging (Fig. 6) and presumably represent a marker for more diffuse inflammation in the subarachnoid spaces. Patients with “communicating” hydrocephalus secondary to inflammation or haemorrhage probably have an obstructive component that may become the predominant underlying mechanism producing hydrocephalus. In a few patients, we have found on postop-

erative CISS imaging that the ventriculostomy was anatomically open but flow voids through the defect were absent. Where CISS imaging has shown residual flow-limiting membranes, it has served as a preoperative guide for a second NTV (Fig. 7). Other membranes in the basal cisterns have less predictable anatomy but are most commonly seen in the prepon-tine cistern between the basilar artery and the poste-

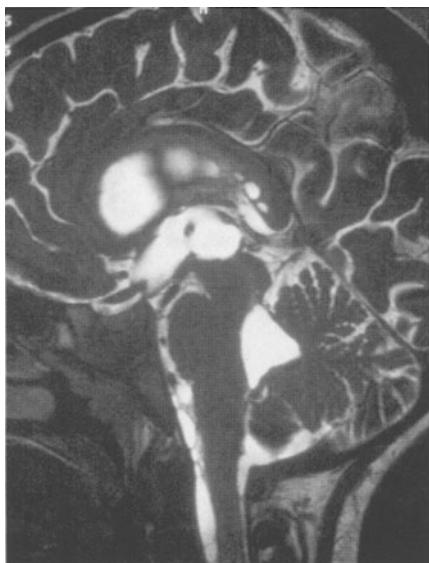


Fig. 6. Post-meningitic hydrocephalus. There are dense matted arachnoid adhesions in the basal cisterns

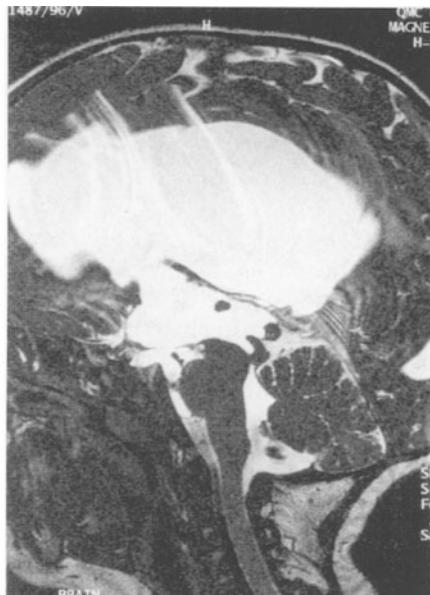


Fig. 7. a Post-operative CISS after NTV for aqueduct stenosis shows absence of a flow void through the defect in the third ventricle floor and a pre-pontine membrane. **b** After division of the membrane at a second neuroendoscopic procedure, a flow void is clearly seen



Fig. 8. Preponitine membrane in association with "communicating" hydrocephalus. The aqueduct is patent

rior aspect of the clivus (Fig. 8). These may be secondary to previous subclinical inflammation or haemorrhage and can also obstruct normal CSF flow in the basal cisterns. They can be seen at endoscopy, and it is possible that division of these membranes at the time of the procedure may improve CSF flow in the basal cisterns, thereby increasing the efficacy of NTV in this patient group. A number of studies have documented the greater conspicuity of intraventricular bands, membranes and cysts on CISS images [5, 8, 14, 26]. An idea of their number and distribution may be helpful to the neuroendoscopist in assessing the suitability for NTV and the approach if the membranes are to be divided.

In conclusion, the CISS sequence provides excellent cisternographic images of the third ventricle and basal cisterns that serve as an accurate preoperative road map for NTV. It also contributes information as to the underlying cause of the hydrocephalus and may be the only way of non-invasively demonstrating some obstructions. Membranes in the basal cisterns or ventricles not seen on conventional MR imaging can be defined using CISS and appear to be related to previous infection or haemorrhage with secondary communicating hydrocephalus. These membranes may be important in CSF flow dynamics and can compromise the success of NTV.

References

- Bradley WG, Kortman KE, Burgoyne DE: Flowing cerebrospinal fluid in normal and hydrocephalic states: appearances on MR images. *Radiology* 159:611-616, 1986
- Buxton N, Vloeberghs M, Punt JA: Liliequist's membrane in minimally invasive endoscopic neurosurgery. *Clin Anat* 11:187-190, 1998
- Casselman JW, Kuhweide R, Deimling M, et al: Constructive interference in the steady state (CISS)-3DFT MR imaging of the inner ear and cerebellopontine angle. *AJNR Am J Neuroradiol* 14:47-57, 1993
- Fukuhara T, Vorster SJ, Ruggieri P, et al: Third ventriculostomy patency: comparison of findings at cine phase-contrast MR imaging and at direct exploration. *AJNR Am J Neuroradiol* 20:1560-1566, 1999
- Govindappa SS, Narayanan JP, Krishnamoorthy VM, et al: Improved detection of intraventricular cysticercal cysts with the use of three-dimensional constructive interference in steady state MR sequences. *AJNR Am J Neuroradiol* 21:679-684, 2000
- Hirsch JF: Percutaneous ventriculocisternostomies in noncommunicating hydrocephalus. *Monogr Neurol Sci* 8:170-178, 1982
- Jack CR, Kelly PJ: Stereotactic third ventriculostomy: assessment of patency with MR imaging. *AJNR Am J Neuroradiol* 10:515-522, 1989
- Jaspan T, Costigan CM, McConachie NS, et al: New features of the Chiari II malformation demonstrated by ultra-high resolution CISS imaging. *AJNR Am J Neuroradiol* (in press)
- Jaspan T, McConachie NS, Punt JA: Ultra-high resolution CISS imaging of the Chiari II malformation. *Child's Nerv Syst* 14:663, 1998
- Jones RFC, Kwok BCT, Stening WA, et al: Neuroendoscopic third ventriculostomy. A practical alternative to extracranial shunts in non-communicating hydrocephalus. *Acta Neurochir Suppl* 61:79-83, 1994
- Jones RFC, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26:86-92, 1990
- Jones RFC, Stening WA, Kwok BCT: Third ventriculostomy for shunt infections in children. *Neurosurgery* 32:855-860, 1993
- Kelly PJ: Stereotactic third ventriculostomy in patients with nontumoral adolescent/adult onset aqueductal stenosis and symptomatic hydrocephalus. *J Neurosurg* 75:865-873, 1991
- Laitt RD, Mallucci CL, McConachie NS, et al: Constructive interference in steady state 3D Fourier-transform MRI in the management of hydrocephalus and third ventriculostomy. *Neuroradiology* 41:324-327, 1999
- Lemmerling M, De Praeter G, Mortele K, et al: Imaging of the normal pontine cisternal segment of the abducens nerve, using three-dimensional constructive interference in the steady state MRI. *Neuroradiology* 41:384-386, 1999
- Lev S, Bhadelia RA, Estin D, et al: Functional analysis of third ventriculostomy patency with phase-contrast MRI velocity measurements. *Neuroradiology* 39:175-179, 1997
- Liliequist B: The anatomy of the subarachnoid cisterns. *Acta Radiol* 46:61, 1956
- Missir O, Dormont D, Pierot L: MR visualisation of CSF flow through a ventriculo-cisternostomy. *Neuroradiology* 31:93-94, 1989
- Nitz WR, Bradley WG, Watanabe AS, et al: Flow dynamics of cerebrospinal fluid: assessment with phase-contrast velocity MR imaging performed with retrospective cardiac gating. *Radiology* 183:395-405, 1992
- Rovira A, Capellades J, Grive E, et al: Spontaneous ventriculostomy: report of three cases revealed by flow-sensitive phase-contrast cine MR imaging. *AJNR Am J Neuroradiol* 20:1647-1652, 1999

21. Sherman JL, Citrin CM: Magnetic resonance demonstration of normal CSF flow. *AJNR Am J Neuroradiol* 7:3-6, 1986
22. Shigematsu Y, Korogi Y, Hirai T, et al: Virtual MRI endoscopy of the intracranial cerebrospinal fluid spaces. *Neuroradiology* 40:644-650, 1998
23. Wilcock DJ, Jaspan T, Punt J: CSF flow through third ventriculostomy demonstrated with colour Doppler ultrasound. *Clin Radiol* 51:127-129, 1996
24. Wilcock DJ, Jaspan T, Worthington BS, et al: Neuro-endoscopic third ventriculostomy: evaluation with magnetic resonance imaging. *Clin Radiol* 52:50-54, 1997
25. Yamamoto M, Oka K, Ikeda K, et al: Percutaneous flexible neuroendoscopic ventriculostomy in patients with shunt malfunction as an alternative procedure to shunt revision. *Surg Neurol* 42:218-223, 1994
26. Yang D, Korogi Y, Ushio Y, et al: Increased conspicuity of intraventricular lesions revealed by three-dimensional constructive interference in steady state sequences. *AJNR Am J Neuroradiol* 21:1070-1072, 2000

Complications of Endoscopic Third Ventriculostomy

CHARLES TEO

Introduction

Justifiably, endoscopic third ventriculostomy (ETV) is considered the greatest breakthrough in the management of hydrocephalus since the introduction of Silastic shunts. Among selected patients, the procedure can render over 70% of children shunt-independent [13, 27, 28]. More recently, however, the procedure has been the focus of scrutiny, with an increased number of reports showing long-term failures and serious complications [1, 4, 8, 11, 16, 17, 23, 25]. Indeed, it is felt among the endoscopic neurosurgical community that the real complication rate may be higher than those published. Although this chapter will review both the well-known and the rarer complications of ETV, complication avoidance will constitute the main body of the text.



Fig. 1. Sharp perforation through an opaque floor with the closed end of a pair of grabbing forceps (Aesculap; Tutlingen, Germany)

Complications Specific to ETV

Bradycardia and Asystole

This common intraoperative complication has been recognized for many years [7, 12]. It was documented in one of the first large series of ETV [27] and identified as a not uncommon occurrence that should be anticipated and detected by turning up the volume of the cardiac monitor. It can occur at any time during manipulation of the third ventricle. It may occur when the scope is introduced, when irrigation is used, or when pressure is placed on the floor (Fig. 1) [2]. The bradycardia resolves with removal of the scope from the third ventricle, removal of irrigant if there is obstruction of outflow, and with release of pressure from the floor. If the bradycardia is not recognized, it will invariably progress to asystole and possible hemodynamic compro-

mise. Handler et. al reported such an occurrence, which fortunately had no long-term adverse consequences [12].

Avoidance

There are several theories behind the genesis of this problem. Among them is the possibility that the scope obstructs both foramina of Monro, resulting in high pressure within the third ventricle when irrigant cannot escape. Another is that the irrigation fluid is either too different to CSF in osmolality or too cold, resulting in irritation of the hypothalamus. Finally, it may be a pure traction phenomenon of either the floor or walls of the third ventricle and hence hypothalamic dysfunction (Fig. 1). Whatever the theory you subscribe to, it would be prudent to obey the following rules:

1. Always check to see that there is an adequate outflow mechanism for the irrigant. Simply having

one of the working channels open does not guarantee egress of fluid. It is not uncommon for a piece of brain or blood clot to obstruct one of these small working/irrigation channels at any time throughout the procedure.

2. Turn up the volume of the cardiac monitor and keep the noise down in the operating room. If the pulse slows, discontinue whatever you happen to be doing, and if possible, reverse the last action.
3. Use isotonic solution, preferably lactated Ringer's, as your irrigant of choice. The fluid should be warmed to approximately body temperature.
4. When puncturing the floor, be sure to use a sharper technique if the floor is thick and nonattenuated (Fig. 1).

Visual Obscuration

There are several causes for a less than optimal view. Of course, the system should be checked before the dura is opened to ensure all components of the video chain are operational. The view can be hindered by fogging of the lenses at any junction, by damaged hardware, and by incorrect assembly of all the different components. The most common cause, however, is *intraventricular hemorrhage* (Fig. 2). This can occur at any time during the procedure, but usually happens when the ependyma is breached as the scope enters the ventricle for the first time. The bleeding can be minor or quite profuse. It is rarely arterial except when small vessels are torn as the stoma is created. Excessively wide excursions of the scope will increase the chances of bleeding. It is surprising how the spilling of such a small amount of blood may result in such a dramatic effect on visualization. The most important point to remember is not to panic, irrigate generously, and maintain access to the ventricle. Once vision is obscured, try to place the end of the scope in the largest cavity. For example, if hemorrhage occurs when the scope is in the third ventricle, the loss in vision may cause the operator to move the scope only a fraction of a centimeter, which could have drastic consequences. A similar movement in the larger lateral ventricle might not have any adverse result. Once hemorrhage has occurred and irrigation is proving unsuccessful, there are several other techniques that can be employed. The scope itself can be placed against the bleeding vessel to tamponade the flow. Of course, one must first identify the responsible vessel, which may prove difficult given the bloody CSF and visual impairment. The

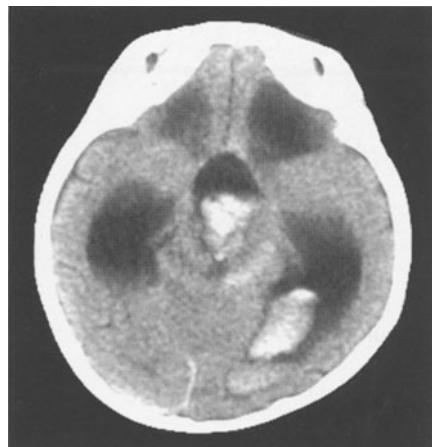


Fig. 2. Postoperative CT of a child who had an ETV complicated by intraoperative hemorrhage. It occurred at the time of the ventriculocisternostomy

next technique is to try and coagulate the vessel with either monopolar or bipolar endoscopic forceps. In reality this maneuver is very difficult. Endoscopic instruments are not readily steerable and the vessel is often floating around in the CSF, creating a moving target with the copious irrigation. If all else fails, CSF can be removed from the ventricle and replaced with air, thereby allowing the surgeon to use standard coagulating techniques without visual obscuration. It is very important to replace the CSF with air to prevent the ventricles from collapsing, as this can create an even worse set of complications.

Avoidance

Prevention of hemorrhage is clearly the optimal way to manage this dilemma:

1. Tap the ventricle with a smaller brain needle before passing the larger sheath. This will give the sheath easier access and, hopefully, less traction on the ventricular walls.
2. Maintain your trajectory. Try not to move the scope from side to side. A small degree of movement may tear the ependymal vessels.
3. When using a rigid scope, make sure the edges are blunt and rounded. Sharp edges tend to damage vessels (Fig. 3).
4. When using a flexible scope, check that the scope is in the neutral position before removing it.
5. If you are using a technique that requires you to remove and replace scopes into the ventricle it would be wise to use a peel-away sheath in order to maintain a tract through the brain (Fig. 4).

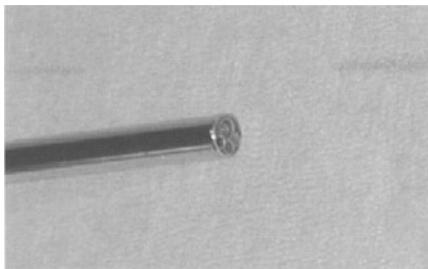


Fig. 3. This particular scope has sharp edges and is capable of damaging neurovascular structures

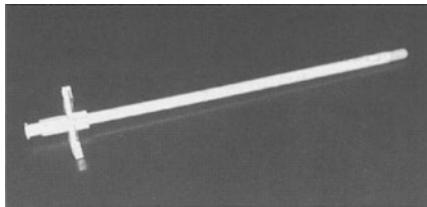


Fig. 4. Peel-away sheath used to maintain the tract through the cerebrum

Damage to the Fornices

This is probably the most common complication of ETV [23, 30]. Thankfully, the clinical consequences are minimal or negligible. It usually occurs with the leading face of the endoscope when it is passed from the lateral ventricle into the third. It may also occur when the scope is manipulated within the third ventricle or, rarely, when the scope is removed from the third ventricle. It has been implicated when patients awake with memory disturbance, although it is difficult to imagine bilateral fornical damage with any of these maneuvers. Bilateral damage is more likely to occur with the initial ventriculostomy, especially when the neurosurgeon uses either the scope itself to tap the lateral ventricle or a peel-away sheath. Another error that may cause bilateral damage is when the scope is placed unknowingly into the contralateral ventricle and the surgeon attempts to pass the scope into the third ventricle.

Avoidance

Damage to the fornix can be avoided by following some simple rules:

1. Optimal burr hole placement (see Chap. 25).
2. Never tap the ventricle with the scope itself or

anything larger in diameter than a brain needle. The thickness of either of these implements is such that if you are off target by only a few millimeters, the consequences can be devastating (Fig. 5). Use a standard brain needle, taking note of the depth at which the ventricle is entered, so that the scope or a sheath can be passed down the same tract for precisely the same distance and not a centimeter more.

3. If you inadvertently enter the contralateral ventricle, it is better to abandon that trajectory, remove the scope, and start again. Similarly, if you find the trajectory is taking you to the posterior third ventricle, it is better to discontinue that attempt, remove the scope, make another burr hole more posteriorly, and start again.
4. It is not uncommon for the foramen of Monro to remain relatively small despite quite dramatic ventricular enlargement. Consequently, the scope may be too wide to pass through the foramen. This has been called scope-to-foramen disproportion [27]. Techniques available to circumvent this problem include choosing a smaller-diameter scope or trying to enlarge the foramen with gentle hydrodissection. A less optimal way of avoiding damage is to remove the outer sheath of the scope and to pass the scope alone into the third ventricle. This would necessitate creating the stoma with the scope itself and without irrigation. Once the scope is within the third ventricle it is important not to wield the scope in wide arcs.



Fig. 5. This hemorrhagic tract was a result of a misguided attempt to access the lateral ventricle with the endoscope itself

- If you are using a flexible scope, it must be in the neutral position before backing out of the third ventricle. Faulty scopes that are poorly cleaned often do not return to the neutral position. To avoid this mistake, take note of the trajectory when the scope first enters the third ventricle and before removing the scope ensure that you have returned to the same trajectory.

Hypothalamic Damage

This is the most common complication of ETV with clinical consequences [23, 27]. It usually occurs at the time the stoma is created and can result in subclinical or clinically devastating complications. Those complications that have been documented in the literature include permanent or transient diabetes insipidus, amenorrhea, loss of thirst [27], death [19], hyperphagia, varying degrees of drowsiness, hyperkalemia [2], hyponatremia [31], and decreased insulin-like growth factor 1 [29]. The hypothalamus is particularly susceptible due to its location in the walls of the third ventricle. Indeed, without ventriculomegaly, the floor of the third ventricle is a narrow median raphe where the walls almost meet in the midline. With hydrocephalus, the walls and the raphe attenuate. In reality, the junction between the thinned-out raphe and the attenuated hypothalamus, which may still be functional, is imperceptible. Clearly, any trauma to the floor may result in trauma to the hypothalamus. Thankfully, most hypothalamic complications will be transient. Of those reported in 1995 by the author [27], all have resolved. The one case of amenorrhea that was reported in the original article resolved after 2 years and the case of loss of thirst after 12 months. All cases of diabetes insipidus improved after 2-14 days.

Avoidance

- In cases of acute hydrocephalus, where the floor has not had the opportunity to become transparently thin, ascertaining the safest area to place the stoma can be difficult. Penetrating the floor too anteriorly will likely damage the hypothalamus, while penetrating it too posteriorly may damage the basilar artery. In these circumstances, aggressive irrigation of the floor may sometimes reveal the thinnest area. Alternatively, if one draws an imaginary line between the infundibular recess and the mamillary bodies, making the ventriculostomy approximately between the anterior and middle thirds should diminish the likelihood of neurovascular damage (Fig. 6).

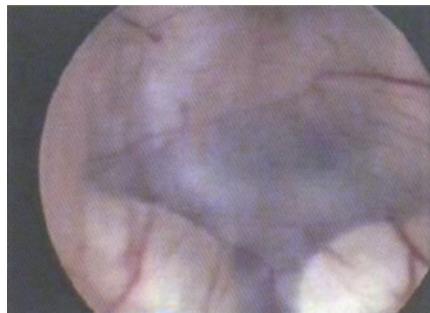


Fig. 6. Endoscopic view of the floor of the third ventricle showing the ideal location for creation of the stoma

- Blunt techniques to penetrate the floor are less often associated with damage to the basilar artery and its branches. However, when the floor is tough, blunt penetration may require excessive force and subsequent traction on the hypothalamus. A sharper technique may be more appropriate in this setting. The author would recommend the closed end of a pair of grabbing forceps followed by balloon dilatation (Fig. 1).
- Make the stoma exactly in the midline. A burr hole placed too laterally will result in the scope aiming to the contralateral side of the third ventricle.

Vascular Damage

Damage to the basilar artery or its branches is the most life-threatening complication when performing ETV. Certainly, the thought of this complication at the moment of penetration causes more anxiety than any other part of the operation. MRI studies have shown us that the location of the basilar artery bifurcation is quite variable. It is mostly just anterior to the mamillary bodies but can be in juxtaposition to the dorsum sellae or somewhere in between (Fig. 7). However, the perforators are consistently posterior to the bifurcation, on their way to supply the brainstem, and consequently any attempt to perforate the floor must be at least anterior to the bifurcation. When the floor is transparent, the safest area can be readily visualized. When the floor is opaque, puncturing the floor is a blind maneuver. Indeed, in reality all techniques used to penetrate the floor are blind maneuvers as the basilar artery cannot be seen until the floor is breached. More common than damage to the bifurcation itself is damage to the perforators (Fig. 8) [23, 25]. These can be injured when the floor is breached with the penetrating instrument but are also at risk when the initial stoma is enlarged. For example, if one uses the blunt end of a

pair of closed forceps and opens the forceps before retracting them into the third ventricle, devastating hemorrhage may result if a small branch of the basilar artery is caught and avulsed from its parent vessel. Similarly, passing a balloon catheter through the floor, expanding it, and pulling it back through the stoma before deflating it may cause avulsion of a perforating vessel. Different techniques have been proposed in an attempt to avoid these complications [6, 18, 24, 28, 33]. An instrument designed to elevate the floor before perforation is theoretically appealing, but the same movement to elevate the floor could also elevate an underlying vessel. The technique recommended by the author uses the endoscope itself to create the initial hole. The face of an endoscope, 4 mm in diameter, is far too large to pen-



Fig. 9. Angiogram of a child taken 7 days after a complicated ETV. The surgeon experienced torrential hemorrhage after creating the ventriculostomy and implicated the sharp edge of the scope as the causative factor

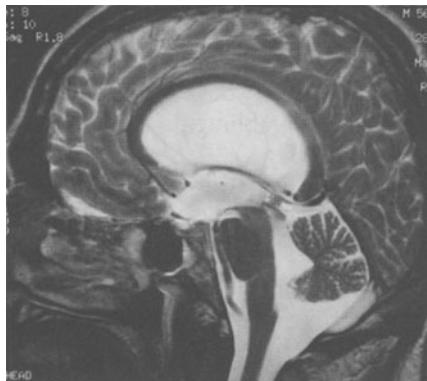


Fig. 7. This midsagittal MRI shows how close the basilar artery can be to the dorsum sellae. Performing an ETV would be relatively dangerous

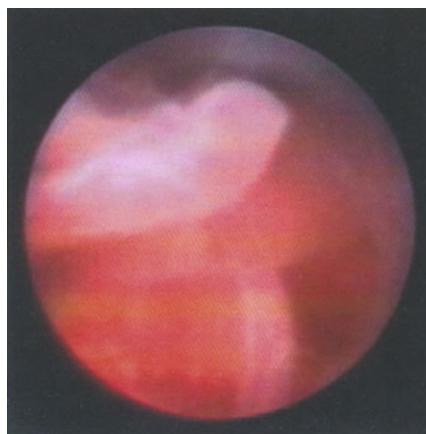


Fig. 8. View of the perforators coming off the back of the basilar complex. If they are damaged, severe neurological sequelae may result

etrate the basilar bifurcation or a perforating vessel. Furthermore, if one uses a 30-degree scope, the face has a leading edge which, when inserted with the leading edge anterior, will naturally push the basilar complex posteriorly, thereby not placing the perforating vessels under any tension. The obvious disadvantage of this technique is the force required to penetrate a thick floor. This added force may stretch the walls of the third ventricle and potentially cause more hypothalamic injury.

Judicious management of hemorrhage from the basilar complex may limit the adverse neurological sequelae of such a disastrous complication [1]. Maintaining access to the ventricle is paramount. Although the endoscope can be removed when visualization is obscured, the sheath should remain within the ventricle so that irrigation can continue until the bleeding stops. This may take up to 45 min. Any attempt to hasten the hemostatic process is usually unsuccessful. Once the bleeding has stopped, the sheath can be removed, an external ventricular drain left within the lateral ventricle, and the wound closed. The patient is then taken to the intensive care unit where the ICP can be monitored and CSF drained if necessary. An angiogram should be arranged when the patient becomes neurologically stable, and if a traumatic aneurysm is found it should be treated appropriately (Fig. 9) [14].

Avoidance

The author has performed over 350 third ventriculostomies using the same technique and has been

fortunate enough to have avoided any vascular complications. The following statements are guidelines based on discussion with colleagues who have had the misfortune to encounter neurovascular injury and who were kind and honest enough to share their experiences. Some of these thoughts have been documented in the literature [1, 16, 23, 25].

1. Choose your endoscope wisely. There are some endoscopic sheaths that have extremely sharp tips that could sever an artery if pushed against it firmly (see Fig. 3). The walls of the sheath need to be smooth.
2. Choose your perforating instrument wisely. Similarly, if you are using a technique that utilizes a smaller instrument passed down a working channel to make the initial hole, the tip of the instrument needs to be blunt. Examples of instruments that have perforated the arterial wall are a pair of grabbing forceps (closed), a 1-mm fiberoptic flexible scope, a Fogarty catheter with stylet, a laser fiber, and a monopolar coagulator.
3. If the floor is opaque and you are relatively inexperienced, it may be wise to abandon the procedure. If you decide to go ahead, then make the hole as anterior as possible, but posterior to the infundibular recess.
4. If you use the scope itself to breach the floor, it is better to use a 30-degree scope with the sloping face looking posteriorly. If the face is directly over the bifurcation, the advancing scope will push the basilar complex posteriorly, avoiding avulsion of the perforators.

Cranial Neuropathies

Damage to cranial nerves is a rare complication that can mostly be avoided by obeying a few simple rules. The cranial nerves most affected are the oculomotor [23] and the abducens. Any damage usually occurs when the floor is bulging downwards, placing the nerves on the stretch; when the floor is perforated, further stretching of the floor causes injury to an already compromised nerve. Diverging from the midline will also put the third cranial nerve at higher risk.

Avoidance

1. Keep to the midline. To achieve this, ensure the burr hole is not too lateral, and make an impres-

sion on the floor before perforating it so that you can pull the scope back slightly to visualize exactly where the stoma will be placed. Do not push the scope or perforating instrument too far below the floor, and do not push too vigorously on an already stretched floor.

2. Be cognizant of aberrant anatomy. The third cranial nerves can follow a course close to the midline on their way to the cavernous sinus.

Subdural Hygroma

This is another complication that is documented in the literature [9] but probably occurs more frequently than reported. The presumed pathophysiology is that CSF forces its way through the frontal tract and into the subdural space. It does so because the newly created “normal” pathways and the absorptive mechanisms need time to mature, so that CSF naturally tries to escape through the pathway of least resistance. Indeed, some of these patients have eventually required extracranial CSF diversion [9], implying that the absorptive mechanisms were always faulty.

Avoidance

It is difficult to identify the true pathogenesis of this condition, but as the author has not had this complication in the last 350 cases, it may be prudent to follow the same protocol:

1. The ventricle should be expanded before removing the sheath from the lateral ventricle.
2. The cortical hole should be plugged with a piece of Gelfoam(Upjohn, Kalamazoo).
3. Lumbar and ventricular drainage should be avoided in the postoperative period.

Others

Several other complications have been documented specifically after ETV. Thomson et al. reported three cases of hypertrophic calcification within the cerebral matter after ETV [26]. They postulated that this complication was iatrogenic from sealing the burr hole with bone dust at the conclusion of the procedure. It may have been from the scope carrying bone dust through the cerebrum.

Postoperative fever is quite common after ETV (see Chap. 25).

General Complications

Seizures

Seizures can occur after any procedure that requires a cortical incision. The incidence may be higher where bone dust is allowed to pollute the cortex. It is important to limit the size of the cortical incision and limit the amount of bone dust once the dura is opened. Patients are not routinely placed on anticonvulsants.

Infection

Any procedure that requires copious ventricular irrigation raises the risk of ventriculitis/meningitis. The author regularly uses prophylactic antibiotics for ETV. The simple act of irrigating the working channels before placing the scope within the ventricle may reduce the incidence of infection. Disposable fiberoptic scopes may further reduce the risk of infection, although this has not been substantiated in the literature. Patients with meningitis following ETV usually present with fever, headache, vomiting, and signs of intracranial hypertension within 2–7 days. The devastating sequel to the meningitis is probable shunt dependence.

Intracerebral Hemorrhage

The true incidence of this complication is probably higher than that documented. The size of the scope is such that hemorrhage is more likely to occur with this passing through the brain than after passage of a smaller-gauge brain needle. Fortunately, the cortical tract is in a relatively noneloquent area and most hemorrhages are asymptomatic. The problem is compounded with collapse of the ventricles after release of CSF.

Avoidance

1. The amount of CSF released with the initial ventricular tap should be limited.
2. The ventricle should be refilled with lactated Ringer's solution at the completion of the operation before the cortical hole is plugged with Gelfoam.
3. The tract can be inspected when withdrawing the scope from the ventricle. Any obvious sites of hemorrhage can be stopped with either coagulation or simple tamponade with the scope itself.
4. *Never* use the scope to find the ventricle. It should only be introduced when the ventricle has been

found with either a stereotactic probe, a ventricular catheter, or a brain needle. Even then, the scope should be marked at a point 5–6 cm from the tip so that it is never blindly introduced further than the depth of the ventricle.

CSF Leak

This is one of the more common and potentially damaging complications. The explanation is simple. Noncommunicating hydrocephalus can give rise to secondary communicating hydrocephalus and, conversely, obstructive hydrocephalus may occur simultaneously with communicating hydrocephalus. Thus, a patient who has an ETV for apparent non-communicating hydrocephalus may have associated communicating hydrocephalus and will therefore fail to absorb the additional fluid load, at least not in the immediate short term. This theory accounts for why some patients need several days or even weeks to improve clinically and radiologically after ETV. CSF within the ventricular and subarachnoid spaces is under pressure in an attempt to create a gradient resulting in bulk flow across the villi into the sagittal sinus. It is not uncommon for patients after ETV to have significant subgaleal CSF collections over the burr hole. This will progress to CSF leak if the wound breaks down or if the absorption from the arachnoid villi continues to be inadequate. External ventricular drainage or lumbar tappings (see Chap. 25) have been advocated by some to address this immediate fluid imbalance. However, draining CSF externally discourages the re-establishment of normal CSF flow, possibly increasing the chance of the stoma closing, which in turn may increase the number of failures. This phenomenon has been well documented by those neurosurgeons who have monitored the CSF pressure in the postoperative period and who have resisted draining off any fluid. It can persist for many days.

Avoidance

1. The author uses Gelfoam (Upjohn, Kalamazoo) to plug the cortical tract. This may help prevent subdural hygromata and CSF leak. The use of bone wax to plug the burr hole appears attractive but probably reduces the healing capacity in the long term and may increase the risk of infection.
2. Water-tight wound closure is imperative.
3. Intermittent lumbar punctures in the immediate postoperative period may reduce the incidence of CSF leak but may also increase the failure rate.

4. The patient should be kept as upright as possible in the postoperative period. This will serve to reduce the CSF pressure on the wound and decrease the sagittal sinus pressure, thereby augmenting the CSF-to-sinus gradient.

Postoperative Neurological Deficit

The two most common causes of neurological deficit after ETV are damage when tapping the ventricle and persevering with the procedure despite poor visualization. The ventricle should never be tapped with the sheath of the scope or a peel-away sheath. Both these instruments are significantly thicker than a brain needle and may cause substantial damage if passed into structures other than the ventricle. The best technique for gaining access to the ventricle is to make the initial trajectory with a thin needle; once access has been achieved, the scope can be passed along the tract under direct visualization. Once the scope is in the ventricle, direct visualization makes the possibility of damaging surrounding neural structures extremely unlikely. However, if one persists in spite of poor visualization, neural injury can happen with very little effort. Nonspecific neurological sequelae after ETV such as confusion, drowsiness, and irritability can be secondary to many events. Some potential steps in the operation where general neurological injury may occur are: irrigating within the ventricles with either cold or nonisotonic solution, stretching of the hypothalamus with third ventricular manipulation, rapid changes in intracranial pressure with irrigation and subsequent brain shifts, subarachnoid hemorrhage

either with the cortical incision or creation of the stoma, and vasospasm secondary to manipulation of the vessels within the interpeduncular cistern.

Avoidance

1. Never tap the ventricle with the scope or the scope sheath.
2. Always check the scope or the sheath for centimeter markings so that it is never passed more than 5 cm below the cortical surface.
3. Once good visualization is obscured with hemorrhage, either clear it with irrigation or, failing this, abandon the procedure. Do *not* persevere with ventricular navigation by feel. There is virtually no tactile feedback in endoscopy.

Subdural Hematoma

Subdural hematoma is a not uncommon complication of any intracranial procedure that causes a significant reduction to intracranial volume. Removing a large tumor, for example, can cause the brain to collapse, with subsequent unilateral, contralateral, or bilateral acute or chronic subdural hematomata. Similarly, permitting excessive loss of CSF during the operation may cause collapse of the cortical mantle and formation of acute subdural hematoma. Almost invariably the collections are small and asymptomatic (Fig. 10), but occasionally they can be massive with serious clinical consequences [17]. Clearly, the solution is to try to keep the ventricles from collapsing.

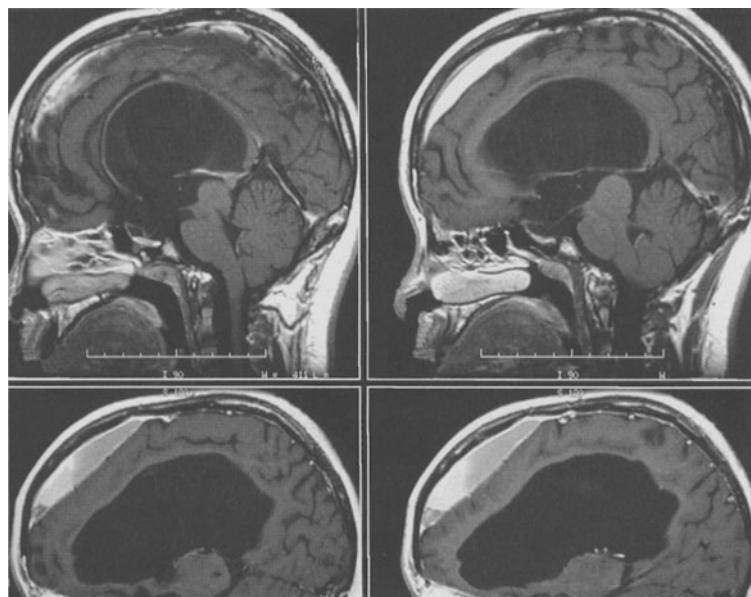


Fig. 10. Asymptomatic subdural hematoma seen 3 months after an ETV. This resolved spontaneously

Avoidance

1. After tapping the ventricle with the thin brain needle, ensure the cortical incision is big enough to admit the endoscope without causing displacement of the underlying brain.
2. Do not allow CSF to escape in large quantities.
3. Refill the ventricles when CSF does escape.
4. Coagulate all cortical bleeding vessels before closing.



Fig. 11. Although this MRI shows clear triventricular ventriculomegaly secondary to aqueduct stenosis, the floor of the third ventricle is extraordinarily thick and hence this patient should not be considered a candidate for ETV

Summary

Surgical Training

The ideal training platform is where the resident learns from the master. This is happening more and more, but there are still a significant number of neurosurgeons who have never been exposed to neuroendoscopy. Unfortunately, these neurosurgeons who did not have the luxury of training in a unit that offered specialized training in endoscopy admit that ETV should be a part of their surgical armamentarium. These practitioners have two options. They can either take time off to visit and learn from a center that does practice endoscopy, or they can enroll in a course. The course should offer teaching in the anatomy of the ventricular system, patient selection, surgical technique, complication avoidance, and postoperative management. It should have a hands-on practical component using cadavers that have been specifically prepared for intraventricular surgery. The course faculty should ideally have extensive experience in endoscopy, and the course should have accreditation for continuing education. Subsequently, the novice neurosurgeon would be well served to have an assistant for his first case who has had some experience with this procedure.

Patient Selection

All patients with noncommunicating hydrocephalus are candidates for ETV. However, to reduce the rate of complications, the ideal candidate would have large ventricles, a third ventricle wider than the diameter of the scope/sheath, an attenuated third ventricular floor, a capacious interpeduncular cistern, and no aberrant anatomy [21]. Of course, with experience, the selection criteria can be liberalized without jeopardizing the patients. The best way to assess

these anatomical prerequisites is with MRI (Fig. 11). The etiology of the hydrocephalus may also be a significant prognosticator [3], e.g., a patient with secondary aqueduct stenosis should do better than one with postmeningitic hydrocephalus.

Postoperative Management

The patient is recovered in the ward and encouraged to mobilize as soon as possible. The author would discourage the use of external ventricular drainage for any period of time or intermittent lumbar punctures. There is no evidence to suggest whether this is a wise move or not. Parents, patients, and caregivers should be warned that all symptoms may not resolve rapidly. Indeed, if they are improved but not absolutely normal, time should be given for possible complete resolution. Serial CT scans may be helpful if they show change, but it should be noted that persistence of ventriculomegaly is usual. Finally, this operation is not a cure. Patients need regular surveillance, like those with shunts, as long-term failures have been known to occur [11, 15].

References

1. Abtin K, Thompson BG, Walker ML: Basilar artery perforation as a complication of endoscopic third ventriculostomy. *Pediatr Neurosurg* 28:35-41, 1998
2. Anand B, Madhusudan Reddy KR, et al: Intraoperative bradycardia and post-operative hyperkalemia in patients undergoing endoscopic third ventriculostomy. *Minim Invasive Neurosurg* 45:154-157, 2002
3. Beems T, Grotenhuis JA: Is the success rate of endoscopic third ventriculostomy age-dependent? An analysis of the

- results of endoscopic third ventriculostomy in young children. *Child's Nerv Syst* 18:605-608, 2002
4. Buxton N, Punt J: Cerebral infarction after neuroendoscopic third ventriculostomy: case report. *Neurosurgery* 46:999-1002, 2000
 5. Buxton N, Vloeberghs M, Punt J: Liliequist's membrane in minimally invasive endoscopic neurosurgery. *Clin Anat* 11:187-190, 1998
 6. Decq P, Le Guerinel C, Brugieres P, et al: A new device for endoscopic third ventriculostomy. *J Neurosurg* 93:509-512, 2000
 7. El-Dawlatly AA, Murshid WR, Elshimy A, et al: The incidence of bradycardia during endoscope third ventriculostomy. *Anesth Analg* 91:1142-1144, 2000
 8. Enya S, Masuda Y, Terui K: [Respiratory arrest after a ventriculoscopic surgery in infants: two case reports]. *Masui* 46:416-420, 1997
 9. Freudenstein D, Wagner A, Ernemann U, et al: Subdural hygroma as a complication of endoscopic neurosurgery. *Neurol Med Chir* 42:554-559, 2002
 10. Fukuhara T, Vorster SJ, Luciano MG: Risk factors for failure of endoscopic third ventriculostomy for obstructive hydrocephalus. *Neurosurgery* 46:1100-1111, 2000
 11. Hader WJ, Drake J, Cochrane D, et al: Death after late failure of third ventriculostomy in children. Report of three cases. *J Neurosurg* 97:211-215, 2002
 12. Handler MH, Abbott R, Lee M: A near-fatal complication of endoscopic third ventriculostomy: case report. *Neurosurgery* 35:525-528, 1994
 13. Hopf NJ, Grunert P, Fries G, et al: Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 44:795-806, 1999
 14. Horowitz M, Albright AL, Jungreis C, et al: Endovascular management of a basilar artery false aneurysm secondary to endoscopic third ventriculostomy: case report. *Neurosurgery* 49: 1464-1465, 2001
 15. Jones R, Kwok BCT, Stening WA: Endoscopic III ventriculostomy. How long does it last? *Child's Nerv Syst* 12:364-365, 1996
 16. McLaughlin MR, Wahlig JB, Kaufmann AM: Traumatic basilar aneurysm after endoscopic third ventriculostomy: case report. *Neurosurgery* 41:1400-1404, 1997
 17. Moharty A, Anand B, Reddy MS, et al: Contralateral massive acute subdural collection after endoscopic third ventriculostomy – a case report. *Minim Invasive Neurosurg* 40:59-61, 1997
 18. Paladino J, Rotim K, Stimac D, et al: Endoscopic third ventriculostomy with ultrasonic contact microprobe. *Minim Invasive Neurosurg* 43:132-134, 2000
 19. Pierre-Kahn A, Renier D, Bombois B, et al: Role of ventriculocisternostomy in the treatment of non-communicating hydrocephalus. *Neurochirurgie* 21:557-569, 1975
 20. Rieger A, Rainov NG, Sanchis L, et al: Ultrasound-guided endoscopic fenestration of the third ventricular floor for non-communicating hydrocephalus. *Minim Invasive Neurosurg* 39: 17-20, 1996
 21. Rohde V, Gilsbach JM: Anomalies and variants of the endoscopic anatomy for third ventriculostomy. *Minim Invasive Neurosurg* 43:111-117, 2000
 22. Schmidt RH: Use of a microvascular Doppler probe to avoid basilar artery injury during endoscopic third ventriculostomy. *J Neurosurg* 90:156-159, 1999
 23. Schroeder HWS, Niendorf WR, Gaab MR: Complications of endoscopic third ventriculostomy. *J Neurosurg* 96:1032-1040, 2002
 24. Schroeder HWS, Wagner W, Tschiutschke W, et al: Frameless neuronavigation in intracranial endoscopic neurosurgery. *J Neurosurg* 94:72-79, 2001
 25. Schroeder HWS, Warzok RW, Assaf JA, et al: Fatal subarachnoid hemorrhage after endoscopic third ventriculostomy. Case report. *J Neurosurg* 90: 153-155, 1999
 26. Thomson S, Tyahi A, Chumas P: Intracranial hypertrophic calcification complicating neuroendoscopy; report of 3 cases. *J Neurosurg* 98: 186-189, 2003
 27. Teo C: Third ventriculostomy in the treatment of hydrocephalus: Experience with more than 120 cases. In: Hellwig D, Bauer BL (eds) Minimally invasive techniques in neurosurgery. Springer, Berlin Heidelberg, pp 73-76, 1998
 28. Teo C, Jones R: Management of hydrocephalus by third ventriculostomy in the patient with myelomeningocele. *Pediatr Neurosurg* 25:57-108, 1996
 29. Teo C, Pihoker K, Aureli S, et al: Anatomical and physiological considerations of third ventriculostomy (abstract). *Child's Nerv Syst* 10:481, 1994
 30. Teo C, Rahman S, Boop FA, et al: Complications of endoscopic neurosurgery. *Child's Nerv Syst* 12:248-253, 1996
 31. Vaicys C, Fried A: Transient hyponatremia complicated by seizures after endoscopic third ventriculostomy. *Minim Invasive Neurosurg* 43: 190-191, 2000
 32. Vloeberghs M, Cartmill M: Improved safety of neuroendoscopic third ventriculostomy by using an operative Doppler ultrasound probe. Technical note. *Neurosurg Focus* 6(4): Article 13, 1999
 33. Wellons JC, Bagley CA, George TM: A simple and safe technique for endoscopic third ventriculocisternostomy. *Pediatr Neurosurg* 30: 219-223, 1999

Repeat Third Ventriculostomy

VITALY SIOMIN, SHLOMI CONSTANTINI

Introduction

The methods of treating hydrocephalus underwent a dramatic evolution in the last few decades. The initial enthusiasm of the neurosurgical community after years of using shunts as the *only* treatment of *all kinds* of hydrocephalus faded despite the fact that dozens of studies have been conducted, and hundreds of significant and seemingly panacean solutions were proposed to improve shunt technology. The reality remains that the overall survival of a shunt and the complication rate have changed only slightly in the last 10-20 years. It seems natural that the alternatives to placement of hardware have been long looked for, and the advent of modern neuroendoscopy in the mid-1980s opened a new page in the history of the war against hydrocephalus, which eventually turned into a war against shunts as well. Endoscopic third ventriculostomies (ETV) have instantly become very popular. ETV is a relatively simple technique, establishes a "natural" pathway for CSF flow, and may help to avoid placement of and reliance upon hardware. ETV is generally considered a safe and effective alternative for patients with triventricular hydrocephalus. If successful, it might eliminate the need for a shunt in 70%-90% of patients in this group [2, 4-13, 15, 17, 18, 20, 23, 27].

While primary ETV has been proven safe and effective, repeat ETV procedures have not been thoroughly studied and analyzed. Some authors have described their experience with repeat ETV [3, 5]. However, if the primary third ventriculostomy fails, most surgeons tend to insert a ventriculoperitoneal shunt (VPS) rather than attempt an additional endoscopic procedure. The purpose of this chapter is to summarize experience and try to define indications for repeat ETV.

Types of ETV Failures

Although ETV is an attractive procedure, in at least 20% of patients who undergo ETV it will fail in the

first year following surgery. Failures of treatment by ETV fall into one of two categories: *early*, and *delayed* failures (Table 1):

1. Early failure is failure recognized in the immediate postoperative period. The primary procedure does not lead to any significant period of clinical and/or radiological improvement. In this group, failure may be attributed to a technical problem during surgery, obliteration of the orifice during the immediate postoperative period, or because the fluid is not absorbed [5].
2. Delayed failure is seen in patients who benefited from a primary ETV for varying periods of time, with their hydrocephalus recurring only after an initial period of success. This period may, actually, last for a few years. However, most of the delayed failures happen within the first 2 years after the procedure. In most such cases the obliteration of the stoma by scar tissue is the most frequent cause of failure. Based on the life-table analysis of patients affected by hydrocephalus and aqueductal stenosis, it was shown that failures of ETV do not occur beyond the 6th year with follow-up periods of at least 10 years [5, 25]. In other words, if the patient remains asymptomatic in the first 5 years after ETV, he/she is probably cured of and will not require surgery for triventricular hydrocephalus.

Table 1. Types of ETV failure

Early failures	Delayed failures
Technical problem e.g., bleeding, obstruction of the orifice by clot, incompletely penetrated membrane	Delayed scarring
Rapid scarring Impaired absorption	

Table 2. Intraoperative findings

	<i>n</i>	%
Occlusion by scar	10	50
Virginal floor	5	25
Pinhole orifice	3	15
Incompletely penetrated membrane	1	5
Blood clot	1	5
Total	20	100

Intraoperative Findings: Causes of Closure of the Third Ventriculostomy

In the series of 20 patients reported by us previously [24], 9 patients (45%) had a hole obliterated by scar tissue. Five patients (25%) had a virginal floor of the third ventricle. A small, “pin hole” opening was found in three cases (15%). Blood clots and an incompletely penetrated membrane were found in one case (5%) each (Table 2).

In the first three groups of patients (90% of all patients) the obstruction or clinically significant narrowing of the orifice was related to development of scar tissue. Radiographically, obliteration of the orifice is demonstrated by absence of flow void phenomenon on MRI, increase in ventricular size, particularly of the third ventricle, and down-bulging of the floor of the third ventricle.

Comparison of Primary vs Repeat ETV

Safety

It appears that repeat ETV is at least as safe as the first ETV. In the series [24] the mortality rate was zero. The complication rate of 5% is similar to that reported elsewhere for primary ETV, and compares favorably to cumulative complication rates for shunting. It is worth mentioning that we did not observe such complications as significant bleeding or infection, both of which occurred after the first ETV in one case each. Nor did we observe most of the other complications described in the literature [1, 14, 15, 19, 21, 22, 26]. The surgeons did not observe any additional intraoperative difficulties, and felt that the repeat procedures were technically similar to the primary surgeries.

Outcome

A successful outcome following an ETV should be defined as resolution of symptoms caused by increased intracranial pressure (ICP) secondary to CSF flow obstruction [16]. On the other hand, the surgeon should view both primary ETV and reoperation for obstruction of the ETV as a process of weaning the patient from shunt. The outcomes of the primary ETV and repeat ETV were similar in our study: 70% and 65% respectively, meaning that the successfully treated patients did not require shunt and the symptoms of increased ICP resolved. A decrease in ventricular size should not be considered a final goal, because in the majority of patients, especially with long-standing triventricular hydrocephalus, the change in the ventricular size is hard to evaluate, unless volumetric techniques are applied. When comparing the MR images of the 13 patients successfully treated with the repeat ETV to those of the 7 patients in whom it failed, it was noticed that none of the “traditional” parameters (i.e., presence of flow void on MRI, decrease in ventricular size) per se are reliable in assessment of the outcome. However, the presence of both flow void phenomenon and decrease in ventricular size correlate well with success.

Patient Selection

As with any surgical procedure, an appropriate selection of patients is crucial for successful outcome of repeat ETV. The original hypothesis was that an ideal candidate for repeat ETV would be (1) an adult patient (2) with an obstructive hydrocephalus (3) who has benefited from the first ETV for a significant period of time (i.e., at least a month).

Contrary to our expectations, our data failed to prove the original hypothesis about the importance of age and interval between surgeries [24]. However, we believe that the significance of these factors should be reevaluated in further larger studies.

The selection of patients for a repeat ETV should be based on essentially the same criteria that are used to recommend a primary ETV. In addition, there are two groups of primary ETV alumni that appear to be likely candidates for successful repeat ETV:

1. Patients for whom the first ETV was a success, as they are more likely to have a patent absorption system with the potential to successfully absorb CSF.
2. Patients for whom the first ETV was a failure, but the surgeon feels some “guilt” that either the procedure was not technically successful, or that bleeding or debris may be blocking the orifice. In such patients repeat ETV might also be successful.

In all these cases a repeat ETV should be attempted, as the potential benefits of a successful ETV that avoids the problems associated with permanent shunting clearly outweigh the risks of repeated surgery. On the other hand, the authors have encountered a subgroup of patients who present with signs of increased ICP after having been asymptomatic for a few years after successful ETV. MRI demonstrates patent ventriculostomy with generous flow void. The authors' recommendation would be that such patients should be treated with shunt, as presence of demonstrable flow void in a symptomatic patient is very suggestive of impaired absorption. The cause of such a delayed failure is hard to understand. A history of meningitis or hemorrhage should be looked for, but our feeling is that in most cases the pathogenesis of delayed failure with patent ventriculostomy remains unclear. Hypothetically, gradual fibrotic changes in the arachnoid granulations or their occlusion by excessive CSF protein or debris might be involved.

Following Surgery: The Definition of Failure

It is expected that about one-third of the patients may experience immediate relief of symptoms and will not require a shunt. The other 70% of patients may remain symptomatic. In our series, nearly half of the symptomatic patients were immediately shunted after the repeat procedure. The other half were treated with temporary CSF diversion. Eighty-five percent of them remained shunt-free. Thus, *temporary CSF diversion* appears to play a key role in the postoperative care of patients after repeat ETV. Since almost half the patients with successful outcome were managed with either external ventricular drain (EVD) or continuous lumbar drain (CLD), or both, and needed time until absorption normalized, we believe in a *patient approach* to such patients. If the neurosurgeon faces a failure, a few things should be attempted before making quick and radical decisions. If the patient's preoperative condition is not stable, the surgeon may choose to leave a tunneled EVD at the end of surgery, or an externalized VPS. However, the most "physiological" way of temporary CSF diversion perhaps would be placement of a *lumbar drain*, as it helps not only to remove the excessive CSF, but also challenge the stoma from below, by encouraging CSF flow through it. It should be noted that the presence of a patent ventriculostomy eliminates the risk of herniation that is traditionally thought to be associated with spinal tap in patients with symptomatic hydrocephalus. Placement of an intraparenchymatous ICP probe might also be very helpful, as it provides a valuable information regard-

ing ICP either while the CSF is drained, or after the drainage is removed.

The treatment is considered a failure only if the patient remains symptomatic after a few attempts at CSF drainage, preferably through the CLD.

Conclusion

1. Failure of an ETV is in most cases due to obstruction of the orifice.
2. Repeat ETV is as safe as the primary ETV.
3. Repeat ETV in selected patients is as effective as the primary ETV and may be preferable to placement of a shunt.
4. The treatment should be considered a failure only if the patient remains symptomatic after a few attempts at CSF drainage, preferably through the lumbar drain.

References

1. Abtin K, Thompson BG, Walker ML: Basilar artery perforation as a complication of endoscopic third ventriculostomy. *Pediatr Neurosurg* 28:35-41, 1998
2. Brockmeyer D, Abtin K, Carey L, et al: Endoscopic third ventriculostomy: an outcome analysis. *Pediatr Neurosurg* 28:236-240, 1998
3. Buxton N, Vloeberghs M, Punt J: Liliequist's membrane in minimally invasive endoscopic neurosurgery. *Clin Anat* 11:187-190, 1998
4. Cinalli G: Alternatives to shunting. *Child's Nerv Syst* 15:718-731, 1999
5. Cinalli G, Sainte-Rose C, Chumas P, et al: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90:448-454, 1999
6. Cinalli G, Sainte-Rose C, Simon I, et al: Sylvian aqueduct syndrome and global rostral midbrain dysfunction associated with shunt malfunction. *J Neurosurg* 90:227-236, 1999
7. Cinalli G, Salazar C, Mallucci C, et al: The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43:1323-7; discussion 1327-1329, 1998
8. Cohen AR: Images in clinical medicine. Endoscopic laser third ventriculostomy. *N Engl J Med* 328:552, 1993
9. Ellenbogen RG, Moores LE: Endoscopic management of a pineal and suprasellar germinoma with associated hydrocephalus: technical case report. *Minim Invasive Neurosurg* 40:13-15; discussion 16, 1997
10. Ferrer E, Santamarta D, Garcia-Fructuoso G, et al: Neuroendoscopic management of pineal region tumours. *Acta Neurochir* 139:12-20, 1997
11. Gaab MR, Schroeder HW: Neuroendoscopic approach to intraventricular lesions. *J Neurosurg* 88:496-505, 1998
12. Gangemi M, Maiuri F, Donati P, et al: Neuroendoscopy. Personal experience, indications and limits. *J Neurosurg Sci* 42:1-10, 1998

13. Grant JA, McLone DG: Third ventriculostomy: a review. *Surg Neurol* 47:210-212, 1997
14. Handler MH, Abbott R, Lee M: A near-fatal complication of endoscopic third ventriculostomy: case report. *Neurosurgery* 35:525-7; discussion 527-528, 1994
15. Hopf NJ, Grunert P, Fries G, et al: Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 44:795-804; discussion 804-806, 1999
16. Jimenez D: Third ventriculostomy. In: Jimenez D (ed) Intracranial endoscopic neurosurgery. American Association of Neurological Surgeons, 108, 1998
17. Jones RF, Kwok BC, Stening WA, et al: The current status of endoscopic third ventriculostomy in the management of non-communicating hydrocephalus. *Minim Invasive Neurosurg* 37:28-36, 1994
18. Jones RF, Stening WA, Brydon M: Endoscopic third ventriculostomy. *Neurosurgery* 26:86-91; discussion 91-92, 1990
19. Kehler U, Gliemroth J, Knopp U, et al: How to perforate safely a resistant floor of the 3rd ventricle? Technical note. *Minim Invasive Neurosurg* 41:198-9, 1998
20. Kobayashi N, Kamikawa S, Miyake S, et al: [Treatment of hydrocephalus without shunt placement: third ventriculostomy]. *No Shinkei Geka* 25:35-40, 1997
21. McLaughlin MR, Wahlig JB, Kaufmann AM, et al: Traumatic basilar aneurysm after endoscopic third ventriculostomy: case report. *Neurosurgery* 41:1400-1403; discussion 1403-1404, 1997
22. Mohanty A, Anandh B, Reddy MS, et al: Contralateral massive acute subdural collection after endoscopic third ventriculostomy – a case report. *Minim Invasive Neurosurg* 40:59-61, 1997
23. Robinson S, Cohen AR: The role of neuroendoscopy in the treatment of pineal region tumors. *Surg Neurol* 48:360-365; discussion 365-367, 1997
24. Siomin V, Cinalli G, Grotenhuis A, et al: Endoscopic third ventriculostomy in patients with cerebrospinal fluid infection and/or hemorrhage. *J Neurosurg* 97:519-524, 2000
25. Tuli S, Alshali E, Drake JM: Third ventriculostomy versus cerebrospinal shunt as a first procedure in pediatric hydrocephalus. *Pediatr Neurosurg* 30:11-15, 1999
26. Vandertop PW: Traumatic basilar aneurysm after endoscopic third ventriculostomy: case report. *Neurosurgery* 43:647-648, 1998
27. Vries JK: An endoscopic technique for third ventriculostomy. *Surg Neurol* 9:165-168, 1978

Economic Analysis of Endoscopic Third Ventriculostomy and Ventricular Shunts

HUGH GARTON¹, PAUL STEINBOK²

Introduction

Endoscopic third ventriculostomy (ETV) is the principal alternative therapy to shunt placement. Fueled by the persistent complications associated with CSF shunt placement and aided by the development of new instruments and better optical and video systems, ETV is becoming performed routinely in the management of hydrocephalus. However, not all patients with hydrocephalus are candidates for this procedure (see Chap. 25). As ETV has become more routinely performed, attempts to determine an optimal strategy for integration of this new technology into the management of hydrocephalus have focused primarily on identifying the subpopulation of patients in whom the procedure is “most effective” in eliminating the need for shunt placement. In selecting patients for ETV on clinical grounds, one weighs the obvious benefits of remaining or becoming shunt-free against the added risk of the procedure itself and, if it is unsuccessful, the added inconvenience and risk of a second surgical procedure for placement of a shunt. A moderately high failure rate is probably acceptable to gain the benefits of shunt independence, but if the chance of success is very low, subjecting the patient to the additional procedure of ETV is unwarranted. In these terms, the procedural success rate at which ETV is preferred as to shunt treatment of hydrocephalus has not yet been defined. Economic evaluations can contribute to this debate, providing evidence of the economic effects of different success rates. As one respected author in the field has commented: “[Ventriculostomy’s] ultimate utility in the armamentarium of the pediatric neurosurgeon will be determined to the point that it represents a more effective and cost efficient means of managing hydrocephalus” [34].

In this chapter, a brief overview of the basic principles of economic analysis is provided by way of back-

ground, followed by a detailed review of the literature as it relates to economic analysis of shunts and ETV. Finally, a cost-effectiveness study done by the authors to compare ETV and shunts is detailed.

Techniques of Economic Analysis

Economic assessment is one type of tool that health care providers use to determine where and how the available resources for providing care are to be spent. Economic questions are always comparative. In order to be truly valid, economic evaluations assume that the tests or therapies under consideration have undergone an assessment of how well they work under ideal and real world conditions, and there is the possibility of distribution or dissemination of the technique or therapy.

Underlying an economic assessment is the assumption that there are resource limitations in providing health care generally, and that understanding the relative costs and benefits of different health care strategies is central to making informed choices about resource allocation. Drummond and colleagues have defined economic evaluation as “the comparative analysis of alternative courses of action in terms of both their costs and consequences.” They state: “the basic tasks of any economic evaluation are to identify, measure, value and compare the costs and consequences of the alternatives being considered” [14]. A corollary to the general idea of resource limitations is that any plan, even one to which there do not seem to be alternatives, has a specific opportunity cost: that is, the value of the item or result given up to achieve the specified plan. Thus, prior to committing resources to an endeavor, one must identify the relevant alternatives and determine whose vantage point is to be used in the assessment: the patient’s, the health care

¹Department of Neurosurgery, University of Michigan, Ann Arbor, Michigan, USA; ²Division of Pediatric Neurosurgery, British Columbia’s Children’s Hospital, and Division of Neurosurgery, Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada

provider's, the health care network, the third party payer, or the national health system's. Each of these groups may consider costs differently, attach a different value to the outcome achieved, and is likely to consider a progressively broader array of competing alternatives [15].

The specific manner and extent to which costs and consequences are measured separates the four basic types of economic analysis common in the health care setting. Readers are cautioned that these terms are frequently used imprecisely in the medical literature, and to assess the methods of an analysis rather than its label.

Cost Minimization

When the effects of competing therapies are felt to be equivalent in both quality and quantity, it is reasonable to compare directly the differing costs of two therapies while assuming equivalent outcome. As an example, let us assume that it could be shown that the complication and reinfection rates for children with shunt infections were the same whether they were managed as outpatients with home nursing or as inpatients on a hospital ward. The common unit of outcome measure would be the number of shunt infections treated, and the results of the assessment would determine the lower cost alternative. The comparison would be made between the costs of hospitalization for treatment versus those of providing home nursing, drug delivery, and travel for follow-up appointments, for example. This type of cost-minimization analysis must be scrutinized for the level of proof of equivalence in outcomes for the compared therapies. In the neurosurgical literature few such comparisons exist.

Cost Effectiveness

When the effects of competing therapies can be compared on a common quality of outcome but the quantity is likely to differ, the question being asked is what is the change in cost for the extra quantity of outcome achieved. The common quality of outcome might be years of life gained, when comparing two chemotherapy protocols, or number of diagnoses made, when comparing diagnostic strategies for identifying hydrocephalus among macrocephalic children. In cost-effectiveness analysis, a more costly therapy may be preferred if it produces more total life-years gained or more diagnoses made, depending on the available resources. By comparing the cost-to-effect ratios for the different therapies, one

can calculate not only the absolute difference in cost versus effect, but also the incremental cost to the more effective strategy, assuming it is more costly also. The disadvantage of this type of analysis is that many comparisons do not lend themselves to similar outcome measures. This would be the case, for example, if one tried to determine whether money is to be spent to provide a multidisciplinary care clinic for children with spina bifida, or to provide prenatal care for indigent pregnant mothers. To assess outcome for the spina bifida clinic, one might follow the preservation of function over a several-year period, as defined perhaps by a measure such as the Functional Independence Measure for Children, while for prenatal care, the numbers of premature births, birthweights, and perinatal complications are the typical measures of interest.

Similarly, when a therapy produces different types of outcomes that need to be considered, a cost-effectiveness analysis offers no ability to combine these. This applies particularly to the question of ETV compared to shunt treatment of hydrocephalus. The main promise of ETV – no reoperation for shunt failure – and the main risk – increased chance of perioperative complications – cannot readily be considered together without conversion to some other common unit of measure.

Cost Benefit

To get around the problem of differing qualities and quantities of outcome, an alternative common ground must be found for comparison. In a cost-benefit analysis both costs and effects are measured in monetary units. Traditional effect measures such as life-years are converted to a dollar value by using average yearly earned income, for example. A variety of simultaneous effects of a therapy can be considered, as long as each can be converted into dollar units. The costs incurred are then subtracted from the value of the benefits achieved to derive a net benefit or loss for each therapeutic option. Both a relative and absolute measure of benefit can be derived. The methods of valuation for outcome events remain controversial and for neurosurgical diagnoses such analyses are rare.

Cost Utility

When it is not possible or desirable to reduce outcomes to their dollar value, but different qualities and quantities of outcomes must still be considered, a cost-utility analysis may be performed. The familiar

Table 1. Types of economic assessment

	Outcome type	Outcome quantity	Outcomes converted to currency	Patient preference for outcome states known
Cost minimization	Same	Same	Not necessary	Not necessary
Cost effectiveness	Same	Different	Not necessary	Not necessary
Cost benefit	Different or multiple	Different	Required	Not necessary
Cost utility	Different or multiple	Different	Not necessary	Required

QALY, or quality-adjusted life-year, is a measure of utility. Done properly, these analyses compare disparate outcomes by multiplying the length of time spent in a particular state by a factor marking the patient's perception of the quality of that time, to produce a quality-adjusted quantitative measure. A cost per additional QALY can then be calculated. Methodologies for eliciting from patients what quality they assign to particular health states are well established, and for some areas of disability, health utility values have been described. Measures such as the Health Utility Index, Quality of Well Being scale, and Euro-Qol are all examples [14]. However, for hydrocephalus in children there is little previous work to act as a guide.

Summarizing then, the type of outcome assessment that should be performed is mostly dependent on the outcome measure being used to compare different therapies. The more similar the outcome, the more straightforward the assessment, but the more limited the comparison with other, different interventions (Table 1).

included in the analysis depends on the analytic perspective taken by the reviewer. A third party payer such as an insurance company will be most concerned with the direct costs and will probably consider indirect costs to be extraneous and not relevant to choice between therapies. Patients would be more likely to find an analysis compelling when it factors in their out-of-pocket expenses for travel and lost income from work missed. Effects on other sectors such as special education costs and disability payments are of particular interest to governmental agencies or, in some cases, employers paying health care premiums for employees.

Once a perspective for the assessment has been determined, the resources that a health care program uses in terms of hospitalized days, provider use, antibiotic and other consumable supplies can be identified, using the perspective as a guide against which potentially relevant items are considered. Next, a cost must be assigned to the resources used. "Cost" is not synonymous with "price". "Cost" refers to the value of items forgone to achieve a particular goal. "Price" is a dollar quantity surrendered to obtain an item from another supplier. While prices often reflect costs, they can be artificially inflated or subsidized. In other situations, the lack of a price might lead one to fail to consider a true cost. For example, donated clinic space may have no price, but has a clear cost in lack of availability of that space for other purposes. The perspective of the analysis and the relative importance of the item help determine when a price can be accepted as a cost. From the perspective of a hospital providing care, the price a supplier charges accurately reflects the hospital's cost, but the fee it charges for its bed use may not. The need to adjust prices to reflect true costs is variable in an analysis. If the resource used between the compared programs is similar then there is little need to adjust prices as they will have a similar effect on both programs.

As is true with outcomes assessment, a decision must be made as to how long the costs are to be tracked into the future. This is particularly important for therapies where there is a trade-off for upfront costs versus long-term benefits. For ETV, the elimi-

Prices, Costs, Perspectives

Costs incurred in the course of a health care program can be broadly divided into three areas. Direct health care costs are the physician and hospital fees and cost for consumed goods and supplies. Indirect costs include those costs borne either by the patient and family, or in some cases by other economic sectors. Readers are again cautioned that the terms "direct" and "indirect" change usage and meaning in different contexts. In some cases, "indirect costs" are those incurred by an organization for activities not directly responsible for patient services, such as housekeeping or administration. However, in the present discussion indirect costs are defined as patient-related costs, excluding hospital or physician fees. These indirect costs include things such as transportation costs, cost for providing care for siblings during the visit, and lost work productivity. The extent to which these various factors should be

nation of future shunt revisions can be captured in part as long-term costs on the CSF shunt side of the evaluation.

Capital and Overhead Costs

Many programs require use of reusable equipment such as CT and MRI scanners. To calculate a per-use cost for items such as these, a typical strategy is to calculate the annual costs of ownership and divide by the number of studies performed. This calculation must include the capital cost of the scanner itself, depreciated over its useful lifespan. Maintenance, film costs, labor, and other consumable items must be considered. Finally, the overhead costs, i.e., those shared resources provided by the hospital, such as payroll, environmental services, and administrative functions, that the CT scanner uses, must be calculated and assigned a cost. Again, this is more important when two programs differ in their resource use. Several methods for apportioning or allocating these shared resources exist. Direct methods require knowledge of the allocation basis for each overhead department, such as number of paid hours for payroll, or square feet for housekeeping. Thus the portion of the payroll office's budget that the CT scanner is responsible for is equal to the person-hours worked by CT personnel divided by the total person-hours worked by all members of the organization. Simultaneous allocation is a more precise method that adjusts for the interaction between overhead departments (i.e., it considers housekeeping's service to payroll and vice versa in calculating costs to end departments) (Fig. 1) [14].

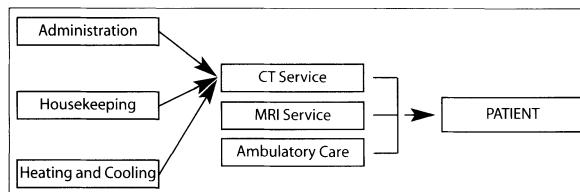


Fig. 1. Overhead and end user costs. In calculating service cost, service units can be divided into overhead and end user departments. The cost of service provided by an end user department is the sum of the department's direct costs, such as labor and supplies, and its overhead costs for payroll, utilities, and environmental services. These overhead costs may be directly allocated on the basis of unit output of work for the overhead department, such as square meters used for housekeeping; alternatively, more precision can be achieved by costing the services provided by overhead departments to each other using simultaneous allocation methods

Accounting for Time Preference

Given the choice, people prefer to receive benefits now and incur costs later. In an economic assessment, this is incorporated as "time preference." This is distinct from inflation. As the costs and benefits of a program are mapped out, year by year, this preference is taken into account by discounting costs and usually, benefits that accrue in future years by a fixed percentage for each additional year into the future in which they occur. The rate of discounting varies, but 5% is a common value used in the medical literature. This implies that a dollar spent today has a present value of 5% more than a dollar spent 1 year from now. Similarly, an improved quality of life today is worth about 5% more than one improved 1 year from now. Discounting benefits is more controversial than discounting costs, but is generally accepted. The rate of discount for time preference is typically between 0 and 5%.

Sensitivity Analysis

Much of the data used in economic analysis, including both resource use and cost data, are point estimates. Often, estimates of rates of therapeutic efficacy are involved in the effectiveness calculations. Therefore, standard stochastic statistical methods using means and standard deviations can be difficult to apply to determine the degree to which chance influences the interpretation of the results of the analysis. In addition, it is usually valuable to know which parameters have the greatest impact on the overall outcome. A sensitivity analysis varies key rates and costs both upward and downward over reasonable ranges to determine the impact on the overall outcome. A robust conclusion withstands these fluctuations, while changes in outcome with specific variations suggest closer scrutiny of the rate, cost, or resource use producing the change.

Incremental Costs

In comparing two therapies A and B for costs and outcomes, there are four possible outcomes: (1) A costs less than B and is more effective, (2) A costs more than B and is less effective, (3) A costs more than B and is more effective, and (4) A costs less than B and is less effective. In either of the first two cases the results point to the obvious acceptance or rejection of choice A. However, in the latter two cases, additional information is necessary to determine the degree of difference in costs and outcomes. The incremental cost-ef-

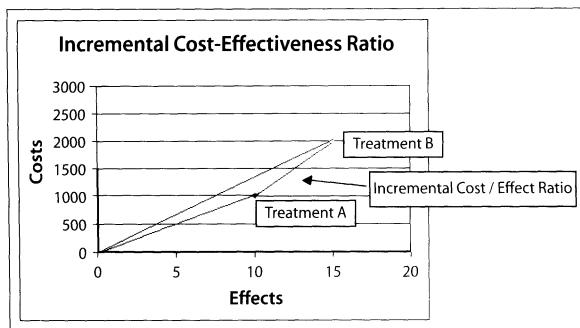


Fig. 2. Cost effectiveness plot. Two therapies, A and B, produce effects of 10 and 15 units at a cost of 1000 and 2000 units respectively. The average cost per effect for A is 1000/10 or 100, while for B the average cost is 2000/15 or 133.3. The incremental cost per effect to move from A to B is $(2000-1000)/(15-10)$ or 200

fectiveness ratio or cost-utility ratio measures the extra expenditure or savings per unit of outcome gained or given up. This is the marginal cost of an additional treatment or diagnosis. Cost-effectiveness plots provide a visual method of demonstrating this (Fig. 2).

Literature Review

An extensive literature search done in May 2000 on Medline, using the key words "ventriculostomy" and "economic" as well as "hydrocephalus" and "economic" identified only one published reference relating to an economic assessment of third ventriculostomy. This study attempted to assess the potential economic impact of the use of third ventriculostomy as a replacement for CSF shunt placement in a mixed pediatric and adult population [1]. No formal cost assessment was performed in this study. Rather, the authors attempted to identify retrospectively the resources saved by ETV by identifying how many additional hospital days and operations could potentially have been avoided over a 2-year period if patients presenting for first-time shunt placement who would have been candidates for third ventriculostomy had in fact had this procedure performed. Of 150 patients with data available for analysis, the authors determined on the basis of clinical and radiographic criteria that 23 patients would have been candidates for third ventriculostomy. There were 29 additional procedures performed and 230 additional hospitalization days as a result of shunt-related complications amongst these 23 patients. Based on an 80% ETV success rate, and a 0% complication rate, they calculated an incremental savings of 18 repeat operations and 148 bed-days over the 2-year study period. The

authors identify several limitations to their analysis: their minimal assumed complication rate, and the assumption that there would be no subsequent admissions for evaluation of possible ETV failure. These are optimistic assumptions in light of other published data [31]. Because there is no information as to the relative costs of the two procedures, the analysis cannot provide much insight into the true economic costs of the two approaches. One of the important issues to determine is the minimum success rate of third ventriculostomy for a financial break-even point. Based on this study alone, if one assumes that the unit cost of shunt placement and ETV are the same, then the rough break-even point in terms of postoperative days and operations saved is at an ETV success rate of 40% at 2-year follow up. This would be expected to increase as the shunted population required subsequent revisions in future years.

Expanding the literature search to include the shunt treatment of hydrocephalus, economic evaluations are still infrequently found. Bondurant and Jimenez obtained data from private US hospital insurers giving an average cost of a shunt procedure of \$2357 (presumably actual amount paid?) in 1991 (US) dollars and estimated the total cost of United States shunt-related procedures at \$94 million dollars. In this same paper the reported prevalence of CSF shunts within the general United States population was 125,000 [4]. The average per patient yearly cost of shunt-related procedures for this population as a whole then is \$750. Other estimates suggest higher costs. In another study of patients suffering grade IV intraventricular hemorrhage (IVH), Pikus et al. [26] reviewed a group of 52 premature neonates cared for over a 10-year period, all of whom had "evidence of massive hemorrhagic parenchymal infarction in addition to having blood in both lateral ventricles and progressive hydrocephalus." All of these children were treated aggressively. Among the 19 survivors, an average of 6.6 shunt revisions were required over a mean of 16 years and a total cost of \$28 500 per patient [26]. This translates into a yearly revision rate of 0.41 revisions per year at a cost of \$4300 per revision and a per-patient-per-year cost amongst survivors of \$1760. McCallum and Turbeville [22] evaluated the costs and outcomes in a series of premature infants with IVH. Amongst 50 children followed over a 5-year period, there was a shunt revision rate of 0.49 shunts per patient per year, at a cost of \$7510 per revision (roughly 1990 US dollars). The shunt infection rate was 4.9% per patient per year at a cost of \$20 661 per infection. The estimated 5-year cost of maintaining the shunt was thus \$4692 per patient per year [22]. These patients would generally be poor candidates for third ventriculostomy, and so their shunt costs may not be re-

flective of those for patients presenting with the option of third ventriculostomy.

The rate of shunt failure, critical to determining the relative benefit of ETV, is probably dependent in part on the etiology of hydrocephalus. Jamjoom and colleagues noted a low 6 % annual rate of shunt revision over a 2-year follow-up of 77 patients with newly placed shunts, all of whom had intracranial neoplasms as the etiology of their hydrocephalus [18]. This compared favorably with other hydrocephalus patients in their practice with nontumor diagnoses, in whom the annual shunt failure rate was 39%. In the Pediatric Shunt Design Trial, children with tumors and aqueductal stenosis had failure rates of 35% compared to 56% for patients with myelomeningocele [33]. These studies highlight the fact that there is a need to consider the comparison population carefully in evaluations of ETV, as shunt failure rates and cost may vary substantially depending on the population studied.

In another costing study Cochrane and colleagues developed an economic model to assess the determinants of the cost of caring for a CSF shunt. This model, based on data from British Columbia, Canada, assessed the effect of different shunt malfunction and infection rates on the overall cost of caring for a pediatric population with hydrocephalus. The median length of stay for shunt insertions and revisions combined was 7 days for those under 2 years of age and 3 days for those over 2 years. Patients with infected shunts had a median length of stay of 12 days and 5 days in the different age groups respectively. The authors provide cost information for their cohort as whole rather than as an average per individual, but comment that 80% of the cost of care was due to the cost of hospitalization. In a series of simulations, similar to a sensitivity analysis, the total cost was most sensitive to the shunt failure rate and the length of hospitalization [10].

Finally, the use of “average yearly failure rates” is problematic given that the published hazard functions for shunt failure suggest that the majority of shunt failures in a cohort will occur soon after shunt insertion. If time preference in the form of discounting of future costs is to be taken into consideration, the timing of shunt or ETV is important to the calculations. In addition, no report including a mean and standard deviation of costs is available for either third ventriculostomy or shunt placement.

Efficacy of Therapy

No randomized comparison of ETV versus shunt treatment for hydrocephalus for the initial management of hydrocephalus has been reported. Efficacy

assessments are available for each therapy individually, with comparisons between the two subject to the myriad of biases and limitations that occur with case series comparisons.

Placement of the CSF shunt system has been the gold standard for treatment of hydrocephalus. Its efficacy in the treatment of hydrocephalus from all causes has been well documented, as have its shortcomings in terms of failure rates requiring shunt revision. Failure rate of shunts, the risk factors, the morbidity and mortality related to shunt revision, and the long-term outcome of treated hydrocephalic children are well known and described elsewhere in this book and in the literature [2, 3, 7, 11, 12, 21, 23–25, 28, 29] (see Chaps. 20–23). The efficacy of third ventriculostomy in the management of hydrocephalus has also been documented in the neurosurgical literature [5, 6, 8, 9, 17, 19, 20, 27, 30, 32] (see Chap. 25). The initial complication rate with ETV appears to be higher than that with the shunt treatment of hydrocephalus. Rates range from 3% to 7% for serious complications [30, 31] (see Chap. 29). The equivalent rates for CSF shunt placement appear to be lower when focused on the perioperative risk for injury rather than the subsequent rate of shunt infection or failure. In an international survey of the complications of first shunt placement, the operative mortality amongst the 773 cases from 4 continents was 0.1% (1 patient) [11]. In the aforementioned pediatric Shunt Design Trial, there was no operative mortality and new neurologic deficits and minor resolving complications occurred at a rate of 1%–2% [13]. One of the important issues in comparing outcomes and costs between ETV and shunting is what is an adequate degree of follow-up. While ETV failure typically occurs within a few weeks to months after the procedure is performed, Tuli and colleagues reported an ETV failure occurring at 4 years after ETV [32]. This suggests that a follow-up period of 4 years should capture the vast majority of ETV failures. Because failure of ETV requires shunt placement, it is tempting to argue that a cost comparison can be simplified to consider only the costs of the ventriculostomy patients to the point of shunt placement, then assume that they perform in a similar fashion to the average shunted patients. This would have the advantage of limiting data collection to the point at which shunting, if any, occurred. A theoretical objection is that a shunt placed after ETV failure might have a different subsequent course than the usual course after initial shunting, with fewer problems because of a more compliant CSF system. There is little evidence to either support or refute this claim. In a case control or cohort design, the safest analytical course would be to continue the analysis of costs in both arms of the cohort, based on the original treatment. In a decision analysis model, the assumption of similar courses might be expected.

British Columbia's Children's Hospital Experience*

We retrospectively reviewed our own experience with ETV at British Columbia's Children's Hospital, British Columbia, Canada, in 1998 to compare the cost-effectiveness of ETV compared to ventricular shunting [16]. Given the retrospective nature of the review, we selected a cost-effectiveness methodology and conducted a case control analysis of 28 consecutive patients undergoing ETV at B.C. Children's Hospital between 1989 and 1998. To compare their costs and outcomes to those seen in the shunt treatment of hydrocephalus, we matched them with a control group of 28 children, treated with shunts by etiology of hydrocephalus, age at the time of the index procedure, and number of prior procedures performed for hydrocephalus using an office practice database. The matching process was designed to produce two groups of patients, as equivalent as possible, relative to the known risk factors for shunt failure. Thus, a 3-year-old patient with hydrocephalus due to aqueductal stenosis, undergoing ETV instead of shunt revision, after three previous CSF shunt placement and revision procedures, would be matched with a child between 2 and 5 years, also with hydrocephalus due to aqueductal stenosis, undergoing his or her fourth shunt procedure. Clinically, the decision as to which therapy a patient received was determined by the practice pattern at the time the patient was evaluated, with most of the control patients being treated in the mid 1980s to 1990, prior to the renewed interest in ETV.

* This section is based on: A cost-effectiveness analysis of endoscopic third ventriculostomy. Garton et al, Neurosurgery 51:69-78, 2002 [16]

Hydrocephalus-related resource consumption and treatment effects were identified by review of office and hospital charts. Cases and controls were followed from the performance of the index ETV or shunt procedure for an equivalent period by limiting consideration to the point of the shorter follow-up between the matched pair. In determining costs, the retrospective nature of the study limited our perspective to that of a third-party payer. We focused on hospital and physician resource use and could not consider items such as out-of-pocket family expenses or changes in parental productivity. We chose for our common effects measure the number of days free of the hydrocephalus treatment, calculated as the total days of follow-up less time spent hospitalized for hydrocephalus-related treatment, plus a 14-day addition to account for prehospitalization illness and postdischarge recovery time. As is evident from the preceding discussion, this effect measure only allows comparison in one area. Complications of therapy were therefore recorded separately. Costs and effects were discounted at a rate of 5% annually.

The indications for third ventriculostomy amongst the cases are as follows: in 13 of 28 patients obstructive hydrocephalus was present as a result of a nonoperative aqueductal mass lesion, mostly tectal gliomas and nongerminomatous germ cell tumors. Ten patients presented with pure aqueductal stenosis. Two patients had imaging characteristics of obstructive hydrocephalus after earlier lesion resection. One patient underwent the procedure prior to subsequent resection of a pineoblastoma. Two patients with myelomeningocele underwent ventriculostomy at the time of shunt malfunction, while two other children suffered from postmeningitic hydrocephalus. Given the matching process, controls had similar etiologies, ages, and number of prior procedures (Table 2).

Table 2. British Columbia's Children's Hospital experience, ETV versus shunt treatment of hydrocephalus: cases versus controls

		ETV	Shunt
Etiology:	Tumor	13	13
	Aqueductal stenosis	10	10
	Myelomeningocele	2	3
	Postmeningitic	2	2
	Other	1	0
Age:	(Median)	4.3 years	5.0 years
	Less than 1 year	10	10
	1-3 years	3	1
	3-7 years	5	6
	7-18 years	10	11
Prior procedures:	0 (Initial treatment)	21	21
	2-4	4	5
	5-6	1	1
	7-10	2	1

We evaluated the index hospitalization, that is, the hospitalization during which the qualifying ETV or matched shunt operation was performed. The third ventriculostomy group used significantly more operative time during the hospitalization, both in the specific comparison of third ventriculostomy to shunt placement and in the total of all operative procedures performed during the admission. The mean total operative time per patient (\pm standard deviation) for the ETV group was 2 h 20 min \pm 48 min, compared to 1 h 35 min \pm 22 min for the shunt group. Four patients underwent reoperation for failed ETV during their initial hospitalization, while 1 patient in the shunt group required immediate revision. Length of stay for the ETV group was 4 days, compared to 3 for the shunt group, but this difference was not significant.

As defined by the need for reoperation, ETV had a procedural success rate of 54% over a median follow-up of 22 months. In one patient a repeat ETV was successful. Most of the failures occurred early in the follow-up period, with 10/13 occurring before 6 months. By Kaplan-Meier survival analysis, the rate and time course of the first failure was not statistically different between the groups (Fig. 3). Similar results have been reported by others [32].

We next assessed the outcomes for patients in terms of readmission and reoperation. The two groups had similar numbers of readmissions, shunt infections, and total admitted hospital days. In the ETV group this included both readmissions for ETV failure and admissions for subsequent failure of CSF shunts placed. Over the 22-month median follow-up the ETV group spent an average of 0.86 days per patient per year in the hospital for hydrocephalus-related treatment compared to 1.21 days for the shunt group. Using previously published costing data from B.C. Children's Hospital along with additional information from the hospital's decision analysis team, we applied a dollar cost to each

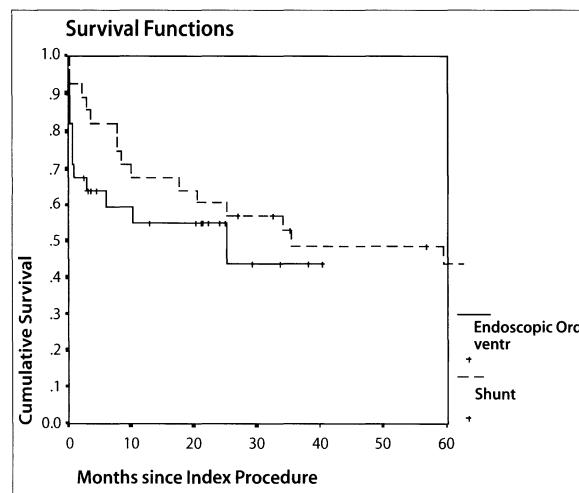


Fig. 3. Kaplan-Meier curve of the “survival” of the index ETV or shunt procedure. Figure reproduced from [16], with permission

item of resource use, including operative procedures, length of stay, neuroimaging studies, relevant laboratory studies, antibiotic use, and clinic and emergency room visits. Table 3 details the effects of the two treatment options, both in terms of resources and costs. Over the short 22-month median follow-up period, we noted little difference in either costs or effects. ETV was less expensive – by about \$1000 per patient – while also minimally more effective: about three extra effect-days per patient over the median 22 month follow-up. When we plotted the time course of the accumulating costs for the two groups over time, the ETV group costs are initially higher, but cross and diverge after the first 30 months.

Importantly, however, ETV was associated a higher rate of complications. A 4-year-old child with aqueductal stenosis underwent ETV as a first treatment procedure. Three months after surgery, a follow-up CT clearly demonstrated a decrease in ventricular

Table 3. British Columbia's Children's Hospital: outcomes after ETV versus shunt treatment. Data for 28 patients per group, with equivalent follow-up periods (median 22 months)

	ETV group	Shunt group
Initial Admission		
LOS	4 days	3 days
Mean cost (2000 Canadian dollars)	\$10,999 \pm \$7,216	\$9,023 \pm \$4,849
Readmissions		
LOS	54 total days for group	91 total days for group
Mean patient days per patient per year	0.86 days	1.21 days
Reoperation	18 (16 shunt revisions and 2 redo ETVs)	26 shunt revisions
Total costs and effects		
Total mean costs	\$17,464 \pm \$12,533	\$18,459 \pm \$14,017
Total days free of symptoms and treatment	26,914	26,828
Cost-effectiveness ratio (cost per day free of symptoms and treatment)	\$18.17	\$19.30

LOS, length of stay

size from the preoperative studies. The child was lost to our follow-up but presented to an outside institution remarkably obtunded 25 months after the procedure was performed, subsequently suffered a respiratory arrest, and died. At autopsy, massive hydrocephalus was present and the third ventriculostomy was noted not to be patent. A 12-year-old boy also suffered a persistent mild hemiparesis after ETV. No mortality or permanent morbidity occurred among the shunt group.

We performed a sensitivity analysis on our cost-effectiveness calculations to determine the effect of some of our assumptions. No significant effect was seen when we varied the discount rate, the posthospitalization days added for recovery, or when we inflated or deflated the costs by 20%. However, when we increased the success rate to 75% the total cost for the ETV cohort and shunt groups crossed at 12 months, with ETV becoming slightly less expensive after 18 months.

Obviously, this single-institution review has a limited sample size, bias-prone case-control design, and short follow-up. In using an effectiveness analysis we limited ourselves to a relatively simplistic measure of the effects of therapy and could only include the complications insofar as they increased the medical costs of therapy, and could not consider the costs, for example, of litigation, or, more importantly, the impact on quality of life.

Conclusion

Although it seems logical that ETV must be more cost effective than the shunt treatment of hydrocephalus, further, more sophisticated analyses will be required to demonstrate this. Regardless of whether analyses are based on models or cohorts of actual patients, readers should look for future analysis to comparatively assess therapies in comparable groups of patients. Outcome measures in future studies will need to incorporate the impact of complications on patients and include patient preference for a shunt free state, if any, as well as any differences that emerge in long term cognitive outcome between the two therapies. Cost-utility analysis would appear to offer the best choice to achieve these goals.

References

1. Barlow P, Ching HS: An economic argument in favour of endoscopic third ventriculostomy as a treatment for obstructive hydrocephalus. *Minim Invasive Neurosurg* 40:37-39, 1997
2. Bierbrauer KS, Storrs BB, McLone DG, et al: A prospective, randomized study of shunt function and infections as a function of shunt placement. *Pediatr Neurosurg* 16:287-291, 1990
3. Billard C, Santini JJ, Gillet P, et al: Long-term intellectual prognosis of hydrocephalus with reference to 77 children. *Pediatr Neurosci* 12:219-225, 1985
4. Bondurant C, Jimenez D: Epidemiology of cerebrospinal fluid shunting. *Pediatr Neurosurg* 23:254-258, 1995
5. Brockmeyer D, Abtin K, Carey L, et al: Endoscopic third ventriculostomy: an outcome analysis. *Pediatr Neurosurg* 28:236-40, 1998
6. Buxton N, Cartmill M, Vloeberghs M: Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 45:795-806, 1999
7. Caldarelli M, Di Rocco C, La Marca F: Shunt complications in the first postoperative year in children with meningocele. *Child's Nerv Syst* 12:748-754, 1996
8. Chumas P, et al: III Ventriculostomy in the management of posterior fossa tumors in children. *Child's Nerv Syst* 11:540, 1995
9. Cinalli G, Sainte-Rose C, Chumas P, et al: Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90:448-454, 1999
10. Cochrane D, Kestle J, Steinbok P, et al: Model for the cost analysis of shunted hydrocephalic children. *Pediatr Neurosurg* 23:14-19, 1995
11. Di Rocco C, Marchese E, Velardi F: A survey of the first complication of newly implanted CSF shunt devices for the treatment of nontumoral hydrocephalus. Cooperative survey of the 1991-1992 Education Committee of the ISPN. *Child's Nerv Syst* 10:321-327, 1994
12. Drake JM, Kestle J: Determining the best cerebrospinal fluid shunt valve design: the pediatric valve design trial. *Neurosurgery* 38:604-607, 1996
13. Drake JM, Kestle JR, Milner R, et al: Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery* 43:294-303, 1998
14. Drummond MF, et al: Methods for the economic evaluation of health care programmes, 2nd edn. Oxford University Press, Oxford, 1997
15. Drummond MF, Richardson WF, O'Brien BJ, et al: Users' guides to the medical literature. XIII. How to use an article on economic analysis of clinical practice. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 277:1552-1557, 1997
16. Garton H, Kestle JR, Cochrane DD, et al: A cost-effectiveness analysis of endoscopic third ventriculostomy. *Neurosurgery* 51:69-78, 2002
17. Goumnerova LC, Frim DM: Treatment of hydrocephalus with third ventriculocisternostomy: outcome and CSF flow patterns. *Pediatr Neurosurg* 27:149-152, 1997
18. Jamjoom AB, Jamjoom ZA, Rahman NU: Low rate of shunt revision in tumoral obstructive hydrocephalus. *Acta Neurochir* 140:595-597, 1998
19. Jones R, et al: Neuroendoscopic third ventriculostomy. In: Manwaring K, Crone K (eds) *Neuroendoscopy*. Liebert, New York, pp 63-77, 1992
20. Jones RF, Kwok BC, Stening WA, et al: The current status of endoscopic third ventriculostomy in the management of non-communicating hydrocephalus. *Minim Invasive Neurosurg* 37:28-36, 1994
21. Kast J, Duong D, Nowzari F, et al: Time related patterns of ventricular shunt failure. *Child's Nerv Syst* 10:524-528, 1994

22. McCallum JE, Turbeville D: Cost and outcome in a series of shunted premature infants with intraventricular hemorrhage. *Pediatr Neurosurg* 20:63-67, 1994
23. O'Brien MS, Harris ME: Long-term results in the treatment of hydrocephalus. *Neurosurg Clin North Am* 4:625-632, 1993
24. Piatt JH: Cerebrospinal fluid shunt failure: late is different from early. *J Neurosurg* 82: 363, 1995
25. Piatt JH Jr, Carlson CV: A search for determinants of cerebrospinal fluid shunt survival: retrospective analysis of a 14-year institutional experience. *Pediatr Neurosurg* 19:233-241, 1993
26. Pikus HJ, Levy ML, Gans W, et al: Outcome, cost analysis, and long-term follow-up in preterm infants with massive grade IV germinal matrix hemorrhage and progressive hydrocephalus. *Neurosurgery* 40: 983-988, 1997
27. Sainte-Rose C: Third ventriculostomy. In: Manwaring K, Crone K (eds) *Neuroendoscopy*. Liebert, New York, pp 47-62, 1992
28. Sainte-Rose C, Piatt JH, Renier D, et al: Mechanical complications in shunts. *Pediatr Neurosurg* 17:2-9, 1991
29. Sgouros S, Mallucci C, Walsh AR, et al: Long-term complications of hydrocephalus. *Pediatr Neurosurg* 23:127-132, 1995
30. Teo C, Jones RF: Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25:57-63, 1996
31. Teo C, Rahman S, Boop FA, et al: Complications of endoscopic neurosurgery. *Child's Nerv Syst* 12:248-253, 1996.
32. Tuli S, Alshail E, Drake JM: Third ventriculostomy versus cerebrospinal fluid shunt as a first procedure in pediatric hydrocephalus. *Pediatr Neurosurg* 30:11-15, 1999
33. Tuli S, O'Hayon B, Drake JM, et al: Change in ventricular size and effect of ventricular catheter placement in pediatric patients with shunted hydrocephalus. *Neurosurgery* 45:1329-1333, 1999
34. Walker M, Petronio J, Carey C: Ventriculostomy. In: Cheek W (ed) *Pediatric neurosurgery: surgery of the developing nervous system*. Saunders, Philadelphia, pp 572-581, 1994

Growth and Puberty in Hydrocephalus

RASA BRAUNER¹, FLORENCE CHOLLEY¹ AND CHRISTINE TRIVIN²

Introduction

Non-tumor-related hydrocephalus may cause short adult height [21, 26], weight gain [11] and/or disorders of puberty [4a, 7, 10, 12]. Although these conditions are believed to be caused by increased pressure on the hypothalamic-pituitary (HP) area of the brain, the exact mechanism is unknown. We will analyze: (1) the expression and incidence of each of these disorders, and their relationship to the quality of the control of the hydrocephalus; (2) the special features of hydrocephalus attributable to a suprasellar arachnoid cyst; and (3) the management of growth and puberty in patients with hydrocephalus.

Growth

Patients with hydrocephalus are at risk of short adult height through: (1) meningomyelocele-induced abnormalities of vertebral growth and structure; (2) growth hormone (GH) deficiency; and (3) early puberty leading to premature fusion of the bone epiphyses.

Adult Height

The mean adult height of patients with meningomyelocele was reported by Rotenstein et al. [21] to be 142 cm in 27 females and 152 cm in 27 males, and by Trollman et al. [26] to be 141 cm in females and 159 cm in males (15 cases). Rotenstein et al. [21] found that patients with thoracic lesions were shorter than those with lumbar lesions, who were in turn shorter than those with sacral lesions. The 109

patients with meningomyelocele in the second study [26] included 47% with short stature; their supine length was influenced by the level of the lesion, their ambulatory status, their skeletal deformities, and their pubertal stage. Those patients with hydrocephalus who had reached their adult height with meningomyelocele were shorter than those with other etiologies of hydrocephalus, who were in turn shorter than the control population [11].

Growth Hormone Secretion

The combined effects of stimulatory (GH-releasing hormone, GHRH, also called GRF) and inhibitory (somatostatin) hypothalamic factors lead to pulsatile GH secretion by the somatotrophic anterior pituitary cells (Tables 1 and 2). GH does not stimulate growth directly, but causes the secretion of insulin-like growth factor (IGF) I by the liver. IGF I stimulates cartilage growth. GH deficiency is diagnosed on the basis of a low GH peak following two pharmacological stimulation tests. However, there are difficulties in this diagnosis because: (1) the limit of the peak defining this deficiency varies from one country to another (7-10 µg/l or ng/ml); (2) the results of the assay depend on the kit used; (3) being overweight and experiencing delayed puberty may lead to a transiently low GH peak; and (4) reports indicate that the evaluation of spontaneous rather than stimulated GH secretion gives a more physiological assessment of a person's capacity to secrete the hormone. GH deficiency can also be diagnosed by measuring the plasma concentrations of IGF I and one of its binding proteins (IGFBP-3) because both depend on GH secretion. Both are excellent tools for diagnosing idiopathic GH deficiency, as their concentrations are low [4].

¹Université René Descartes, Paris, France; ²Physiology Laboratory, Hôpital Necker-Enfants Malades, Assistance Publique - Hôpitaux de Paris, Paris, France

Table 1. Hypothalamic-pituitary secretions

Hypothalamus	GHRH	TRH	CRF	GnRH
Anterior pituitary	GH	TSH	ACTH	FSH-LH
Gland		Thyroid	Adrenals	Gonads
Hormone		Thyroxin	Cortisol	Testosterone, estradiol-progesterone

ACTH, adrenocorticotropin; CRF, adrenocorticotropin-releasing factor; FSH, follicle-stimulating hormone; GH, growth hormone; GHRH, GH-releasing hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone

Table 2. Laboratory tests for assessing hypothalamic-pituitary function

Hormone	Basal value	Stimulation test
antidiuretic hormone (ADH)	Plasma and urinary osmolalities	Water deprivation
ACTH	Cortisol at 08.00 a.m.	
GH	IGF-I and IGFBP-3	Arginine, insulin, ornithine
Gonadotropins (LH and FSH)	Testosterone in boys, estradiol in girls	GnRH
Prolactin	Prolactin	TRH
TSH	Thyroxin	TRH

ACTH, adrenocorticotropin; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid stimulating hormone

The diagnosis of GH deficiency is particularly difficult in patients with hydrocephalus because: (1) despite having normal GH, their growth rate may be decreased through abnormalities of vertebral growth in meningomyelocele; (2) early puberty and/or weight gain may lead to a normal growth rate despite GH deficiency; and (3) weight gain may decrease the GH response in stimulation tests. The abnormal vertebral growth in meningomyelocele is partly responsible for the short trunk, so arm span evaluation can be used to exclude the effect of vertebral growth. The influence of HP dysfunction on short stature is suggested by the fact that those patients with hydrocephalus requiring a ventriculoperitoneal shunt are shorter than those without a shunt. In 7/47 patients with meningomyelocele, Hochhaus et al. [10] found a GH peak after two stimulation tests below 10 ng/ml, and low IGF I concentrations. Magnetic resonance imaging showed that those patients with hydrocephalus and a poor GH response to stimulation tests also had significantly smaller pituitary glands than those with a normal GH response [13]. When treated with GH (0.5 U/kg body week), seven patients with meningomyelocele and hydrocephalus associated with GH deficiency increased their growth rate from 3.7 to 7.2 cm during the first year of treatment [27], but there are no data on their adult heights. Hochhaus et al. [10] found normal cortisol (62 cases) and low free thyroxine concentrations in only 2/62 cases.

Weight

Overweight is frequent, particularly in those with meningomyelocele [11]. These patients have a decreased body cell mass and increased body fat mass [23].

Puberty

Normal Puberty

Puberty includes the appearance of sexual characteristics and the acceleration of the growth rate. It is initiated by the activation or disinhibition of the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. This leads to increased secretion of gonadotropins (luteinizing hormone, LH, and follicle-stimulating hormone, FSH) from the anterior pituitary, and to changes of LH pulsatility with increased frequency and amplitude of LH peaks. Gonadotropin secretion induces gonadal development and sex steroid secretion: in boys, testosterone from the testes; and in girls, estradiol and, later, progesterone from the ovaries. This phase of puberty is gonadarche. The

other is adrenarche, corresponding to the increased secretion of dehydroepiandrosterone sulfate (DHAS) from the adrenals, which is partly responsible for the development of pubic and axillary hair. This occurs at 7-8 years, before gonadarche. It is probably controlled by a central factor that is different from gonadotropins and adrenocorticotropic.

In 95% of cases, sexual characteristics appear between 8 and 13 years in girls, and between 9 and 14 years in boys. Pubertal stages are rated from stage 1 (prepubertal) to stage 5 (adult development) according to Marshall and Tanner [14, 15]. There are differences in the age of onset of puberty, but the sequence of pubertal development is usually similar. In girls, the first sign is breast and/or pubic hair development, which occurs at a mean age of 11 years. The mean time interval between the onset of breast development and the occurrence of the first menstruation is 2 years. Menstruation becomes cyclic after 1-2 years, and the first cycles are anovulatory. In boys, the first sign is enlargement of the testes, which occurs at a mean age of 12 years. It corresponds to the development of the seminiferous tubules. The size of the testes before puberty are 20×10 mm; dimensions greater than 30×20 mm indicate activation of the HP-testicular axis.

The growth rate accelerates during puberty. Annual height gain increases from 5 cm before puberty to 7-9 cm during the pubertal growth spurt. The mean age at the time of this spurt is 12 years in girls and 14 years in boys. The mean total height gain between the clinical onset of puberty and adult height is 25 cm in girls and 28 cm in boys [25]. It represents 16% of the standing adult height. The mean total height gain between the first menstruation and the adult height is 7 cm when first menstruation occurs at 13 years. It varies between 3 and 14 cm and is higher when the first menstruation occurs earlier. Adult height is reached at a mean age of 16 years in girls and 18 years in boys. Acceleration of the growth rate during puberty is due to the effect of increased sex steroid, GH, and IGF I secretions.

Precocious puberty is defined as the onset before 8 years in girls and 10 years in boys; advanced puberty by an onset at between 8 and 10 years in girls; and delayed puberty by the absence of puberty after 13 years in girls and 14 years in boys.

Disorders of Puberty

Patients with hydrocephalus may have early (precocious or advanced) puberty, or fail to make normal progress through it.

Early Puberty

This may be premature adrenarche, which is a variation of normal pubertal development, or central or true early puberty, which is due to premature activation of the HP-gonadal axis. Hydrocephalus is responsible for 5%-8% of cases of central precocious puberty. The frequency of central precocious puberty among patients with hydrocephalus is 5% to 16%. Proos et al. [20] found early puberty (onset before 9.2 years) in 52% of girls with meningocele, with an inverse relationship between head circumference at birth and age at breast development. In hydrocephalus, the mean age at the menarche was significantly lower in the female patients than in their controls (11.7 vs 13.2 years) and lower than it had been for their mothers (13.1 years) [12]. The mechanism by which the HP lesions cause premature activation of the HP-gonadal axis is unknown. The role of the increased pressure on the HP area has been discussed [7, 10], but this activation also occurs in patients with functional derivation of hydrocephalus and normal ventricular size or minimal enlargement on neuroradiological examination. Chronic minimally increased intraventricular pressure may be involved, as suggested by the fact that central precocious puberty occurs almost exclusively in those patients with meningocele who have also had hydrocephalus [10], and that shunt malfunction preceded precocious puberty in four patients with hydrocephalus [7]. Treatment with GnRH analog is used in central precocious puberty to slow the bone maturation induced by the early secretion of sex steroids. Trollmann et al. [28] found no improvement in the predicted adult height in 7 seven patients treated for more than 2 years.

Delayed Puberty

In patients with hydrocephalus, delayed puberty may be due to gonadotropin deficiency (hypogonadotropic hypogonadism) or to "hypothalamic dysregulation", as suggested by the occurrence of amenorrhea despite a normal gonadotropin peak.

Suprasellar Arachnoid Cyst

A suprasellar arachnoid cyst [19] may also cause short adult height [17], weight gain [17] and/or disorders of puberty [3, 5, 6, 16-18, 22, 24, 29]. We routinely evaluated the growth, puberty, and HP function of 30 patients with a suprasellar arachnoid cyst [2]. Only two

patients (with precocious menstruation or tall stature) had these disorders themselves drawn attention to the cyst. In the other cases the cyst was discovered in the course of routine ultrasound evaluation (5 cases), or revealed by macrocranial (17 cases), neurological (16 cases), and/or visual symptoms (9 cases). Twenty-three patients (77%) had an abnormal height, weight, or puberty; these were short (5 cases) or tall (10 cases) stature, being overweight (6 cases), precocious puberty (10 cases), and/or no progression of pubertal development (3 cases). Half the patients had a low GH peak.

Low GH peaks have been reported by Hoffman et al. [9] and short stature by Obenchain and Becker [17]. Half of our cases were abnormally short or tall, and 20% of them were overweight. The GH peak was low in more than half the patients, but it did not correlate with the height or growth rate. Its negative correlation with body mass index (BMI) and a low GH peak in 4/6 of the overweight patients, in spite of their normal height and growth rate, suggest that being overweight is responsible for the low GH peak of some patients. However, its negative correlation with plasma fasting insulin concentrations, and the absence of a correlation between these concentrations and BMI, suggest that the hyperinsulinism due to the suprasellar arachnoid cyst itself is the primary phenomenon.

The way in which a suprasellar arachnoid cyst causes disorders of puberty and HP function is unknown. It induces deficiencies of GH and thyroid-stimulating and adrenocorticotropin hormones, but stimulates the HP-gonadal axis, leading to central precocious puberty. The hyperinsulinism and/or excess weight may be partly responsible for the precocious puberty and tall stature in one-third of our patients, but does not account for these features in the majority of them. Central precocious puberty occurred in a third of our cases. About 16 cases of central precocious puberty have been reported in patients with suprasellar arachnoid cyst [3, 5, 6, 16-18, 22, 24, 29], and with the regression of pubertal development after draining of the cyst in 6 of them [5, 24, 29]. Menstruation may be the first sign in girls, as in

2/6 of our patients. Regular menstrual menstruations were reported in one case [5]. The precocious puberty is evolutive [8], as suggested by the pubertal level of plasma sex steroids and the response of gonadotropins to the GnRH test, and by the short adult height of patients with precocious puberty who were not treated with GnRH analog. This puberty is therefore an indication for treatment with GnRH analog to prevent excessive bone maturation. In spite of a normal plasma gonadotropin response to a GnRH test, one girl had primary amenorrhea and two boys had low plasma testosterone. Two of them had had central precocious puberty. This sequence has been reported, as well as irregular menstruations, abnormal fertility, or amenorrhea [17]. The other HP disorders that have been reported are thyroid and cortisol deficiencies, galactorrhea, and hyperprolactinemia.

Management

The growth and pubertal development of patients with hydrocephalus must be monitored (Table 3). GH secretion should be evaluated in those with low growth rate and/or short stature before puberty, routinely in those with precocious puberty or with no acceleration of growth rate in spite of puberty at a normal age and with associated decreased arm span in the case of meningocele, and/or low plasma IGF I and IGFBP-3 concentrations. A low GH peak in a patient following two stimulation tests must be interpreted as a function of weight, as it may be caused by excess weight. Plasma thyroxin concentration should be evaluated regularly.

The early development of sexual characteristics may be due to premature adrenarche, which is a variation of normal pubertal development, or to central or true early puberty, which is due to premature activation of the HP-gonadal axis. A check should be made for isolated pubic and/or axillary hair development, and for clinical signs of central

Table 3. Management of growth and puberty in hydrocephalus

Evaluate GH secretion:

1. If low growth rate and/or short stature before puberty
2. Routinely in precocious puberty or when no acceleration of growth rate in spite of puberty at a normal age
3. If meningocele, when there is associated decreased arm span
4. When plasma concentrations of IGF-I and IGFBP-3 are low

Early development of sexual characters:

Central puberty or isolated pubic and/or axillary hair development

If central puberty → bone age, sex steroids, gonadotropin response to GnRH, GnRH analog treatment

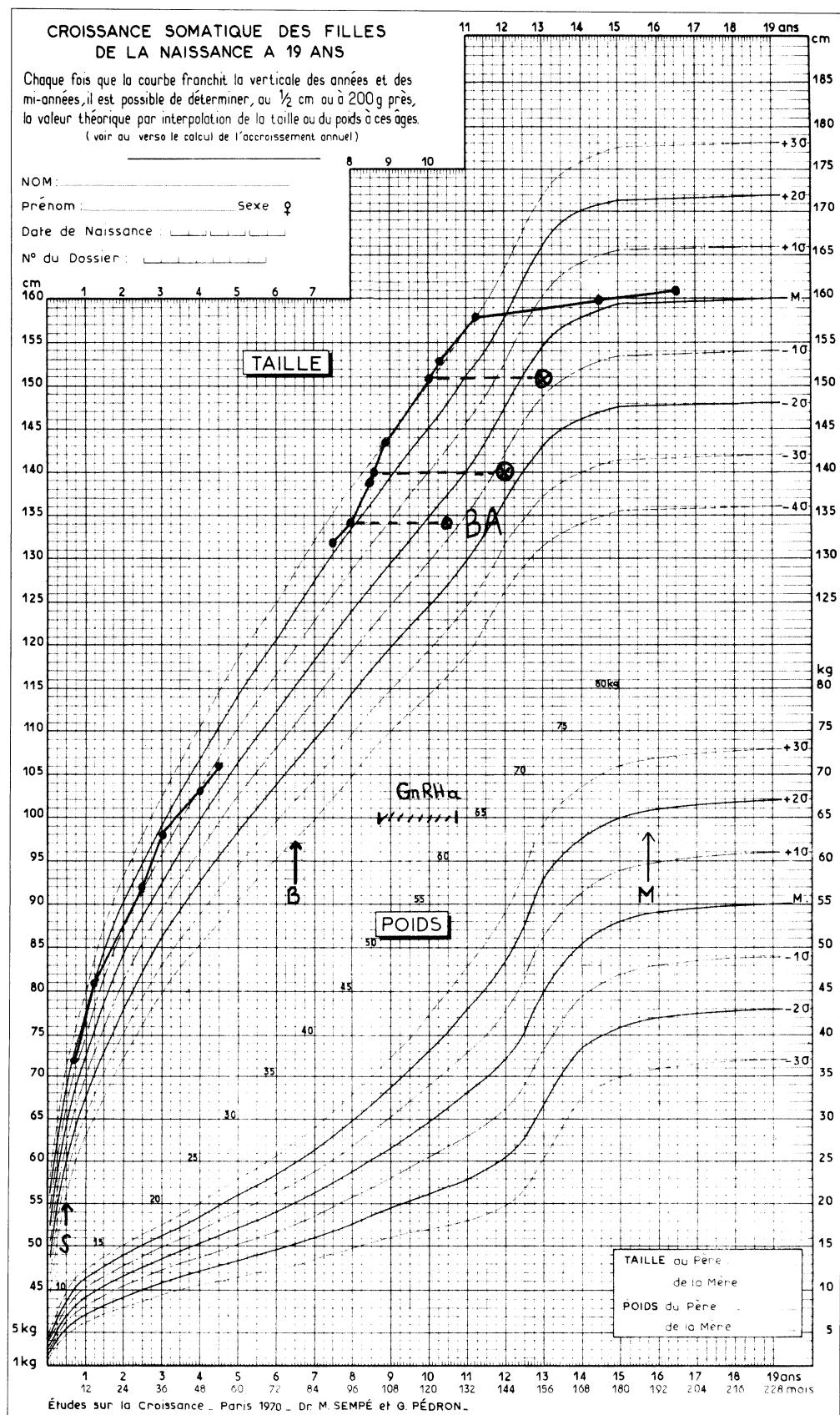


Fig. 1. Growth chart of a girl with central precocious puberty due to hydrocephalus, treated by shunt at 0.5 years (S). Breast development (B) occurred at 6.5 years. She had advanced bone age. She was treated with GnRH analogue between 8.75 and 10.75 years, which slowed the bone age progression. She menstruated (M) at 14.5 years and her adult height is 160.5 cm

puberty. In premature adrenarche there is no increase in growth rate or advance in bone age, no breast development in girls, and no increased testicular volume in boys. In these circumstances there is no premature secretion of sex steroids, and thus no risk of premature fusion of the bone epiphyses leading to short adult height. Conversely, in central early puberty there is an increase in growth rate, premature onset of breast development in girls, and increased testicular volume in boys before 9 years. In this situation bone age, basal plasma concentrations of sex steroids, and gonadotropin response to a GnRH test should all be evaluated. Central early puberty is characterized by an advance in bone age, and increase in plasma sex steroid concentrations (estradiol >20 pg/ml in girls and testosterone >0.2-0.5 ng/ml in boys) and in the pubertal response of the gonadotropins (LH and FSH) to a GnRH test. This response is characterized by LH/FSH peak ratio greater than 0.6 in girls and greater than 2 in boys. Early puberty is an indication for GnRH analogue treatment. This treatment has little effect on the predicted adult height of patients with meningomyelocele, but it probably prevents deterioration of the growth potential. Patients with associated GH deficiency and early puberty must be treated with GH and GnRH analogue [1].

Acknowledgments. We thank the neurosurgeons, Drs. G. Cinalli, E. Hirsch, Prs. A. Pierre-Kahn, D. Renier, C. Sainte Rose and M. Zerah of the Pediatric Neurosurgery Department, Pr. F. Brunelle of the Pediatric Radiology Department, and the nurses of the Pediatric Endocrinology Department (M. Faivre, M. Bichet, C. Robertson) of the Hôpital Necker-Enfants Malades in Paris. We are grateful to Drs. G. Watts and O. Parkes for editorial help.

References

1. Adan L, Souberbielle JC, Zucker JM, Pierre-Kahn A, et al: Adult height in 24 patients treated for growth hormone deficiency and early puberty. *J Clin Endocrinol Metab* 89: 229-233, 1997
2. Adan L, Bussières L, Dinand V, Zerah M, et al: Growth, puberty, and hypothalamic-pituitary function in children with suprasellar arachnoid cyst. *Eur J Pediatr*, 159: 348-355, 2000
3. Bercovici JP, Besson G, Caroff J: Puberté précoce, kyste arachnoidien du 3^e ventricule et acétate de cyproterone. *Ann Endocrinol* 37: 467-468, 1976
4. Bussières L, Souberbielle JC, Pinto G, Adan L, et al: The use of insulin-like growth factor I reference values for the diagnosis of growth hormone deficiency in prepubertal children. *J Endocrinol* 52: 735-739, 2000
- 4a. Cholley F, Trivin C, Sainte-Rose C, Souberbielle JC, Cinalli G, Brauner R: Disorders of growth and puberty in children with non-tumoral hydrocephalus. *J Pediatr Endocrinol Metab* 14: 319-327, 2001
5. Clark SJ, Van Dop C, Conte FA, Grumbach MM, et al: Reversible true precocious puberty secondary to a congenital arachnoid cyst. *Am J Dis Child* 142: 255-256, 1988
6. Dos Santos FM, Campistol J, Ruscalleda J, Fernandez-Alvarez E: Quiste aracnoideo parasellar asociado a pubertad precoz isosexual. *An Esp Pediatr* 18: 141-144, 1983
7. Elias ER, Sadeghi-Nejad A: Precocious puberty in girls with myelodysplasia. *Pediatrics*: 521-522, 1994
8. Fontoura M, Brauner R, Prevot C, Rappaport R: Precocious puberty in girls: early diagnosis of a slowly progressing variant. *Arch Dis Child* 64: 1170-1176, 1989
9. Hoffman HJ, Brice Hendrick E, Humphreys RP, Armstrong EA: Investigation and management of suprasellar arachnoid cysts. *J Neurosurg* 57: 597-602, 1982
10. Hochhaus F, Butenandt O, Schwarz HP, Ring-Mrozik E: Auxological and endocrinological evaluation of children with hydrocephalus and/or meningomyelocele. *Eur J Pediatr* 156: 597-601, 1997
11. Löppönen T, Saukkonen A-L, Serlo W, Lanning P, Knip M: Slow prepubertal linear growth but early pubertal growth spurt in patients with shunted hydrocephalus. *Pediatrics* 95: 917-923, 1995
12. Löppönen T, Saukkonen A-L, Serlo W, Tapanainen P, et al: Accelerated pubertal development in patients with shunted hydrocephalus. *Arch Dis Child* 74: 490-496, 1996
13. Löppönen T, Pääkkö E, Laitinen J, Saukkonen A-L, et al: Pituitary size and function in children and adolescents with shunted hydrocephalus. *Clin Endocrinol* 46: 691-699, 1997
14. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in girls. *Arch Dis Child* 44: 291-303, 1969
15. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in boys. *Arch Dis Child* 45: 13-23, 1970
16. Mori K: Precocious puberty with fits of laughter and with a large cystic mass on the floor of the third ventricle. *Arch Jpn Chir* 38: 800-804, 1969
17. Obenchain TG, Becker DP: Head bobbing associated with a cyst of the third ventricle. *J Neurosurg* 37: 457-459, 1972
18. Okamoto K, Nakasu Y, Sato M, Handa J: Isosexual precocious puberty associated with multilocular arachnoid cysts at the cranial base. Report of a case. *Acta Neurochirur* 57: 87-89, 1981
19. Pierre-Kahn A, Capelle L, Brauner R, Sainte-Rose C, et al: Presentation and management of suprasellar arachnoid cysts. *J Neurosurg* 73: 355-359, 1990
20. Proos LA, Dahl M, Ahlsten G, Tumevo T, Gustafsson J: Increased perinatal intracranial pressure and prediction of early puberty in girls with myelomeningocele. *Arch Dis Child* 75: 42-45, 1996
21. Rotenstein D, Adams M, Reigel DH: Adult stature and anthropomorphic measurements of patients with myelomeningocele. *Eur J Pediatr* 154: 398-402, 1995
22. Segall HD, Hassan G, Ling SM, Carton C: Suprasellar cysts associated with isosexual precocious puberty. *Radiology* 111: 607-616, 1974
23. Shepherd K, Roberts D, Golding S, Thomas BJ, Shepherd RH: Body composition in myelomeningocele. *Am J Clin Nutr* 53: 1-6, 1991
24. Sweasey TA, Venes JL, Hood TW, Randall JB: Stereotactic decompression of a prepontine arachnoid cyst with resolution of precocious puberty. *Pediatr Nerosci* 15: 44-47, 1989

25. Tanner JM, Whitehouse RH., Marubini E, Resele LF: The adolescent growth spurt of boys and girls of the Harpenden growth study. *Ann Hum Biol* 3: 109-126, 1976
26. Trollmann R, Dörr HG, Strehl E, Katalinic A, et al: Growth and pubertal development in patients with meningomyelocele: a retrospective analysis. *Acta Paediatr* 85: 76-80, 1996
27. Trollmann R, Strehl E, Dörr HG: Growth hormone deficiency in children with myelomeningocele (MMC) - effects of growth hormone treatment. *Eur J Pediatr Surg* 7, Suppl 1: 58-59, 1997
28. Trollmann R, Strehl E, Dörr HG: Precocious puberty in children with myelomeningocele: treatment with gonadotropin-releasing hormone analogues. *Dev Med Child Neurol* 40: 38-43, 1998
29. Turgut M, Ekin Ozcan OE: Suprasellar arachnoid cyst as a cause of precocious puberty and bobble-head doll phenomenon. *Eur J Pediatr* 151: 76, 1992

Epilepsy in Childhood Shunted Hydrocephalus

MARIE BOURGEOIS¹, CHRISTIAN SAINTE-ROSE¹, GIUSEPPE CINALLI², WIRGINIA MAIXNER³ AND JEAN AICARDI⁴

Introduction

Although the association between hydrocephalus and epilepsy is well recognized, much controversy still exists about the incidence of epilepsy amongst hydrocephalic children. The reported occurrence varies from 6% to 59% in the literature [4, 6, 7, 12, 14, 16, 18, 22, 28-30, 36, 39, 41-43]. There are many factors that may account for this, including the etiology of the hydrocephalus, its subsequent treatment and any resulting complications. A few studies indicate that the presence of a shunt [2, 13, 16, 26, 39], the number of shunt revisions [5-7, 13, 16, 28, 41], a history of shunt infection [2, 4-6, 16, 28, 39] and perhaps the shunt location [3, 7] increase the risk of developing seizures. However, long-term follow-up has rarely been provided and a number of important questions still remain unanswered. For example, the relationship between raised intracranial pressure and seizures and the way in which seizures in hydrocephalic children may affect developmental outcome have been poorly documented. In addition, there is little information available concerning the type and frequency of seizures or the EEG findings. The aim of this chapter is to address all of these questions, through the analysis of a series of hydrocephalic children, in order to gain a more complete picture of epilepsy in this population.

Materials and Methods

In the period between 1980 and 1990, 1320 hydrocephalic children were treated with ventricular shunts in the Hôpital Necker, Enfants-Malades. Hydrocephalus requiring shunting of cerebrospinal fluid (CSF) was in all cases diagnosed by CT and/or MRI scan. The criteria used to determine the need for shunting included clinical evidence of raised in-

tracranial pressure in association with radiological studies revealing either evidence of hydrocephalus at the initial examination or of progressive ventricular enlargement.

For the purpose of this study, 45 children who did not survive for more than 2 years after shunt insertion were excluded as it was felt that the information available would have been inadequate. Two hundred and fifty-seven patients with hydrocephalus in association with a tumor were excluded to avoid any potential effects that a tumor may have on any epileptic activity. Also excluded were 216 children in whom data were incomplete, resulting in 802 children entering the study.

Data obtained from the medical records included: sex, etiology, prenatal and perinatal history, familial history of nonfebrile seizures, developmental history, and school performance. In addition, we also recorded the presence or absence of seizures, age at onset of seizures, EEG findings, age at first shunt, type of shunt procedure, number of shunt revisions, and complications.

Seizures were divided into different categories: simple partial seizures, complex partial seizures, simple partial plus secondarily generalized tonic-clonic seizures, complex partial plus secondarily generalized tonic-clonic seizures, mixed simple partial-complex (focal clonic or tonic with complex symptomatology) i.e., unilateral motor seizures in addition to complex partial seizures. Seizure frequency was also divided into four groups: daily with an average of at least one seizure per day (and sometimes many more), weekly, monthly, and occasional (e.g., febrile convulsions without consequent epilepsy) seizures.

Standard EEG records were obtained using a 21-channel electroencephalograph. All the EEG records were read by the two same electroencephalographers. The interictal surface EEG was assessed for baseline activity, the presence and topography of focal spikes, and the presence of general-

¹ Department of Pediatric Neurosurgery, Hôpital Necker-Enfants Malades, Paris, France; ² Department of Pediatric Neurosurgery, Santobono-Pausilipon Hospital, Naples, Italy; ³ Department of Neurosurgery, Royal Children's Hospital, Melbourne, Australia; ⁴ Department of Pediatric Neurology, Hôpital Robert Debré, Paris, France

ized paroxysmal discharges in each child. Baseline activity was classified as normal, asymmetrical, or slow. Focal spikes were localized, regional or multifocal, with or without focal, regional, or diffuse slow waves. Generalized paroxysmal discharges included diffuse irregular spike-and-wave activity or multiple spike-and-waves but excluded diffuse high-voltage slow bursts.

During follow-up, serial neurological evaluations and developmental testing were performed. The type of evaluation depended upon the age of the child. Generally evaluations were performed every 6 months for the first 2 years of life and yearly thereafter. IQ results according to the Brunet Lezine or the Wechsler tests were categorized into: "normal" – either verbal or performance IQ over 90; "slightly retarded" – either verbal or performance IQ under 90; "moderately retarded" – between 50 and 90, and "severely retarded" – IQ under 50. The last group was characterized by learning disabilities including memory deficit, attention deficit, speed factor, and problem solving. Behavioral and psychosocial aspects were divided into four groups: normal behavior, psychological impairment (e.g., inhibition, obsession), hyperactivity, and psychosis. School performance was also studied and children were grouped as follows: normal schooling; moderate difficulties with a school delay of under 2 years; significant difficulties with a delay of over 2 years; children with no possibility of schooling; and children who were too young (<6 years) for school. In addition, some children who did not receive formal testing were judged to be of average intelligence because of their academic performance and progress in regular school, even though some in this group may have unrecognized learning disabilities. Standard statistical methods were used to analyze the different variables.

Results

During the specified period, all 802 children included in the study were treated for hydrocephalus with CSF shunts. The median follow-up after shunt insertion was 7.6 years (range 1 to 26 years).

Etiologies

The distribution of the different etiologies of the hydrocephalus is summarized in Table 1, and is characteristic of the usual causes of hydrocephalus in children in Western countries. The majority of children

Table 1. Distribution of etiologies of hydrocephalus

Myelomeningocele	20%
Hemorrhage	23%
Infection	18%
Malformation	16%
Prenatal	8%
Other	6%
Unknown	9%

(73%) had severely enlarged ventricles on preoperative CT scans.

Shunt History

All children were treated with conventional differential, medium-pressure valves. The ventricular catheter was placed according to the site of maximum ventricular dilatation. This was usually in the occipital horn of the lateral ventricle (92%). The right side was the preferred approach (85%). In 51.3% of the children the age at first shunt insertion was under 3 months, in 32% the age at first shunt insertion was between 3 months and 1 year, and 16.7% of the children were older than 1 year.

A total of 1637 operations were performed with an average of 2 operations (range 1-18) per patient in the given study period.

Shunt Complications

Half of the children have not had any complications so far. Shunt complications requiring one surgical intervention occurred in 401 of the 802 children (50%), of whom 220 (28%) have had one complication, 90 (11%) more than two, and 91 (11%) more than three complications. Approximately one-third of the children (36%) experienced a mechanical shunt malfunction, 4.4% suffered infective complications, and another 9.6% a combination of both mechanical and infective complications. Thus the infection rate for the entire series was 14% per patient and 6.8% per procedure. Revisions were equally distributed between proximal, distal, and complete replacement.

Postoperative CT Scan

On postoperative CT scan the majority of the patients had either normal-sized ventricles (34%) or slit ventricles (30%), with the remainder showing some degree of enlargement.

Seizures

Seizures occurred in 255 of the 802 children (32%) at some time during the follow-up period. Of these, 73 patients (28.6%) had their first epileptic seizure prior to initial shunting, whilst the remaining 182 patients (71.4%) developed their seizures after shunting (Figs. 1, 2). Analyzing the time interval between the onset of epilepsy and the time of shunt insertion, there was a peak incidence of seizure occurrence around the time of shunt insertion with the majority being observed in the days preceding shunt insertion.

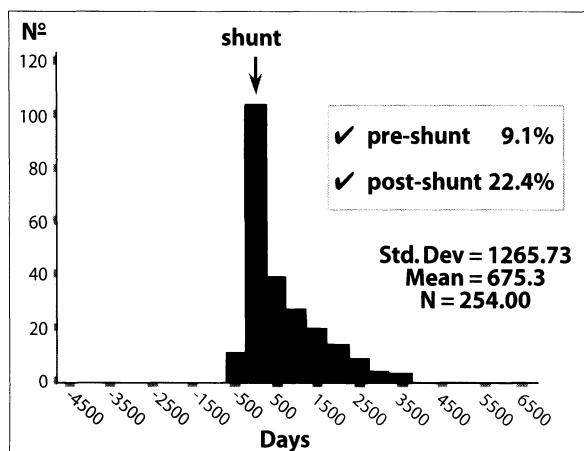


Fig. 1. Time of seizure occurrence versus time of first shunt: seizures peak at the time of diagnosis of hydrocephalus and shunt insertion

Classification of seizures

The overall incidence of seizures in children with shunts was 32%, with two types of patients emerging. The minority were those who had only occasional seizures (35 children or 4.5% of the 802 patients), often with recognized associated causes such as high fever or meningitis. Most of the epileptic patients, however, had recurrent unprovoked seizures (220 children or 27.5% of the 802 patients) for at least 2 years and were poorly controlled with medication. Recurrences were observed even after the commencement of antiepileptic medication, and most had seizures that did not respond well to antiepileptic drug regimens consisting, for the most part, of two or three anticonvulsants. The seizure frequency in these children was at least one prolonged convolution per month, but, unfortunately, most experienced several seizures per week.

There was a significant difference ($p < 0.001, \chi^2$ test) in the severity of epilepsy between the patients who developed seizures before and after shunt insertion. In the preshunt group, a high incidence of occasional seizures (86%) was observed, whereas in the postshunt group most of the children (80%) had recurrent epilepsy. Of the 72 patients in the preshunt seizure group, 33% had a seizure in the first month of life, and 80% before one year. Of the 255 shunted children who experienced seizures, 82 (32.2%) had secondarily generalized tonic-clonic seizures and 111 (43.5%) had simple partial seizures, 95 of whom (37.2%) had focal clonic seizures and 16 (6.3%) focal seizures with complex symptomatology. A further 39 (15.3%) have manifested a combination of several types of epilepsy and the remaining 23 children (9.2%) had catastrophic epilepsy with infantile spasms.

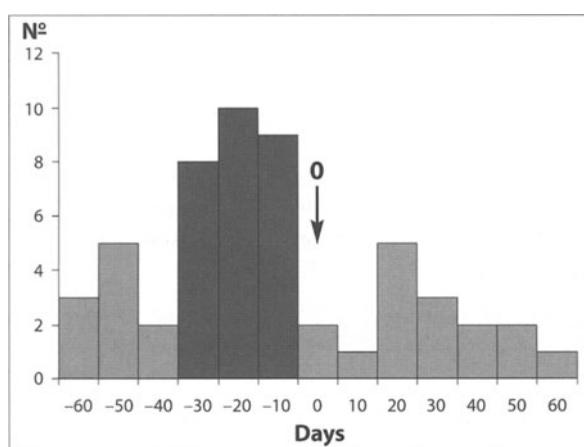


Fig. 2. Detail of Fig. 1, showing the seizure peak concentrated in the month preceding shunt insertion

Seizures Characteristics

Significant differences in the seizure characteristics were observed between pre- and postshunt groups. In the preshunt group a high incidence of generalized epilepsy was observed whereas in the postshunt group a high incidence of partial epilepsy was noted. In both pre- and postshunt groups, in about a third of patients the epilepsy was not controlled by an adequate trial of a "first-line" conventional antiepileptic drug, either as sole therapy or in combination, and proved to be severe epilepsy. Seizure frequency varied among patients but was in most cases high: 108 (43%) suffered seizures daily, 47 (18%) weekly, 53 (21%) monthly, and 47 (18%) had rare attacks of seizures. Common to the children with daily seizures was the occurrence of attacks of clusters of seizures lasting a few days at a time with an average seizure frequency of 10-20 attacks per day. Episodes of

partial status epilepticus were documented in 126 (50%) patients and required admission to hospital.

Seizures vs Hydrocephalus Etiologies

In comparing the proportions of children with seizures, a significant difference emerged between groups with different etiologies (χ^2 test, $p=0.001$). Children with myelomeningocele experienced a significantly lower overall prevalence of epilepsy (7%) than did those in the premature group or those with cerebral malformations (30%), and those with prenatal hydrocephalus (38%). Moreover meningitis and postinfective hydrocephalus carried a high risk for epilepsy in the order of 50%.

Radiological Abnormalities and CNS Malformations

The presence of radiological abnormalities on CT (33% of the patients) was associated with a high incidence of epilepsy at 45%. A CNS malformation seen on CT scan, such as agenesis of the corpus callosum, focal migration abnormalities, encephalocele, holoprosencephaly, absent or hypoplastic cerebellum, and posterior fossa cyst, was a statistically significant variable in predicting seizure occurrence with a higher incidence of epilepsy. The presence of malformations not known to involve the CNS, such as polymalformative syndrome, was also found to be a predisposing factor for the occurrence of seizures in the hydrocephalic children.

Birth Insults

One-third of the children had a history of one or more insults at their birth (anoxia 8%, hemorrhage 9%, infection 10%, multiple 8%). The existence of birth insults was another significant risk factor for the development of seizures (χ^2 test, $p<0.001$). There was a higher incidence of epilepsy among children who suffered hemorrhage (41%), infection (47%), or anoxia (68%) in the neonatal period than among children who did not have a positive birth history (27%).

Influence of Shunt Complications and Raised Intracranial Pressure on Epilepsy

Table 2 shows the relative frequency of shunt complications in three groups, divided into those who had no seizures, those who had occasional seizures, and those who had recurrent epilepsy. The average number of shunt revisions in children with seizures was significantly greater than in those who did not have seizures.

There was a higher incidence of epilepsy among children who had shunt malfunction, infection, or a combination of both. Moreover, there was direct correlation between the incidence of epilepsy and the number of shunt revisions, ranging from only 20% (no revisions) to 52% (3 or more revisions) (Fig. 3).

This study also attempted to determine whether onset of seizures or increased frequency of seizures is a reliable indicator of increased intracranial pressure secondary to shunt dysfunction. The temporal relationship of seizures to shunt dysfunction was defined as seizure activity that occurred within a few days preceding the diagnosis of shunt malfunction and that was not accounted for by an obvious precipitating event such as a febrile illness, an intercurrent infection, or a seizure disorder with lowered therapeutic blood anticonvulsant levels. As shown in Table 3, the

Table 2. Shunt problems in relation to incidence of epilepsy

	No seizures (%)	Occasional fits (%)	Epilepsy (%)
No shunt problems	76	4	20
Malfunction	63	4	33
Infection	51	12	37
Malfunction + infection	53	4	43

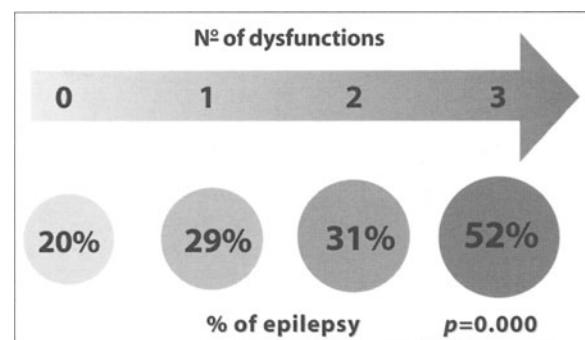


Fig.3. The number of shunt malfunctions correlates significantly with the incidence of epilepsy

Table 3. Presenting symptom of shunt malfunction in relation to seizure history

	History of seizures (%)	No history (%)
Intracranial hypertension	56.5	94.8
Seizures	28.3	3.5
Seizures + intracranial hypertension	9.4	1.0
Other	5.7	0.7

majority of the 407 children admitted for shunt dysfunction presented with clinical evidence of intracranial hypertension; however, seizures alone were the presenting symptom of shunt dysfunction in 8.6% of the whole series. Furthermore, seizures were the sole presenting symptom of shunt dysfunction in 28.3% of the children with a previous history of epilepsy. An EEG was obtained in all of these patients, showing abnormal electrical activity, either diffuse or focal. Some of the children were diagnosed as having had infantile spasms while the remaining children had either generalized seizures, partial motor seizures – sometimes in clusters or of the “hemiconvulsive-hemiplegic” type – or complex partial seizures.

Role of the Ventricular Catheter in Postshunt Epilepsy

The trauma of catheter placement and the subsequent presence of a foreign body within the substance of the brain are potential causes of focal cerebral dysfunction. For this reason we elected to investigate children before and after shunting procedures with EEGs.

Paroxysmal discharges were tabulated as focal if only one focus (spikes isolated, continuous, or in bursts) was demonstrated on all records for a given child. If two or more foci of spikes were demonstrated, the tracing was classified as a multifocal paroxysmal discharges record. It is interesting that most children including some with CNS malformations were reported as having generalized seizures, although the common EEG finding was of focal paroxysmal features, suggesting that a focal onset of the seizure may not have been recognized.

In EEG examinations performed before shunt insertion we found a 27% incidence of a single epileptic focus. This increased to a 50% incidence in the post-

operative EEGs. However, a significant number of patients in this series (45%) had radiological abnormalities which could be an epileptic focus in their own right, as we found a direct relationship between the side of the abnormalities and the side of EEG focus (Table 4). This made it difficult to know whether it was these lesions or the brain injury related to the shunt which were responsible for the focal EEG paroxysmal discharges or slow waves.

To explore this further, we selected from our patients a small subgroup of children with epilepsy, no radiological abnormalities on the CT or MRI, and right posterior parietal ventricular catheters which remained in that site even after revision. A more detailed analysis of the nature of the EEG abnormalities of the 33 patients that fitted these criteria showed that bilateral abnormalities occurred in 76% in the group prior to shunting. In only 8% of the 33 children was spike and wave activity found in the EEG prior to the initial shunting, while in the postshunt group an epileptic focus appeared in the right hemisphere in 30% (Table 5) and on the posterior parietal area in 39.4%, localized to the general region of the shunt (Table 6). So, in most of the children with no evidence of a cerebral parenchymal lesion on CT, the focal side of interictal EEG anomalies was identical to the area of shunt insertion.

In some children who had hemiconvulsions followed by transient hemiplegia, the discharges of slow or spike waves started in the right parietal area where the valve was inserted and involved the anterior regions. Therefore in most of the cases, the spikes were present at the onset of the first seizure, but were preceded by a focus of slow waves. With regard to the site of shunt and its influence on epilepsy, due to the fact that nearly all our patients had been treated via a posterior approach, a valid statistical comparison with the frontal entry point could not be drawn.

Table 4. Location of brain lesions in relation to location of EEG abnormalities

	Bilateral EEG abnormalities (%)	Right-sided EEG abnormalities (%)	Left-sided EEG abnormalities (%)
Bilateral lesion	67	9	24
Right lesion	17	79	4
Left lesion	3	3	94

Table 5. Side of EEG abnormalities in the preoperative and the postoperative period

	Bilateral EEG abnormalities (%)	Right-sided EEG abnormalities (%)	Left-sided EEG abnormalities (%)
Preshunt	76	8	16
Postshunt	52	30	18

Table 6. Location of postoperative EEG abnormalities

Anterior (%)	Posterior (%)	Multilobar (%)	Diffuse (%)
18	39.4	33.3	9.1

Seizure Prognosis

Overall, the prognosis for seizure control was not good. Only 70 among the 255 hydrocephalic children had their antiepileptic medication discontinued for any period of time. Withdrawal of antiepileptic drugs was successful in 35 children who had been seizure-free for at least 3 years and in whom seizures were attributed to transient conditions. None of these 35 children have had recurrent seizures at follow-up. Thirty-five other children whose seizures were considered to represent a more chronic seizure disorder were treated for longer seizure-free periods before medication was stopped. Fourteen of them have remained seizure-free but 21 suffered a relapse within 6 months of cessation of antiepileptic drug therapy. Thus in these children it was concluded that antiepileptic drug monotherapy was necessary to provide an acceptable degree of seizure control.

To summarize in terms of seizure outcome, two different patterns could be observed between those who developed seizures before shunting and those who developed them afterwards. The nature of the seizures in the preshunt group was often generalized and outcome was clearly related to shunt insertion, with two-thirds (63%) improving following this, and one-third remaining with severe epilepsy. On the other hand, the nature of the seizures in the postshunt group was mainly of a focal type, and the seizures were refractory to medical treatment in most cases, with only one-third improving (35%) with antiepileptic medication.

Developmental Assessments

Of the 547 hydrocephalic children without epilepsy, 409 underwent a developmental IQ assessment which showed that 12% had mild retardation, 13% were moderately retarded, and 9% were severely retarded. In the majority (66%) development was normal. In contrast, of the 255 hydrocephalic children with epilepsy, only 24% had normal development, with 23% having mild, 18% moderate, and 35% severe retardation. Mental retardation was statistically significantly higher in children continuing to require medi-

cine for their seizures compared with those whose seizures remitted and for whom treatment was discontinued. This indicated that epilepsy correlated strongly with poor cognitive outcome.

With regard to psychological outcome, there was a striking difference between hydrocephalic patients with seizures, of whom only 32% were normal and 20% were psychotic, and those without seizures, of whom 80% were normal.

Educational outcome also demonstrated the dramatic influence that seizures have on the academic achievement of these children. The majority of the hydrocephalic children without seizures had normal schooling, whereas half of those with seizures were institutionalized.

Discussion

There have been many reports and publications, in particular with regard to epilepsy, concerning the follow-up and complications associated with the treatment of hydrocephalus by ventricular distal shunts. However, the relationship between shunts and their complications and seizures, the interaction between intracranial hypertension and seizures and the influence that these may have on developmental outcome have been poorly documented.

Incidence of Epilepsy Among Hydrocephalic Children

Many studies have investigated the incidence of epilepsy in children with hydrocephalus. Although the results are conflicting as the incidence of epilepsy ranges widely from 9% to 65%, there is general agreement in most of the literature that the incidence of epilepsy in hydrocephalic children of all etiologies is around 30%, which agrees with the incidence of 32% observed in our series.

This incidence is significantly greater than would have been expected at this age in life. This suggests that hydrocephalic children are at a greater risk of having or developing seizures than the general population. In a recent paper Keene and Ventureyra [19] did not find any correlation between the occurrence of epilepsy and shunt malfunction, number of shunts placed, age at first shunt insertion, or the location of the shunt. In the opinion of these authors, patients with hydrocephalus who had significant cognitive delay or significant motor disability were significantly more likely to develop seizures than patients who did not, and they concluded that the occurrence of epilep-

sy was related to an underlying diffuse encephalopathy and not to the hydrocephalus or to the procedures related to its treatment. Klepper et al. [20] believed that associated malformations of the cerebral cortex are probably related to the development of seizures and considered that epilepsy as a complication of intracranial shunting might be overestimated in the literature. However, a high number of their hydrocephalic children had no brain abnormality, the hydrocephalus being considered as idiopathic. Moreover, the epilepsy itself led to a poorer intellectual and neurological outcome. Ruge recently suggested (editorial comment) that analysis of MRI and PET data between the two groups, those with and without brain lesions, could yield some support for the authors' conclusions.

In this context, valid criteria identifying epilepsy related to the surgical procedure need to be defined in order to answer the question of whether having a shunt significantly increases the risk of having epileptic seizures.

Seizures or Epilepsy?

The terms "epilepsy" and "seizures" are often used interchangeably in the literature and perhaps this contributes to the variability of the reported incidence. For a patient to be diagnosed with epilepsy, seizures must occur repeatedly. There is general agreement in most of the literature that the incidence of epilepsy in hydrocephalic children of all etiologies is around 30%, which is comparable with the incidence of 32% observed in our series. However, in contrast to most publications, which only report on the overall frequency of seizures, this study differentiates between transient seizures and epilepsy, finding an incidence of occasional or transient seizures in 4.5% of the children and recurrent seizures in 27.5%.

Influence of Etiology

With regard to the influence that the original etiology of the hydrocephalus may have on the incidence of epilepsy, there remains a diversity of opinion in the literature. Contrary to the findings of the majority of authors [2, 4, 16, 18, 28, 29, 31] who have noted a correlation, others [6, 36, 39] have found no correlation between etiology and the incidence of epilepsy. Lorber et al. [25] and Hosking [16] attributed the high prevalence of epilepsy to underlying brain anomalies or disease. In most reports, the children with myelomeningocele experienced a significantly lower overall prevalence of epilepsy [2, 4, 5, 18, 29], whereas

meningitis [4, 16] and cerebral malformations [2, 28, 29, 39, 41] are strongly correlated with epilepsy. Analyzing our results has shown a correlation quite clearly, not only for those with postinfective hydrocephalus but also with other etiologies. Overall we found that myelomeningocele carries a low risk at 7%, cerebral malformations and intraventricular hemorrhage a medium risk at around 30%, and infection a high risk in the order of 50%.

Influence of Birth Injury

We have also found that other factors, such as history of birth injury or insult, may play a significant role in the development of seizures in hydrocephalic children. Such a history has not been previously found to correlate with the development of epilepsy in such children [28, 29, 39]. However, in contrast, we found a high correlation with children sustaining a birth insult and subsequent epilepsy, with anoxia showing the highest incidence (68%), followed by infection (47%) and hemorrhage (41%).

Influence of Age at Shunt Insertion

The age at shunt insertion is reported to influence occurrence of seizures, the risk being highest in the youngest [6, 42]. Like other authors, we were not able to find such a correlation in our series [7, 25, 28, 29].

Influence of Shunt Location

Much controversy [1, 3, 7, 22, 29, 39, 43] exists about the relative advantages and disadvantages of anteriorly vs posteriorly placed shunts in terms of infection rate, duration of function, and risk of epilepsy. A transfrontal shunt placement was reported to carry a risk of postshunt epilepsy by Dan and Wade [7], but this was disputed by others [1, 22, 43]. In our series, the relationship between shunt site and epilepsy cannot be adequately evaluated, since in our series all shunts were placed in a parietal location except for 15% of patients who had shunt inserted via the frontal region.

Influence of Slit Ventricle

The overdrainage of CSF can cause "slit ventricle syndrome", with clinical signs of CSF overdrainage such as low-pressure headache, vomiting, drowsiness, disturbance of consciousness, motor deficit, and an in-

crease in the frequency of epileptic seizures [11]. Saukkonen et al. [35] demonstrated in a series of 113 shunt-treated hydrocephalic children that repeated EEG evaluation is a valuable aid in the follow-up: if EEG abnormalities appear after shunting, particularly spike and sharp wave activity, with or without slow wave, CSF overdrainage should be expected. In the opinion of the authors, these data justified prophylactic anticonvulsive therapy.

Influence of Shunt Malfunction and Shunt Infection

With respect to how shunt complications may affect the subsequent development of seizures, one must consider the role of shunt infection and shunt dysfunction separately. With few exceptions [25, 31, 36], most reports agree that shunt infection predisposes to epilepsy [2, 4-6, 16, 28, 39, 41]. Disagreement remains on the influence that shunt malfunction may have on the risk of epilepsy. In some series [4, 25, 29, 31, 36, 39], epilepsy was not commonly associated with shunt malfunction, thus not confirming the results of other investigators [2, 5-7, 16, 18, 41].

In our series, however, there was a higher incidence of epilepsy among children who had shunt malfunctions, infection, or a combination of both. Moreover, and perhaps surprisingly, there was direct correlation between the incidence of epilepsy and the number of shunt dysfunctions requiring revisions (Fig. 3). These results contradict those previously reported in the literature [4, 39].

Are First-Time Seizures or a Recurrence of Seizure Activity the Presenting Symptom of a Shunt Dysfunction?

Another important issue that has attracted debate in the past is whether seizure activity can be the presenting symptom of shunt dysfunction. Some reports mention an increased number of seizures or reappearance of seizures when the shunt is malfunctioning [10, 18, 26, 38]. Faillace and Canady [10] emphasized the importance of the onset of a first-time seizure or new seizure activity in a previously shunted child, despite a relatively low incidence of 2%. A relationship between seizure and shunt dysfunction or raised intracranial pressure was proposed but not clearly identified. Others do not agree with these findings [4, 28], whereas some take an intermediate view and conclude that, although seizures alone are not a good predictor of shunt malfunction, they may be seen as one of the presenting symptoms [9, 15, 16, 39].

We found that in patients with a previous history of epilepsy, seizures (either a new onset after a long period of controlled epilepsy or increased activity) were the presenting symptom of malfunction in 28%, whereas the figure was only 3% among children without such a history.

Could the Shunt Induce Seizures?

Considerable controversies surround the influence of a ventricular catheter on the total risk of epilepsy. In contrast to hydrocephalic children, in whom the overall reported rate is around 30%, the incidence of epilepsy following subdural shunts and ventriculostomy is very low [24, 37]. Moreover, the development of epilepsy occurring specifically after shunt placement for hydrocephalus could be directly related to the shunting, as evidenced by the widely varying reported values of newly occurring post-shunt epilepsy, ranging from the 24% and 18% quoted by Copeland et al. [6] and Marossero et al. [27], respectively, to the 7.2% reported by Venes and Dauser [43].

Ines and Markand [17] later evaluated a large series of hydrocephalic children for EEG abnormalities and seizures. Of 65 patients with right-sided shunts, half had recurrent seizures. The authors noted that the majority of seizures began within 4 years after placement of the shunt. Varfis et al. [42] reported similar data and observed that the irritative focus usually became evident during the 2nd year following surgery, and that a slow wave pattern usually preceded the occurrence of paroxysmal discharges.

In another study, Johnson et al. [18] suggested that the incidence of epilepsy could increase proportionally to the duration that the brain was exposed to the catheter, because the majority of seizures occurred months after the shunt was inserted. Collectively these reports suggest that cortical injury at the time of shunt placement could be a factor in the development of seizures.

The influence of the ventricular catheter has been further explored by studying EEG abnormalities, which have been frequently found in shunted patients [12, 14, 17, 23, 41, 42]. For Saukkonen [34], a focal slow-wave focus was frequently seen within the 1st year of life in children with hydrocephalus and may have originated from enlargement of the third ventricle rather than as an effect of the ventricular catheter.

Sulaiman and Ismail [40] concluded that, whatever the cause, hydrocephalus in children may be associated with generalized or focal EEG abnormalities, reflecting the underlying disease disorder.

Most interestingly, focal paroxysmal discharges

have been reported to be significantly more frequent in shunted than in nonshunted patients [21, 30]. One of the first indications of potential seizure disorder following shunting was reported by Laws and Niedermeyer [21], who noted that 15 of 18 patients with shunts had EEG abnormalities. Lateralization of the abnormality was to the right hemisphere in 11 children. In a comparative group of infants with hydrocephalus and no shunting, there was a high incidence of normal traces and no significant lateralization. The matter was pursued further by Graebner and Cellesia [14], who also compared a group of shunted hydrocephalic patients with a nonshunted group and found a higher incidence of abnormal records in the shunted group. Further, they found focal specific paroxysmal discharges and slow waves in the area of the ventricular catheter in 85% of shunted hydrocephalic children as compared with 62% of nonshunted hydrocephalic children. These authors concluded that shunts could be responsible for cortical injury.

It is difficult to relate the onset of epilepsy to the insertion of a ventricular catheter through the cerebral mantle, and not to the etiology of the hydrocephalus or to a focal cerebral lesion as identified on neuroradiological examination [5, 22, 28, 29, 31, 34-36, 39, 43]. In this context, the influence of a single surgical procedure is difficult to assess, and valid criteria identifying epilepsy related to the surgical intervention are difficult to define. Among the criteria most commonly used are: postoperative onset of epilepsy, focal discharges at the site of the shunt and contralateral seizures [6, 9, 14, 17, 27, 36, 43].

In our series, 71% patients developed epilepsy after the shunt placement, with a high incidence of partial seizure and focal contralateral EEG abnormalities. However, in patients with radiological abnormalities, we found a direct relationship between the side of the lesion and the side of EEG focus. Thus, it was difficult to know whether these lesions or the brain injury related to the shunt were responsible for the EEG focal abnormality.

To clarify this point, we selected a small group of 33 patients with postshunt epilepsy who had no radiological abnormalities, and who had right posterior parietal ventricular catheters that remained on that site even following revision. In this subgroup there was a right posterior parietal focus in as many as 39.4%. Moreover, the seizures in this subgroup of children without radiological abnormalities were partial and originated at the irritative "shunt-linked" focus. Of particular interest, this irritative focus was always located where the catheter was first inserted, was not present before the operation, and developed about 1 or 2 years after the insertion of the shunt, often on a focus of slow waves.

Having dealt with all the factors that may cause the seizures, it is important to identify any factors that could predict seizure remission and subsequent cessation of medical therapy. Noetzel and Blake [28, 29] attempted to determine this. Their study indicated that mental retardation or CNS malformations were poor predictors of seizure remission, whilst children older than 3 years at seizure onset, who had no EEG abnormalities and had been seizure-free on anticonvulsants for 3 years, had a good chance of remaining seizure-free after withdrawal of medical treatment. Our results have led us to similar conclusions, where cessation of antiepileptic drugs, albeit in a small proportion of our patients, was successful in 35 children who had been seizure-free for at least 3 years and in whom seizures were attributed to transient conditions.

Cognitive Level

In the current literature there are many conflicting views regarding the effects of hydrocephalus on cognition and memory. Research on multiple shunt revisions, and their effect on the child's overall cognitive functioning, is limited and has produced inconsistent findings in the literature [32]. It was generally concluded that the cognitive defects were not related to hydrocephalus but rather to other developmental brain anomalies.

In a recent study, Ralph et al. [33] demonstrated that the underlying "lesion" causing the hydrocephalus may have the greatest influence on cognitive functioning, as opposed to the number of shunt revisions. Their study suggested that multiple shunt revisions do not impact significantly on the subject's overall cognition and memory compared to single shunt placement. However, children with shunted hydrocephalus performed at a lower level on measures of cognition and memory. The authors concluded that seizures were the only variable to significantly account for the variance in scores of cognition, verbal comprehension, and perceptual organization.

Perhaps one of the most important points is the universally accepted fact that the presence of seizures in children predisposes to poor intellectual outcome [2, 8, 28, 29, 39]. In our series, we not only found that epilepsy correlated strongly with poor cognitive outcome, but that in addition there was a similar strong negative correlation between epilepsy and psychological and educational outcome as well.

These findings have practical implications as these children may benefit from early and serial neuropsychological evaluations to determine appropriate education.

Future Directions

Having become aware of potential predisposing factors for seizure development in hydrocephalic children, we must focus on ways to reduce their occurrence. One way is to avoid shunts altogether by using alternative procedures such as neuroendoscopic third ventriculostomy to treat the hydrocephalus when anatomically possible, both as a primary treatment and in cases of shunt malfunction [37]. Another is to avoid shunt complications by taking meticulous steps to reduce infection, and also prevent subsequent shunt malfunction by striving to improve surgical technique and to develop improved materials and valves. In this way, some impact may be made on improving intellectual and psychological outcome in these patients by reducing their overall incidence of epilepsy.

Conclusion

We conclude from our data that epilepsy is associated with infantile hydrocephalus in one-fourth to one-third of children and its onset occurs around the same time that the diagnosis of hydrocephalus is made. The etiology of the hydrocephalus and the presence of radiological abnormalities were found to be strong predictors of epilepsy. In addition, episodes of intracranial hypertension related to hydrocephalus or shunt dysfunction may further predispose to epileptic seizures. We feel it is essential to emphasize the importance of the onset of a first-time seizure or new seizure activity in a shunted child. Shunt complications, both infective and mechanical, predispose to epilepsy, but even the presence of a shunt catheter on its own can promote an epileptogenic focus. Finally, epilepsy appears to be an important predictor of poor intellectual outcome in shunted hydrocephalic children. A prospective study is needed to clearly identify and confirm avoidable factors predisposing to seizures in these children, so that we can strive to reduce seizure incidence and improve the children's quality of life.

References

1. Albright A, Haines S, Taylor F: Function of parietal and frontal shunts in childhood hydrocephalus. *J Neurosurg* 69: 883-886, 1988
2. Bartoshesky L, Haller J, Scott R, et al: Seizures in children with meningomyelocele. *Am J Dis Child* 139: 400-402, 1985
3. Bierbrauer K, Storrs B, D'Ml, et al: A prospective, randomized study of shunt function and infections as a function of shunt placement. *Pediatr Neurosurg* 16:287-291, 1990-1991
4. Blaauw G: Hydrocephalus and epilepsy. *Z Kinderchir* 25: 341-345, 1978
5. Chadduck W, Adametz J: Incidence of seizures in patients with myelomeningocele: a multifactorial analysis. *Surg Neurol* 30: 281-5, 1988
6. Copeland G, Foy P, Shaw M: The incidence of epilepsy after ventricular shunting operations. *Surg Neurol* 17: 279-281, 1982
7. Dan N, Wade M: The incidence of epilepsy after ventricular shunting procedures. *J Neurosurg* 65: 19-21, 1986
8. Dennis M, Fitz C, Netley C, et al: The intelligence of hydrocephalic children. *Arch Neurol* 38: 607-615, 1981
9. Di Rocco C, Iannelli A, Pallini R, et al: Epilepsy and its correlation with cerebral ventricular shunting procedures in infantile hydrocephalus. *Ann Rev Hydrocephalus* 4: 74-75, 1986
10. Faillace W, Canady A: Cerebrospinal fluid shunt malfunction signaled by new or recurrent seizures. *Child's Nerv Syst* 6: 37-40, 1990
11. Faulhauer K, Schmitz P: Overdrainage phenomena in shunt treated hydrocephalus. *Acta Neurochir (Wien)* 45: 89-101, 1978
12. Fernell E, Hagberg B, Hagberg G, et al: Epidemiology of infantile hydrocephalus in Sweden: a clinical follow-up study in children born at term. *Neuropediatrics* 19: 135-142, 1988
13. Finney H, Arlant P: Focal seizure disorder secondary to multiple shunt revisions. A case report. *Child's Brain* 3: 62-64, 1977
14. Graebner R, Celesia G: EEG findings in hydrocephalus and their relation to shunting procedures. *Electroencephalogr Clin Neurophysiol* 35: 517-521, 1973
15. Hack C, Enrike B, Donat J, et al: Seizures in relation to shunt dysfunction in children with meningomyelocele. *J Pediatr* 116: 57-60, 1990
16. Hosking G: Fits in hydrocephalic children. *Arch Dis Child* 49: 633-635, 1974
17. Ines DF, Markand ON: Epileptic seizures and abnormal electroencephalographic findings in hydrocephalus and their relation to the shunting procedures. *Electroencephalogr Clin Neurophysiol* 42: 761-768, 1977
18. Johnson D, Conry J, O'Donnell R: Epileptic seizure as a sign of cerebrospinal fluid shunt malfunction. *Pediatr Neurosurg* 24: 223-227; discussion 227-228, 1996
19. Keene D, Ventureyra E: Hydrocephalus and epileptic seizures. *Child's Nerv Syst* 15: 158-162, 1999
20. Klepper J, Büssé M, Straburg H: Epilepsy in shunt-treated hydrocephalus. *Dev Med Child Neurol* 40: 731-736, 1998
21. Laws EJ, Niedermeyer E: EEG findings in hydrocephalic patients with shunt procedures. *Electroencephalogr Clin Neurophysiol* 29: 325, 1970
22. Leggate J, Baxter P, Minns R, et al: Role of a separate subcutaneous cerebro-spinal fluid reservoir in the management of hydrocephalus. *Br J Neurosurg* 2: 327-337, 1988
23. Liguori G, Abate M, Buono S, et al: EEG findings in shunted hydrocephalic patients with epileptic seizures. *Ital J Neurol Sci* 7: 243-7, 1986
24. Litofsky N, Raffel C, McComb J: Management of symptomatic chronic extra-axial fluid collections in pediatric patients. *Neurosurgery* 31: 445-450, 1992
25. Lorber J, Sillanpää M, Greenwood N: Convulsions in children with hydrocephalus. *Z Kinderchir Grenzgeb* 49: 346-351, 1978

26. Majewska Z, Szelozynska K: Epileptic fits in children with hydrocephalus. *Acta Universitatis Carolinae Medica Monographia* 75: 92-93, 1976
27. Marossero F, Massarotti M, Migliore A: [EEG abnormalities in infantile hydrocephalic subjects after ventriculo-atrial shunts]. [In Italian]. *Riv Neurol* 40: 239-241, 1970
28. Noetzel M, Blake J: Prognosis for seizure control and remission in children with myelomeningocele. *Dev Med Child Neurol* 33: 803-810, 1991
29. Noetzel M, Blake J: Seizures in children with congenital hydrocephalus: long-term outcome. *Neurology* 42: 1277-1281, 1992
30. Pampiglione G, Laurence K: Electroencephalographic and clinical pathological observation in hydrocephalic children. *Arch Dis Child* 37: 491-499, 1962
31. Piatt JJ, Carlson C: Hydrocephalus and epilepsy: an actuarial analysis. *Neurosurgery* 39: 722-727; discussion 727-728, 1996
32. Prigatano G, Zeiner H, Pollay M, et al: Neuropsychological functioning in children with shunted uncomplicated hydrocephalus. *Child's Brain* 10: 112-120, 1983
33. Ralph K, Moylan P, Canady A, et al: The effects of multiple shunt revisions on neuropsychological functioning and memory. *Neurol Res* 22: 131-136, 2000
34. Saukkonen A: Electroencephalographic findings in hydrocephalic children prior to initial shunting. *Child's Nerv Syst* 4: 339-343, 1988
35. Saukkonen A, Serlo W, von Wendt L: Electroencephalographic findings and epilepsy in the slit ventricle syndrome of shunt-treated hydrocephalic children. *Child's Nerv Syst* 4: 344-347, 1988
36. Saukkonen A, Serlo W, von Wendt L: Epilepsy in hydrocephalic children. *Acta Paediatr Scand* 79: 212-218, 1990
37. Scarff J: Treatment of hydrocephalus: an historical and critical review of method and results. *J Neurol Neurosurg Psychiatry* 26: 1-26, 1963
38. Sekhar L, Moossy J, Guthkelch A: Malfunctioning ventriculoperitoneal shunts. Clinical and pathological features. *J Neurosurg* 56: 411-416, 1982
39. Stellman G, Bannister C, Hillier V: The incidence of seizure disorder in children with acquired and congenital hydrocephalus. *Z Kinderchir* 41 (Suppl 1): 38-41, 1986
40. Sulaiman A, Ismail H: Pattern of electroencephalographic abnormalities in children with hydrocephalus. *Child's Nerv Syst* 14: 124-126, 1998
41. Talwar D, Baldwin M, Horbatt C: Epilepsy in children with meningomyelocele. *Pediatr Neurol* 13: 29-32, 1995
42. Varfis G, Berney J, Beaumanoir A: Electro-clinical follow-up of shunted hydrocephalic children. *Child's Brain* 3: 129-139, 1977
43. Venes J, Dauser R: Epilepsy following ventricular shunt placement [letter]. *J Neurosurg* 66: 154-155, 1987

Subject Index

- Abscess 205, 207
Achondroplasia
 genetics 8-9
 radiology 88
Acquired hydrocephalus 96
Adult hydrocephalus, classification 105
Aicardi syndrome 3
Alzheimer 48
Anatomy, endoscopic, of the brain 352-359
 aqueduct 358
 basilar artery 356-357, 374-375, 414-415
 choroid plexus 353-355, 371
 infundibular recess 356, 372, 373
 interthalamic adhesion 358
 mammillary bodies 347, 356-357, 372, 373
 Monro foramen 352-356, 371
 posterior commissure 358-359
 septal vein 354
 thalamostriate vein 353-354
 third ventricle 356-359
Anti siphon device 54-56, 300, 338
Appendicitis, in ventriculo-peritoneal shunts 315-319, 325
Aqueduct, sylvian
 anatomy 279-280
 CSF flow through 49, 283-284
 endoscopy 357-359
 syndrome 287-289
Aqueductal stenosis
 congenital 84
 in Dandy-Walker malformation 266
 etiology 281-283
 genetics 1
 hydrocephalus, in 283
 anatomical changes 284-285
 pathophysiology 283-284
 prognosis 290
 radiology 284-287, 289-290
 symptoms 287-288
 treatment 362
 pathology 280
 post CMV infections 204
 post-haemorrhagic 85
 post-toxoplasmosis 202-203
 post viral infections 209
 radiology 83
 X-linked hydrocephalus 1-2
Aqueductoplasty 237-240
Arachnoid
 embriology 22
Arachnoid cyst
 in posterior fossa 86-87, 263
 suprasellar 169, 437-438
Arachnoid villi 36, 37, 50
Arachnoiditis
 in Dandy-Walker malformation 267
 neoplastic 191
“Arrested” Hydrocephalus 139, 140
Ascites 320-322
Astrocytoma
 radiology 85
ATPase, Sodium-Potassium 26
Atrial diverticula, *see* diverticula
Atrial Natriuretic Peptide 31
“B” waves 55, 57
Bacterial infection 205-207
Basal ganglia, in hydrocephalus 70-72
Basilar artery 356-357, 374-375, 414-415
Blood flow, cerebral (CBF) 67-68
Blood vessels 67
Blood-brain barrier
 ontogenesis 33-35
Blood-CSF barrier
 ontogeny 35-36
Bowel perforation, in shunts 322-323
Brain
 atrophy 53
 compliance 51
 energy metabolism 68
 extracellular space 69
 morphological changes in hydrocephalus 66
 volume 47
 water content 69
 white matter 69-70
Brain stem
 in Chiari II 134

- Candida albicans 204, 206
 Catheter, in shunts 301
 Causes of hydrocephalus 81
 Cavum Septi Pellucidi 240-242
 Cavum Vergae 240-242
 Cephalocranial disproportion 339-340, 344
 Cerebral blood flow *see* Blood flow
 Cerebral cortex, in hydrocephalus 68-71
 Cerebrospinal fluid (CSF)
 circulation 49, 79
 computerized infusion test 53
 drainage 50
 dynamics model 50-52
 in shunted patients 54-55
 embriology of CSF pathways 19-37
 metabolism 69
 overdrainage 59
 overproduction 82
 production 47-49
 reabsorption 36, 50
 resistance to outflow (R_{csf}) 52
 measurement 56
 relations with cerebral autoregulation 60
 secretion and circulation 29, 47-49
 vascular compensation 57, 59
 Cestode 246
 Chromosomal abnormalities 1
 in Dandy-Walker malformation 3, 265-266
 Chiari I malformation
 radiology 88
 in slit ventricle syndrome 343
 Chiari II malformation
 hydrocephalus and 133-134
 radiology 88
 Chimaeras 23
 Choroid plexus
 embriology 24-33
 endoscopic anatomy 352-356
 enzymes 26
 morphogenesis 28
 regulation of functions 30
 cholinergic innervation 30
 endocrine regulation 31-33
 peptidergic innervation 31
 sympathetic innervation 30
 removal 47
 Cisterna Magna, Prominent 263
 Classification, of hydrocephalus 95
 Clinical trial randomized 329
 Coccidioidomycosis 213-214
 Collier's sign 288
 Colloid cyst
 epidemiology 171-172
 histogenesis 173
 histology 172
 hydrocephalus in 173
 pathophysiology 173
 immunohistochemistry 172
 management 175
 endoscopy 176-180
 shunting 175
 stereotaxy 176
 surgical removal 181-182
 mortality 172
 neuroradiology 174
 pathology 172
 sudden death 174
 symptoms 173-174
 "Communicating" hydrocephalus 49
 external hydrocephalus 91
 metastasis 90
 post-meningitic 90
 post-hemorrhagic 89
 venous hypertension 91
 Complication 315-317, 319, 321-326, 411, 412, 414-417
 radiology 92
 Computed tomography 80
 Congenital hydrocephalus, *see* fetal hydrocephalus
 Corpus callosum agenesis 2
 in Aicardi syndrome 4
 Cortex, cerebral, *see* cerebral cortex
 Craniopharyngioma 164
 Cryptococcal meningitis 211-213
 Cryptococcus neoformans 211
 CRASH syndrome 1-2, 3
 CSF, *see* Cerebrospinal fluid
 CSF Shunt, *see* Ventriculoperitoneal shunts
 Cyst, tumor
 endoscopic drainage 169
 stereotactic drainage 168
 Cysticercosis
 CSF in 250
 diagnosis 250-251
 epidemiology 245
 hydrocephalus in 245, 252-255
 incidence 245-246
 life cycle 246-247
 meningitis in 250
 pathology 247-249
 prophylaxis 255
 symptoms 249-251
 treatment 251
 endoscopy 253-254
 medical 251
 Cysticercus 248
 Cytomegalovirus (CMV) 203-204
 Dandy-Walker Complex, *see* Dandy-Walker Malformation
 Dandy-Walker malformation 3
 chromosomal abnormalities in 3-5, 265-266
 definition 259-263
 hydrocephalus in 266

- pathophysiology 266
epidemiology 269
outcome 275
symptoms 269
treatment 270-275
mendelian disorders 3-5
pathogenesis 4, 264-266
pathology 263-264
 Cerebellum 264
 Cyst wall 263
radiology 86, 269-270
teratogens in 3-5
Davson's equation 59
Definition of hydrocephalus 95
Delta valve 55, 329-333, 338, 342
Dementia 106
Diverticula, atrial, in aqueductal stenosis 286-287
- Echinococcus 245
Ectoderm 19-25
Embriology 19-45
Encephalocele
 in Dandy-Walker malformation 4
 genetics 8
Endocrinology in hydrocephalus 435-440
 growth hormone 435-436
 puberty 436-437
 treatment 439-440
 weight 436
Endoscope 351-352
 flexible 368
 rigid endoscope 351-352, 368
 rigid fiberscope 368
 steerable 368
Endoscopic third ventriculostomy, *see* third ventriculostomy
Engrailed-1 transcription factor 4
Ependyma
 changes in hydrocephalus 66
Ependymoma
 radiology 85
Epilepsy, in hydrocephalus 443-453
 characteristics 445-446
 cognitive level 451-452
 etiological factors 449-450
 incidence 443-445, 448-449
 prognosis 448
 in shunt complications 450
 ventricular catheter 449-450
Escherichia Coli 204
"External" Hydrocephalus 145, 146
 classification 103-104
 radiology 91
- Failure 421-423
Fetal hydrocephalus 96
- classification 96
diagnosis 97
genetics 1-3, 99
infection 202
management 98
models 98
pathophysiology 65
FGFR3 (Fibroblast Growth Factor Receptor) 9
- Fibrinogen
 and spinal cord tumors 190
- Foramen magnum
 obstruction 88
 radiology 88
- Foraminocephaly, of Monro foramen 233
- Forking, of the sylvian aqueduct 280
- Fornix 347, 353
- Fourth ventricle
 choroid plexus formation in, 28
 isolated
 aqueductoplasty 237-238
 clinical signs 234
 definition 219, 233
 endoscopy 237
 etiology 234
 forms 234
 open surgery 237
 radiology 87, 234-235
 shunt 236
 treatment 236
 roof of the 30
 tumors 85
 radiology 85
- Gastrulation 20
- Genetics 1, 14
Germ cell tumors, hydrocephalus in 169
- Germinal matrix 121-122
- Gliosis, in aqueductal stenosis 280
- Glucocorticoid hormone 32
- Glucose metabolism in hydrocephalus 68
- Growth hormone 435-436
- Hakim programmable valve 55, 298-299, 342
- Hakim triad 105-107
- Haemophilus influenzae 206, 207
- Histoplasmosis 255
- Holoprosencephaly
 alobar 5
 associated malformations 5
 genetics 5
 lobar 5
 semilobar 5
- Hydatidosis 245
- Hydroxytryptamine 31
- Hypotension, intracranial 338-339, 342
- Hysteresis 56

- Histoplasma capsulatum 255
 Histoplasmosis 255-256
- Imaging, in hydrocephalus 79-93
 post-operative 81
 pre-natal 81
- Infundibular recess 356-357
- Infusion test 51, 53, 55-57, 60
- Insulin 32
 Insulin-like Growth Factor II 32
- Interthalamic adhesion 358
- Intracranial hypertension 187, 189-192, 194, 195
- Intracranial hypotension 338, 341, 342
- Intracranial pressure 48, 56, 113, 114
 monitoring 56-57
 in slit ventricle syndrome 337-340
- Intraventricular septa 223
- Isolated compartments hydrocephalus 100-102
- Joubert syndrome 3
- Koerber-Salus-Elshnig syndrome 288, *see also* Aqueduct syndrome
- Lactate metabolism in hydrocephalus 68
- Leukomalacia, *see* periventricular leukomalacia
- L1 gene 3
- L1CAM proteine 2
- Longstanding Overt Ventriculomegaly in Adults 107
- LOVA, *see* Longstanding Overt Ventriculomegaly in Adults
- Lumboperitoneal shunt
 in slit ventricle syndrome 342
- Luschka foramen
 CSF flow through 49
 atresia of, in Dandy-Walker malformation 266
- Magendie foramen
 CSF flow through 49
 atresia of, in Dandy-Walker malformation 266
- Magnetic Resonance Imaging (MRI)
 CISS sequence 405-410
 dynamic MRI 397-402
 in hydrocephalus 80
 third ventriculostomy assessment 400-401
- Mammillary bodies 347, 356-357, 372, 373
- MASA syndrome 2
- Meckel-Gruber syndrome 3, 4
- MEDOS valve 299
- Medulloblastoma
 radiology 85
- Melatonin 31
- Meninges 19, 22-25, 33
 embryology 23
- histogenesis 24
 meningeal cells 25
 structure 22
- Meningitis 206-207
- Merlin 12
- Mesoderm 21-23
- Methabolism in hydrocephalus 68
- Midbrain-Hindbrain organizer 4
- Migraine 340
- Monro, foramen of
 damage of, during ETV 371-372, 413
 endoscopic anatomy 352-356, 371
 in slit ventricle syndrome 335-337
 obstruction by colloid cyst 173, 178
 obstruction in neoplasms 232
 obstruction in unilateral hydrocephalus 82, 100-102, 232
 treatment 233
- Monro-Kellie doctrine 47
- Multiloculated hydrocephalus, *see also* Isolated compartments hydrocephalus
 classification 219
 clinical features 224
 congenital 222
 definition 219
 etiology 220
 hemorrhage in 221
 pathogenesis 220-221
 pathology 223
 prognosis 229
 radiology 224
 repeated shunt surgery 222
 shunt infection 221
 treatment
 craniotomy 227
 endoscopy 227-228
 shunts 226
 stereotaxy 227
 tumor surgery 222
 ventriculitis in 221
- Mumps 208
- Mycobacterium 211
- Mycotic infections 206
- Myelination 70, 73
 hydrocephalus 114-117
 intracranial pressure 113-114
 magnetic Resonance 114, 117
 neurodevelopment 115-116
- Myelomeningocele hydrocephalus
 aqueduct stenosis, role of 134
 arrested hydrocephalus 139
 Chiari II malformation, role of 134
 closure of the 135
 epidemiology 133
 intrauterine repair 135
 natural history 133

- pathophysiology 133
 psychomotor development 140
syringomyelia 141
 treatment 137
 pitfalls 138
 shunts 137
 timing 138
 third ventriculostomy 138
 venous abnormalities 135
Myelomeningocele
 genetics 6-8
- Neural tube defects** 6-8
 folic acid 6, 8
 genetics 6
 mouse models 7-8
- Neurocele, central** 20
- Neurocele, spinal** 21
- Neurocysticercosis, see** *Cysticercosis*
- Neurodevelopment** 113-118
- Neurofibromatosis** 10-13
 aqueductal stenosis in 11, 282
 Neurofibromatosis type I 10-12
 genetics 11
 Mouse models 12
 Moya-Moya in 11
 Neurofibromin 11
 optic nerve gliomas in 11
 tumors in 11
 UBO (Unidentified Bright Objects) in 11
 Neurofibromatosis type II 10, 12-13
 genetics 12
 schwannomas 12
- Neuropore**
 anterior 5
 posterior 5
- Neurulation** 20-21
- “Non-communicating” hydrocephalus** 54
- Normal pressure hydrocephalus**
 definition 105
 diagnosis 106
 terminology 106
- NPH, see** *Normal Pressure Hydrocephalus*
- Obex, cyst of the** 191
- Obstruction** 421-423
- “Obstructive” hydrocephalus**
 aqueduct obstruction 83
 3rd ventricle obstruction 83
 radiology 82
- Optic Pathways Glioma (OPG)** 165
- Orbis Sigma valve** 299-300, 329-333, 338, 342
- Osteochondrodysplasia, see** *Achondroplasia*
- OSV II, see** *Orbis Sigma valve* 342
- Overdrainage** 54-56, 298-301, 338-339
- Pallister-Hall syndrome** 5
- Papile grading scale** 123
- Paramyxovirus, see** *mumps*
- Parinaud’s sign**
 in aqueductal stenosis 287
 in sylvian aqueduct syndrome 288
- Pathology** 192
- Pathophysiology** 65
- Pericerebral collections** 145, 146-149
 clinical features 146
 incidence 145
 natural history 148
 pathophysiology 103-104, 145
 post-meningitic 207
 radiology 91, 146-147
 subdural hematoma 148-151
 treatment 150-152
- Peritoneal pseudocyst** 315, 319, 320
- Periventricular leukomalacia** 222
- Perspective Classification of**
 Congenital Hydrocephalus (PCCH) 96
- Pia mater**
 embriology 22-23
- Pneumoencephalography** 193
- Poiseuille’s law** 296
- Posterior fossa**
 arachnoid cyst 86
 tumors and hydrocephalus 155
 external drainage 155-156
 third ventriculostomy 158, 160-161
 shunts, in Dandy-Walker 271-273
 shunts, in isolated fourth ventricle 236
 volume in Chiari II 134
- Posthemorrhagic hydrocephalus**
 clinical presentation 123-124
 complications 128
 epidemiology 122
 medical treatment 126-127
 outcome 128-129
 pathophysiology 121, 126
 periventricular leukomalacia 222, 223
 radiology 89
 risk factors 125
 surgical treatment 127
 ultrasonography 123
 VP shunts in 128
- Posterior commissure** 358-359
- Postinfectious hydrocephalus** 201
- Post-traumatic hydrocephalus** 104
- Pregnancy, in shunts** 325-326
- Prenatal hydrocephalus, see** *congenital*
- Pressure gradients**
 in aqueductal stenosis 283-286
 in slit ventricle syndrome 337
 within skull 49
- Prolactin** 33

- Proteus mirabilis 205
 Pseudotumor cerebri 92
 Puberty, in hydrocephalus 436-437
- Repeat third ventriculostomy 421-423
 RIMLF (rostral interstitial nucleus of the medial longitudinal fasciculus) 288
 Rubenstein-Taybi syndrome 5
- Scolex 246
 Septa, intraventricular 223
 Septal vein 354
 Septostomy
 in suprasellar tumors 168
 in unilateral hydrocephalus 232
 Septum, in aqueductal stenosis 280
 Septum pellucidum
 changes in hydrocephalus 66, 353
 endoscopic anatomy 352-353
 in multiloculated hydrocephalus 226
 Shunts, *see* Ventriculo-peritoneal shunts
 Sigma valve, *see* Orbis Sigma valve
 Siphon-control device, *see* Delta valve
 Skull X-Rays 79
 Slit ventricle syndrome 335-348
 cephalocranial disproportion in 339-340
 Chiari malformation in 342-343
 ICP monitoring 337
 intermittent ventricular catheter occlusion 339
 intracranial hypertension in 339-340
 intracranial hypotension 338
 migraine 340
 pathophysiology 337
 radiology 93
 treatment 341-348
 in cephalocranial disproportion 344
 in IC hypotension 342
 in intermittent occlusion 342-343
 lumboperitoneal shunts 342
 shunt removal 344-348
 third ventriculostomy 344-348
 Smith-Lemli-Opitz syndrome 5
 Somites 22-23
 Spina bifida aperta, *see* myelomeningocele
 Spinal tumor, hydrocephalus in
 extradural 189
 extramedullary 189
 intramedullary tumors 188
 literature 188
 management of 194
 pathophysiology 189
 radiology 89, 194
 Spirometry 245
 Stereotaxy
 in colloid cysts 176
- in multiloculated hydrocephalus 227
 Subarachnoid hemorrhage 192
 Subarachnoid space
 embriology 24
 Subdural haematoma 145, 148, 149, 151
 Subdural shunt 151, 152
 Suboccipital decompression, in slit ventricle syndrome 343
 Subtemporal decompression, in slit ventricle syndrome 343-344
 Superficial Glia Limitans 24-25
 Suprasellar tumors, hydrocephalus in
 clinical signs 164
 complications 169
 endoscopy 166
 incidence 164
 management of 166
 pathophysiology 164
 radiology 165
 septostomy 168
 shunts 168
 surgery 166
 timing 166
 Sylvian aqueduct syndrome, *see* Aqueduct
 Syringomyelia
 in Dandy-Walker malformation 268
 in myelomeningocele 141
 Taenia solium 245
 Temporal horn, entrapped
 clinical features 230
 definition 219-220, 229
 treatment 230
 Thalamostriate vein
 endoscopic anatomy 353-354
 in foraminoplasty 233
 Thanatophoric dysplasia 9
 Third ventricle 356-359
 Third Ventriculostomy, Endoscopic (ETV)
 complications 411-420
 bradycardia 411-412
 CSF leak 370, 377-379
 damage to the fornix 413-414
 damage to the hypothalamus 414
 infection 417
 seizures 417
 subdural hygroma 416, 418-419
 vascular damage 414-417
 visual obscuration 412-413
 in Dandy-Walker malformation 273, 364-365
 economic analysis 425-433
 failure 421
 hardware 367-368
 history 361
 indications
 aqueductal stenosis 362
 neonatal hydrocephalus 365

- post-infectious hydrocephalus 367
shunt malfunction 364, 389-396
slit ventricle syndrome 344-348, 364
tetraventricular hydrocephalus 366-367
Toxoplasmosis 202-203
tumoral hydrocephalus 155-161, 362-364
vein of Galen malformation 366
obstruction 382-383
post-operative period 377-379, 392
 ICP monitoring 378-379
 lumbar puncture 379
repeat third ventriculostomy 421-424
results 379-383, 392-395
technique
 burr hole 370, 391
 floor perforation 372-375
 irrigation 371
 Liliequist membrane 376-377
 navigation 371, 391-392
 position 369
 preparation 369
 skin incision 369
 stoma dilatation 375
Thyroid Hormone 32
Toxoplasmosis 66, 201-203
Transcallosal approach
 in colloid cysts 181
 in multiloculated hydrocephalus 227
Transthyretin 33
Triploidy 3
Trisomy 3
Tuberculosis 65, 209-211
Tuberous Sclerosis 10
 CNS tumors in 13
 diagnostic criteria 13
 genetics 13
 hamartomas in 13
 tuberin 14
Ultrasonography 80
Unilateral hydrocephalus
 radiology 82
Vasopressin 32
Venous hypertension
 in Dandy-Walker malformation 267-268
Ventricles 24-26, 28, 31
 formation 20
 fourth, *see* fourth ventricle
 third, *see* third ventricle
Ventricular volume, regulation 335
Ventriculitis 205, 206, 221
Ventriculography
 in Dandy-Walker malformation 266
 in spinal cord tumors 193
Ventriculo-cardiac shunts 308
Ventriculoperitoneal shunt 329
 abdominal complications in 315-327
 ascites 320-322
 appendicitis 318
 epidemiology 316
 hernias 323-324
 hydroceles 323-324
 lost catheters 324
 management 317
 peritoneal pseudocyst 319-320
 pregnancy, in shunts 325-326
 design 302
 failure 329-333
 long-term shunt survival 329-330
 outcome 332
 shunt trial 329
hydrodynamics 296-297
history 295
in Dandy-Walker malformation 271
infection 221
 multiloculated hydrocephalus
repeated surgery 222
siphoning 297-298
surgery 302-310
 insertion 303
 revision 308-310
 selection 302
 surgical technique 303-307
third ventriculostomy, in shunt malfunction 389-396
unblocking shunts 301-302
valves 298
 antisiphon device 300
 differential pressure 298
 flow-regulating 299-300
 gravity actuated 300
 programmable 298-299
Ventriculo-pleural shunts 307-308
Vermis, cerebellar 259
 anatomy 259
 in Dandy-Walker malformation 260-263
Virus 208-209
Waardenburg syndrome 8
Walker-Warburg syndrome 3, 4
White matter 66, 68-70, 72, 73
X-linked hydrocephalus 1-3