Childs Nerv Syst (2003) 19:540–550
DOI 10.1007/s00381-003-0792-3

ORIGINAL PAPER

David G. McLone
Mark S. Dias

The Chiari II malformation: cause and impact

Received: 10 April 2003
Published online: 12 August 2003

D. G. McLone (✉) · M. S. Dias
Division of Pediatric Neurosurgery,
The Children's Memorial Hospital,
2300 Children's Plaza, Chicago, IL 60614,
USA
e-mail: dmclone@nwu.edu
Tel.: +1-312-8804373
Fax: +1-312-8824311

Abstract *Introduction:* It is the Chiari II malformation and its effects that determine the quality of life of the individual born with spina bifida. *Discussion:* The cause of this malformation has been a source of debate for many years. Understanding the cause enables strategies for the management of problems created by this malformation to be developed. An open neural tube defect allows fluid to escape from the cranial vesicles, altering the intracranial environment and leads to all of the brain changes seen in the Chiari II malformation. Decompression of the intracranial vesicles causes overcrowding, decrease in the size of the third ventricle, and changes in the fetal skull. It also permanently links the intracranial ventricular system to the spinal cord central canal.

Keywords Chiari II malformation · Spina bifida · Embryonic and fetal development · Open neural tube

Introduction

Myelomeningoceles occur with a frequency of approximately 0.4 per 1,000 live births [40]; associated hydrocephalus occurs in approximately 85–90% of afflicted patients [29]. The mortality rate continues to decline and the likelihood of independent living continues to improve [6]. It is the hydrocephalus and the other manifestations of the Chiari II malformation more than anything else that will determine the outcome for survival and independence in these children (Fig. 1, Table 1). Without the Chiari II malformation these children would have a prognosis similar to individuals with traumatic paraplegia or spinal cord lipomas. The treating neurosurgeon would therefore do well to have a thorough understanding of the development and pathophysiologic processes associated with the Chiari II malformation in myelodysplasia.

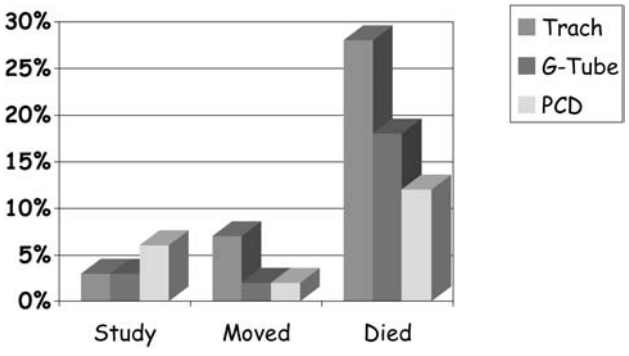

Fig. 1 Children born between 1975 and 2001 with long-term follow-up demonstrate the impact of the Chiari II malformation on children with spina bifida. *PCD* posterior cervical decompression

Discussion

Several pathophysiologic mechanisms may act alone or in concert to cause hydrocephalus in patients with myelomeningoceles [27]. Aqueductal occlusion, fourth ventricular outlet obstruction, obliteration of the subarachnoid space by the crowded posterior fossa contents, and obstruction at the level of the tentorial hiatus have all been implicated [26]. All these mechanisms potentially have a common origin in the caudal hindbrain anomaly of the Chiari II malformation.

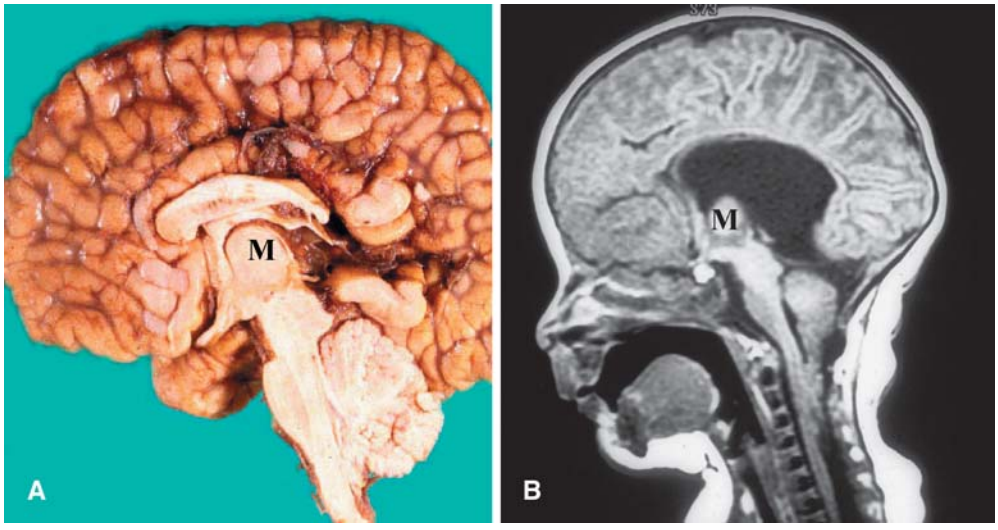

Fig. 2 **A** Specimen of brain of a child who died. **B** Mid-sagittal section shows the typical changes of the Chiari II malformation. *M* large massa intermedia

Table 1 Manifestations of the Chiari II malformation

Manifestation
Apnea
Tongue fasciculations
Stridor
Facial palsy
Gastro-esophageal reflux
Swallowing difficulties
Poor feeding
Ataxia
Hypotonia
Upper extremity weakness
Hydrocephalus
Hydromyelia
Attention deficit
Seizures
Extra-ocular movement abnormalities
Nystagmus
Increased mortality

Table 2 Chiari-associated central nervous system malformations

Malformation
Disorders of the skull
Lückenschädel of the skull
Small posterior fossa
Low-lying tentorium cerebelli with large incisura
Scalloping of the petrous bone
Shortening of the clivus
Enlargement of the foramen magnum
Disorders of the cerebral hemispheres
Polymicrogyria
Cortical heterotopias
Dysgenesis of the corpus callosum
Large massa intermedia
Disorders of the posterior fossa
Descent of the cerebellar vermis through the foramen magnum
Caudal displacement of pons and medulla
Rostral displacement of superior cerebellum through the tentorium
Kinking of the brainstem
Loss of pontine flexure
Aqueductal stenosis or forking
Beaking of the tectum

The Chiari II malformation is present in virtually all patients with myelomeningoceles and encompasses a broad constellation of malformations (Table 2) involving both the neuroectoderm (both supratentorial and infratentorial) and the surrounding mesoderm (membranous skull and basicranium) [29]. This is a pancerebral malformation. The most striking of these involve the posterior fossa (Fig. 2). Neuroectodermal abnormalities include caudal displacement of the cerebellar tonsils and vermis, as well as the caudal brainstem (medulla and, variably, the pons), through an enlarged foramen magnum into the cervical spinal canal. In some instances, the brainstem becomes kinked (the medullary kink) as the more cranial portions are translocated dorsal to more caudal tissue held by the first dentate ligament (Fig. 3). Additionally, the superior vermis and cerebellar hemispheres are displaced cranially through the tentorial incisura and lie, to a variable extent, within the middle fossa of the supratentorial compartment (Fig. 4). Associated mesenchymal abnormalities produce a small posterior fossa, a low-lying tentorium with a much-enlarged tentorial incisura, a foreshortened clivus, and scalloping of the petrous bone.

However, the Chiari II malformation also encompasses several abnormalities (both neuroectodermal and mesenchymal) that involve the supratentorial compartment (Table 2). Neuroectodermal malformations include an enlarged massa intermedia of the thalamus, small third ventricle, dysgenesis of the corpus callosum, beaking of the quadrigeminal plate, polymicrogyria, and cortical

heterotopias. Mesenchymal abnormalities produce the lückenschädel deformity of the skull.

Animal models of human disease offer an opportunity to understand the embryonic and fetal mechanisms that lead to congenital malformations [14]. In this case the Splotch mouse model is an excellent model of human neural tube defects, both morphogenically and molecular biologically (Fig. 5). Both cranial and spinal neural tube defects occur in this mouse due to a defect in the Pax-3 gene. The same gene, Hup-2 in humans, produces neural tube defects in man [22, 31].

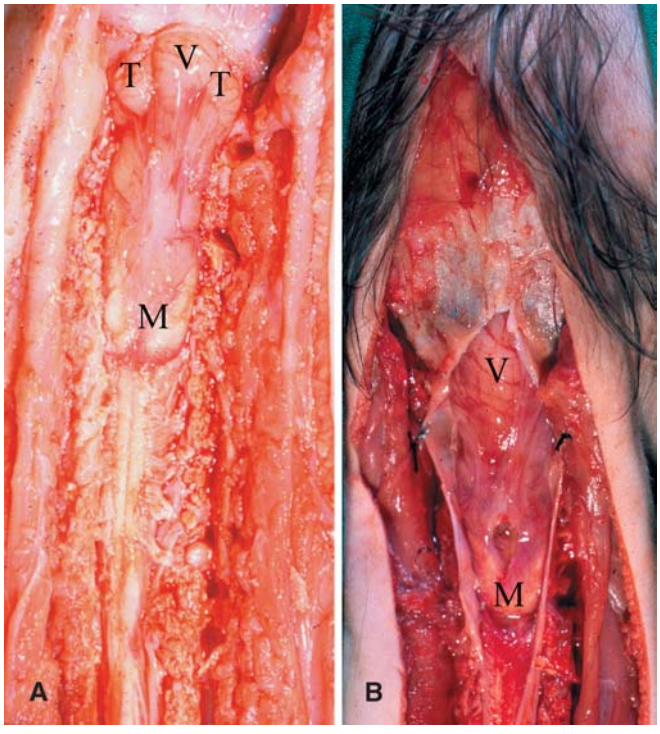

Fig. 3A, B Autopsy specimens show the herniation of cerebellar vermis (*V*) and tonsils (*T*) through the foramen magnum. *M* medullary kink

It has been possible to observe the evolution of the Chiari II malformation in the embryo and fetal mouse (Fig. 6). Additional experiments in chick embryos demonstrated that venting ventricular fluid from the cerebral vesicles produced a malformation similar to the Chiari II malformation in the posterior fossa of the chick.

We recently proposed a unified theory to explain the pancerebral anomalies involved in the Chiari II malformation [24, 27]. According to this theory, the presence of an open neural tube allows venting of cerebrospinal fluid from the entire central nervous system through the caudal end of the open neural tube during embryonic and fetal life. Under normal circumstances, just prior to neural tube closure in humans, there is a temporary period of spinal neurocele occlusion, during which the central canal of the developing spinal cord is temporarily obliterated for at least 2 days and perhaps as long as 8 days (Fig. 7) [11]. The ventricular fluid is held within the cranial compartment under pressure and this maintains the distention of the developing ventricles [34]. During this time, the isolated ventricular system (vesicles of the embryo), and cranial neuroectoderm undergo tremendous growth and development [35]. One important function of the resultant growth of the cranial neurocele is to provide an inductive stimulus for the growth of the surrounding mesenchyme (membranous skull and basicranium). This outward pressure and volume expansion determines the volume of the cranial cavities (Fig. 8). A similar phe-

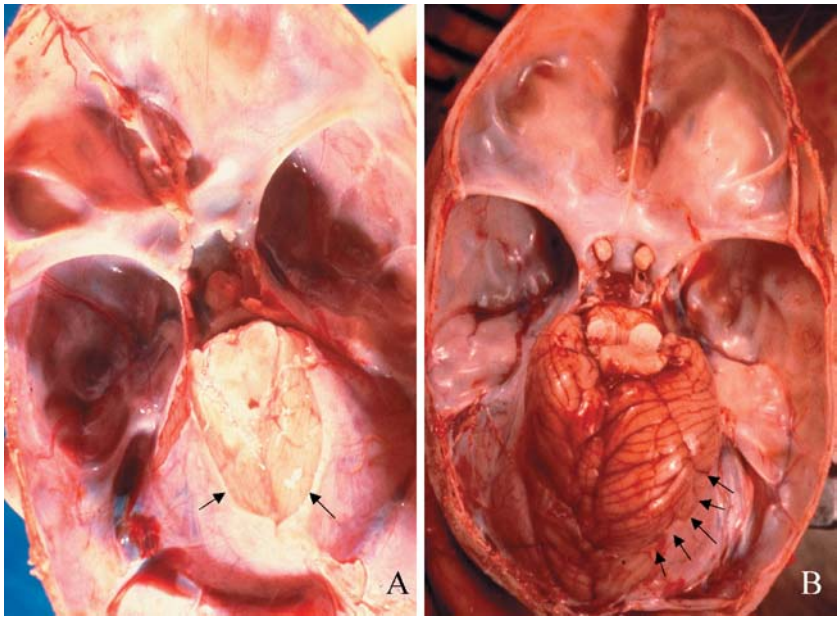

Fig. 4A, B Autopsy specimens demonstrate the herniation of the dorsal cerebellum through the wide incisura (*arrows*)

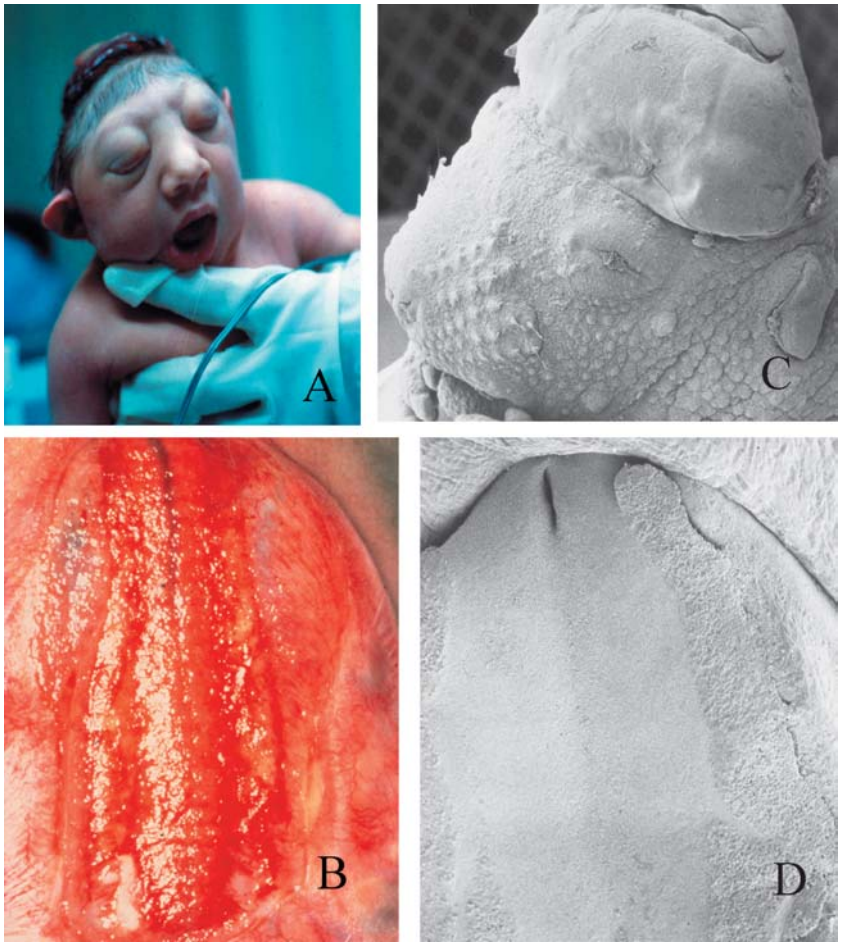

Fig. 5A–D Neural tube defects in children and fetal Splotch mice: **A** is a child with anencephaly, **B** a child with a myelomeningocele, **C** a fetal mouse with exencephaly, the same as anencephaly, and **D** a fetal mouse with a myelomeningocele

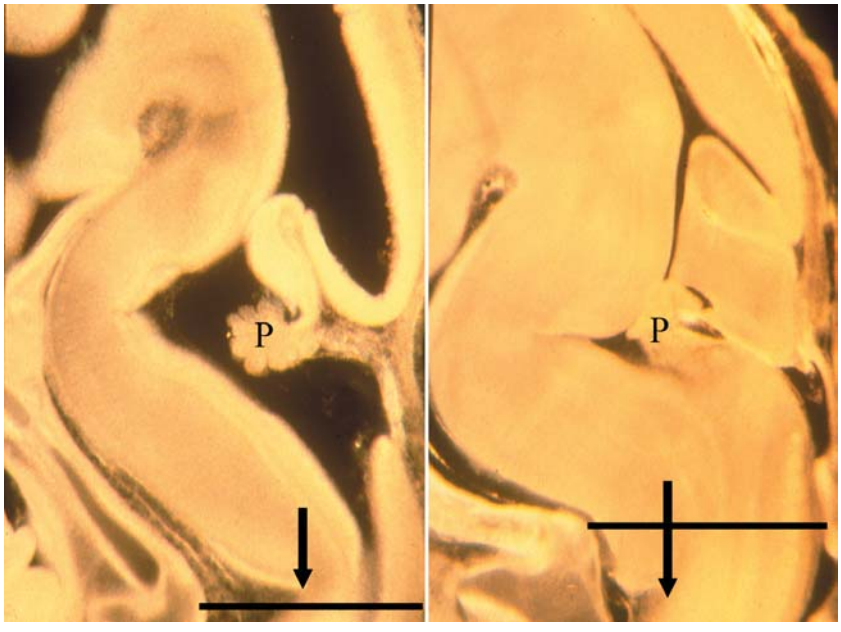

Fig. 6 Splotch mice embryos on the *left*, without an open neural tube defect, and on the *right* with an open defect. *Line* indicates the opening at the base of the skull and the *arrow* indicates the level of the inferior edge of the brain stem. Note collapsed space and descent of the stem in the defective embryo. *P* choroid plexus

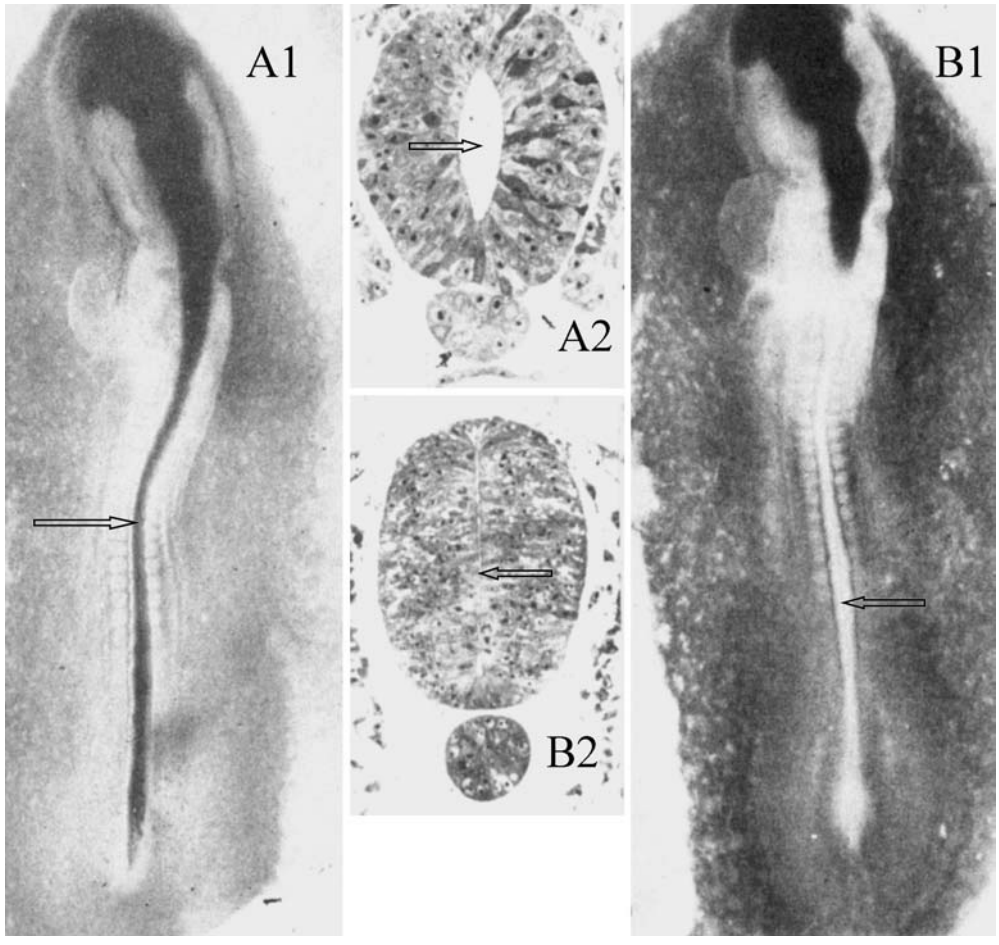

Fig. 7A, B Chick embryos with contrast injected into the neurocele. Note in **A1** the contrast fills both the cranial and spinal neurocele. **A2** is a cross section of the spinal neural tube demonstrating the open neurocele (*arrow*). **B1** and **B2** show the spinal neurocele is closed and the contrast is restricted to the cranial neurocele during the period of "occlusion" [13]

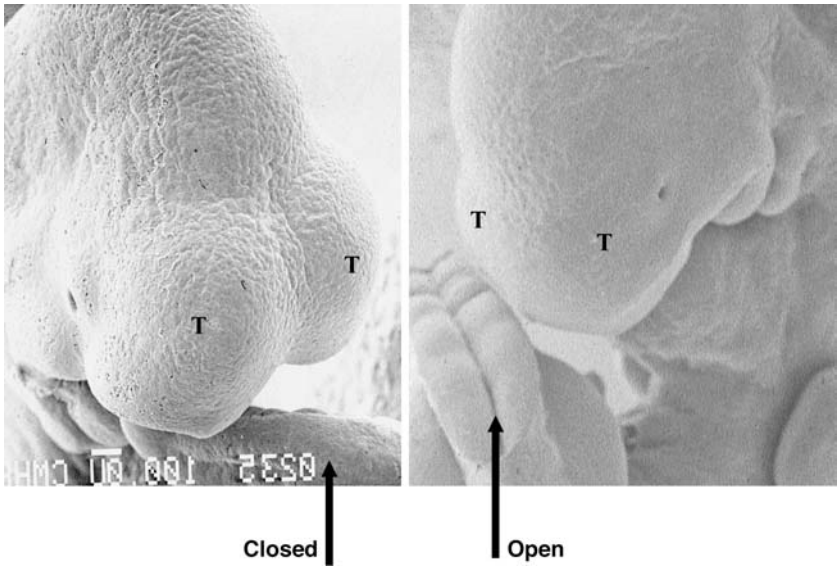

Fig. 8 Scanning electron micrograph of two mouse embryos with their caudal neural tube next to the cranial end. *Arrow* indicates that the normal mouse neural tube is closed and the Splotch mouse neural tube is open. The telencephalic (*T*) vesicles are distended in the normal mouse and collapsed in the Splotch

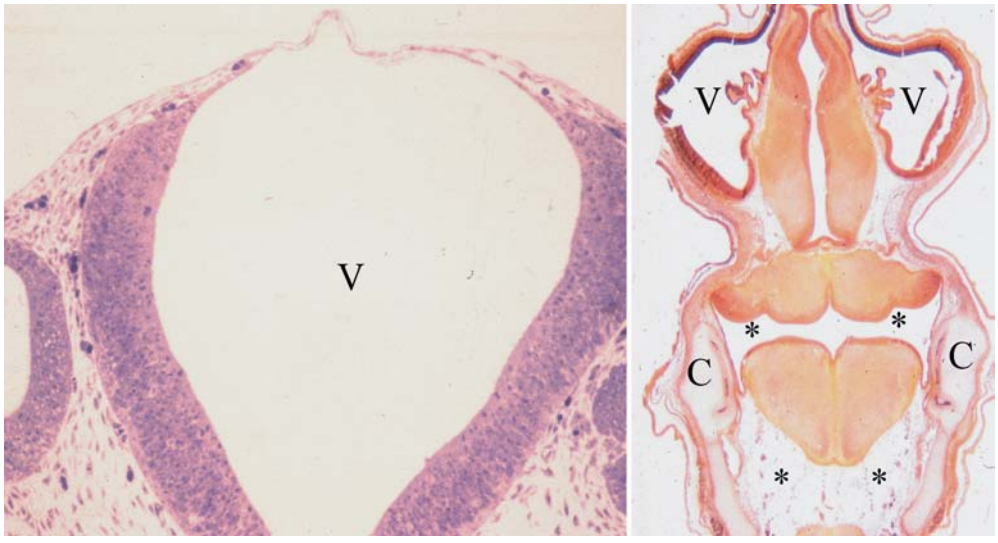

Fig. 9 Light micrographs from *left* a mouse embryo and *right* a 35 to 37-day-old human embryo. The *left* image shows the distended hindbrain neural vesicle (*V*) of the mouse and the sounding mesenchyme that will establish the volume of the posterior fossa prior to the development of the cerebellum. The *right* image demonstrates the presence of cartilage (*C*) very early in development forming a rigid posterior fossa prior to cerebellar development. *Asterisks* indicate the space that anticipates the development of the cerebellum and (*V*) the telencephalic vesicles are collapsed anteriorly, which is an artifact of fixation

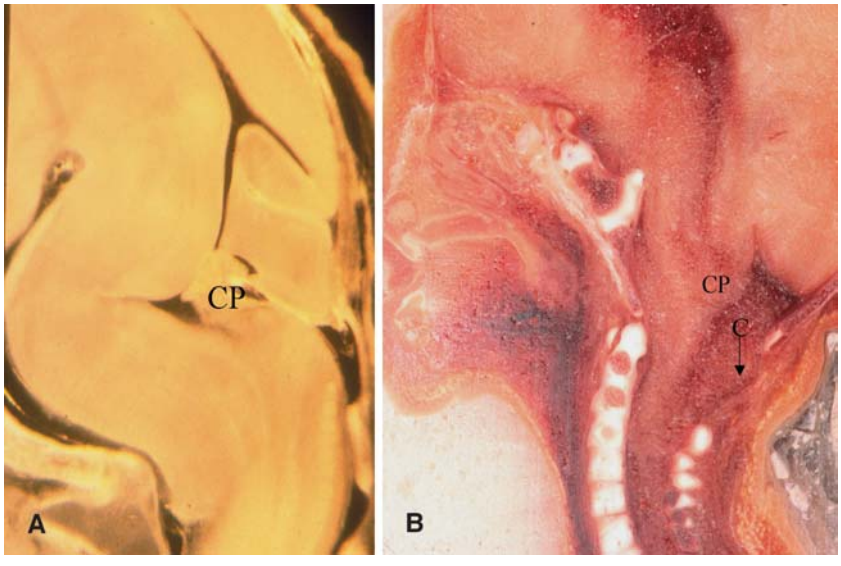

Fig. 10 s**A** Mouse embryo with a neural tube defect and **B** a spontaneously aborted human fetus with a myelomeningocele. *CP* collicular plate, *C* early cerebellum with herniation (*arrow*)

nomenon has been described in both avian and mammalian embryos [12, 13, 20, 35, 37, 38, 39].

During this period of occlusion of the spinal neurocele, the process of neural tube closure is completed. When occlusion reverses and the neurocele reopens, the distention of the cranial vesicles of the embryo (ventricular system in fetal development) is maintained by a closed neural tube (Fig. 8). If, however, the neural tube closure was defective and the neural tube remains open, the fluid drains from both the spinal and cranial nervous system (Fig. 8). A failure of proper ventricular growth during these critical periods results in inadequate and disorganized neural development [10, 12, 19, 35] as well as secondary effects on the growth of the surrounding mesenchyme (Fig. 9) [27]. The development of the Chiari II malformation and its impact on the developing nervous system begins in the embryo and continues throughout fetal development. The distention of the caudal embryonic vesicles (rhombencephalic and metencephalic), and later the fetal posterior fossa cerebrospinal fluid spaces, is essential to determine the size of the posterior fossa prior to and during cerebellar and brain stem development. These spaces must be large enough to anticipate the blossoming cerebellum that will soon fill these spaces. The lack of distention leads to secondary mesenchymal defects, miscoding of volume determination, resulting in a smaller posterior fossa, which, during subsequent cerebellar development, is inadequate to house the rapidly enlarging hindbrain. As a consequence, the hindbrain is displaced both cranially (through the incisura) beaking the collicular plate and compressing the aqueduct. Caudal displacement (through the foramen

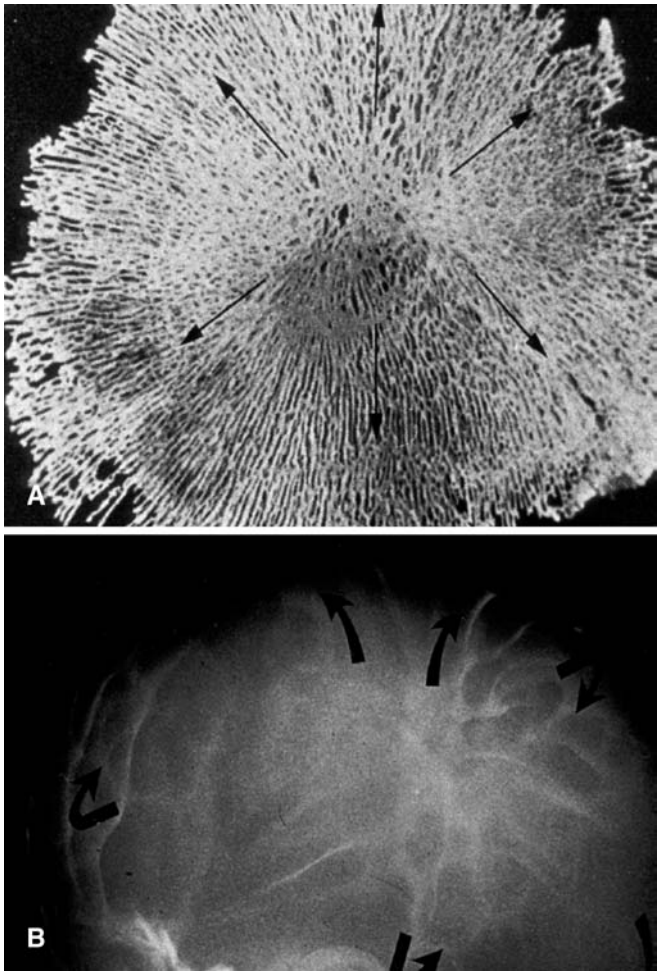

Fig. 11 **A** is a parietal plate from a normal infant skull, which demonstrates the calcified bundles radiating out (*thin arrows*) from the growth center. **B** is an X-ray of an infant with a myelomeningocele and Chiari II malformation. *Thick arrows* indicate the dense bundles turning into an abnormal lückenschädel pattern

magnum) of the vermis and cerebellar tonsils with medullary elements produces the hindbrain anomaly at the foramen magnum and cervical spinal canal (Fig. 10).

Distention of the ventricular system also acts as scaffolding for the development of the supratentorial neural elements [35]. Normal neuronal migration from the ventricular germinal zone to the cortical layers occurs along the radially oriented glial processes. Collapse of the ventricles disorganizes this process leading to the cerebral malformations of the Chiari II. These primary disorders of neuronal histogenesis include polymicrogyria, heterotopias, and callosal dysgenesis. Through secondary effects on disordered surrounding mesenchyme, lückenschädel develops [27]. The cranial plates develop from ectoderm. The frontal and parietal plates grow from the growth center in the middle of the plate. Collagen bundles radiate out from these centers and are drawn out in response to growth stimulated by the underlying developing brain. Decompression of the cerebral hemispheres disrupts this and causes the collagen bundles to follow a chaotic course leading to the lückenschädel skull deformity (Fig. 11). This also causes the frontal plates to deform with an inward concavity referred to on ultrasound as the "lemon sign." Collapse also results in a small third ventricle and the approximation of the thalami with a large massa intermedia (Fig. 2).

The result of this disproportionate growth between the hindbrain and surrounding mesenchyme is a tightly compacted posterior fossa with little room [25]. This impedes the development of the cerebrospinal fluid spaces and the normal flow of cerebrospinal fluid (CSF) from the third to the fourth ventricle through the cerebral aqueduct, from the fourth ventricle to the posterior fossa subarachnoid space through the ventricular outlets, and from the posterior fossa subarachnoid space through the incisura to the cerebral convexities (Fig. 12) [23, 27, 28], resulting in hydrocephalus. Therefore, hydrocephalus is

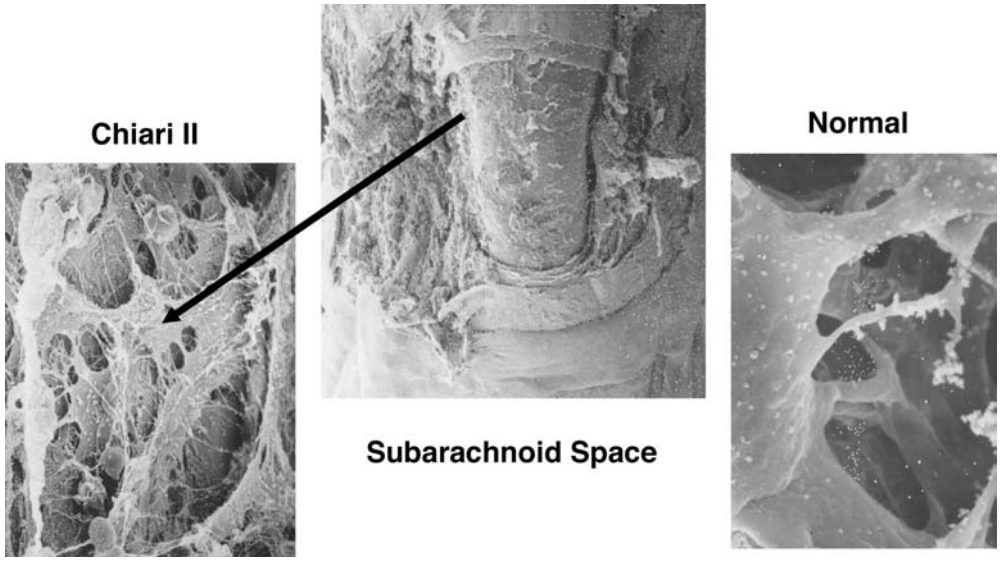

Fig. 12 Scanning electron micrographs from a Splotch fetal mouse with a Chiari II malformation and the developing subarachnoid space of a normal fetus. The image on the *left* is a higher power view of the *middle* image from a fetal mouse with an open neural tube. The image on the *right* is the normal developing subarachnoid space

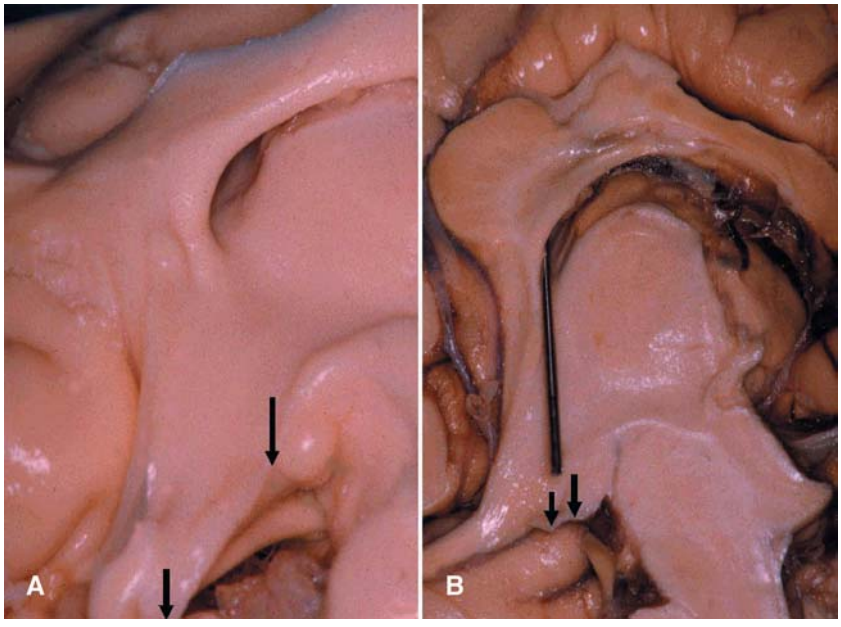

Fig. 13 **A** is a midsagittal view of a normal brain third ventricle. Note the long floor, between *arrows*, of the third ventricle and no identifiable massa intermedia. **B** shows an extremely short floor between the *arrows*. Note the ventriculoscope entering through a small foramen of Monro. Also seen are a large massa intermedia, deformed corpus callosum, and peaked collicular plate

a result of the Chiari II malformation and not the cause of the malformation. Studies of aborted fetal brains clearly show that the Chiari II malformation precedes the onset of hydrocephalus (Fig. 10) [33]. While hydrocephalus is not the cause of Chiari II malformation, the onset of hydrocephalus, during either fetal or postnatal life, further deforms and impedes the development of the nervous system. Hydrocephalus exacerbates and accelerates the clinical manifestations of hindbrain compression.

The cause of the Chiari II malformation is the open neural tube. This has important implications for the management of the neural tube defect. Prevention of the defect or early repair would obviously eliminate or diminish the severity of the malformation.

In addition to their importance in producing hydrocephalus, the pancerebral anomalies of the Chiari II malformation have important practical implications for the management of hydrocephalus in patients with myelodysplasia. For example, the presence of callosal dysgenesis, cortical heterotopias, and polymicrogyria confer a characteristic shape to the ventricular system, in which the atria and occipital horns are disproportionately large, a condition known as colpocephaly. Consequently, mild or moderate enlargement of only the posterior ventricular system, as occurs in callosal agenesis, may not necessarily connote hydrocephalus in the absence of other signs of progressive ventriculomegaly.

The Chiari II malformation may interfere with the proper functioning of a ventricular shunt. For example, the presence of a small third ventricle with an enlarged massa intermedia, together with an eccentric bulge from the head of the caudate nucleus, prominent commissural fibers extending across the anterior third ventricle, and anteriorly pointing frontal horns may distort and functionally obstruct the interventricular foramen of Monro and result in isolated lateral ventricles after unilateral shunt placement [4, 5, 32]. The small third ventricle makes the use of a third ventriculostomy difficult at any time and almost impossible in the neonate (Fig. 13).

In one series, 6 of 42 patients with myelomeningoceles and hydrocephalus had congenital abnormalities at the foramen of Monro that could potentially result in isolated ventriculomegaly [4]. The use of distal slit valves, with strong siphoning effects, appears to be particularly associated with the phenomenon of isolated ventriculomegaly after shunting and has led to the suggestion that distal slit valves should be avoided in managing hydrocephalus in myelodysplastic patients [5].

Hindbrain compression or distortion may be exacerbated by associated hydrocephalus and result in caudal brainstem signs and symptoms, either as an initial manifestation of hydrocephalus in the neonate or as a feature of shunt malfunction in the older child [1, 8, 9, 18, 21, 23].

The role the spinal cord's central canal plays in the development of the Chiari II malformation permanently links the cranial and spinal ventricular system. Thus, the onset of progressive hydrocephalus, or more commonly the first shunt malfunction, can result in hydromyelia (Fig. 14) [16, 17]. Prompt shunting, or revision of the present shunt, will reverse the hydromyelia and may return the spinal cord to its normal form.

The clinical features and management of hydrocephalus in the patient with a myelomeningocele can be divided into two phases: an initial neonatal phase, during which the decision is made as to whether or not to shunt, and a late phase, lasting the patient's entire life, during which the child is closely followed for signs and symp-

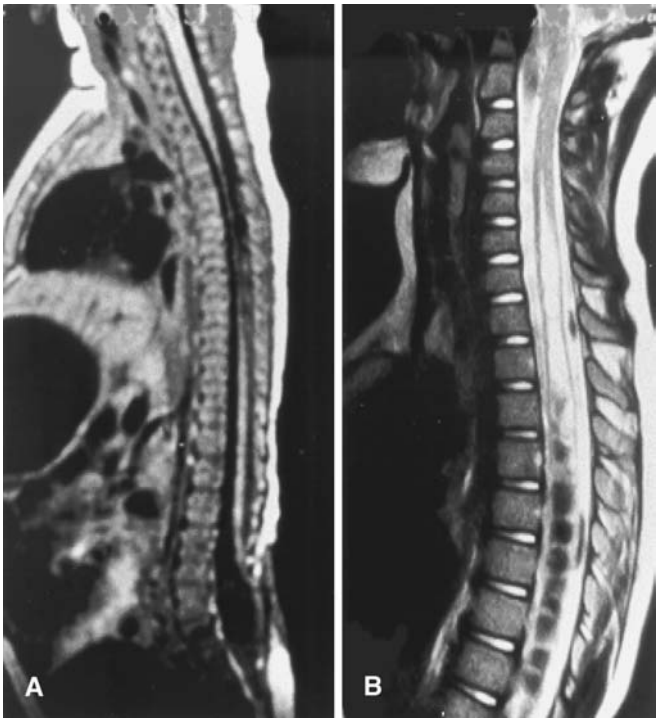

Fig. 14A, B MR images of an infant with a myelomeningocele, Chiari II malformation, and hydrocephalus. **A**, note the normal cord during shunt function and **B**, that a shunt malfunction produced hydromyelia

toms of hydrocephalus (if not previously shunted) or shunt malfunction (if previously shunted). During each of these periods, the presence of the myelomeningocele and Chiari II malformation has a profound impact on the evaluation and management of associated hydrocephalus. Overt hydrocephalus is clinically evident early (that is, at the time of birth and before closure of the placode) in about 15% of infants with myelomeningoceles, and is often the result of aqueductal stenosis or occlusion [36]. More frequently, however, overt hydrocephalus is absent at birth but becomes evident during the days or weeks following closure of the myelomeningocele. This delayed hydrocephalus is due to the loss of the central canal venting of CSF and the blockage to CSF flow through either the incisura or the subarachnoid space [26].

The infant with worsening hydrocephalus may first develop symptoms of lower brainstem compromise from the Chiari II malformation with attendant stridor, facial palsy, a weak, high-pitched cry, swallowing difficulties and poor feeding, nasal regurgitation, or recurrent bouts of aspiration pneumonitis [3]. Additionally, upper extremity weakness and hypotonia may arise from cervicomedullary compression from the Chiari or from syringomyelia. These symptoms, although related anatomically to the Chiari II malformation, are often exacerbated by the presence of hydrocephalus [18]. Accordingly, in many cases they will resolve after appropriate treatment for the hydrocephalus, and more complex (and morbid) cervical decompressive procedures will be avoided.

Seizures are estimated to occur in approximately 15–25% of children with myelomeningoceles [2, 7, 15, 30], and are most likely to be related to cerebral anomalies such as cortical heterotopias and polymicrogyria that are associated with the Chiari II malformation. Seizures may occur de novo in patients not previously known to have seizures, or may be exacerbated in patients with a known seizure disorder.

Lower brainstem dysfunction in association with shunt malfunction is attributed to an exacerbation of brain stem compression from the hindbrain Chiari II anomaly, and often improves after shunt revision [1, 8, 9, 18, 21, 23]. As mentioned above, signs of lower cranial nerve dysfunction include stridor, a weak or high-pitched cry in the infant and a hoarse, nasal, or high-pitched voice in the older child or adult, frequent choking or sputtering on foods, nasal regurgitation during feeding (particularly liquids), frequent gastro-esophageal reflux, recurrent bouts of aspiration pneumonitis, facial weakness and tongue fasciculations, and extraocular movement abnormalities. In the extreme, apnea may occur [8, 9, 18] and is probably a common cause of spontaneous death in this population. Additional signs of brain stem compromise include changes in upper or lower extremity muscle strength or tone, and cerebellar dysfunction (truncal ataxia or appendicular dysmetria).

Progressive motor dysfunction in the upper or lower extremities may occur in association with shunt malfunction, and is manifested as muscle weakness, an increase in tone (spasticity), worsening muscle contractures, or a disturbance in gait. These signs suggest progressive spinal cord dysfunction due to hindbrain compression, tethered cord, or syringomyelia [17]. Many patients are dramatically improved following shunt revision and thus avoid a more extensive surgical procedure. For these reasons it is imperative that optimal function of the shunt be established prior to any procedure involving the hindbrain, hydromyelia, or tethered cord.

Conclusion

In summary, the presence of myelomeningocele and associated intracranial abnormalities collectively referred to as the Chiari II malformation considerably alters the presenting features of hydrocephalus, both at the time of presentation in infancy and later in life. Hydrocephalus in patients with myelomeningoceles differs in several respects from other forms of hydrocephalus. The signs and symptoms of shunt malfunction are diverse and may suggest a symptomatic Chiari II malformation,

tethered spinal cord, or syringomyelia. When presented with any of the above signs or symptoms, it is our practice to always assess shunt function before proceeding with posterior fossa decompression, an untethering procedure, or treatment for syringomyelia. This has two benefits:

1. It obviates a more extensive (and potentially more morbid) surgical procedure.
2. It may prevent disastrous clinical deterioration from herniation syndromes that might otherwise occur after removing CSF from the spinal subarachnoid space in the presence of a shunt obstruction.

References

1. Adeloye A, Singh SP, Odeku EL (1970) Stridor, myelomeningocele, and hydrocephalus in a child. Arch Neurol 23:271–273
2. Bartoshesky LE, Haller J, Scott RM et al (1985) Seizures in children with myelomeningocele. Am J Dis Child 139:400–402
3. Bell WO, Charney EB, Bruce DA et al (1987) The symptomatic Arnold-Chiari malformation: review of experience. J Neurosurg 66:812–816
4. Bell WO, Sumner TE, Volberg FM (1987) The significance of ventriculomegaly in the newborn with myelodysplasia. Childs Nerv Syst 3:239–241
5. Berger MS, Sundsten J, Lemire RJ et al (1990) Pathophysiology of isolated lateral ventriculomegaly in shunt myelodysplastic children. Pediatr Neurosurg 16:301–304
6. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA (2001) Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg 34:114–120
7. Chadduck W, Adametz J (1988) Incidence of seizures in patients with myelomeningocele: a multifactorial analysis. Surg Neurol 30:281–285
8. Charney EB, Rorke LB, Sutton LN et al (1987) Management of Chiari II complications in infants with myelomeningocele. J Pediatr 111:364–371
9. Cochrane DD, Adderley R, White CP et al (1990–1991) Apnea in patients with myelomeningocele. Pediatr Neurosurg 16:232–239
10. Coulombre AJ, Coulombre JL (1958) The role of mechanical factors in brain morphogenesis. Anat Rec 130:289–290
11. Desmond ME (1982) Description of the occlusion of the spinal cord lumen in early human embryos. Anat Rec 204:89–93
12. Desmond ME, Jacobson AG (1977) Embryonic brain enlargement requires cerebrospinal fluid pressure. Dev Biol 57:188–198
13. Desmond ME, Schoenwolf GC (1986) Evaluation of the roles of intrinsic and extrinsic factors in occlusion of the spinal neurocele during rapid brain enlargement in the chick embryo. J Embryol Exp Morphol 97:25–46
14. George TM, McLone DG (1995) Mechanisms of mutant genes in spina bifida: implications from animal models—a review. Pediatr Neurosurg 23:236–245
15. Hack CH, Enrile BG, Donat JF et al (1990) Seizures in relation to shunt dysfunction in children with myelomeningocele. J Pediatr 116:57–60
16. Hall P, Lindseth R, Campbell R et al (1979) Scoliosis and hydrocephalus in myelocele patients. The effects of ventricular shunting. J Neurosurg 50:174–178
17. Hall PV, Campbell RL, Kalsbeck JE (1975) Meningomyelocele and progressive hydromyelia. Progressive paresia in myelodysplasia. J Neurosurg 43:457–463
18. Holinger PC, Holinger LD, Reichert TJ et al (1978) Respiratory obstruction and apnea in infants with bilateral abductor vocal cord paralysis, meningomyelocele, hydrocephalus, and Arnold-Chiari malformation. J Pediatr 92:368–373
19. Jelinek R, Pexeider T (1970) Pressure of the CSF and the morphogenesis of the CNS. Folia Morphol 18:102–110
20. Kaufman MH (1983) Occlusion of the neural lumen in early mouse embryos analysed by light and electron microscopy. J Embryol Exp Morph 78:211–228
21. Kirsch WM, Duncan BR, Black FO et al (1969) Laryngeal palsy in association with myelomeningocele, hydrocephalus, and the Arnold-Chiari malformation. J Neurosurg 28:207–214
22. Mayanil CSK, George D, Freilich L, Miljan EJ, Bremer CL, Mania-Farnell B, McLone DG, Bremer EG (2002) Microarray analysis detects novel Pax3 downstream target genes. J Biol Chem 49299–49309
23. McLone DG (1991) Spinal dysraphism: pathogenesis and treatment. Spinal Surg 5:3–20
24. McLone DG, Knepper PA (1989) The cause of Chiari II malformation: a unified theory. Pediatr Neurosurg 15:1–12
25. McLone DG, Naidich TP (1992) Developmental morphology of the subarachnoid space, brain vasculature and contiguous structures, and the cause of the Chiari II malformation. Am J Neuroradiol 13:463–482
26. McLone DG, Dias L, Kaplan WE et al (1985) Concepts in the management of spina bifida. Concepts Pediatr Neurosurg 5:97–106
27. McLone DG, Nakahara S, Knepper PA (1991) Chiari II malformation: pathogenesis and dynamics. Concepts Pediatr Neurosurg 11:1–17
28. Naidich TP, McLone DG, Fulling KH (1983) The Chiari II malformation. IV. The hindbrain deformity. Neuroradiology 25:179–197
29. Naidich TP, Maravilla K, McLone DG (1986) The Chiari II malformation. In: McLaurin RL (ed) Proceedings of the Second Symposium on Spina Bifida. Praeger, New York, pp 164–173
30. Noetzel MJ, Blake JN (1991) Prognosis for seizure control and remission in children with myelomeningocele. Dev Med Child Neurol 33:803–810
31. Nye JS, Balkin N, Lucas H, Knepper PA, McLone DG, Charrow J (1998) Myelomeningocele and Waardenburgh syndrome (type 3) in patients with interstitial deletions of 2q35 and the PAX3 gene: possible digenic inheritance of a neural tube defect. Am J Med Genet 75:401–408
32. Oi S, Matsumoto S (1985) Pathophysiology of nonneoplastic obstruction of the foramen of Monro and progressive unilateral hydrocephalus. Neurosurgery 17:891–896
33. Osaka K, Matsumoto S, Tanimura T (1978) Myeloschisis in early human embryos. Childs Brain 4:347–359
34. Pacheco MA, Marks RW, Schoenwolf GC et al (1986) Quantification of the initial phases of rapid brain enlargement in the chick embryo. Am J Anat 175:403–411

35. Pexeider T, Jelinek R (1970) Pressure of the CSF and the morphogenesis of the CNS. II. Pressure necessary for normal development of brain vesicles. Folia Morphol 18:181–192
36. Rekate HL (1991–1992) Shunt revision: complications and their prevention. Pediatr Neurosurg 17:155–162
37. Schoenwolf GC, Desmond ME (1984) Descriptive studies of occlusion and reopening of the spinal canal of the early chick embryo. Anat Rec 209:251–263
38. Schoenwolf GC, Desmond ME (1984) Neural tube occlusion precedes rapid brain enlargement. J Exp Zool 30:405–407
39. Schoenwolf GC, Desmond ME (1986) Timing and positioning of reopening of the occluded spinal neurocele in the chick embryo. J Comp Neurol 246:459–466
40. Windham GC, Edmonds LD (1982) Current trends in the incidence of neural tube defects. Pediatrics 70:333–337