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Two Hundred Thirty-Six Children With Developmental Hydrocephalus: Causes and Clinical Consequences

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Abstract

Few systematic assessments of developmental forms of hydrocephalus exist. We reviewed magnetic resonance images (MRIs) and clinical records of patients with infancy-onset hydrocephalus. Among 411 infants, 236 had hydrocephalus with no recognizable extrinsic cause. These children were assigned to 1 of 5 subtypes and compared on the basis of clinical characteristics and developmental and surgical outcomes. At an average age of 5.3 years, 72% of children were walking independently and 87% could eat by mouth; in addition, 18% had epilepsy. Distinct patterns of associated malformations and syndromes were observed within each subtype. On average, children with aqueductal obstruction, cysts, and encephaloceles had worse clinical outcomes than those with other forms of developmental hydrocephalus. Overall, 53% of surgically treated patients experienced at least 1 shunt failure, but hydrocephalus associated with posterior fossa crowding required fewer shunt revisions. We conclude that each subtype of developmental hydrocephalus is associated with distinct clinical characteristics, syndromology, and outcomes, suggesting differences in underlying mechanisms.

Keywords

hydrocephalus, aqueductal stenosis, myelomeningocele, encephaloceles

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Hydrocephalus, characterized by progressive accumulation of cerebrospinal fluid within the ventricular system of the brain, affects approximately 1 in 1000 births.[1] Hydrocephalus is a well-established consequence of acquired events such as intraventricular hemorrhage, but also occurs without a clear extrinsic cause, especially in infants. Our understanding of the causes of nonextrinsic forms of hydrocephalus, which we refer to as developmental hydrocephalus, is particularly limited.

When hydrocephalus develops during infancy, it has significant clinical implications. Early-onset hydrocephalus conveys a high risk of neurodevelopmental impairment, but because developmental subtypes of hydrocephalus are often not defined, the extent to which outcome depends upon subtype is unclear. Similarly, the extent to which surgical outcome (in particular, the rate of shunt failure) differs by subtype is also unclear. As a result, most available information about both the causes and the clinical consequences of developmental hydrocephalus is generic, rather than subtype-specific.

Using existing medical records, we investigated the clinical characteristics of a large cohort of infants with hydrocephalus, with particular emphasis on hydrocephalus without an extrinsic cause. We sought to better define the major clinical-radiographic subtypes of developmental hydrocephalus and their relative frequency, as well as the additional physical malformations and syndromes seen within each group, which could hold clues to underlying functional mechanisms. We then compared subtypes on the basis of concrete and quantifiable markers of developmental and surgical outcome.

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Methods

Patient Identification

With the intention of performing a retrospective review, and with the approval of the Seattle Children's Hospital Institutional Review Board, we searched the hospital's imaging database using the terms "hydrocephalus," "ventriculomegaly," and "aqueductal stenosis" for magnetic resonance images (MRIs) that had been performed in children 12 months of age or less.

Patient Inclusion and Exclusion Criteria

We used the definition of hydrocephalus proposed by the International Hydrocephalus Working Group: "an active [and progressive] distension of the ventricular system ... resulting from inadequate passage of cerebrospinal fluid from its point of production ... to its point of absorption."[2] Accordingly, we included children with ventricular distension, regardless of whether they had clinical signs of increased intracranial pressure. We excluded children with hydranencephaly, children in whom excessive cerebrospinal fluid was purely extra-axial, and children with hydrocephalus ex vacuo, unless progressive ventricular distension was also evident.

Confirmation of Hydrocephalus and Review of Anatomy

Two authors (HMT, GEI) assessed scans to confirm ventricular dilation. When we observed only equivocal ventricular dilation, we looked for evidence of progression on follow-up imaging studies, or accelerated head growth on growth charts. To quantify ventricular dilation, we calculated an Evans index using standard methods.[3] We also assessed brain anatomy in detail.

Clinical Information

We reviewed the medical records of all identified children. In addition to basic demographic characteristics, date of birth, and date of death or last follow-up, we recorded associated medical conditions, results of diagnostic testing, surgical history, and cause of death (if known, and if applicable). Time of onset of hydrocephalus was defined as the age at which it was first confirmed on imaging. We recorded whether children of any age were able to eat safely by mouth and whether they required physical or speech therapy. We also recorded whether children had epilepsy. We recorded whether children 2 years of age and older were able to walk independently. We recorded the type and timing of all hydrocephalus-related surgical procedures, and whether there was a history of shunt infection or mechanical shunt failure.

Classification of Subtypes

We sought to delineate subtypes of developmental hydrocephalus on the basis of major radiographic findings, particularly the apparent point of cerebrospinal fluid obstruction. Since infants with developmental forms of hydrocephalus may have multiple points of cerebrospinal fluid obstruction, not all of which can be easily defined on MRI,[2] we classified them as having apparent obstruction at the level of the aqueduct, at the level of the posterior fossa, or neither. We also incorporated readily apparent imaging findings such as intracranial cysts and encephaloceles, as well as the distinctive Chiari II malformation seen in association with myelomeningoceles.

Statistical Analysis

To compare differences in outcome variables across subtypes of hydrocephalus, we performed chi-square, Fisher exact, analysis of variance, and nonparametric mean tests. All analyses were performed using Stata12 software (*Stata Statistical Software: Release 12* [College Station, TX: StataCorp LP]).

Results

We identified 424 infants who were diagnosed with or treated for hydrocephalus between 2002 and 2012, 411 of whom had sufficiently detailed records to allow assessment of etiology (Supplementary Table 1). Of these infants, 155 (37.7%) had hydrocephalus attributable to a known extrinsic event, including intraventricular (n = 96) or intraparenchymal (n = 10) hemorrhage, neoplasm (n = 20), infection (n = 16), and trauma (n = 8). Another 20 had clinical or imaging signs that implied a cryptic extrinsic cause, including chorioretinal scarring (suggesting intrauterine infection), or apparent hemosiderin on MRI (suggesting intrauterine hemorrhage). The remaining 236 patients had hydrocephalus without any evident extrinsic cause, so they were classified as having developmental hydrocephalus.

Subtypes of Developmental Hydrocephalus

A total of 232 of 236 children could be placed in 1 of 5 clinical-radiographic categories (Table 1, Supplementary Table 2): hydrocephalus associated with myelomeningocele (Figure 1; n = 78); hydrocephalus associated with apparent aqueductal obstruction (Figure 2; n = 59); hydrocephalus associated with posterior fossa crowding (Figure 3; n = 25); hydrocephalus associated with cysts or cephaloceles (Figure 4; n = 40); and communicating hydrocephalus, with no radiographic evidence of obstruction (Figure 5; n = 31). Four children could not be categorized: 2 with vein of Galen malformations and 1 with a dural arteriovenous fistula, none of whom had detailed presurgical imaging to allow the point of obstruction to be determined, and 1 with neurocutaneous melanosis, with multiple subarachnoid adhesions. These children were included in the overall analyses, but not within subgroup analyses.

Additional Brain Malformations (Supplementary Table 3)

All but 2 children with myelomeningocele-associated hydrocephalus had classic Chiari II malformations. The other 2 had the brainstem features of a Chiari II, but with a partially absent cerebellum, a feature presumed to be the result of a prenatal disruption.[4] Among children with hydrocephalus associated with apparent aqueductal obstruction, 14 had additional midline brainstem and cerebellar malformations. Three had nodular aqueductal obstruction, and 2 had the characteristic features of muscle-eye-brain disease. Posterior fossa crowding was associated with Chiari I malformations in 11 children, 4 of whom had megalencephaly.

Table 1. Basic Characteristics of 236 Children With Developmental Hydrocephalus.

	All hydrocephalus (n = 236)	MM (n = 78)	Proximal obstruction (n = 60)	Distal obstruction (n = 25)	Cysts and celes (n = 38)	Communicating (n = 31)
Male, n (%)	131 (55.3)	43 (55.1)	14 (56.0)	14 (56.0)	18 (47.4)	22 (71.0)
Age at diagnosis, n (%)						
Prenatal and <1 wk	166 (72.2)	78 (100.0)	51 (86.4)	2 (8.0)	24 (64.9)	11 (35.4)
1 wk–6 mo	37 (16.1)	0 (0.0)	7 (11.9)	9 (36.0)	9 (24.3)	12 (38.7)
>6 mo–12 mo	27 (11.7)	0 (0.0)	1 (1.7)	14 (56.0)	4 (10.8)	8 (25.8)
Age at last visit (y), M ± SD (minimum, maximum)	4.6 ± 3.1 (0.0, 13.1)	4.9 ± 3.1 (0.1, 11.7)	4.9 ± 3.2 (0.0, 11.8)	5.2 ± 3.2 (0.3, 11.3)	4.7 ± 3.1 (0.4, 13.1)	3.0 ± 2.1 (0.1, 10.0)
Evans index, median (minimum, maximum)	0.44 (0.26, 0.88)	0.41 (0.30, 0.76)	0.56 (0.34, 0.88)	0.41 (0.31, 0.71)	0.43 (0.31, 0.59)	0.37 (0.26, 0.80)

Abbreviations: M, mean; MM, myelomeningocele; SD, standard deviation.

Table 2. Clinical Syndromes and Additional Anomalies by Category.

Clinical syndrome/additional anomalies	Genetic cause (n/n tested)
MM-associated	
Defined syndrome: 0/78 (0%)	
Additional physical anomalies: 3/78 (4%)	
MM with structural cardiac (1), atypical thoracic MM with vertebral segment defects, absent left kidney, absent right testis, structural cardiac (1), atypical thoracic MM with multiple vertebral segment defects (1)	
Proximal obstruction	
Defined syndrome: 8/59 (14%)	
Aqueductal stenosis without additional findings (47), including HSAS	*L1CAM* (6/8)
Muscle-eye-brain (2)	*POMGNT1* (2/2)
Additional physical anomalies without defined syndrome: 1/51 (2%)	
Unilateral anophthalmia (1)	
Distal obstruction	
Defined syndrome: 15/25 (60%)	
Crouzon (4)	*FGFR2* (1/1)
Pfeiffer (3)	*FGFR2* (3/3)
Carpenter (1)	Not tested
Achondroplasia (3)	*FGFR3* (1/1)
Thanatophoric dysplasia (1)	*FGFR3* (1/1)
Spondyloepiphyseal dysplasia (1)	Not tested
Undefined skeletal dysplasia	*FGFR3* (0/1)
MPPH (1)	*PiK3CA/AKT3* pathway genes not tested
Additional physical anomalies without defined syndrome 2/10 (20%)	
Additional anomalies: unilateral microphthalmia (with megalencephaly), upper cervical fusion anomaly	
Cysts and cephaloceles	
Defined syndrome: 3/39 (8%)	
Chudley-McCullough (1)	*GPSM2* (1/1)
Oro-facial-digital type 1 (1)	*OFD1* not tested
Opitz G/BBB (1)	*MID1* not tested
Additional physical anomalies without defined syndrome: 7/36 (19%)	
Cysts in multiple organ systems and polysyndactyly (1), multicystic kidneys (1), ambiguous genitalia and polydactyly (1), syndactyly and limb reduction with skin appendages (1), structural renal with vertebral segment defects and interrupted aortic arch (1), vertebral segment defects and cleft palate (1), structural renal (1), TEF (1)	(*OFD1* 0/1, other genes not known/not tested)
Communicating	
Defined syndrome: 2/31 (6%)	
Cardio-facio-cutaneous with pulmonic stenosis (1)	*BRAF* (1/1)
Gorlin (1)	*PTCH1* not tested
Additional physical anomalies without defined syndrome: 4/29 (14%)	
CDH (3), structural cardiac (1)	(genes not known)

Abbreviations: HSAS, hydrocephalus with stenosis of the aqueduct of Sylvius (associated with *L1CAM* mutations); MM, myelomeningocele; MPPH, megalencephaly, polydactyly, polymicrogyria and hydrocephalus syndrome; TEF, tracheoesophageal fistula.

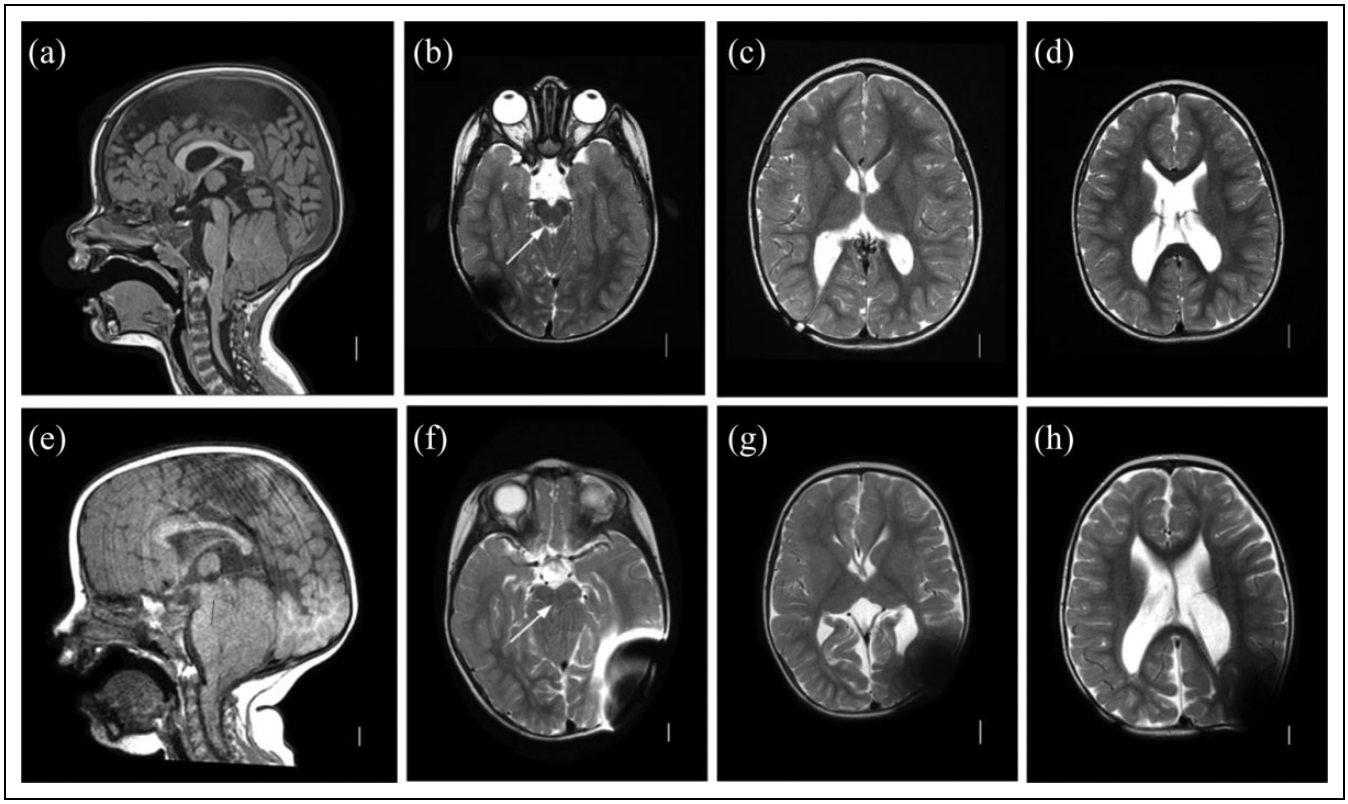

Figure 1. Myelomeningocele-associated hydrocephalus. (A-D) Classic Chiari II malformation. Sagittal T1 magnetic resonance image (MRI) demonstrating classic features of a Chiari II malformation including elongated pons and downwardly displaced medulla, tectal beaking, small posterior fossa with vertically oriented tentorium, with cerebellar tonsillar ectopia below the foramen magnum line (A). Axial I T2 images (B-D). Note patency of aqueduct in B (arrow). (E-H) Chiari II with aqueductal compression. Sagittal T1 image (A) demonstrating similar anatomic configuration as A but with more prominent posterior fossa crowding and aqueductal compression. Axial T2 images (F-H). Note absence of patent aqueduct in F (arrow).

Among children in the cysts and cephaloceles group, agenesis of the corpus callosum was seen in 7, always in conjunction with midline cysts. Cortical dysplasia, sometimes extensive, was seen in 8 children. Only 2 children in this category had classic Dandy-Walker malformations. Among children with communicating hydrocephalus, 2 had midline malformations, including agenesis of the corpus callosum and absent septum pellucidum; otherwise, brain malformations were uncommon.

Additional Physical Malformations and Identifiable Clinical Syndromes

Additional physical anomalies were identified in 48 of 232 children (21%), 27 of whom had been diagnosed with specific syndromes (Table 2). No specific syndromes were present in patients with hydrocephalus associated with myelomeningocele, and additional physical malformations were rare. Among children with hydrocephalus associated with apparent aqueductal obstruction, 8 of 59 (14%) had a defined syndrome, including 6 with hydrocephalus with stenosis of the aqueduct of Sylvius associated with *L1CAM* mutations (sometimes referred to as Bickers-Adams syndrome). Only 1 additional physical anomaly was seen.

Only 3 of 39 children (6%) with cysts and cephaloceles had an identifiable syndrome, but 7 (19%) had additional malformations, most conspicuously renal cysts and digit abnormalities.

Among children with communicating hydrocephalus, only 2 of 31 (6%) had a defined syndrome, but 5 had major physical anomalies, including 2 structural cardiac defects and 3 congenital diaphragmatic hernias. Remarkably, 15 of 25 children (60%) with posterior fossa crowding had defined disorders, most frequently multisuture craniosynostosis or skeletal dysplasia syndromes. Additional physical malformations were seen in 2 of the 10 remaining children (20%).

Developmental and Surgical Outcome

After assessing basic characteristics of children with hydrocephalus (Table 3), we compared children on the basis of objective clinical criteria. At an average age of 5.3 years, 87% could eat by mouth, and 72% of children more than 2 years of age (86% of children without myelomeningocele) were walking independently. Seventy percent required physical therapy (56% of those without myelomeningocele), 41% were receiving speech therapy, and 18% had epilepsy. We noted

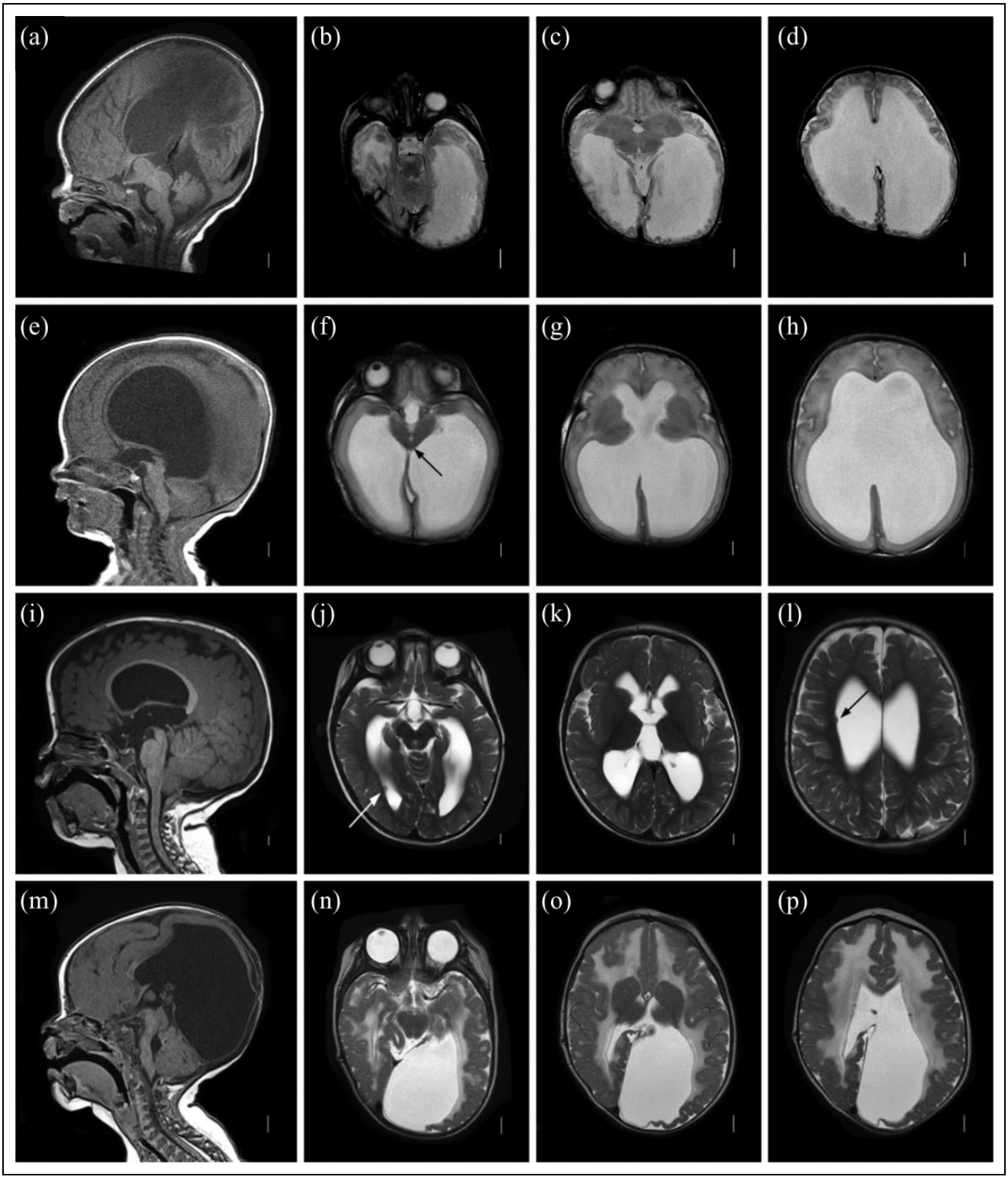

Figure 2. Aqueductal obstruction. (A-D) Aqueductal obstruction associated with *L1CAM* mutation. Sagittal T1 MRI image (A) showing complete aqueductal occlusion (arrow) and small cerebellum. Axial T2 images (B-D) demonstrating extensive dilation of lateral ventricles. (E-H) Mesencephalosynapsis. Sagittal T1 images (A) demonstrating inferior aqueductal occlusion with funneling (arrow). Axial T2 images (F-H) showing fused inferior colliculi (arrow) and severe ventricular dilation. (I-L) Periventricular nodular heterotopia with aqueductal nodule. Sagittal T1 image (A) showing obstructive nodule within aqueduct (arrow). Axial T2 images (J-L) demonstrating moderate ventricular dilation and periventricular nodular heterotopia (arrows). (M-P) Muscle-eye-brain disease. Sagittal T1 image (M) showing enlarged tectum with complete aqueductal obstruction (arrow), hypoplastic and kinked brainstem, and cerebellar dysplasia with cysts. Axial T2 images (N-P) showing cobblestone cortex and abnormal white matter.

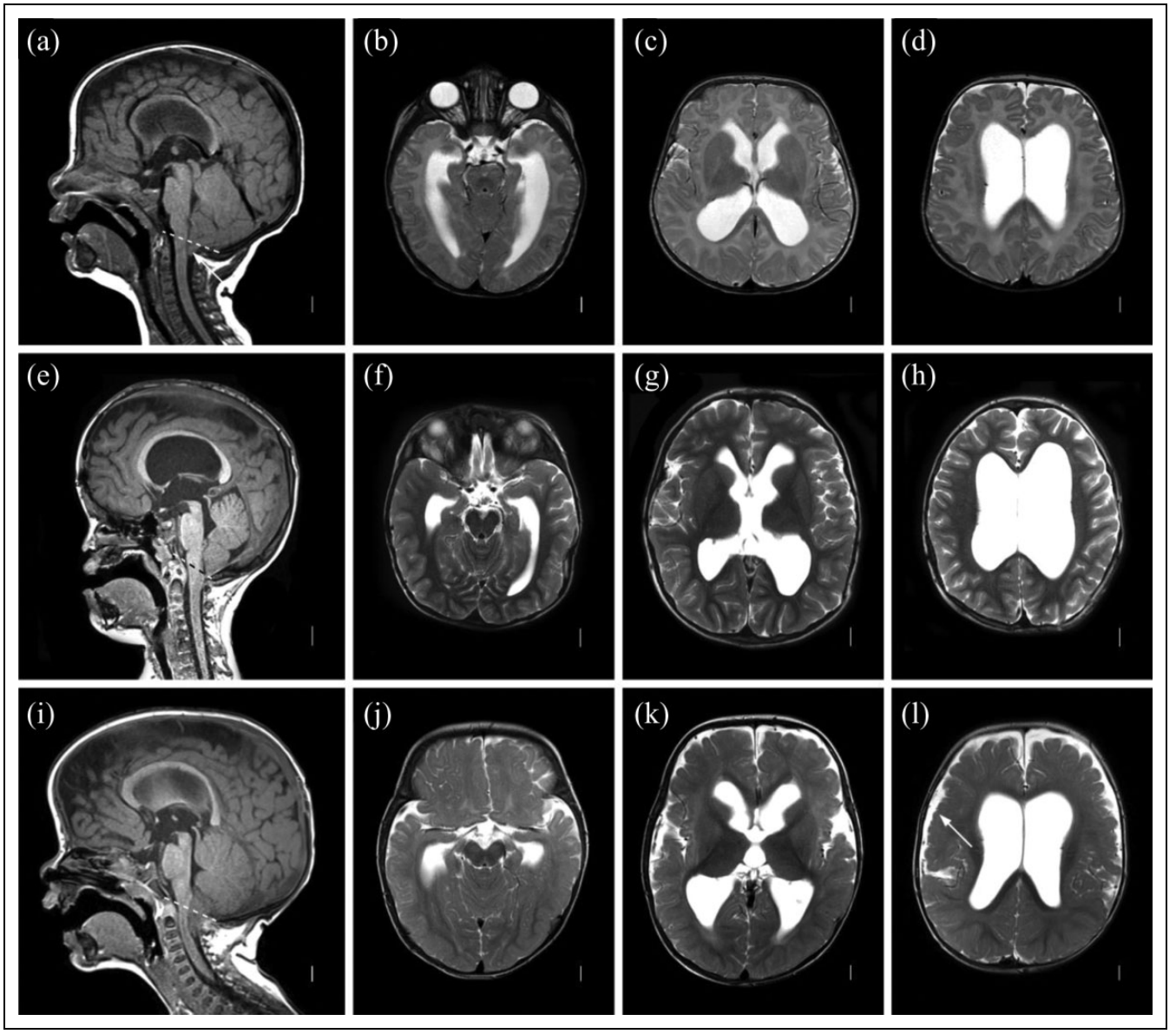

Figure 3. Posterior fossa crowding. (A-D) Chiari I malformation. Axial T1 MRI image (A) showing open aqueduct and relatively large-appearing cerebellum, with herniation of tonsils below foramen magnum (dashed line). Axial T2 images (B-D) showing moderate dilation of lateral ventricles. (E-H) Pfeiffer syndrome with multisuture synostosis. Sagittal T2 images (E) showing midface retrusion, widely patent aqueduct, and small, crowded posterior fossa with tonsillar herniation below the foramen magnum (dashed line) in patient with a confirmed *FGFR2* mutation. Axial T2 images (F-H) showing moderate ventricular dilation. (I-L) Megalencephaly, polydactyly, polymicrogyria, and hydrocephalus syndrome. Sagittal T1 image (I) showing widely patent aqueduct with tonsillar herniation through foramen magnum (dashed line). Axial T2 image showing moderate ventricular dilation (J-L) and extensive bilateral perisylvian polymicrogyria (L, arrow).

statistically significant differences in the need for physical therapy, speech therapy, and the presence of epilepsy across subtypes.

Surgery for hydrocephalus was performed in 72% of children, with the highest proportion in hydrocephalus associated with myelomeningocele (87%) and the lowest in communicating hydrocephalus (19%) (Table 4). Among patients who underwent ventriculoperitoneal shunt placement, 53% experienced at least 1 shunt failure, a result that did not differ statistically by subtype. However, the 10-year shunt failure rate demonstrated highly statistically significant difference across subtypes, a result driven by the lower revision rates seen in children with posterior fossa crowding.

Discussion

We investigated a large series of infants with hydrocephalus and found that 58% had no obvious extrinsic cause of their condition. Almost all children could be placed into 1 of 5 subtypes based on key clinical and radiographic features. The additional malformations and syndromes seen within subtypes suggest distinct underlying mechanisms, a notion further underscored

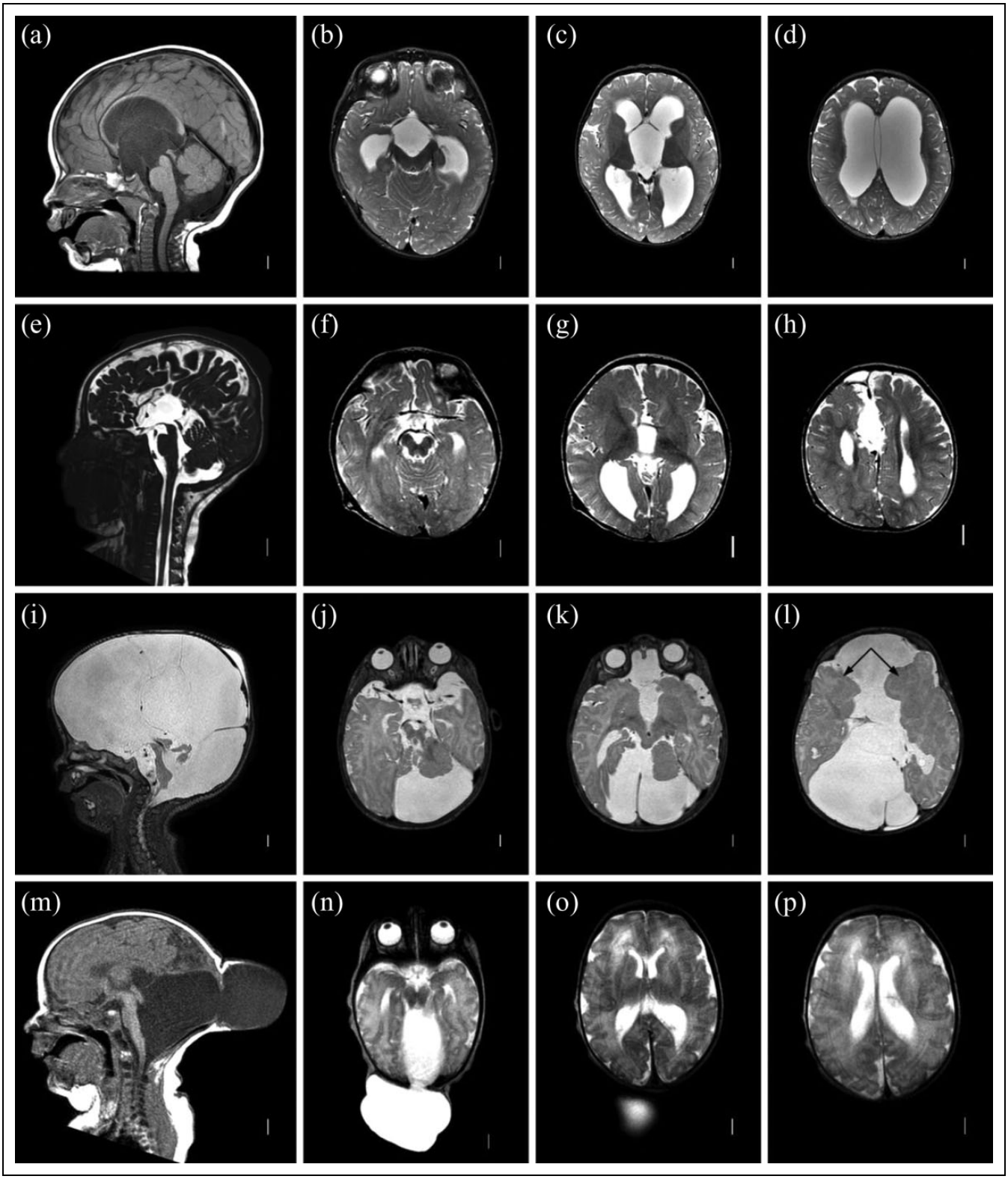

Figure 4. Cysts and cephaloceles. (A-D) Third ventricular cyst. Sagittal T1 (A) and axial T2 (B-D) MRI images demonstrating small, obstructive cyst with lack of additional brain malformations or cortical dysplasia. (E-H) Interhemispheric cyst. Sagittal constructive interference in steady state and axial T2 images showing interhemispheric cyst with absent corpus callosum. (I-L) Complex cystic malformation. Sagittal (I) and axial (J-L) T2 images demonstrating brainstem hypoplasia and extensive infolded, dysplastic cerebral hemispheres (L, arrows). (M-P) Encephalocele. Sagittal T1 images (M) showing cephalocele, with fluid collection in continuity with posterior fossa. Axial T2 images (N-P) demonstrating relatively normal-appearing cerebral hemispheres.

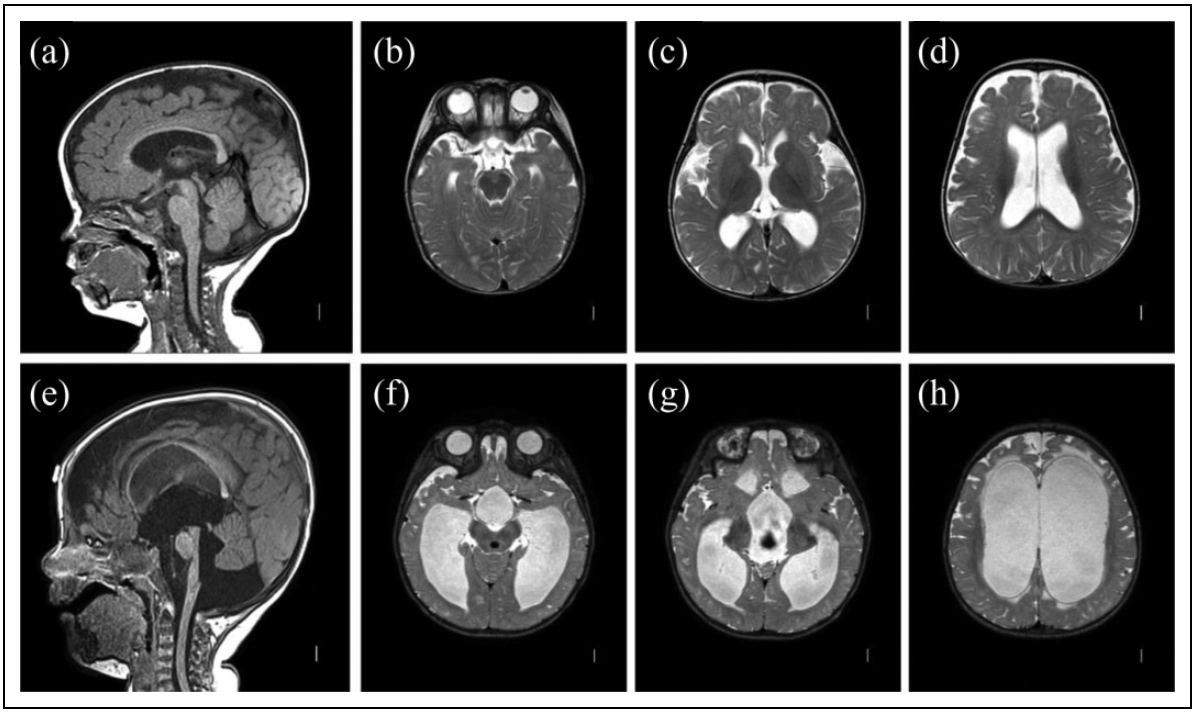

Figure 5. Communicating hydrocephalus. (A-D) Mild idiopathic communicating hydrocephalus. Sagittal T1 MRI image (A) showing open aqueduct and absence of posterior fossa crowding. Axial T2 images (B-D) showing rounded, mildly dilated ventricles with generous extra-axial space. (E-H) Severe idiopathic communicating hydrocephalus. Sagittal T1 image (E) showing enlarged aqueduct, fourth ventricle, and excess fluid within the posterior fossa. Axial T2 images (E-H) demonstrate marked ventriculomegaly with transependymal flow.

by differences in basic clinical characteristics, developmental and surgical outcomes.

Hydrocephalus Associated With Myelomeningocele

The myelomeningocele-associated Chiari II malformation is characterized by several anatomic features that combine to cause apparent aqueductal and posterior fossa crowding,[5] which may contribute to the earlier onset and greater ventricular dilation seen in this group of children compared to those with posterior fossa crowding alone. Though these children had mobility problems as a result of their myelomeningoceles, the proportion of children requiring speech therapy, who had epilepsy and who were deceased was relatively low.

Mechanistically, the Chiari II malformation is usually viewed as a consequence of chronic intrauterine cerebrospinal fluid leakage,[6,7] a notion supported by animal models[7-9] and by the results of clinical trials in utero repair of myelomeningocele, which show improvement in hydrocephalus.[10] Of note, mutations in planar cell polarity genes play a role in the pathogenesis of some neural tube defects in humans,[11-13] whereas mutations in other planar cell polarity genes give rise to hydrocephalus independent of myelomeningocele in mice,[14] postulated to be the result of impaired development and function of ependymal cilia.[15] The hydrocephalus that accompanies myelomeningocele may therefore be both a consequence of mechanical obstruction and, in a subset of patients, genetically based differences in cerebrospinal fluid flow.

Aqueductal Obstruction

Hydrocephalus associated with aqueductal obstruction was early in onset and associated with the greatest severity of ventricular dilation. Not surprisingly, this group of children had the worst developmental outcomes of any group, though the need for multiple surgeries and the total number of surgical procedures undergone by each patient was similar to most other subtypes.

Of the 8 children with aqueductal obstruction tested, 6 had mutations in *L1CAM*, which plays key roles in neuronal migration and axon guidance.[16] Two children had muscle-eye-brain disease caused by mutations in *POMGNT1*, which also leads to aberrant migration of neurons and likely contributes to an obstructive brainstem malformation.[17,18] Notably, 15 children with aqueductal obstruction had additional mid-hindbrain malformations, most often mesencephalosynapsis with or without rhombencephalosynapsis. These malformations are thought to be genetically based, though the genes involved are not known.

Though we excluded patients with known intraventricular hemorrhage or infection, some children in this group could have aqueductal obstruction as the result of an unrecognized extrinsic event. Evidence of obstructive microhemorrhage in a structurally normal aqueduct is sometimes evident only upon autopsy.[19] Intraventricular hemorrhage has also been shown to induce nodules of neural progenitor cells within the ventricular system.[20] This mechanism could potentially explain the nodular obstruction seen in 3 children.

Table 3. Clinical Outcome of Children With Developmental Hydrocephalus.

	All hydrocephalus (n = 236)	MM (n = 78)	Proximal obstruction (n = 60)	Distal obstruction (n = 25)	Cysts and cephaloceles (n = 38)	Communicating (n = 31)	*P* value for heterogeneity
NGT- or GT-fed, n (%)	29 (12.8)	6 (7.9)	10 (17.0)	5 (20.8)	4 (11.1)	4 (12.9)	.40
Mobility (age ≥2 y)							.28 (excluding MM)
Walking independently	114 (65.9)	19 (31.1)	32 (74.4)	19 (95.0)	24 (85.7)	16 (94.1)	
Crutches or walker	14 (8.1)	12[a] (19.7)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Wheelchair	45 (26.0)	30[a] (49.2)	9 (20.9)	1 (5.0)	4 (14.3)	1 (5.8)	
Physical therapy n (%)	126 (70.0)	63[a] (92.7)	28 (68.3)	10 (47.6)	17 (68.0)	8 (32.0)	.02 (excluding MM)
Speech therapy n (%)	71 (40.5)	19 (29.2)	23 (59.0)	12 (54.6)	10 (58.3)	7 (28.0)	.02
Epilepsy n (%)	40 (17.3)	5 (6.5)	20 (33.3)	2 (8.0)	11 (29.0)	2 (6.5)	<.001
Deceased n (%)	14 (6.0)	1 (1.3)	7 (11.5)	2 (8.0)	2 (5.3)	2 (6.5)	.16

Abbreviations: GT, gastric tube; NGT, nasogastric tube; MM, myelomeningocele; SD, standard deviation.
[a]May primarily reflect disability from myelomeningocele.

Table 4. Surgical Outcome of Children With Developmental Hydrocephalus.

	All hydrocephalus (n = 236)	MM (n = 78)	Proximal obstruction (n = 60)	Distal obstruction (n = 25)	Cysts and cephaloceles (n = 38)	Communicating (n = 31)	*P* value for heterogeneity
Any surgery [a] n (%)	167 (72.0)	68 (87.2)	47 (78.3)	13 (52.0)[b]	33 (86.8)	6 (19.4)	<.001
Total surgeries[b] Mean ± SD (min, max)	2.3 ± 1.6 (1, 9)	2.3 ± 1.7 (1,9)	2.3 ± 1.5 (1,6)	1.3 ± 0.8 (1, 3)	2.8 ± 1.8 (1, 7)	1.8 ± 1.2 (1, 3)	.04
VP shunt n (%)	162 (68.6)	67 (85.9)	47 (78.3)	11 (44.0)	28 (73.7)	6 (19.4)	<.001
Any shunt failure[c] n (%)	85 (52.8)	39 (58.2)	26 (55.3)	2 (18.2)	15 (55.6)	2 (33.3)	.13
Failure rate[c] (number of failures per 10 child-years)[c]	2.0 ± 3.9	2.0 ± 3.6	1.8 ± 3.6	0.4 ± 0.9	3.0 ± 5.5	1.4 ± 2.8	<.001

Abbreviations: MM, myelomeningocele; SD, standard deviation; VP, ventriculoperitoneal.
[a]Shunt, ETV, or cyst fenestration.
[b]Among children who underwent surgery.
[c]Among children with VP shunt.

Posterior Fossa Crowding

Posterior fossa crowding, with or without hydrocephalus, is often described in conjunction with alterations of skull shape.[21-24] Skeletal dysplasias and multisuture synostosis syndromes were seen in more than half the patients in this category, with mutations in *FGFR* genes found in all but one of those children who underwent testing. The bony changes associated with *FGFR*-related syndromes are well recognized. However, mutations in *FGFR*-mediated signaling pathways can also cause excessive growth of the brain itself.[25-28] This provides a link between *FGFR*-associated hydrocephalus and megalencephaly-associated hydrocephalus, which was present in 6 children in this category.

The mechanism leading to this subtype of hydrocephalus may be a progressive mismatch between skull size and brain size, which is underscored by the relatively late onset of hydrocephalus seen in this group of children. Clinical outcomes were similar to the group as a whole, though fewer children had epilepsy. Notably, children in this category who underwent hydrocephalus-related surgery were much less likely to experience shunt failure, possibly because many also underwent skull surgery, probably rendering these children less shunt-dependent through improved cerebrospinal fluid flow dynamics.

Cysts and Cephaloceles

Cysts and cephaloceles are known causes of hydrocephalus,[29,30] but the pathogenesis of these malformations is poorly understood. Simple cysts have been attributed to accidental entrapment of cerebrospinal fluid within a split layer of arachnoid.[31] However, more complex cystic malformations can have a genetic basis, with numerous syndromes described in the literature, including oro-facial-digital syndrome,[32] Chudley-McCullough syndrome[33] and Aicardi syndrome.[34] This subtype was associated with the highest proportion of children with epilepsy, likely reflecting the inclusion of complex cystic malformations and encephaloceles with associated cortical dysplasia.

We suspect that several molecular mechanisms underlie cyst- and cephalocele-associated hydrocephalus, which is supported by the spectrum of MRI findings seen in this group of children. Only 3 patients had a defined syndrome, but additional physical anomalies were more common in this subtype than in any other. Several of the malformations seen in association with complex cystic malformations and encephaloceles, including renal cysts and poly- or syndactyly, hint at defective ciliary signaling.[35]

Communicating Hydrocephalus

Hydrocephalus without apparent obstruction is a known consequence of intraventricular hemorrhage and infection, presumably due to inflammation in the subarachnoid space. The pathophysiology of idiopathic communicating hydrocephalus is less clear, with cryptic hemorrhage,[36] immaturity of the arachnoid granulations,[37,38] excessive skull growth,[39] lymphatic dysplasia,[40] and elevated venous outflow resistance[41-43] all invoked as possible causes. A genetic underpinning of idiopathic communicating hydrocephalus has long been suspected, based on the observation that a substantial minority of affected children have close family members with macrocephaly.[38,44,45] In our series, this subtype had a much higher proportion of males than others, which suggests an X-linked contribution.

The highly variable age of onset and severity seen among children with communicating hydrocephalus suggests that multiple functional mechanisms may be operating. Notably, 5 patients in this group had malformations associated with increased vascular pressure, confirming that high venous outflow resistance may be important in this form of hydrocephalus.

Limitations of This Study

This study provides detailed anatomic and clinical information on a large cohort of children; however, it is limited to those who underwent MRI scans. Those who underwent only CT or ultrasound were not included, which could bias the results towards more severely affected children. This study is also limited by its retrospective and observational nature. Children with multiple medical needs are likely to have frequent medical appointments with detailed documentation available for review; children who are more mildly affected may be more easily lost to follow-up. Therefore, this study may be biased toward more severely affected children, with a resulting overestimation of the proportion with disabilities. In contrast, this study may underestimate the frequency of outcomes such as epilepsy and shunt failure; these outcomes accrue over time and would be expected to increase if the cohort were followed longer.

Conclusion

Among 411 infants with hydrocephalus, 60% had no recognizable extrinsic cause of their condition. All but 4 of these infants could be placed in 1 of 5 categories based on key clinical and radiographic features. The clinical characteristics, patterns of additional malformations and syndromes, as well as statistically significant differences in developmental and surgical outcome observed across subtypes suggest distinct underlying mechanisms. We suspect that these mechanisms will be better elucidated, and subtypes further refined, with advances in imaging and discovery of new genes. This in turn will allow for more nuanced counseling of affected families and more clinically relevant comparisons of outcome and response to treatment.

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Author Contributions

HMT designed the study, collected and analyzed the data, and drafted the manuscript; GEI reviewed MRIs; TCR and JCP performed statistical analysis of the data; SRB, KJM, DD, and WBD provided conceptual framework for delineating subtypes of hydrocephalus as well as clinical outcomes.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was reviewed by the Human Subjects Protection Program of the Seattle Children's Research Institute and was granted approval number 14299.

Supplemental Material

The online [appendices/data supplements/etc] are available at http://jcn.sagepub.com/supplemental

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