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Infantile hydrocephalus: a review of epidemiology, classification and causes

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Abstract

Hydrocephalus is a common but complex condition caused by physical or functional obstruction of CSF flow that leads to progressive ventricular dilatation. Though hydrocephalus was recently estimated to affect 1.1 in 1,000 infants, there have been few systematic assessments of the causes of hydrocephalus in this age group, which makes it a challenging condition to approach as a scientist or as a clinician. Here, we review contemporary literature on the epidemiology, classification and pathogenesis of infantile hydrocephalus. We describe the major environmental and genetic causes of hydrocephalus, with the goal of providing a framework to assess infants with hydrocephalus and guide future research.

Keywords

Hydrocephalus; Aqueductal stenosis; L1CAM; Intraventricular hemorrhage; Genetics

Introduction

Hydrocephalus is a common problem, heterogeneous in nature and complex in pathogenesis. As a consequence, hydrocephalus has multiple competing definitions and classification systems that make it a difficult condition to approach as a scientist or as a clinician. Congenital forms of hydrocephalus are particularly complicated, both anatomically and mechanistically. In this paper, we undertake a comprehensive review of hydrocephalus, focusing on those forms that are apparent prenatally and within the first year of life. We describe contemporary views on the underlying mechanisms that lead to infantile hydrocephalus and discuss its most common associations, both acquired and genetic.

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Defining hydrocephalus

Hydrocephalus has been defined broadly as any increase in cerebrospinal fluid (CSF) within the skull, including brain edema [1], and more narrowly as ventricular enlargement that causes accelerated head growth or requires surgical intervention [2]. Our preferred definition is that proposed as part of the International Hydrocephalus Working Group, which describes “an active distension of the ventricular system...resulting from inadequate passage of cerebrospinal fluid from its point of production within the cerebral ventricles to its point of absorption into the systemic circulation [3].” Embedded in this definition is the notion of hydrocephalus as a progressive process; however, the progression does not have to be so rapid or relentless as to cause clinical symptoms or require surgical intervention. Non-progressive ventricular enlargement, such as that seen in the setting of atrophy, injury, or certain brain malformations, would be excluded from this definition of hydrocephalus.

Epidemiology of hydrocephalus

Prevalence estimates for infantile hydrocephalus vary between one and 32 per 10,000 births, depending on the definition used and the population studied. The most recent estimate of prevalence comes from a large, population-based investigation of idiopathic infantile hydrocephalus in Denmark over a 30 year period [4]. The authors included children diagnosed before one year of age with no known extrinsic cause of their condition. Chiari I and Dandy-Walker malformations were included, but neural tube defects were excluded from their study population. The authors found an estimated prevalence of 1.1 per 1,000 infants.

Pathophysiology of hydrocephalus

In the most familiar model of cerebrospinal fluid (CSF) flow, CSF is produced primarily by the choroid plexi, unique secretory structures located within the lateral, third, and fourth ventricles [5]. According to this “bulk flow” model, CSF travels slowly and unidirectionally through the ventricular system, exits the fourth ventricle into the subarachnoid space, and is absorbed through arachnoid granulations into the venous sinuses and systemic circulation. In this model, hydrocephalus is a consequence of physical or functional obstruction within the ventricular system, the subarachnoid space, or the venous sinuses. Within the ventricular system, an obstructive malformation or gliosis can cause physical blockage of CSF flow. Outside the ventricular system, inflammation and scarring of the subarachnoid space, or elevated pressures within the venous sinuses, can impair translocation of CSF into the systemic circulation.

Notably, up to one third of CSF exits the skull along cranial nerve sheaths and into the lymphatic system rather than into the venous sinuses [6]. Disturbances of this lymphatic exit pathway have been implicated in rat models of hydrocephalus [7], but whether they play a role in the pathogenesis of human hydrocephalus is not yet known.

Superimposed upon unidirectional CSF flow is pulsatile movement of CSF during the cardiac cycle. With each beat of the heart, CSF flows through the foramen magnum, into the spinal subarachnoid space and then back into the skull. Recently, CSF has also been found to flow in a pulsatile manner from the intracranial subarachnoid space into the brain

parenchyma, and then into the systemic circulation, along paravascular pathways [8, 9]. Augmentation of pulsatile ventricular pressure waves in animal models results in hydrocephalus [10]. Altered pulsatility of CSF flow has repeatedly been described in conjunction with human hydrocephalus [11-15], but whether it is cause or consequence remains unclear [16].

Classification of hydrocephalus

Acquired vs. developmental (congenital)

In infants, hydrocephalus without an obvious extrinsic cause is usually referred to as congenital hydrocephalus, since it is often present at birth. When hydrocephalus occurs as a complication of another condition such as hemorrhage, infection or neoplasm, it is usually called acquired or secondary hydrocephalus. However, forces such as hemorrhage and infection can act prenatally and also cause “congenital” hydrocephalus. Moreover, some genetic forms of hydrocephalus are not evident at birth, but develop over time. Therefore, we prefer to distinguish between acquired (extrinsic) and developmental (intrinsic) forms of hydrocephalus.

Obstructive vs communicating

One of the earliest classifications for hydrocephalus was the obstructive/communicating dichotomy devised by neurosurgeon Walter Dandy in 1913 [17]. This binary system remains in common use, but a more nuanced system that takes advantage of tremendous advances in imaging is now possible. In the neurosurgical literature, a multifactorial classification system that incorporates the exact point of CSF obstruction has been introduced [18]. However, developmental forms of hydrocephalus often have multiple points of obstruction, and so have proved resistant to classification within a precise obstruction-based system. In children with hydrocephalus, we have found it helpful to specify whether the primary point of obstruction is proximal (at the level of the third ventricle or aqueduct), distal (at the level of the fourth ventricle, fourth ventricular outflow tracts, or foramen magnum), or whether there is no apparent source of obstruction (communicating hydrocephalus).

Syndromic vs non-syndromic

Hydrocephalus has traditionally been divided by geneticists into syndromic and non-syndromic forms, depending on whether additional congenital anomalies are present [2]. However, no consensus exists about how to classify patients with defined genetic syndromes that lack major clinical features outside the brain. For example, the hydrocephalus associated with mutations in *LICAM* has been classified both as non-syndromic [2] and as syndromic [19]. We prefer to distinguish between hydrocephalus in which the clinical phenotype is characterized predominantly by brain findings, and hydrocephalus that is only one part of a condition characterized by major physical abnormalities or clinical signs. When a particular clinical syndrome or genetic basis can be identified, we describe the hydrocephalus as being associated with that syndrome (e.g., *LICAM*-associated hydrocephalus).

Causes of hydrocephalus

Hydrocephalus can be the result of an extrinsic event acting upon a structurally normal brain. It can also occur in the setting of an identifiable clinical or molecular syndrome, or can be purely idiopathic. In a recent series of 411 infants with hydrocephalus, 175 had a confirmed or suspected extrinsic cause of their condition, most commonly prematurity-associated intraventricular hemorrhage. The remaining 236 patients had no clear extrinsic cause of their condition, but 28 of them had an identifiable genetic syndrome (Tully, unpublished data).

Acquired hydrocephalus

The most common cause of acquired hydrocephalus in infants is hemorrhage, most often as a consequence of prematurity. Other important causes include neoplasm and infection, usually bacterial meningitis. In these clinical situations, there is little ambiguity about the cause of the hydrocephalus. However, intraventricular blood can also cause progressive ventricular dilatation even in the absence of a clinically obvious hemorrhage. In a series of 28 autopsies performed on fetuses from pregnancies that were terminated because of hydrocephalus, four fetuses were found to have evidence of cryptic microhemorrhage (red blood cells and hemosiderin-laden macrophages) within a structurally normal aqueduct [20]. Thus, some apparently idiopathic hydrocephalus may in fact be due to unrecognized prenatal intraventricular hemorrhage.

Similarly, unrecognized intrauterine infection could conceivably cause hydrocephalus. Intrauterine infections with enterovirus [21], lymphocytic choriomeningitis [22], CMV and toxoplasmosis [23] have all been associated with hydrocephalus, but their contribution to the total burden of infantile hydrocephalus remains unknown. A recent pilot study [23] found that infants with hydrocephalus were more likely to have evidence of toxoplasmosis or CMV infection on neonatal blood spot cards than infants without hydrocephalus. The odds ratio was not statistically significant, which the authors attributed to reduced sensitivity of stored specimens and to small numbers of affected patients overall. Information was not available about whether children with evidence of infection on neonatal blood spot card had other clinical evidence of viral infection. Nevertheless, these results suggest that at least some idiopathic infantile hydrocephalus may be due to unrecognized viral infections.

Several medications have been described in association with infantile hydrocephalus when taken during pregnancy, including misoprostol [24]metronidazole [25], and antidepressants [26]. The best documented association is with isotretinoin [27]. Though isotretinoin-associated hydrocephalus is incompletely characterized, it is presumably caused by a disruption of retinoic acid morphogen gradients in the hindbrain [28] that results in an obstructive malformation.

Developmental hydrocephalus

When an overt extrinsic cause has been excluded, clinicians must carefully assess clinical and imaging findings to see if a particular genetic syndrome can be identified. In our cohort of patients, a specific clinical syndrome or genetic cause was found in only a minority,

underscoring our still-limited knowledge of the causes of hydrocephalus. In patients without distinctive clinical features, only a very few causative genes have been discovered. Yet in the Danish population-based study described earlier, the authors found strong evidence of familial aggregation of developmental hydrocephalus, which suggests a major contribution from yet-unrecognized genetic factors [4].

Hydrocephalus without major additional physical features (Table 1)

Of patients whose clinical phenotype is characterized by hydrocephalus without additional major clinical exam findings, the majority have obstruction at the level of the aqueduct (Tully, unpublished data). Of these patients, *L1CAM* mutations remain the single most common cause, although mutations in this gene still explain only a minority of hydrocephalus.

L1CAM-associated hydrocephalus

X-linked hydrocephalus associated with stenosis of the aqueduct of Sylvius (HSAS) is the most common heritable form of hydrocephalus, thought to account for up to 10% of males with isolated idiopathic hydrocephalus [29]. Mutations in *L1CAM* are the main genetic cause of HSAS, which occurs within a broader spectrum of disease that also includes isolated agenesis of the corpus callosum as well as X-linked spastic paraplegia (SPG1). The *L1CAM* gene product is a neural recognition molecule that plays key roles in neuronal migration and axon guidance [30]. When mutated, it gives rise to several structural malformations that obstruct CSF flow, most commonly at the level of the aqueduct (Figure 1A-D).

Though mutations in *L1CAM* are the best known cause of X-linked hydrocephalus, there is still limited consensus about what clinical findings should prompt testing in children without a family history. In a recent series of 138 autopsy subjects that had been referred specifically for *L1CAM* testing [31], 57 (41%) were found to have pathogenic mutations. Of those mutation-positive patients, 98% had abnormalities of the corpus callosum, 98% had hypoplasia or aplasia of the corticospinal tracts, 90% had aqueductal stenosis, and 88% had adducted thumbs. However, none of these findings was specific to *L1CAM*-associated hydrocephalus: Among the 79 autopsy subjects without *L1CAM* mutations, callosal abnormalities were seen in 73%, corticospinal tract abnormalities in 59%, aqueductal stenosis in 46%, and adducted thumbs in 27%. Though the hit rate for detecting an *L1CAM* mutation increases in the setting of a positive family history and compatible clinical and radiographic features [29], no single finding or combination of findings can confirm or exclude the diagnosis. Therefore, *L1CAM* testing should be strongly considered in all males with unexplained hydrocephalus, but should be regarded as mandatory for those with a family history or adducted thumbs.

AP1S2-associated hydrocephalus

Fried syndrome, first described in 1972 [32], was once thought to be an example of L1 syndrome before it was recognized as a separate X-linked disorder [33]. Now known to be caused by mutations in the *AP1S2* gene [34], Fried syndrome is characterized primarily by intellectual disability with prominent basal ganglia iron deposition or calcifications [35] on

CT scan (which may not be obvious on MRI), and variable hydrocephalus. Mutations in the same gene have now been recognized as the cause of other overlapping X-linked intellectual disability syndromes [35] that are often accompanied by hydrocephalus. The severity and radiographic appearance of the hydrocephalus associated with mutations in *APIS2* has not been well characterized, but has been described as aqueductal stenosis in at least some affected individuals [32], though others may have retrocerebellar or 4th ventricular (Dandy-Walker spectrum) cysts [35]. We recommend considering *APIS2* testing in males with intellectual disability and imaging abnormalities that suggest deposition of iron or calcium with the basal ganglia. Since both iron calcium may be subtle on basic MRI sequences, we recommend assessing for these with a head CT, or by MRI sequences that are particularly sensitive to both iron and calcium (GRE, SWI).

Walker-Warburg/Muscle-Eye-Brain disease

α -dystroglycanopathies are often classified as muscular dystrophies, but hydrocephalus may be an early-onset feature that dominates the clinical phenotype. These related conditions are caused by mutations in enzymes that result in defective neuronal binding to the extracellular matrix, abnormal glial limiting membrane, and disrupted neuronal migration [36, 37]. The result is a distinctive brain malformation consisting of a cobblestone cortex with abnormal white matter in the cerebral hemispheres, as well as brainstem abnormalities characterized by a flattened pons, enlarged tectum, and kinked medulla, often with associated aqueductal obstruction (Figure 1, E-F). Cerebellar cysts are sometimes seen. These radiographic findings may not be readily apparent on perinatal scans [38], particularly if the associated hydrocephalus is severe. We recommend careful assessment of the MRIs of children diagnosed with aqueductal stenosis specifically for these findings. Follow-up MRIs done at a later age (as opposed to perinatal scans) may be particularly valuable to review. Serum creatine kinase levels and eye exams can also be useful in establishing a diagnosis. *POMT1*, *POMT2*, *POMGNT1*, *FKTN*, *FKRP*, *LARGE*, *ISPD* have all been associated with Walker-Warburg and Muscle-Eye-Brain phenotypes, so a multi-gene panel could be considered if available. *POMGNT1* in particular is associated with cerebellar cysts, so could be prioritized if those are seen [39].

New Mendelian causes of hydrocephalus

Mutations in two additional genes have recently been discovered to underlie severe autosomal recessive forms of hydrocephalus. *MPDZ* encodes for a protein that localizes to tight junctions [40] and may help regular planar cell polarity [41]. Previously studied in the context of addiction [42], alcohol withdrawal [43], and retinal degeneration [44], *MPDZ* was recently implicated as the cause of hydrocephalus in two consanguineous Saudi families [45]. The hydrocephalus associated with *MPDZ* appears to be severe and is described variably by the authors as supratentorial (which implies aqueductal obstruction) and communicating (which implies absence of intraventricular obstruction).

CCDC88C encodes DAPLE, a ubiquitously expressed protein that regulates cellular migration through its interaction with *dishevelled* in the non-canonical wnt pathway [46]. A mutation in *CCDC88C* was first suggested as the cause of hydrocephalus in a single consanguineous Algerian family [47], and was subsequently validated in a non-

consanguineous Ashkenazi Jewish family and a consanguineous Palestinian family [48]. In all three families, the hydrocephalus appears to be very severe. MRI revealed apparent aqueductal obstruction, though an autopsy performed on an affected 20-week gestational age fetus demonstrated an aqueduct that was patent at that time.

Other causes of hydrocephalus without additional physical features

Hydrocephalus can occur as an inconstant accompaniment to several other brain malformations including holoprosencephaly [49], rhombencephalosynapsis [50], Aicardi syndrome [51], agenesis of the corpus callosum [52], lissencephaly (though mostly in the context of severe forms such as X-linked lissencephaly with abnormal genitalia) [53] and periventricular heterotopia [54], among others.

Hydrocephalus accompanied by other physical features (Table 2)

Many clinical and genetic syndromes are accompanied by hydrocephalus. For infants with these disorders, diagnosis is usually made on the basis of characteristic clinical findings; however, brain MRI findings can sometimes provide additional clues to diagnosis.

Neural tube defects (NTDs)

The vast majority of patients with neural tube defects have hydrocephalus. NTD-associated hydrocephalus may be multifactorial in origin. Animal models suggest that chronic intrauterine CSF leakage produces the distinctive Chiari II malformation [55, 56], which obstructs CSF flow. However, mutations in planar cell polarity genes such as *Fuzzy (FUZ)* [57], *VANGL1* [58] and *CELSR1* [59] contribute to NTDs. Other planar cell polarity genes such as *CELSR2* [60] and *MPDZ* [45] can cause hydrocephalus independent of NTDs. The mechanism for this remains unknown, but could involve disrupted function of the ependymal cilia [61]. Alternatively, mutations in these genes could contribute to an obstructive structural malformation, such as that seen in *MPDZ*-associated hydrocephalus.

Syndromes associated with intracranial cysts

Intracranial arachnoid cysts are a well-recognized cause of hydrocephalus [62, 63]. Small, simple cysts have been attributed to an entrapment of CSF within the meninges [64], which could conceivably be a developmental accident. Since simple arachnoid cysts are seen in approximately 15% of individuals with deletion 22q13.3 (Phelan-McDermid) syndrome [65], this diagnosis should be considered in anyone in whom the severity of developmental delay seems disproportionate to the degree of hydrocephalus.

The genetic basis of complex cystic malformations has long been recognized. Several syndromes with overlapping phenotypes are characterized by complex cystic brain malformations that can cause progressive hydrocephalus, including oro-facial-digital syndrome type 1 [66], acrocallosal syndrome, hydroletharus syndrome [67], Pallister-Hall syndrome [68], and Grieg cephalopolysyndactyly [69]. Chudley-McCollough syndrome [70] is associated with intracranial cysts, polymicrogyria and profound sensorineural hearing loss. Mutations in *CC2D2A*, which cause both Joubert and Meckel syndromes, were recently found to be strongly associated with ventricular enlargement in a cohort of 209 Joubert

patients [71]. Dysfunction of the primary (non-motile) cilium is emerging as a major disease mechanism in several of these syndromes.

FGFR-associated craniosynostosis syndromes and skeletal dysplasias

Craniosynostosis syndromes are strongly associated with progressive hydrocephalus. In these conditions, mutations in fibroblast growth factor receptor (FGFR) genes cause cranial changes that obstruct flow of CSF and reduce absorption into the systemic circulation by increasing venous pressure [72, 73]. Mutations in these genes can also cause excessive growth of the brain itself, thereby compounding the problem [74-77]. Interestingly, hydrocephalus can accompany FGFR-associated skeletal dysplasias as well, likely reflecting the same underlying mechanisms.

RASopathies

Mutations in the RAS pathway cause several overlapping phenotypes including Noonan, cardio-facio-cutaneous and Costello syndromes [78, 79], as well as neurofibromatosis type 1 (NF1). The hydrocephalus associated with these conditions is likely multifactorial, due to both direct effects of the genetic defect as well as downstream effects. Cerebellar overgrowth is well-documented in Costello syndrome [80]. Chiari I malformations are frequently described in association with both Noonan and CFC syndromes, suggesting cerebellar overgrowth may also be present in those conditions. Noonan, CFC and Costello are also associated with structural heart disease, so elevated venous pressures may create a pressure gradient that impedes absorption of CSF into the systemic circulation. Hydrocephalus in NF1 is likely due to a combination of brain overgrowth and, in some infants, obstructive hamartomas.

Megalencephaly syndromes

PI3K-AKT pathway-related and other megalencephaly syndromes are increasingly recognized as a cause of progressive hydrocephalus [81]. As in the RASopathies, the cause may be multifactorial, related to both direct effects of the genetic defect combined with progressive brain overgrowth that causes posterior fossa crowding and distal obstruction of CSF flow.

VACTERL-H

The association of VACTERL features with hydrocephalus was first reported in 1984 [82], and was subsequently designated VACTERL-H syndrome. One subset of patients VACTERL-H was found to have X-linked inheritance and Fanconi anemia [83] in association with mutations in FANCB [84]. However, another subset of patients with VACTERL-H does not have Fanconi anemia or excess chromosome breakage [85]. Recently, our group found that several patients with non-FANCB-associated VACTERL-H have rhombencephalosynapsis [50, 86], a distinctive brain malformation in which the cerebellar vermis is at least partially absent, and the cerebellar hemispheres are fused across the midline. The genes that underlie rhombencephalosynapsis remain unknown.

Other syndromes

Several additional syndromes are associated with hydrocephalus, including the mucopolysaccharidoses [87], Sotos syndrome [87], Peter's Plus syndrome [88], primary ciliary dyskinesia [89, 90], Gorlin syndrome [91], and Rothmund-Thomson syndrome [92]. In addition to these single-gene disorders, many cytogenetic abnormalities have been linked to hydrocephalus, including microdeletion 9q22.3 [93], partial trisomy 1 [94], deletion 6q26q27 [95, 96], terminal duplication of 7q [97], as well as Trisomy 13, 18, 21 and triploidy [2].

Conclusions

Infantile hydrocephalus is a complex condition with both genetic and environmental causes. In acquired hydrocephalus, an extrinsic cause is often readily apparent by history or on the basis of imaging findings. In the majority of infants with hydrocephalus, however, an extrinsic cause is not easily discerned. In some of these children, an intrauterine microhemorrhage or prenatal viral infection may have gone unrecognized. However, we believe that hydrocephalus in many children is a marker of abnormal brain development. This can be assumed to be genetic, although most of the underlying genes are still unknown.

For children who are presumed to have developmental as opposed to acquired hydrocephalus, a detailed physical exam and careful review of imaging findings are critical to arriving at a diagnosis. The majority of genes known to cause hydrocephalus were discovered in the setting of clinical syndromes characterized by additional physical findings. FGFR-associated craniosynostosis syndromes (and, to a lesser extent, FGFR-associated skeletal dysplasias), RAS pathway-associated syndromes, and PI3K-AKT-pathway-associated megalencephaly syndromes have a particularly prominent association with hydrocephalus.

However, in many infants with hydrocephalus, there are no major additional physical findings to guide a genetic workup. For these children, MRI may reveal important diagnostic clues. However, only a few genetic causes of “just hydrocephalus” are known; most children without additional physical phenotypic clues still elude diagnosis. *LICAM* is the most commonly identified form of hydrocephalus without major additional physical findings (adducted thumbs are a suggestive clinical feature, but are neither completely sensitive nor completely specific). Other more recently discovered genetic causes include *AP1S2*, *MPDZ*, and *CCDC88C*. The genes that underlie congenital muscular dystrophies (dystroglycanopathies) are probably an under-recognized cause of hydrocephalus, since the characteristic clinical and radiographic features may be overlooked.

Though our understanding of infantile hydrocephalus has deepened over the past several decades, much remains unknown. Ongoing research is imperative. As new genetic technologies lead to discovery of additional causative genes, and as the phenotypes associated with these genes are better characterized both clinically and radiographically, we will be better able to counsel patients and families about the causes and consequences of this common condition.

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Figure 1. Hydrocephalus without major additional physical findings

A-B: HSAS in a 5-year-old girl with a mutation in *L1CAM*, for which she was tested only after a mutation was found in her affected younger brother. **A:** Sagittal T1 demonstrates aqueductal obstruction and stretched, dysplastic or disrupted corpus callosum. **B:** Axial T2 showing markedly and reduced white matter, particular in the posterior horns. **C-D:** HSAS in a newborn boy (brother of patient seen in A-B) caused by a mutation in *L1CAM*. Note similar, though more severe findings when compared to his older sister. **C:** Sagittal T1 demonstrates complete aqueductal obstruction and stretched corpus callosum. **D:** Axial T2 showing severely dilated lateral ventricles. **E-F:** Muscle-eye-brain disease. This girl had been given a diagnosis of aqueductal stenosis at birth. Radiographic features of Muscle-Eye-Brain disease were recognized only after she underwent a repeat MRI at age 3, after which her CK level was tested and found to be markedly elevated she was subsequently found to have a homozygous mutation in *POMGNT1*. **E:** Sagittal T1 demonstrates stretched, disrupted corpus callosum, thick tectum (arrow), kinked brainstem and cerebellar cysts. **F:** Axial T2 reveals cobblestone cortex and abnormal white matter signal in addition to decompressed lateral ventricles.

Figure 2. Hydrocephalus with major additional physical findings

A-C: 9-year-old girl with oro-facial- digital syndrome, Type 1. **A:** mid-sagittal T1 showing midline cysts with agenesis of the corpus callosum. **B, C:** axial and coronal T2s showing multiple midline cysts associated with cortical dysplasia. **D-F:** 6- month-old boy with Chudley-McCollough syndrome. **D:** sagittal T1 showing third ventricular cyst exerting mass effect on the brainstem and cerebellum. **E, F:** axial and coronal T2 showing third ventricular cyst, dilated lateral ventricles (particularly the posterior horns) and frontal polymicrogyria (final figure will have arrows). **G-I:** Hydrocephalus associated with previously unrecognized multisuture synostosis in a 13-month-old girl who underwent a head CT after a breath-holding spell. She was subsequently discovered to have a mutation in FGFR2. Craniosynostosis had not been recognized clinically. **G:** Sagittal view revealing dilated aqueduct and distal obstruction (posterior fossa crowding with Chiari I malformation). **H, I:** axial and coronal T2 showing dilated lateral ventricles and absent septum pellucidum.

Table 1

Hydrocephalus without major additional physical features

Condition	Point of Obstruction	Major Clinical Features	Major Imaging Features	Genes	Inheritance
HSAS	Proximal (aqueduct)	Adducted thumbs (in most patients with <i>LICAM</i> mutations, but not specific)	None (hypoplasia or agenesis of the corticospinal tracts is present in most patients with <i>LICAM</i> mutations, but may not be visible on MRI)	<i>LICAM</i> , others still unknown	X-linked (<i>LICAM</i>)
Fried syndrome, Fried-Pettigrew Syndrome	Not fully characterized, but some with proximal obstruction (aqueduct)	Intellectual disability	Basal ganglia calcification on CT or MRI (GRE or SWI sequences most sensitive)	<i>AP1S2</i>	X-linked
Walker-Warburg/Muscle-Eye-Brain Disease	Proximal (aqueduct), with probable overlay of communicating hydrocephalus from involvement of subarachnoid space	Variable eye findings, including microphthalmia, hypoplastic optic nerves, and anterior chamber malformations; elevated serum CK	Cobblestone cortex with abnormal white matter (may not be apparent on perinatal scans), kinked brainstem, enlarged tectum, cerebellar cysts (may be missed if hydrocephalus is severe)	<i>POMT1</i> , <i>POMT2</i> , <i>POMGNT1</i> , <i>FKTN</i> , <i>FKRP</i> , <i>LARGE</i> , <i>ISPD</i>	AR
Severe autosomal recessive	Not yet fully characterized	Not yet fully characterized	Not yet fully characterized	<i>MPDZ</i> , <i>CCDC88C</i> , likely others	AR

AR: autosomal recessive, CK: creatine kinase

Table 2

Hydrocephalus with major additional physical features

Type of Hydrocephalus	Point of obstruction	Major Clinical Features	Major Imaging Features	Genes	Inheritance
NTD-associated	Distal, with variable additional proximal obstruction	Neural tube defect	Chiari II malformation	<i>Fuzzy (FUZ)</i> , <i>VANGL1</i> , <i>CELSR1</i> (susceptibility genes)	Probably complex gene-environment interactions
Complex cystic malformations with overlapping phenotypes	Varies with location of cysts	OFD type 1: Trilobed tongue, accessory frenulae, Polydactyly or syndactyly	Variable, but may include ACC and cysts	<i>OFD1</i>	X-linked (lethal in males)
		Acrocallosal/hydrolethrus/Grieg: Postaxial Polydactyly (hands), hallux duplication in some	Variable, but may include ACC, hypothalamic hamartoma, molar tooth sign	<i>KIF7</i> , <i>GLI3</i>	AD (GLI3), AR (KIF7)
		Chudley McCollough: deafness	Polymicrogyria and ACC	<i>GPSM2</i>	AR
Craniosynostosis syndromes and skeletal dysplasias	Distal	Characteristic craniofacial features	Characteristic skull findings. Subtle areas of brain overgrowth likely not visible on MRI.	<i>FGFR1</i> , <i>FGFR2</i> , <i>FGFR3</i> , others	AD
		Characteristic skeletal features			
RASopathies	Variable (distal, communicating, or both)	NF1: café au lait spots, neurofibromata	Variable, including “unidentified bright objects” (punctate T2 hyperintensities), gliomas, hamartomas	<i>NF1</i>	AD
		Noonan: short stature, characteristic facial features, structural cardiac defects (especially pulmonic stenosis)	Not characterized	<i>PTPN11</i> , <i>SOS1</i> , <i>RAF1</i> , <i>KRAS</i> , <i>NRAS</i> , <i>BRAF</i> , <i>MAP2K1</i>	AD
		CFC: structural cardiac defects, characteristic craniofacial features, skin and hair abnormalities	Not characterized	<i>BRAF</i> , <i>MAP2K1</i> , <i>MAP2K2</i> , <i>KRAS</i>	AD, usually de novo
		Costello: characteristic craniofacial features, structural cardiac	Relatively large cerebellum, posterior fossa crowding	<i>HRAS</i>	AD, usually de novo
Megalencephaly syndromes	Distal	MCAP: capillary malformations, segmental overgrowth, syndactyly, polydactyly	Megalencephaly, posterior fossa crowding	<i>PIK3CA</i> , <i>CCND3</i>	Usually due to post-zygotic mosaicism
		MPPH: postaxial polydactyly	Megalencephaly, posterior fossa crowding, polymicrogyria	<i>PIK3R2</i> , <i>AKT3</i>	AD, usually de novo
VACTERL-H	Not characterized	VACTERL features	Not characterized	<i>FANCB</i>	XL
	Proximal (aqueduct)		Rhombencephalosynapsis	unknown	Usually sporadic

NTD: neural tube defect, OFD: oro-facial-digital syndrome, MCAP: megalencephaly capillary malformation syndrome, MPPH: megalencephaly-polydactyly-polymicrogyria-hydrocephalus syndrome, NF1: neurofibromatosis type 1, CFC: cardio-facial-cutaneous syndrome. ACC: agenesis of the corpus callosum