HHS Public Access

Author manuscript

Neurosurg Clin N Am. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Neurosurg Clin N Am. 2022 January ; 33(1): 67–79. doi:10.1016/j.nec.2021.09.006.

Syndromic Hydrocephalus

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Keywords

hydrocephalus; syndromic hydrocephalus; hydrocephalus genetics

Introduction

Hydrocephalus is characterized by abnormal accumulation, and impaired circulation and clearance, of cerebrospinal fluid (CSF). CSF accumulation results in distention of the ventricular system, leading to accelerated head growth and increased intracranial pressure, and often requires surgical intervention[1,2]. Syndromic hydrocephalus encompasses a diverse group of disorders and genetic variants in which hydrocephalus is a symptom, due to congenital structural malformations, or a range of emerging pathology associated with recently described genetic variants[3]. In this review we discuss several of the major syndromic causes of hydrocephalus, as well as emerging research on the genetic basis for congenital hydrocephalus as part of recently described genetic mutations (Table 1).

L1 Syndrome, and X-Linked Hydrocephalus

X-linked hydrocephalus comprises 5% of all cases of congenital hydrocephalus (Table 1)[1].X-linked hydrocephalus, associated with stenosis of the aqueduct of Sylvius (cerebral aqueduct), is the most severe phenotype associated with L1 syndrome, an X-linked recessive disorder (Fig. 1)[4]. Other phenotypes of L1 syndrome include MASA (mental retardation, aphasia, spastic paraplegia, adducted thumbs) and X-linked complicated corpus callosum and/or pyramidal tract agenesis[3,5]. Many of these phenotypic features commonly co-occur with X-linked hydrocephalus, especially intellectual disability[6].

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DISCLOSURE STATEMENT

The Authors have nothing to disclose.

This syndrome results from mutations in *L1CAM* on chromosome region Xq28, affecting the locus of a gene coding for the neural cell adhesion molecule *L1*. Mutations in this gene are associated with disordered neuronal migration which is considered a key mechanism in the pathogenesis of this syndrome[7]. Knockout rat models of the disease have revealed early pathologic changes of periventricular white matter tracts following the development of hydrocephalus, evidenced by reductions in fractional anisotropy and axial diffusivity on DTI in the corpus callosum, external capsule, and internal capsule. Histology also revealed hypomyelination and increased extracellular fluid in the corpus callosum, yielding some insight into how mutations of *L1CAM* contribute not only to hydrocephalus, but also to the developmental delays and intellectual deficits observed in this condition[8].

Point mutations at branch points in introns of *L1CAM,* causing abnormal splicing, were among the first mutations implicated in the disease. Recently, duplication affecting the intracellular domain, frameshift mutations affecting translation of fibronectin type-III of *L1CAM*, and novel nonsense mutations affecting ependymal cilia have also been implicated in this syndrome[9,10,11,12,13].

Beyond *L1CAM*, other X-linked mutations have recently been associated with syndromic hydrocephalus including missense mutations in *OTUD5* resulting in severe neurodevelopmental delay, hydrocephalus, and early lethality[14]. Duplications of Xp22.33 also lead to an L1-like phenotype of hydrocephalus associated with stenosis of the cerebral aqueduct, and dysgenesis of the corpus callosum[15]. Modern sequencing techniques may reveal other X linked mutations associated with L1-like syndromic hydrocephalus, though *L1CAM* remains the most common and thoroughly explored locus causing this condition.

Once an *L1CAM* pathogenic variant has been identified in a family, carrier testing, prenatal testing, and preimplantation genetic testing are available to patients and families. Treatment of individuals with X-linked hydrocephalus may vary depending on the timing of presentation; however, because many of these patients present with symptomatic hydrocephalus at birth, treatment often involves ventriculoperitoneal shunting (VPS), as the efficacy of endoscopic third ventriculostomy (ETV) with choroid plexus catheterization (CPC) in young infants is variable[4].

Syndromic Craniosynostosis

Syndromic craniosynostosis is associated with an increased incidence of hydrocephalus[16]. Hydrocephalus is more common in syndromic compared to non-syndromic or isolated craniosynostosis, and is seen in Crouzon's and Pfeiffer's syndromes[17]. Mechanisms underlying hydrocephalus in this group of syndromes relate to primary cerebral maldevelopment and residual structural outflow obstruction, not significantly ameliorated by posterior vault distraction strip craniectomy or cranial vault reconstruction commonly utilized in the treatment of craniosynostosis[16,18]. Conversely, early shunting (or over-shunting) can cause iatrogenic premature fusion of the cranial sutures in patients without craniosynostosis[19]. Treatment of hydrocephalus in patients with syndromic craniosynostosis includes VP shunt and ETV +/− CPC and is usually influenced by future need for cranial

vault reconstruction; therefore, location of shunt placement may vary to accommodate future planned surgeries.

Pfeiffer Syndrome

Of the syndromes associated with craniosynostosis, Pfeiffer syndrome is most frequently associated with hydrocephalus, with up to 60–80% of patients requiring ventriculoperitoneal shunt insertion or other treatment for hydrocephalus[20,21]. This syndrome is also associated with speech, language, hearing and feeding issues related to mutations in *FGFR2*[21,22].

Crouzon Syndrome

Crouzon syndrome, related to mutations in *FGFR2*[23], can be associated with a small foramen magnum and outlet obstruction associated with hydrocephalus.[24] Because of the structural predisposition to developing hydrocephalus in this form of craniosynostosis, up to 40% of patients with Crouzon's can present with or develop ventricular dilation[25]. While ventriculomegaly is common, a smaller number will ultimately require surgical treatment of hydrocephalus[26].

Apert Syndrome

Apert syndrome, also related to mutations in *FGFR2,* is characterized by multi-suture craniosynostosis, midface retrusion, syndactyly of the hands, fusion of the second through fourth nails, and nonprogressive ventriculomegaly[27,28]. Fewer patients with Apert syndrome have true or progressive hydrocephalus[29]. Rates of ventriculoperitoneal shunt placement in one study of a cohort of patients with Apert syndrome was 24.3%, lower that that seen in Crouzon or Pfeiffer syndromes[30].

Muenke Syndrome

Muenke syndrome is an autosomal dominant syndrome associated with mutations in *FGFR3* characterized by coronal craniosynostosis and variable extracranial anomalies[31]. Though this syndrome is not regularly associated with hydrocephalus, there has been a rare familial variant of this syndrome (p.Pro250Arg) with hydrocephalus, without craniosynostosis[32].

Achondroplasia

Achondroplasia is an autosomal dominant skeletal dysplasia caused by a gain of function G380R mutation in *FGFR3* on chromosome 4[33,34]. This mutation alters bone growth resulting in obstruction or stenosis of the cranial skull base foramina. Increases in venous pressure secondary to stenosis of the jugular foramen can result in macrocephaly, ventriculomegaly and hydrocephalus[33,34,35]. The etiology of hydrocephalus in achondroplasia is likely multifactorial, with contributions from alterations in CSF flow at the foramen magnum, venous outflow alterations, and potentially decreased CSF egress along cranial nerve sheaths due to narrowing of their respective foramina [34,36,37].

Many patients with achondroplasia have some degree of ventriculomegaly which stabilizes overtime [37,38]. As the natural history of this ventriculomegaly and the contributions from stenosis at the foramen magnum and cervical medullary junction is better understood, there

are far fewer patients who receive treatment with ventriculoperitoneal shunting, which in the past was associated with significant complications[39]. Some patients are successfully treated with cervicomedullary decompression, which is associated with decreased need for shunting and stabilization of both ventriculomegaly and intracranial pressure[40,37].

NF 1 and NF 2

Neurofibromatosis 1 (NF1), also known as von Recklinghausen's disease, is an autosomal dominant disorder caused by mutations on chromosome 17q11.2 that affect neurofibromin production[41,42]. NF 1 has variable expression and predisposes individuals to several tumors and hamartomas in the central and peripheral nervous system, including optic pathway gliomas (OPG) and gliomas outside the optic pathway, which in some cases can lead to obstructive hydrocephalus (Fig. 2) [43,44,45,46]. Hydrocephalus in NF-1 can occur from alterations in CSF circulation that results from OPGs, as well as periaqueductal gliosis, aqueductal webs, nontumor hamartomatous changes, and tectal and midbrain tumors causing obstruction or narrowing of the ventricular system, particularly at the level of the cerebral aqueduct.[45,47]. Treatment may involve the tumor directly, or in some cases, surgical treatment for symptomatic hydrocephalus. [42,47]. Direct treatment of a tumor may involve surgical removal or treatment with chemotherapy including BRAF/MEK inhibitors [47]. Finally, treatment of NF-1 associated hydrocephalus with ETV can be successful regardless of the type or level of obstruction[48].

Neurofibromatosis 2 (NF2), another autosomal dominant disorder, is caused by deletions or loss of function of the tumor suppressor gene on chromosome 22q12 that encodes the protein *Merlin*[49,50]. Compared to NF1 with a prevalence of 1 in 4,000–5,000 births, NF2 is more rare with an incidence of 1 in 40,000 births[43,51]. Patients with NF2 can develop bilateral vestibular schwannomas or other intracranial tumors that can rarely cause hydrocephalus through obstruction of CSF circulation[50,52].

Down Syndrome

There have been several case reports of hydrocephalus in patients with Down syndrome. Two early reports from the 1970s describe children with Down syndrome and hydrocephalus, aqueductal stenosis, and partial agenesis of the corpus callosum[53,54]. A more recent case report describes a patient with hydrocephalus detected during pregnancy who required treatment with ventriculoperitoneal shunt[55]. Two additional case reports describe two patients with Down syndrome and normal pressure hydrocephalus, both of whom were treated with ventriculoperitoneal shunts[56]. The second report describes a patient with tetraventricular hydrocephalus caused by obstruction of the foramina of Luschka and Magendie treated using ETV[57].

Although Down syndrome is not associated with hydrocephalus, mouse models have demonstrated ventriculomegaly related to the genetic abnormalities in Down syndrome. The Ts1Rhr mouse model, with a shorter trisomic segment than previous models, exhibits PcP4-dependent ciliopathy sufficient to trigger ventricular enlargement[58]. Thus, it is possible that despite their varying presentations and treatment, some of the reported human

hydrocephalus cases may be related to trisomy 21 itself rather than non-syndromic findings. Finally, there is an increased prevalence of ventriculomegaly in very low birthweight (VLBW) infants with Down syndrome compared to other VLBW infants, suggesting that some Down Syndrome-related pathologic process may contribute to the development of hydrocephalus or ventriculomegaly in a subset of patients with this condition[59].

Tuberous Sclerosis

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic syndrome with dysfunction of the mTOR pathway resulting in cortical and subcortical tubers, subependymal nodules along the lateral ventricles, and subependymal giant cell astrocytomas (SEGAs) [60,61]. SEGAs are associated with obstructive hydrocephalus in the first two decades of life, and are monitored for growth using frequent, serial imaging in patients with TSC[60,61]. Though they grow slowly, SEGAs can cause obstructive hydrocephalus secondary to blockage of CSF circulation at the Foramen of Monro.[62].

Management of hydrocephalus in these cases depends on management of the SEGAs themselves. Treatment strategies include surgical resection or mTOR inhibition. Early surgical resection was once the standard for management of SEGAs that showed growth on serial imaging, and surgery was curative for small lesions, with low complication rates[63]. However for larger or bilateral lesions, complication rates were higher, and in many patients with both SEGA and hydrocephalus, VPS was still necessary[63,64]. More recently, medical management using mTOR inhibitors has been used alone or in combination with surgical resection, though some concerns remain about its long-term safety considering effects on linear growth, puberty, and immunosuppression[65,66,67,68]. In patients with SEGA and asymptomatic obstructive hydrocephalus, mTOR inhibition is effective in treating hydrocephalus even in the setting of acute, symptomatic increases in intracranial pressure, though surgery is often still considered in these cases[66,69]. Endoscopic tumor removal, laser interstitial thermal therapy (LITT), and biologics targeting of the MAPK/ERK pathway, may also be utilized in the treatment of SEGA and associated hydrocephalus in TSC patients[70,71].

Walker-Warburg Syndrome/ Brain-muscle-eye disease

Walker-Warburg Syndrome (WWS), the most severe congenital muscular disorder, is caused by an autosomal recessive mutation that leads to type II Lissencephaly and severe hydrocephalus (Fig. 3)[72,73]. WWS is characterized by defective O-glycosylation of α-dextroglycan but the disease is highly heterogenous, as hypoglycosylation can occur in the Protein O-Mannosyltransferase 1 (*POMT1*) gene, present in 10–20% of patients, as well as in the POM *T2, POMGNT1, FKTN, FKRP, LARGE, ISPD* or other genes associated with dystroglycanopathy phenotypes[73,74,75].

While the incidence of WWS is rare, estimated at 1.2 per 100,000 births, many cases of WWS are complicated by hydrocephalus[76,77,78]. Similar to the clinical and genetic variability of WWS, the nature of the concurrent hydrocephalus is also variable. Hydrocephalus can be associated with tectal enlargement resulting in aqueductal stenosis as well as cobblestone cortex[79]. One patient with WWS presented with ventriculomegaly

and a bulging third ventricle along with progressive hydrocephalus, while another WWS patient presented with macrocephaly, triventricular enlargement, hypoplasia of the corpus collosum, and obstructive hydrocephalus; both were treated with VP shunts[77]. Other case studies reported prenatal findings of posterior fossa anomalies and associated hydrocephalus with a *POMT2* mutation confirming WWS, and three affected siblings with varying levels of fetal and congenital hydrocephalus, all with fatal prognosis [76,78]. ETV-CPC was used to treat a patient with cobblestone lissencephaly, increased bulging of the anterior fontanelle and sutural separation, with a *POMT1* mutation[80].

It is important to note that the etiology of hydrocephalus in WWS is likely due to stenosis of the aqueduct secondary to altered brain development and an enlarged tectum. This differs from an aqueductal web, in which the brain stem is otherwise normal. Given the rates of hydrocephalus and abnormal brain development in WWS, close monitoring for hydrocephalus is warranted, although many patients present at birth with symptomatic hydrocephalus requiring treatment[76]. Given the early presentation, although many patients do have aqueductal stenosis, VP shunting may be more efficacious than ETV or ETV-CPC due to the young age at presentation.

Primary Ciliary Dyskinesia/Kartagener's

Primary ciliary dyskinesia (PCD) is a rare, genetically heterogeneous syndrome associated with defects in cilia and flagella motility[81,82]. Many of the mutations associated with PCD affect the *dynein axonemal heavy chain 5* or *dynein axonemal intermediate chain 1* genes which encode the outer dynein arms of cilia[83,84,85]. PCD has a worldwide prevalence of 1 in 16,000 children[86]. Common manifestations include Kartagener's syndrome (bronchiectasis, situs inversus, and chronic sinusitis), as well as neonatal respiratory distress, and male infertility[86]. While hydrocephalus is infrequently seen in humans with PCD, mouse models of this disease frequently develop severe symptomatic hydrocephalus[82]. Insertional mutations in the mouse axonemal dynein heavy chain gene, *Mdnah5*, cause loss of axonemal outer arms, and reproduce most of the classic features of PCD such as recurrent respiratory infections, situs inversus, and ciliary immobility[87]. In these mice, the mutation also causes hydrocephalus and death in the perinatal period and this mouse model suggest that the degree of ciliary dysfunction caused by the mutation is causally related to the severity of PCD and the development of hydrocephalus[87]. In both human and mouse models, functional loss of the *Ccdc151* gene has also been associated with PCD, as this gene is expressed by ependymal cells and affects the ciliary axoneme. This mutation, too, is associated with hydrocephalus and perinatal death in mouse models[88]. The exact role of ciliary motion in the development of hydrocephalus has yet to be determined, including whether cilia are capable of producing or maintaining bulk flow of CSF throughout the ventricular system.

While there are case reports of hydrocephalus in Kartagener's syndrome or PCD, in humans hydrocephalus is relatively infrequent [82,89,90,91,92]. One case of PCD and hydrocephalus was associated with aqueductal stenosis and abnormal ultrastructure of the respiratory epithelium cilia[93]. Another report of autosomal recessively inherited PCD and intellectual disability in 3 generations of a Jordanian family notes that 4 of 9 affected individuals also had hydrocephalus[94]. Mutations in the multicilin gene (*MCIDAS*) are associated with choroid

plexus hyperplasia and hydrocephalus in humans, possibly related to reduced generation of motile cilia[95]. Finally, mutations in *FOXJ1*, encoding a transcription factor involved in ciliogenesis, are associated with an autosomal dominant motile ciliopathy like PCD, with obstructive hydrocephalus in all reported cases. Hydrocephalus in these cases was associated with the inability to maintain patency, and resulting stenosis, of the aqueduct and/or foramina of Luschka/Magendie due to insufficient motile ciliary function[96]. In all affected individuals, pathological specimens showed mis-localized basal bodies and incorrect localization of adhesion proteins, leading to deficits in ciliary function and inadequate fluid flow[96]. Overall, while PCD is not consistently linked with hydrocephalus in humans, findings from mouse models and several human reports suggest that severe dysfunction of ciliary motility may contribute to hydrocephalus in some cases of PCD and related ciliopathies. Possible mechanisms for symptomatic hydrocephalus include stenosis of the aqueduct due to decreased flow of fluid across this channel or from collapse of the ependymal walls around the aqueduct due to changes in the integrity of the ependyma. Finally, as in other syndromes, the concurrent altered brain development may play a role in the development of hydrocephalus.

Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a group of disorders of connective tissue that affects bone growth and fragility, caused by defective *COL1A1* and *COL1A2* genes and is grouped into four types— Type II, type III, type IV and type I — ordered from most to least severe[97,98]. OI can be associated with macrocephaly, hydrocephalus, basilar invagination and cerebral atrophy[99]. Concurrent basilar invagination can lead to obstructive hydrocephalus. While the true incidence of hydrocephalus in OI is not well known, several studies and case reports have documented OI with associated hydrocephalus[99,100].

In one study, OI was associated with sulcal prominence and hydrocephalus with no clear intraventricular obstruction in 22% of patients[99]. In another study of 5 neonates with OI, 4 had hydrocephalus associated with foramen magnum stenosis, cerebral parenchymal and intraventricular hemorrhage, and occipital-bone fractures[101]. All 4 infants died soon after birth[101]. One other case reported a patient that presented with a novel mutation of the *COL1A2* gene and was diagnosed with type II OI with obstructive hydrocephalus; in this case the patient was treated with ETV[98].

Emerging Genetic Syndromes

Through the use of next generation sequencing, novel genetic mutations associated with hydrocephalus have been identified, accounting for many cases previously classified as sporadic or as “congenital hydrocephalus”[3,102,103]. It is unclear in all cases how these genetic alterations directly lead to hydrocephalus, however mechanisms beyond disruptions to CSF dynamics or structural barriers to CSF flow such as abnormal neuronal proliferation, differentiation, and maintenance may be involved in hydrocephalus[102].

Pettigrew Syndrome

Pettigrew syndrome is an X-linked disorder, characterized by mutations in the *AP1S2* gene that encodes a subunit of the AP1 adaptin protein essential in regulating lysosomal protein sorting[104]. Mutations lead to intellectual disabilities, iron and calcium deposition, and hydrocephalus[3]. The related Lethal giant larva (Lgl) protein is involved in maintaining cell polarity in mice. Loss of this protein in *Lgl1−/−* mice pups leads to severe hydrocephalus and neonatal death[105].

RASopathies

Various RASopathies, through mutations in the RAS-MAPK pathway, have been associated with hydrocephalus; among these disorders are NF1, discussed previously, Costello syndrome, Noonan syndrome and cardio-facio-cutaneous (CFC) syndrome, all with autosomal dominant inheritance[3]. Noonan syndrome is associated with mutations in *CBL* (regulators of activated TRKs), *KRAS, NRAS* (RAS proteins), *PTPN11, SOS1, SHOC2* (modulators of RAS function) and *RAF1* (downstream signal transducers); it is also associated with hydrocephalus in addition to hindbrain herniation and syringomyelia[106,107]. Costello syndrome is caused by mutations in the *HRAS* protooncogene that lead to failure-to-thrive, along with macrocephaly, posterior fossa crowding, low cerebellar tonsil position and hydrocephalus[108]. CFC syndrome is most frequently caused by mutations in *BRAF,* but can occur due to mutations in *MEK1, KRAS* and *MEK2* as well. This can lead to cervical stenosis, torticollis, Chiari malformation, and hydrocephalus[109].

RAS has a multifaceted role in CNS development. Through its involvement in the RAS-ERK pathway, it is involved in the regulation and maintenance of neural stem cells, as well as in the regulation of oligodendrocyte differentiation[110,111]. Through its regulation of the PI3K-AKT pathway, RAS is also involved in synaptic plasticity[112,113]. Despite these interactions with CNS cell growth, differentiation, and maintenance, the role of RAS in CSF clearance and flow is not well characterized, and it is possible that structural deficits due to defective neurogenesis and differentiation contribute to hydrocephalus in these cases rather than direct effects on CSF flow.

PI3K-AKT-mTOR pathway

Four different mutations of genes in the PI3K-AKT-mTOR pathway, involved in cell proliferation, growth and function, have been shown to cause megalencephaly-associated symptoms, leading to hydrocephalus[3]. Mutations in the *AKT3, CCND2* and *PIK3R2* genes cause different types of Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH), while mutations in the *PIK3CA* gene causes Megalencephaly-capillary-malformations (MCAP). Both MPPH and MCAP cause megalencephaly, polymicrogyria and ventriculomegaly that can lead to hydrocephalus[114]. PI3K pathway genes, including *PIK3CA, PTEN, and MTOR* contribute to neural stem cell growth, proliferation, and differentiation, especially in the developing ventricular zone, and mutations in these genes predispose patients to tumorigenesis and overgrowth syndromes[115,103]. As these syndromes have only recently been characterized, it remains to be seen whether therapeutics targeting affected molecular pathways will eventually aid in the treatment of hydrocephalus in these cases.

Discussion

Hydrocephalus occurs in the setting of many well-characterized syndromes of childhood. Treatment involves a combination of treating the primary pathology (e.g. tumors that cause outflow obstruction) and treatment for hydrocephalus with VPS and/or ETV +/− CPC. Next-generation sequencing has allowed for the characterization of novel genetic syndromes associated with hydrocephalus and the identification of mutations in sporadic cases of hydrocephalus. These mutations shed light on how alterations to development and proliferation of neurons and neural stem cells contribute to sporadic hydrocephalus, and may eventually contribute to our understanding of novel syndromic causes of hydrocephalus.

Four genes regulating neural stem cell fate have recently been described in congenital hydrocephalus[102]. *TRIM71* loss is associated with defective neural tube closure, and decreased proliferation of neural progenitor cells (NPCs) in mouse models[116]. *SMARCC*1 encodes a subunit of a chromatin remodeling complex important to the survival of NPCs and transcriptional control of telencephalon development, and knockouts are associated with hydrocephalus and aqueductal stenosis[117]. *PTCH1* is involved in the mechanism by which primary cilia in neuroepithelial cells sense and respond to SHH gradients, which is important in NPC differentiation and fate[118]. *SHH* encodes the ligand responsible for NPC migration along the dorsal-ventral axis of the neural tube[119]. *TRIM71* mutations are associated with communicating hydrocephalus, while *SMARCC1* and *PTCH1* mutations are more likely to be associated with aqueductal stenosis. These mutations highlight that abnormal neurogenesis or brain development likely play a role in the development of hydrocephalus, beyond deficits in CSF accumulation or clearance[102]. In a follow-up study, mutations in the PI3K pathway genes previously discussed, as well as *FOXJ1, FMN2, and FXYD2* were present in up to 22% of sporadic congenital hydrocephalus cases. Their involvement is likely related to their role in supporting embryonic neurogenesis[103]. These findings highlight that the dysregulation of neurogenesis, proliferation, or migration, especially in the ventricular zone, are emerging areas of interest that may contribute to CSF accumulation or disordered circulation in some cases of hydrocephalus.

Summary

Hydrocephalus is a common phenotype in various syndromes of childhood with diverse genetic etiologies. The mechanisms behind these disorders include structural deficits, mutations affecting neuronal adhesion, vesicle trafficking, growth factors, PI3K-AKT-mTOR pathway and Dystroglycanopathies, Ciliopathies and RASopathies[3]. The pathophysiology of syndromic hydrocephalus is multifactorial, and treatment is often multimodal, addressing both the underlying condition and the associated hydrocephalus. While the incidence or the underlying pathogenesis of hydrocephalus in certain conditions is not fully known, next generation genetic sequencing has begun to shed light on the complex underlying pathways affecting development of the brain which result in hydrocephalus.

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KEY POINTS

- Hydrocephalus is a phenotypic feature associated with a diverse set of genetic syndromes in childhood
- Pathogenesis and accompanying phenotypic features,as well as inheritance patterns,vary between and within syndromes
- Next-generation sequencing studies now identify underlying genetic causes of hydrocephalus, previously categorized as “congenital hydrocephalus”.

SYNOPSIS

Hydrocephalus, the abnormal accumulation and impaired circulation/clearance of cerebrospinal fluid, occurs as a common phenotypic feature of a diverse group of genetic syndromes. In this review we outline the genetic mutations, pathogenesis, and accompanying symptoms underlying syndromic hydrocephalus in the context of: L1 syndrome, syndromic craniosynostoses, achondroplasia, NF 1/2, Down's syndrome, tuberous sclerosis, Walker-Warburg syndrome, primary ciliary dyskinesia, and osteogenesis imperfecta. Further, we discuss emerging genetic variants associated with syndromic hydrocephalus.

CLINICS CARE POINTS

- Management of syndromic hydrocephalus may require direct surgical treatment with VPS or ETV (±CPC) and/or treatment of associated pathology resulting in hydrocephalus such as tumors obstructing CSF flow.
- Treatment options vary depending on a variety of patient- and syndrome-specific factors.
- In sporadic cases of congenital hydrocephalus, genetic screening for recently described variants may eventually influence treatment decisions, though at this stage few pathway-specific therapeutics are available

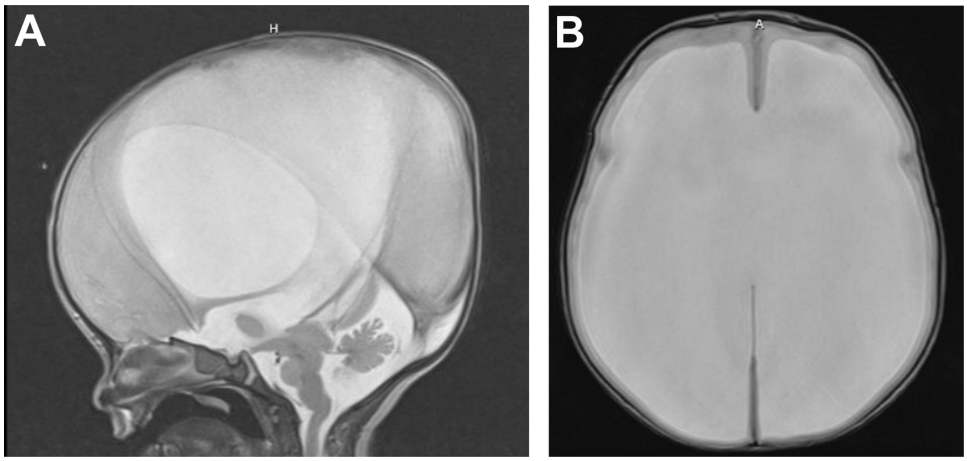

Figure 1.

1-day-old with L1 syndrome resulting in hydrocephalus and aqueductal stenosis treated on day-of-life 1 with a VP shunt. T2-weighted MRI (A) sagittal and (B) axial views.

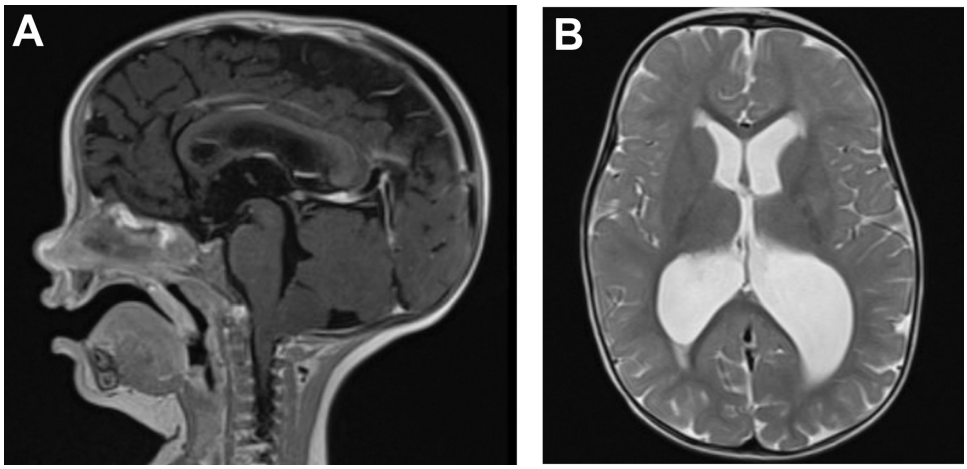

Figure 2.

14-month-old with NF-1 presented with enlarged ventricles, transependymal CSF, and low tonsil position. Patient underwent Chiari decompression and subsequent treatment with ETV. T2-weighted MRI (A) sagittal and (B) axial views

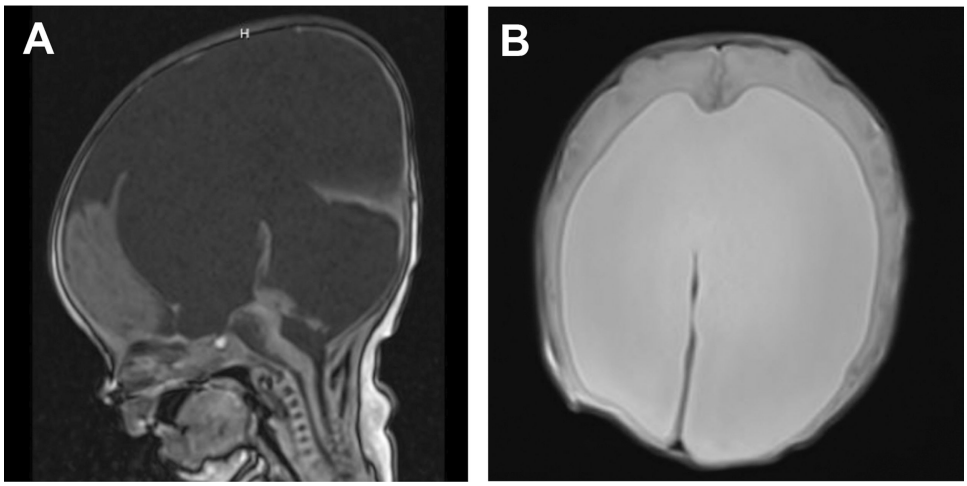

Figure 3.

1 day old with POMT-1 P273L Walker-Warburg syndrome, born at 35 weeks gestation. MRI A) sagittal (T1) and B) axial (T2) views showing hydrocephalus with tectal dysplasia contributing to aqueductal stenosis. This patient was treated with a VP shunt on day of life 4

Table 1.

Genetic Basis of Syndromes Associated with Hydrocephalus

Syndrome	Type of Disorder	Mode of Inheritance	Genetic Locus
L1 Syndrome, and X-Linked Hydrocephalus	Neuronal Adhesion	X-linked	L1CAM
Syndromic Craniosynostoses (Pfeiffer, Crouzon, Apert, Muenke)	Primary cerebral maldevelopment	Heterogeneous	FGFR1 (Pfeiffer), FGFR2 (Crouzon; Apert; Pfeiffer), FGFR3 (Muenke)
Achondroplasia	Growth Factor	Autosomal Dominant	FGFR3
NF 1	RASopathy	Autosomal Dominant	NF1 (17q11.2)
NF 2	RASopathy	Autosomal Dominant	NF2 (22q12)
Down's Syndrome	Trisomy	Non-disjunction	Chromosome 21
Tuberous Sclerosis	mTOR related	Autosomal Dominant	*DNAH5, DAIC1, CCDC151, MCIDAS, FOXJ1*
Walker-Warburg Syndrome/ Brain-muscle-eye disease	Dystroglycanopathies	Autosomal Recessive	POMT1, POM*T2, POMGNT1, FKTN, FKRP, LARGE, ISPD*
Primary Ciliary Dyskinesia	Ciliopathy	Heterogeneous	DNAH5, MCIDAS, FOXJ1
Osteogenesis Imperfecta	Connective tissue	Autosomal Dominant	COL1A1 and COL1A2
Pettigrew Syndrome	Vesicle trafficking	X-linked	AP1S2
Costello Syndrome	RASopathy	Autosomal Dominant	HRAS
Noonon Syndrome	RASopathy	Autosomal Dominant	CBL, KRAS, NRAS, PTPN11, SOS1, SHOC2 and RAF1
Cardio-facio-cutaneous (CFC) syndrome	RASopathy	Autosomal Dominant	BRAF, MEK1, KRAS and MEK2
Megalencephaly-polymicrogyria-polydactyly-hydrocephalus (MPPH)	PI3K-AKT-mTOR pathway	Autosomal Dominant	AKT3, CCND2 and PIK3R2
Megalencephaly-capillary-malformation (MCAP)	PI3K-AKT-mTOR pathway	N/A	PIK3CA