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Genetics and Molecular Pathogenesis of Human Hydrocephalus

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Abstract

Hydrocephalus is a neurological disorder with an incidence of 80–125 per 100,000 live births in the United States. The molecular pathogenesis of this multidimensional disorder is complex and has both genetic and environmental influences. This review aims to discuss the genetic and molecular alterations described in human hydrocephalus, from well-characterized, heritable forms of hydrocephalus (e.g., X-linked hydrocephalus from *L1CAM* variants) to those affecting cilia motility and other complex pathologies such as neural tube defects and Dandy–Walker syndrome. Ventricular zone disruption is one key pattern among congenital and acquired forms of hydrocephalus, with abnormalities in cadherins, which mediate neuroepithelium/ependymal cell junctions and contribute to the pathogenesis and severity of the disease. Given the relationship between hydrocephalus pathogenesis and neurodevelopment, future research should elucidate the genetic and molecular mechanisms that regulate ventricular zone integrity and stem cell biology.

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Full Text

Hydrocephalus is the most common disease treated by pediatric neurosurgeons[1] with an incidence of 0.3–0.7 per 1,000 live births in the US.[2] Current treatments are largely limited to cerebrospinal fluid (CSF) diversion including CSF shunts or endoscopic third ventriculostomy with or without choroid plexus cauterization.[3],[4] While nonsurgical treatments have long been sought, the pathophysiology of this disorder is complex, involving myriad genes and environmental factors.[1]

This review focuses on the genetics and molecular pathogenesis of human hydrocephalus. We begin by describing the ventricular system and neuroepithelium/ependyma in normal development before reviewing the genetics and molecular biology associated with hydrocephalus. We then describe in detail ventricular/subventricular zone (VZ/SVZ) disruption and dysregulation of cell–cell junctions as one critically important common molecular trigger in the

pathogenesis of hydrocephalus.

The ventricular system, CSF dynamics, and neuroepithelium/ependyma

According to the bulk-flow hypothesis, CSF moves from the two lateral ventricles to the third ventricle through the foramina of Monro, and from there to the fourth ventricle through the aqueduct of Sylvius. CSF exits the fourth ventricle to the subarachnoid space through the foramina of Luschka and Magendie, after which it is reabsorbed into the bloodstream.[5],[6],[7] Moreover, while beyond the scope of this review, it is now appreciated that CSF movement is considerably more complex, with a dynamic exchange flow between blood, interstitial fluid, and CSF occurring throughout the entire brain.[7] The glymphatic system, formed by perivascular channels and astrocytes, eliminates soluble protein and metabolites, and distributes different molecules such as glucose or amino acids.[8],[9] CSF flows from the subarachnoid space, to the perivascular spaces in the dura, and from there to the brain parenchyma through Aquaporin-4 water channels, mixing with the interstitial fluid. Parenchymal interstitial fluid flows through perivenous spaces and is collected in the meningeal and cervical lymph nodes.[8],[9],[10],[11],[12]

At the interface between the brain parenchyma and the ventricles, the VZ develops as a neuroepithelium, maturing to a single-cell, ciliated ependymal layer.[13] During development, neurogenesis in the neuroepithelium involves radial glial cells.[14],[15] A subpopulation of radial glial cells matures into nonproliferative ependymal cells, while some radial glia cells are retained as stem cells, constituting a neurogenic niche in the SVZ.[13],[16],[17] The VZ has several critical functions, serving as a barrier with polarized cells that regulate CSF composition, mediating CSF flow via motile cilia, and secreting signals involved in the development and physiology of the brain.[13]

Neuroepithelial cells are joined by tight junctions at their apical surface, and while VZ ependyma loses tight junctions during development, they continue to express adherens junctions on their lateral surfaces.[14],[15] Adherens meetings are primarily composed of N-cadherins, transmembrane proteins that interact with catenin proteins and the actin cytoskeleton, as well as other proteins and transcription factors.[18] N-cadherins are also involved in the regulation of catenin to modulate signal transduction and developmental patterning.[18] Ependymal cells elaborate cilia, organelles present on the surface of the cells that beat in rhythmic waves. These cilia project into the ventricles, contributing to the ependymal planar polarity. Ciliary beating also contributes to CSF flow, especially in the narrowest parts of the ventricular system, that is, the aqueduct,[13] although myriad other mechanisms, such as pulsatility and pressure gradients, influence CSF flow.[19]

Hydrocephalus

Hydrocephalus is a neurologic condition resulting from an imbalance in CSF production and absorption, typically producing ventricular enlargement and increased intracranial pressure.[1],[20],[21] Traditionally, hydrocephalus has been classified as communicating or noncommunicating,[22] with communicating etiologies presumably resulting from the reduction of the CSF transport or occult obstruction at the level of the subarachnoid space.[23] Noncommunicating etiologies result from an obstruction in the ventricular system, frequently at the level of the aqueduct.[23] It is now recognized that hydrocephalus is more complex and may have multiple points of potential pathology or obstruction,[21] with impairment of CSF absorption occurring anywhere in the cranial cavity. Hydrocephalus may also be described broadly as congenital (developmental) or acquired.[1] Acquired hydrocephalus may result from intracranial hemorrhage (e.g. subarachnoid or intraventricular hemorrhage (IVH)) or other lesions developing after birth, while developmental hydrocephalus may be genetic or syndromic in origin or observed with anomalies, the pathogenesis of which is not yet understood.[1] In North America, IVH is a common cause of severe neurological injury in very preterm infants, and resultant post-hemorrhagic hydrocephalus (PHH) represents the most common cause of pediatric hydrocephalus.[24],[25]

Genetics of congenital/developmental hydrocephalus

Congenital hydrocephalus includes (1) X-linked hydrocephalus with congenital aqueduct stenosis (AS), (2) neural tube defects (spina bifida), (3) Dandy–Walker syndrome, (4) holoprosencephaly, (5) primary ciliary dyskinesia and other ciliopathies, and (6) nonsyndromic autosomal recessive hydrocephalus. Hydrocephalus has been associated with other less common syndromes such as Fried-type syndrome; RAS-opathies; and vertebral, anal, cardiac,

tracheoesophageal, renal, and limb anomalies plus hydrocephalus (VACTERL-H).[1],[26] The most frequent gene mutations involved in these syndromes/pathologies are shown in [Table 1].{Table 1}

X-linked hydrocephalus with aqueduct stenosis (XLH)

XLH is associated with a gene mutation in the neural cell adhesion molecule L1-CAM located on chromosome X.[1], [26] It is the most common genetic form of hydrocephalus (1/30,000 births).[20],[27] L1-CAM is a member of the immunoglobulin-like CAM family located on chromosome Xq28.[27],[42] L1-CAM is a glycoprotein that mediates cell-cell adhesion, playing an important role in neural adhesion, migration, growth, and morphology.[26],[27] In 254 unrelated families, 211 mutations in the L1-CAM have been found, affecting different sites,[26] with correlations between the mutation class and the severity of the ventricular dilation: (1) Class I mutations are present in the cytoplasmic domain of the protein, (2) Class II are in the extracellular domain, (3) Class III provoke a premature stop codon in the extracellular domain and loss of the protein function, and (4) mutations in the noncoding regions.[26]

L1-CAM mutations have long been linked to Corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus (CRASH) syndrome.[43] Ventriculomegaly is present in 100% of the cases, although its severity can vary.[26],[27] XLH is also commonly associated with AS, fused thalami, and cerebellar lesions.[26], [27] Adle-Biassette et al.[27] reported that 89% of patients with XLH exhibited AS, probably from severe ventriculomegaly and high-pressure causing deformation. However, it has also been suggested that impairment of the cell L1-CAM junctions is related to maldevelopment of midline structures[26] [Figure 1].{Figure 1}

Fried-type syndrome is an X-linked disorder caused by mutations in the AP1S2 gene.[38] The clinical symptoms include intellectual disability, basal ganglia iron deposition, and hydrocephalus. AS and/or retrocerebellar or fourth ventricular cysts have been detected in some hydrocephalic cases.[20]

Neural tube defects

Neural tube defects (NTDs) occur due to failure of closure of the neural tube during embryological development. Myelomeningocele (spina bifida aperta (SBA)), which results from impaired closure of the caudal neuropore, is the most frequent NTD and occurs in 1–2 cases per 2700 births.[26] In SBA, the meninges, dorsal spinal arch, and skin do not develop properly; thus, the neural placode is exposed.[46] Hydrocephalus is present in almost 80% of these cases and may be related to genetic variations that cause the loss of the ependymal cell polarity and ciliary beating[26] or genes related to neural tube development.[46] However, there is no single genetic locus mutation; its origin is likely a combination of multiple genes and environmental factors. What is well established is that intake of folate during pregnancy decreases the incidence of the disease. It has been shown that genetic variants of single genes encoding folate-homocysteine metabolism or gene-related interactions between different folate pathways are risk factors.[46],[47],[48],[49] Notably, in utero closure of SB reduces both the post-natal incidence of hydrocephalus and the need for shunting while also positively impacting Chiari II malformation and neurological outcomes.[50],[51] These improvements further underscore the complexity and multifactorial nature of the disease.

Dandy–Walker malformation

Dandy–Walker malformation (DWM) is a common cerebral malformation (1/35,000 births) characterized by hypoplasia and rotation of the cerebellar vermis; enlargement of the fourth ventricle and posterior fossa; and rostrally shifted position of the lateral sinus, tentorium, and torcula herophili.[26],[52] Hydrocephalus is present in 80% of DWM cases, along with corpus callosum dysgenesis, schizencephaly, and glial heterotopia.[53] DWM is associated with at least 18 types of chromosomal abnormalities such as trisomy 9, but it has also been associated with exposure to different viruses, alcohol, or diabetes during brain development.[26],[53] Mutations in the genes POMT1, POMT2, POMGNT1, FKTN, FKRP, LARGE, ISPD have been associated with the disease.[20],[30] Furthermore, DWM may also be linked to other genetic syndromes such as, ectopic brain, and NTD.[53]

Holoprosencephaly (HPE)

HPE is a brain malformation caused by neural differentiation abnormalities that lead to failure of separation of the left

and right cerebral hemispheres before neural tube closure.[54] HPE incidence is 1/10,000 births. It may be associated with hydrocephalus, DWM, and craniofacial abnormalities,[54] with three types based on the grade of separation: alobar, semi lobar, and lobar HPE.[26] Like other neurodevelopmental anomalies, the pathogenesis of HPE may have genetic and environmental influences or chromosomal abnormalities, such as trisomy 13, 18, or triploidy (25%–50%). The other 50% of the cases may be related to glucose levels in mothers with diabetes, mutation in 7-dehydrocholesterol reductase, and at least 16 other genes, including SHH, ZIC2, SIX3, and TGIF.[26]

Primary ciliary dyskinesia and other ciliopathies

With a prevalence of 1/15–30,000 births,[35] primary ciliary dyskinesia originates from a defect in ciliary and flagellar motility or orientation that causes cilia dysfunction. Motor cilia are composed of an axoneme with 9 + 2 microtubules and a basal body to anchor the axoneme to the cell membrane. Another motile cilium is only present during fetal neurodevelopment, presenting 9 + 0 microtubular structure, and functioning as an activator of a signaling cascade that establishes left-right sidedness and body laterality.[35]

Motility is dependent on dynein proteins.[35] Primary ciliary dyskinesia in motor cilia is caused primarily by mutations in genes that create immotile monocilia, that is, NEK10 or GAS2L2 genes encoding Hydin or polycystin-1 proteins,[55],[56] although more than 50 genes have been identified.[35] Hydin regulates dynein arm activity in the central pair of microtubules of the 9 + 2 axoneme in motile cilia;[57] thus, the mutation in this gene can impair cilia motility.[58] MCIDAS mutations have been shown to strongly correlate with hydrocephalus.[36]

In primary ciliary dyskinesia, hydrocephalus is usually present with other pathologies, such as situs inversus congenital heart disease, asplenia, or polysplenia.[55] It is thought that hydrocephalus appears as a consequence of impaired ependyma cilia beating in narrow CSF passages, provoking AS.[36] As ependyma and choroid plexus are involved in CSF production, changes in the CSF microenvironment secondary to beating loss may affect CSF production, also contributing to hydrocephalus.[36]

Nonsyndromic autosomal recessive hydrocephalus: Beyond X-linked hydrocephalus

Nonsyndromic congenital hydrocephalus comprises 2%–11% of congenital hydrocephalus cases.[37] Distinct from XLH, nonsyndromic congenital hydrocephalus includes the autosomal recessive variations of the CCDC88C or MPDZ genes.[1] CCDC88C encodes the actin-binding protein DAPLE involved in cell migration. Three domains have been described in DAPLE mutations, generating an absence of the entire protein (families I and III) or an absence of the binding domain (family II).[37] Autosomal recessive hydrocephalus typically is characterized by ventricular dilatation with an interhemispheric cyst, small vermis, and enlarged posterior fossa.[37]

Hydrocephalus associated with other less common syndromes

Hydrocephalus associated with intracranial arachnoid cysts, indicative of impaired CSF absorption within the meninges,[59] has been related with mutations in the CC2D2A gene in Joubert and Meckel syndromes and with deletion 22q13.3 Phelan–McDermid syndrome.[20] RAS-opathies, which include Noonan, cardio-facio-cutaneous, and Costello syndromes,[20] originate from mutations in the RAS pathways (e.g., NF1, KRAS, BRAF, and PTPN11).[1],[39] Hydrocephalus is present in these pathologies and may be caused directly by the genetic abnormality or by downstream effects on the brain itself. Similar to RAS-opathies, hydrocephalus may be observed in megalencephaly syndromes and may have multiple causes, often related to mutations in genes of the PI3K–AKT pathway.[40] Hydrocephalus is also present in craniosynostosis syndromes where mutations in fibroblast growth factor receptor genes have been identified. Alterations in the skull or skull base configuration may create an obstruction of CSF flow or reduced absorption from venous hypertension.[30] VACTERL-H is a syndrome related to FANCB gene mutations and Fanconi anemia or excess chromosome breakage.[20]

Molecular biology of hydrocephalus: Cell junctions and ventricular zone disruption

The neuroepithelium lines the ventricular walls during brain development and generates ependyma, which covers the mature periventricular areas.[13] As described above, neuroepithelial/ependymal cells are joined by adherens

junctions formed by N-cadherin.[13] It has been shown that abnormalities in the cell junctions during ependymal development can trigger or affect the evolution of hydrocephalus.[13],[23],[60],[61],[62],[63]

Disruption of the VZ/SVZ in hydrocephalus is a common event that involves the disassembling, disorganization, or loss of the VZ cells.[60] The VZ/SVZ disruption follows a temporal and spatial program: progression proceeds from caudal to rostral regions, and during neurodevelopment, impairment begins in early fetal stages when the tight junctions disappear.[60] In human fetuses with SB, VZ disruption has been observed in the pallium at 21–22 GW, with the disruption extending throughout the lateral ventricles in fetuses by 40 weeks.[64] Interestingly, the disruption does not seem to correlate with ventricular volume but with the stage of neurodevelopment.[65]

Additionally, VZ/SVZ disruption seems to follow a common pattern in different hydrocephalic etiologies. Neuroepithelium/ependymal loss has been detected in cases with hydrocephalus associated with SB[61],[62],[64] and communicating hydrocephalus,[66] as well as IVH,[65] demonstrating that disruption is not only present in congenital hydrocephalus but also in acquired hydrocephalus, such as PHH.[65]

The alterations in cell junctions appear to contribute to the developmental and physiological abnormalities of VZ associated with hydrocephalus,[13] such as the alterations in L1CAM and Aquaporin-4 levels seen in human fetal-onset hydrocephalus [Figure 1].[44],[45] These patients exhibited abnormal cellular location of N-cadherin and connexin 43 as both proteins were detected in the cytoplasm of the cells instead of the cell membrane.[61],[62] This hypothesis has been tested in chick embryos where the immunologic blockage of N-cadherin resulted in the loss of ependyma and formation of rosettes,[67] and it has been observed in several experimental in vivo and in vitro models.[60],[67],[68],[69],[70],[71],[72],[73]

In humans, VZ disruption is associated with anomalous ependymal rosettes or heterotopia,[74] abnormalities in neurogenesis that cause SVZ stem cell loss and disruption[60] and AS.[13] Large rosettes have been detected in the areas where VZ disruption is present.[62] These rosettes are characterized by a group of cells organized in a "wheel" shape that lose their polarity and cell junctions.[62] Subependymal rosettes near the VZ disruption site have been detected expressing GFAP and without N-cadherin.[64] Heterotopia have been observed with large clusters of βIII tubulin-positive cells near the SVZ.[64] Abnormalities in neurogenesis can be due to an impairment of migration of neuroblasts caused by N-cadherin defects, displacing neural stem cells (NSC) and neuroblasts.[66] Human fetuses with communicating hydrocephalus exhibit SVZ NSC abnormalities resulting from the loss of the germinal ependyma layer, disorganization of the SVZ, and abnormal migration of the neuroblasts.[66] In human fetuses with IVH, SVZ alterations also occur, including areas with NSC and ependyma loss and translocation of cells into the lateral ventricles[65] [Figure 1]. Finally, AS can occur from the loss of neuroepithelium/ependyma[60]; when complete obliteration takes place, noncommunicating hydrocephalus develops. The subcommissural organ-Reissner's fiber complex (SCO-RF) may play a role in AS.[22],[75] The SCO creates a large mass of negatively charged, sialylated glycoproteins, the RF, which remains CSF-soluble in normal conditions. In hydrocephalus, the SCO-RF is absent, possibly contributing to AS.[75]

It is likely that the denuded ependyma is replaced by reactive astrocytes.[23],[61],[62],[65],[66] While experimental models clearly support this response, the role of astrocytes in the development and severity of hydrocephalus in humans is still unclear. In congenital and acquired animal models, it has been shown that the astrocytes covering the denuded ventricular walls formed a new and organized layer.[69] Thus, they create a new layer that may mimic the lost ependyma, expressing vimentin, which lacks tight junctions, gap junctions, microvilli in contact with the ventricle, the water channel Aquaporin-4, caveolae, paracellular permeability, and endocytosis.[69] More analyses are needed in human fetuses to elucidate any possible role of astrocytes in replacing the ependyma.

Inflammation can play an important role in the pathogenesis of hydrocephalus, especially in acquired hydrocephalus such as PHH. The levels of pro-inflammatory molecules, such as interleukins IL-6, tumor necrosis factor-alpha (TNF-alpha), or transforming growth factor-beta (TGF-beta) in the CSF correlate with the severity of hydrocephalus.[76] Limbrick et al.[77],[78],[79],[80] have shown promising candidates of biomarkers: IL-6, IL-8, CCL-3, TNF-alpha, interferon-gamma, or TGF-beta; growth factors, such as nerve growth factor; and cell adhesion and cytoskeleton makers NCAM, tau, or GFAP. In addition, the neuropathological examination of human fetuses has identified signs of inflammation such as microglial activation and reactive gliosis.[61],[65],[76] Pro-inflammatory cytokines, such as the

ones mentioned above, can modulate epithelial barriers, regulating paracellular permeability.[81] In this regulation, the pro-inflammatory cytokines modulate the internalization of cell junction proteins.[81] However, the relationship between inflammation and VZ disruption still needs to be understood, and further studies are needed to focus on this relationship.

Future work on investigating hydrocephalus

Recently, novel genetic variants related to hydrocephalus have been discovered, at once elucidating important mechanisms in its pathogenesis, but also underscoring the complexity of the disease. Molecular biological studies are urgently needed to rigorously investigate these novel pathways, including those involved in inflammation, VZ disruption, alterations in cell–cell junctions, and aberrant precursor cell biology. The development and analysis of experimental models of hydrocephalus are a fundamental step in this process. Further research should be performed to uncover the genetic and molecular mechanisms behind the pathophysiology of hydrocephalus to develop new diagnostic and treatment strategies.

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There are no conflicts of interest.

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