

Hydrocephalus: Myths, New Facts, Clear Directions

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Background

Hydrocephalus is a neurological disorder that spans all ages. The primary clinical characteristic of this disorder is excessive accumulation of cerebrospinal fluid (CSF) in the brain, which typically appears as very large ventricles on imaging studies.

Hydrocephalus may be congenital or acquired. Congenital hydrocephalus is present at birth, may be caused by genetic abnormalities, and may be associated with other developmental disorders such as neural tube defects like spina bifida, or Dandy-Walker malformation. Often the cause is unknown. Acquired hydrocephalus develops at the time of birth or at some point afterward, and may be secondary to damage to the brain caused by hemorrhage, stroke, infection, tumor, or traumatic injury. Normal pressure hydrocephalus, in which the pressure of CSF is not elevated, occurs most often among the elderly due to unknown causes.

Symptoms of hydrocephalus vary with age, disease progression, and individual differences.

Hydrocephalus can mimic many other diseases making diagnosis difficult. In infancy, the most obvious indication of hydrocephalus is an abnormal increase in increased or an unusually large head size. In older children and adults, symptoms may include headache followed by vomiting, nausea, problems with balance, poor coordination, gait disturbance, urinary incontinence, drowsiness, changes in personality, and trouble thinking or memory loss. Normal pressure hydrocephalus (NPH) can be confused with Parkinson's or Alzheimer's disease, as it can cause gait abnormalities, as well as dementia and incontinence. As our population ages, the prevalence of NPH is expected to increase.

Hydrocephalus is most often treated with the surgical placement of a shunt system which diverts the flow of CSF from the central nervous system to a site elsewhere in the body. A limited number of patients are treated with an alternative procedure called third ventriculostomy, in which a small hole is made in the floor of the third ventricle, allowing the CSF to bypass the obstruction and be reabsorbed. Shunts may malfunction and have many of the other problems that a foreign device has in the human body. Some sources report shunt failure rates of up to 40-50% within the first several years after placement; considering that many shunt recipients are the very young, and that shunts are lifelong commitments in these children for the most part, these statistics underscore importance of research and therapeutics development.

Diagnosis, Natural History, and Treatment

Hydrocephalus spans every age. While hydrocephalus is commonly seen in the clinic, the epidemiological data is scant. Additional well designed epidemiological studies are needed. Data from Canada suggests this disorder may be declining in incidence: despite this, it remains a common reason for a neurosurgeon to operate, and pediatric neurosurgeons in particular spend a large percentage of their practice treating hydrocephalus and dealing with treatment complications (such as shunt failure). There are no clear diagnostic "gold standards" for most categories of hydrocephalus. All currently used diagnostic tests have false positives and negatives. There is significant variability among

neuroradiologists, neurologists, and neurosurgeons in diagnostic approaches, especially, regarding the decision to operate/re-operate. The standard of care for diagnosis and treatment, including selection of shunts, strategies for treating shunt failures, treatment complications, and other surgical approaches, are not typically evidence based.

Hydrocephalus is a heterogeneous group of disorders rather than a single disorder, which contributes to the challenges in this field. Some known causes include intraventricular hemorrhage, myelomeningocele and other congenital abnormalities, infections, trauma (including shaken infant syndrome), tumors, venous hypertension (as in, but not limited to, achondroplasia, craniofacial syndromes, spina bifida, congenital heart disease, and other syndromes). Each of these may have very different requirements in terms of hydrocephalus treatments. Causes and clinical features vary greatly by age; for example, in infants, the ventricles do not necessarily expand at the time of shunt failure, whereas they do in adults.

Current treatment strategies (i.e., shunting) focus on CSF removal. Other strategies could include reduced CSF production, enhanced CSF absorption, neuroprotection, and recovery/regeneration enhancement post shunt. The trials targeting these other strategies have not shown benefit to date. Changes in trial design and development of better therapies specific to these goals may improve this, and animal model studies suggest there are several options which may warrant further testing pre-clinically (including, but not limited to, nimodipine and MgSO₄).

Shunts have complications on initial placement and also may malfunction thereafter. Frequent revision may be necessary due to normal growth of the patient as well as due to malfunction, which in itself increases the risk for complications. Problems can include shunt obstruction, over-drainage (“slit ventricle syndrome”), infection, device migration, disconnection and fracture. These can cause significant illness, brain injury, or even death. The symptoms of shunt malfunction can resemble other, less life-threatening diseases which adds to diagnostic difficulties. Although most shunts currently use peritoneal drainage, it is not clear that this is the optimal drainage location and this is an area for exploration. Additional diagnostic methods for identifying the site(s) of shunt obstruction are also needed. The risk factors for shunt malfunction and differences between shunts in their functionality are not well known. Additional studies to address how to avoid shunt obstruction, infection, and other complications are needed. Standardization of shunt performance would allow head-to-head shunt comparisons.

Improved outcome measures are needed in order to compare treatments. Several scoring systems have been used and others are in development for predicting prognosis in certain clinical subgroups. Because the appropriateness of any given treatment depends on multiple factors (including age), targeted therapies need to take these matters into account, especially for infants and children (where technology should not be simply scaled down from what is used for adults, for example). What is often termed neonatal hydrocephalus may well begin in utero. It is possible, with ultrasound and other imaging methods, to diagnose hydrocephalus antenatally in many instances. In utero shunt surgery is currently limited/not performed, due to confusion over any benefits thereof based on the published in studies from 1970s-1980s; some advances in technology suggest that this question may be worth asking once again. However, it is not clear what patients (mother/child) would benefit. Management strategies are currently lacking for the cohort shunted as neonates or during childhood once they enter into adulthood.

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Suggested outcome measures for NPH include videotaping and timing of gait, neuropsychological batteries to be developed specifically for NPH (including anterograde memory, timed tests, and naming, activities of daily living tests) and assessment of incontinence. Movement analysis is another area which may assist in differential diagnosis and for objective treatment evaluation. For example, gait is quantitatively and qualitatively different between NPH, Parkinson's disease, and other disorders; in the former, there is an enlarged step width and foot angles, poor step height, unsuccessful response to external cues, and improvement of gait velocity after tapping, suggesting that this disorder involves not only the basal ganglia but also the fronto-cerebellar pathways. While gait analysis has been extensively studied in NPH, hand movement has not been systematically investigated, although there are clear abnormalities of the upper limb movements in this disorder in addition to the problems with gait. Electrophysiology might also be a useful adjunct for clinical characterizations. Attention to head size is not typically measured in adults, but this may be a useful and simple bedside measure, even in adults.

It is not known to what extent the hydrocephalus itself is responsible for therapeutic outcome, versus other co-morbid factors (such as tumor, injury, neurodegenerative disorders). Improved monitoring methods would assist in deciphering this dilemma. Improvements in primary outcomes should lead to improvements in the very important areas of quality of life as well. Treatment by an interdisciplinary team of medical professionals, rehabilitation specialists, and educational experts is likely critical to a positive outcome.

CSF Production, Absorption, and Dynamics

The normal and abnormal cellular process of production and absorption of CSF is not well understood. The mechanisms of ventricular dilatation and whether or not this is directly injurious to the nervous system is also not known. Balance between CSF production and drainage needs to be understood in more sophisticated ways.

The cerebrospinal fluid (CSF) has many putative roles including mechanical protection of the brain, distribution of neuroendocrine factors, and facilitation of pulsatile cerebral blood flow. Understanding cardiovascular dynamics is valuable as the flow pattern of arterial blood must be tightly regulated within the brain in order to assure consistent brain oxygenation. CSF movement allows arterial expansion and contraction by acting like a spring, which prevents wide changes in intracranial blood flow. When disorders of CSF flow occur, they may therefore impact not only CSF movement, but, may also impact intracranial blood flow and subsequent neuronal and glial vulnerabilities. The venous system is also important in this equation. Infants and patients shunted as small children may have particularly unexpected relationships between pressure and ventricular size, possibly due in part to venous pressure

dynamics. This may have significant treatment implications but the underlying pathophysiology needs to be further explored.

CSF connections with the lymphatic system have been demonstrated in several mammalian systems. Preliminary data suggest that these CSF-lymph connections form around the time that the CSF secretory capacity of the choroids plexus is developing (in utero). There may be some relationship between CSF disorders, including hydrocephalus, and impaired CSF lymphatic transport. Further study of these relationships may help us better understand CSF production and resorption, as well as identify therapeutic strategies.

Pressure regulation and volumetric control issues relative to shunting are not yet well understood. Studies of patients, animal models, and mathematical models all will be important to help us decipher these factors in hydrocephalus.

Neuronal and Glial Mechanisms in Hydrocephalus

It is postulated that at least some injured brain tissue has the potential for recovery once the pathological process causing hydrocephalus is corrected. While shunting is the most widely used treatment, other treatment modalities may, and likely will, be important towards this goal. In order to develop such modalities, we must first better understand the mechanisms leading to hydrocephalus. Also, we need to explore what might protect the nervous system and enhance its ultimate chance for recovery. Mechanisms which may lead to insult in hydrocephalus may include a number of factors. Grossly, these include compression, stretch, edema, ischemia, breakdown of the blood-brain barrier (BBB), and toxicity due to poorly circulation of CSF. On the cellular level, pathways of cell death (neurons and glia), axonal degeneration and demyelination, neurotransmitter alterations, gliosis, changes in metabolism, and aberrant regeneration are probably important.

Microscopically, we will need to better understand neuronal and glial mechanisms during the pathological process of hydrocephalus including ischemia, neuronal stretch/stress/shear, regulation of cellular volume, white matter loss, inflammation, and the genetic regulation of cellular processes. Identification of gene expression patterns during insult and recovery may be useful towards this aim. Studies in animal models suggest that calcium (Ca^{++}) mediated damage may contribute to the insult in hydrocephalus. Manipulations of pathways or molecules (for example, those in inflammatory cascades) may help manage or even prevent complications such as post hemorrhagic/inflammatory hydrocephalus.

Developing and adult progenitor cells may be vulnerable to the effects of hydrocephalus. Injury is likely to vary with developmental age, as well as the form of hydrocephalus, and is likely influenced by genetic background. Future investigations may include identifying neural stem cells and progenitors in hydrocephalic animal models, determining the timing and location of changes of these cells in hydrocephalus in response to treatment, and evaluating clinical measures which correlate with progenitor cell damage.

Lessons from Related and Overlapping Disorders

Genetic studies are useful for identifying primary causes of multi-factorial diseases. They are particularly useful because phenotypically-defined disorders are not driven by a priori assumptions about molecular cause. Additionally, complementary usage of mouse and human gene discoveries allow rapid improvement in understanding of the underlying molecular pathways of a number of disorders.

There are several congenital disorders with a constellation of abnormalities, of which hydrocephalus is one. These include Dandy Walker Malformation, Aicardi syndrome, Miller Dieker Syndrome (lissencephaly), MEG-PMG-Polydactyly-Hydrocephalus syndrome (MPPH), Lissencephaly X-linked with ambiguous genitalia (XLAG), Cobblestone Walker Warburg syndrome, and others. Because many of these may be single gene disorders, the tools of linkage analysis and transgenics can be used to dissect the biology of these diseases and how/when they impact brain development. For example, in mouse models, loss of Dkk1 (an antagonist of canonical Wnt signaling), Lis/Reln double mutations, dystroglycan conditional nulls, and others have profound hydrocephalus. Mouse models in order to sort out pathways of single gene disorders in the developing brain should be carefully phenotyped for hydrocephalus, as this may not only identify valuable models for hydrocephalus but also reveal predisposing factors to neonatal hydrocephalus which can be further explored molecularly.

Many individuals with spina bifida have hydrocephalus. Genetic heterogeneity controls both spinal cord lesion and brain development. The brain anomalies are related to a behavioral profile, which includes core deficits (in timing, attention orienting, and movement) and functional deficits (in how information is represented, how problems are solved). Combining imaging and neuropsychological testing allows better characterization and understanding of neuroanatomical correlates of behavioral and cognitive deficits in spina bifida, which in turn segregate with given genetic polymorphisms. The role of imaging may similarly be useful in diagnosis, management, and natural history prediction of hydrocephalus, especially when used in combination with behavioral and genetic assessments.

Glaucoma, a complex disorder, informs many aspects of hydrocephalus research. In glaucoma, increased intraocular pressure is associated with the death of cells in the optic nerve. While glaucoma was originally viewed as a “plumbing problem”, in which a buildup of fluid led to disease (much as we often view hydrocephalus today), it is clearly not that simple as demonstrated by research advances. In fact, extensive studies of aqueous humor physiology and dynamics have not yet improved understanding of the primary causes or molecular mechanisms of glaucoma. Important questions in glaucoma, which likewise would inform the field of hydrocephalus, include determining which genetic and non-genetic risk factors predispose to glaucoma, determining which tissues are affected when, and how the different pathways of disease interact.

Further study of disorders in other organ systems may inform hydrocephalus research. Additionally, comorbid conditions in hydrocephalus are important areas worthy of future study. Studying possible connections of fundamental principles of the development of hydrocephalus, cysts, and syringomyelia is worthwhile. Of note, risk factors for NPH may include hypertension based on both clinical and animal studies, and periventricular vascular disease is a pathological feature of NPH. The role of amyloid burden in contributing to NPH is controversial.

Research Resources for Hydrocephalus

A number of animal models exist of acquired perinatal, juvenile, and adult hydrocephalus. Animal hydrocephalus models have been made in hamster, guinea pig, dog, rat, lamb, cat, and monkey. Many of these have histopathological similarities to what has been seen in human hydrocephalus. Despite this, better animal models are needed, especially for NPH and congenital hydrocephalus. An online database of existing animal models or a review of these and their relative strengths and limitations would be a valuable resource.

Standardized assessments for animal models of hydrocephalus are needed in order to allow comparisons across models and with human clinical findings so that features can be interpreted in

therapeutically meaningful ways. In order to improve the process of moving from animal models into clinical trials, several suggestions were made which are consistent with recommendations for studies in other fields (such as stroke), including: assuring that animal trials are appropriately randomized and the evaluations are blinded, having both short and long term outcome measures in animals, validating results in separate laboratories prior to human trials, and testing any therapy in more than a single non-human species prior to human intervention. Animal models of hydrocephalus would be useful for evaluation of prenatal treatments as well as surgeons to develop expertise in fetal techniques.

Models need not be animal models: for example, mathematical modeling is a very useful tool as are the tools of the biomedical engineer. Improved understanding of the biomechanics of the brain and skull need to be elucidated and applied to models in ways that approximate human biomechanics. Biomechanical models should evaluate both the pulsatile and the bulk flow issues.

New technologies (such as nanotechnologies) should be explored and extended into the development of new treatment modalities. Additionally, development of biomaterials which may act to lessen the problems seen in hydrocephalus therapy (such as anti-biotic coating for shunts, means to prevent bacterial attachment) should be explored.

Long term studies are important for determining how the early management of hydrocephalus impacts long term outcomes. A clinicopathological database, with the possibility of linking longitudinal, genetic, and pathophysiological data would allow systematic studies. Development of non invasive markers (for example, imaging methods, metabolic markers) would help with developing clear diagnostic subcategories and to predict outcomes. In order to study bulk flow on imaging studies, high molecular weight tracers would be valuable. Imaging methods (including fMRI, DTI, CSF flow imaging) would be useful not only diagnostically, possibly, but as primary research tools to delve into a better understanding of hydrocephalus and its causes.

Overview

Hydrocephalus represents a significant portion of those patients seen in clinical practice for pediatric neurosurgeons, as well as some neurologists, neurosurgeons, and other clinicians, but the incidence, prevalence, and burden of illness to individuals and caregivers is not well known. Treatment requires an interdisciplinary team of medical professionals, and training to develop a cadre of specialists as well as researchers with perspective on this complex disorder would be welcome. Evidence based guidelines for treatment are greatly needed for all subgroups of hydrocephalus patients, as are carefully designed and conducted natural history studies. Development of non invasive markers and imaging methods may improve diagnostic accuracy and also serve as research tools. Standardization of shunt performance and comparison of shunt function and complications, as well as improved shunt designs are needed. Additional inroads into biomedical engineering and device design will ideally be done in parallel with and informed by pathophysiology studies. New technologies (such as nanotechnologies, the development of biomaterials to enhance shunt function) and their application to hydrocephalus should be explored. Issues related both arterial and venous blood flow, as well as lymphatic flow, must be evaluated in relation to the development and progression of all types of hydrocephalus. Combining the use of genetics with cell and molecular biology is recommended in order to decipher molecular pathways of disease and targets for therapeutics. While several useful animal models exist, additional models may be helpful especially for primary hydrocephalus. Current treatment strategies (i.e., shunting) focus on CSF removal. Other strategies could include reduced CSF production, enhanced CSF absorption, neuroprotection, and recovery/regeneration enhancement. Pursuing these strategies can be informed by research in overlapping and related disorders, including glaucoma, syringomyelia, and

others. Laboratory based studies to decipher the role of CSF, brain, glia and other factors in the pathogenesis of this complex disorder are needed. Because hydrocephalus is a heterogeneous group of disorders, rather than a single disease entity, hydrocephalus research will require a multifaceted approach to the many questions remaining in this important scientific area. Our understanding of the pathogenesis of hydrocephalus, the risk factors in associated disorders, and the fundamentals of normal CSF production and clearance are poorly understood. There is a wide spectrum of research questions remaining in the field.

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