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Pathophysiology of congenital and neonatal hydrocephalus

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S U M M A R Y

The pathophysiology of congenital and neonatal hydrocephalus is not well understood although the prognosis for patients with this disorder is far from optimal. A major obstacle to advancing our knowledge of the causes of this disorder and the cellular responses that accompany it is the multifactorial nature of hydrocephalus. Not only is the epidemiology varied and complex, but the injury mechanisms are numerous and overlapping. Nevertheless, several conclusions can be made with certainty: the age of onset strongly influences the degree of impairment; injury severity is dependent on the magnitude and duration of ventriculomegaly; the primary targets are periventricular axons, myelin, and microvessels; cerebrovascular injury mechanisms are prominent; gliosis and neuroinflammation play major roles; some but not all changes are preventable by draining cerebrospinal fluid with shunts and third ventriculostomies; cellular plasticity and physiological compensation probably occur but this is a major under-studied area; and pharmacologic interventions are promising. Rat and mouse models have provided important insights into the pathogenesis of congenital and neonatal hydrocephalus. Ependymal denudation of the ventricular lining appears to affect the development of neural progenitors exposed to cerebrospinal fluid, and alterations of the subcommissural organ influence the patency of the cerebral aqueduct. Recently these impairments have been observed in patients with fetal-onset hydrocephalus, so experimental findings are beginning to be corroborated in humans. These correlations, coupled with advanced genetic manipulations in animals and successful pharmacologic interventions, support the view that improved treatments for congenital and neonatal hydrocephalus are on the horizon.

1. Introduction

Viewed in its simplest form, hydrocephalus occurs when cerebrospinal fluid (CSF) cannot be absorbed adequately, usually forcing the cerebral ventricles (and occasionally the subarachnoid spaces) of the brain to enlarge substantially. Whereas hydrocephalus can begin at any age, fetal, perinatal and neonatal onsets, with a reported incidence of 0.48 to 0.81 per 1000 live births,[1,2] are particularly difficult to treat and often result in the poorest neurological outcomes. Some studies suggest that up to 78% of patients with congenital or neonatal hydrocephalus suffer with residual neurological deficits,[2–5] others indicate that disability rates are decreasing and have now reached 28%.[6] No doubt a major factor in these poor outcomes is the extraordinarily high failure of the surgical treatments designed to shunt CSF from the ventricles to alternative absorption sites. Shunt malfunctions occur at the rate of 30–40% during the first year and exceed 50% during the second year of treatment.[7] In addition, the very early onset of ventriculomegaly in fetuses and neonates results in a protracted course of cellular damage that often is not reversible. The goal of this review is to summarize the cellular mechanisms that contribute to the pathophysiology of congenital and neonatal hydrocephalus and to identify some promising pharmacologic interventions that may improve outcome in the future.

2. Multifactorial nature of hydrocephalus

Congenital and neonatal hydrocephalus can be caused by a wide variety of developmental abnormalities or insults; the primary culprits are neural tube defects, infection, intraventricular hemorrhage, trauma, and tumors. In children, this condition is especially damaging because the expanding ventricles, accompanied by increasing CSF pressure, cause the flexible skull to enlarge; this in turn both compresses and stretches adjacent brain tissue.

It is important to recognize that the pathophysiology of congenital hydrocephalus almost always includes two separate mechanisms: primary genetic abnormalities that may affect outcome individually, and secondary injury mechanisms that occur mainly as a result of expanding ventricles and/or altered CSF physiology. An excellent review has recently summarized the genetic factors that contribute to congenital hydrocephalus.[8] This review will highlight some of the specific cellular consequences

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that accompany genetic abnormalities, but will also focus on the secondary effects of ventriculomegaly in the developing brain. Rodent studies, which have recently been corroborated by preliminary observations in humans, suggest that (in addition to gross malformations such as Chiari II and Dandy–Walker) the main congenital mechanisms involve aqueductal stenosis or obstruction, ependymal denudation, and alterations in the subcommissural organ (SCO).

Furthermore, the clinical presentation and course of hydrocephalus contain many features that contribute to the multifactorial nature of this disorder. Multiple etiologies and classifications exist – so many that the straightforward separation of 'communicating' (flow of CSF from the ventricular system to the subarachnoid spaces) and 'obstructive' (blockage of CSF flow anywhere within the cerebral ventricles) has been challenged.[9] This challenge promotes the concept that all ventriculomegaly is 'obstructive' in the sense that CSF absorption can be impaired by structural blockage or reduced physiological transport at the arachnoid membrane and its granulations, cranial nerve lymphatics, and capillaries of microvessels. Major variations can also occur in the different temporal and spatial progressions of hydrocephalus, and these differences could have important clinical consequences. For example, a relatively slow progression of ventriculomegaly over weeks and months may allow cellular plasticity to occur and thus promote intrinsic repair mechanisms. Likewise, preferential expansion of the occipital horns of the lateral ventricle may impact the optic radiations and thus cause selective visual deficits without involving locomotion and motor function. Regional effects such as this raise the caveat that much of our knowledge of the pathophysiology of hydrocephalus has been determined by examination of the cerebral cortex, probably because it is easily accessible and is more distorted than most other structures.[10] Consequently, extrapolations to other critical structures such as the hippocampus, basal ganglia, hypothalamus, and especially the cerebellum and brainstem, should be viewed with caution. The age of onset may influence outcome; e.g. perinatal induction should primarily affect neuronal differentiation rather than the neurogenesis that occurred in early gestation. Finally, although it is widely accepted that multiple shunt malfunctions play a major role in outcome, the specific effects of these repetitive insults have never been studied at the cellular level. Taken together, all of these variables highlight the multifactorial nature of hydrocephalus and make targeted studies particularly difficult.

3. Overlapping and interrelated injury mechanisms in hydrocephalus

Several reviews have discussed the many injury mechanisms known to occur in most types of hydrocephalus.[11–17] Briefly, the most acute mechanisms initiated hours to a few days after the onset of ventriculomegaly include compression and stretch of periventricular tissue, ischemia and hypoxia, and increased CSF pulsatility, most notably in the cerebral aqueduct. Additional mechanisms are recruited as ventriculomegaly becomes chronic and/or progresses to more severe forms: gliosis and neuroinflammation, periventricular edema, demyelination, axonal degeneration and slow axoplasmic transport, metabolic impairments, stagnant CSF flow, altered blood–brain barrier transport that can lead to toxicity as with reduced amyloid clearance, dendritic and synaptic deterioration resulting in altered connectivity, and cell death. The role of neuronal cell death in the overall pathophysiology of hydrocephalus is interesting because apoptosis and necrosis of cortical neurons seem to occur only after prolonged hydrocephalus, and while statistically significant reductions have been reported it may be that these changes are not biologically significant, since the total number of apoptotic neurons in the cerebral cortex is so low compared to all neurons in that region that the overall effect is probably negligible. By contrast, oligodendrocytes appear to be vulnerable during early stages of hydrocephalus and undergo significant apoptosis in the periventricular white matter. Thus, myelin formation in the developing hydrocephalic brain can be impeded by multiple simultaneous events: stretch, compression, interstitial edema, hypoxia, and oligodendrocyte death. Much work remains in order to determine the sequence of these events, their time course, and their ultimate contribution to neurological outcome.

4. Overview of brain damage in hydrocephalus

Although our understanding of the pathophysiology of congenital and neonatal hydrocephalus is far from complete and many critical questions remain unanswered, the collective evidence, obtained mostly from experimental studies, indicates that the following conclusions can be drawn at this time. (a) The age of onset strongly influences the degree of impairment. Whereas developing brains may be more capable of plasticity and recovery, overall the impact of in-utero or perinatal onsets usually predicts a worse neurological outcome. (b) Regardless of the injury mechanisms, the severity of the pathology is dependent on the magnitude and duration of ventriculomegaly. (c) The primary, or at least the earliest affected, targets are periventricular axons, myelin, and microvessels. (d) Secondary changes in neurons reflect responses to axonal disconnection, diminished cerebral blood flow and ischemia, and altered metabolism. (e) Cerebrovascular injury mechanisms are prominent (e.g. hypoxia, ischemia, capillary damage). (f) Gliosis and neuroinflammation play major roles in acute and chronic (subthreshold) injury. (g) Altered efflux of extracellular fluid, slow CSF flow, and altered capillary transport mechanisms cause accumulation of toxins. (h) Some but not all changes are preventable by draining CSF with ventricular shunts, extraventricular drains, and third ventriculostomy. (i) Considerable plasticity and compensation probably occurs, although this is a major area requiring further study; one example is the newfound lymphatic absorption of CSF that occurs adjacent to some cranial nerves as they exit the cranium. (j) Pharmacologic protection of the brain holds promise but more preclinical research is required.

5. Animal models of congenital and neonatal hydrocephalus

The H-Tx rat model is most often employed in experimental research. This strain develops congenital obstructive hydrocephalus following aqueductal stenosis in the late fetal and perinatal periods,[18–21] which correspond to the third trimester of human brain maturation. The hydrocephalic phenotype is characterized by four chromosomes within a heterozygous background[20] and incomplete penetrance.[22] Ventriculomegaly becomes severe by the second postnatal week (Fig. 1A) and animals will usually expire by 20–25 days of age if CSF is not drained with either ventriculo-peritoneal or ventriculo-subcutaneous shunts. Behavioral and cytopathologic studies clearly indicate that these shunts are more effective if placed early (3–5 days of age) rather than late (12–14 days of age) during the progression of ventriculomegaly. A few studies have taken advantage of the fact that about 10–15% of H-Tx offspring will only develop mild ventriculomegaly and will survive for months to years. The benefit of this chronic subtype within this strain is that the slowly progressive nature of hydrocephalus can be examined over a long period of time. Inbred strains of Wistar–Lewis (LEW/Jms) rats also develop aqueductal stenosis through non-Mendelian mechanisms as early as 4 days before birth,[23] and are excellent models for studying neonatal and