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Neonatal Brain Hemorrhage (NBH) of Prematurity: Translational Mechanisms of the Vascular-Neural Network

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Abstract

Neonatal brain hemorrhage (NBH) of prematurity is an unfortunate consequence of preterm birth. Complications result in shunt dependence and long-term structural changes such as post-hemorrhagic hydrocephalus, periventricular leukomalacia, gliosis, and neurological dysfunction. Several animal models are available to study this condition, and many basic mechanisms, etiological factors, and outcome consequences, are becoming understood. NBH is an important clinical condition, of which treatment may potentially circumvent shunt complication, and improve functional recovery (cerebral palsy, and cognitive impairments). This review highlights key pathophysiological findings of the neonatal vascular-neural network in the context of molecular mechanisms targeting the post-hemorrhagic hydrocephalus affecting this vulnerable infant population.

Keywords

Cerebral palsy; experimental; germinal matrix hemorrhage; hydrocephalus; mental retardation; neonatal rats; neurological dysfunction; pathogenesis; stroke

INTRODUCTION

Neonatal brain hemorrhage (NBH) occurs at a rate of approximately 3.5 times per 1,000 live births, and this is the most common neurological disorder of newborns [1]. The injury is defined as blood vessel rupture of subependymal immature (i.e. germinal–matrix) near the ganglionic eminence (neural and glial progenitor cell region) [2-3]. Severity of the bleeding is defined as grade I: isolated in the germinal matrix (i.e. GMH); grade II: GMH with intraventricular extension (IVH) without ventricular enlargement; grade III: GMH with IVH with ventricular enlargement; grade IV: GMH/IVH with intraparenchymal extension [4-5]. Others further subdivide the sub-types, according to less common bleeding location (i.e.

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

epidural, between skull and dura; subdural, between dura and arachnoid membranes; and subarachnoid) [6].

Extent of bleeding is the factor ultimately most associated with increased morbidity and mortality [7]. Grade 1-2 hemorrhage has been related to developmental disabilities; while grade 3-4 hemorrhages are associated with increased risk of hydrocephalus, as well as long-term sequelae like mental retardation and cerebral palsy [8-9]. Ultimately, up to 85% of survivors of neonatal brain hemorrhage will exhibit major cognitive dysfunction; the majority of which eventually having special educational needs [10-11].

Despite extensive work in both human and animal studies regarding pathogenesis and prevention of neonatal brain bleeds, the incidence has remained relatively the same over the last two decades [12]. The risk and severity of neonatal brain hemorrhage are inversely related to the gestational age and weight at time of birth: there is a 1% incidence in human infants born between 38 and 43 weeks, and a 50% incidence between 24-30 weeks [13]. Occurring with nearly 15% of premature births (<37 weeks); and gestational age (often clinically related to body weight) is the most important clinical predictor of brain hemorrhage. Premature infants with weights between 500-750g have a 45% incidence of NBH [14]; 20% incidence for those <1000g (extremely low birth weight; ELBW); and about 10% of <1500g (very low birth weight; VLBW) infants [15]. Importantly, since both preterm birth rates and neonatal survival have increased over the past two decades [16], the collective management of these newborns has become an ever increasing social and economic burden.

Post-hemorrhagic hydrocephalus often develops as a consequence of NBH [1-2]. Infants surviving this brain injury will often suffer from long-term neurological deficits from the expansion of the cerebroventricular system and subsequent mechanical compression of brain tissue [17]. This has been associated with other diseases of prematurity, and progressive neurologic sequelae such as epilepsy, cerebral palsy, and learning disability [18]. Factors related to neonatal brain hemorrhage include: vaginal delivery, low Apgar scores, seizure, hyaline membrane disease, hypoxia, hyper-/ hypo-carbia, patent ductus arteriosus, infection, thrombocytopenia, venous congestion, intravascular volume expansion, arterial hyper-/ hypo-tension, serum osmolarity changes, and local fibrinolytic activity [2, 5, 19-28]. Taken together, three overall factors seem to predispose NBH: 1) relative vascular fragility of the germinal matrix in comparison to other brain regions, 2) changes in cerebral blood flow (CBF), and 3) changes in hemostatic forces. Intracerebroventricular blood clots and thrombin have been implicated as causative factors for hydrocephalus development. Blood clots damage proper cerebrospinal fluid (CSF) absorption and circulation [17, 29]. Thrombin leads to obstruction of the cerebroventricular system by inducing proliferation of extracellular matrix (ECM) proteins, gliosis, and inflammatory responses [7, 30].

Therefore, NBH is a problem that generates much research interest, as ameliorating the hematoma consequences may alleviate permanent neurological impairments [31-32]. This article will review the pathogenesis of hydrocephalus with particular focus on the effect on neuronal structure and function. Long-term pathogenic outcomes from both animal and human studies show: 1) dissolution of the periventricular ependymal layer; 2) compression-

induced ischemia of local microvessels; 3) reactive processes that include proliferation and activation of glial cells; and; 4) neuronal stretching potentially leading to neuronal dysfunction and death [33-38].

POST-HEMORRHAGIC VENTRICULAR DILATATION (PHVD)

Post-hemorrhagic ventricular dilatation (PHVD), commonly known as hydrocephalus is a serious complication of neonatal brain hemorrhage (see Fig. **1**). Although this brain bleed usually occurs unilaterally, early bilateral non-communicating hydrocephalus can develop from cerebrospinal fluid outflow obstruction at the cerebral aqueduct or foramina of Magendie and Luschka. This is quite common, as over 50% of premature newborns with NBH studied at one institution had either died or required neurosurgical intervention with shunt placement; however in the early stage of brain bleed, most infants remain asymptomatic with incidental perinatal diagnosis by screening transcranial ultrasound or by other brain imaging technique [8]. PHVD can be physically evident with subtle or obvious neurologic changes in alertness, behavior, tone, respirations or cranial enlargement; later in life, the neurologic impairments become apparent, with many individuals developing cognitive or motor deficits [39-41].

PHVD results in periventricular white matter injury by a variety of mechanisms, such as: hypoxia-ischemia, altered interstitial flow from compressive forces, free radical injury, and cytokine abnormalities [38]. In addition, lack of regional autoregulation in cerebral vasculature and inadequate vascularization to periventricular regions may exacerbate hypoxia-induced injury [28, 42-44]. Both acute and chronic symptoms can be partially explained by periventricular white matter disease and dysfunction, which likely begins with ventricular expansion [5, 38]. Direct intraparenchymal extension of the hemorrhage can also damage proximal structures, such as the head of the caudate nucleus and the internal capsule [45], and delayed periventricular hemorrhagic infarcts were observed in the white matter from ischemic insult [5], could both partially explain the long-term neurologic dysfunctions observed clinically.

Early ventriculo-peritoneal shunting is often the treatment of choice, as it is associated with rapid improvement of some symptoms and short and long-term physiologic normalization [38]. However, despite its usefulness, this has expected complications, such as shunt failure at some point; and unexpected ones, specifically infection, or migration of individual parts. Less invasive therapies, including repeated lumbar or ventricular tapping of cerebrospinal fluid (CSF), intraventricular infusion of fibrinolytics, or diuretics have not yet been found effective [46-48].

Anatomic and pathologic descriptions of PHVD brains have been largely described, and immunohistochemical techniques have yielded valuable information [25, 49-50]. Fukimizu *et al* have described increased hemosiderin deposition, nodular gliosis, ependymal cell loss and underlying subependymal rosette formation in the ventricular wall following PHVD [51-52]. Other investigators have shown growth of glial progenitor cells in areas of ependymal cell loss after hydrocephalus, as indicated by high expression of nestin and vimentin in those brain regions [53]. Together, it was observed that pathologic findings were

greater in PHVD brains in comparison to those lacking ventricular dilation after IVH; suggesting the difference may be accounted by rapid increases of intracranial pressure. Regardless of the cause, hydrocephalus is associated with specific functional and behavioral deficits, with recent attempts made to isolate exact brain regions responsible [54-55].

The neonatal age of hydrocephalus development is possibly an important descriptor in the perinatal and infant period as it pertains to neurodevelopment. In animal models, hydrocephalus can be induced prenatally via genetically-engineered predisposition (i.e. the hydrocephalic Texas [H-Tx] rat [56]), or at later time of infancy using kaolin or silicone injections [57-58]. Studies comparing rat models using both techniques demonstrated that the resultant hydrocephalus causes abnormal cell proliferation in the periventricular germinal layer [56, 59-60].

PHVD delays myelination in white matter regions, which shows reversibility with early surgical shunting [61-63]. Parallel findings were found in humans using magnetic resonance imaging techniques [64] and post-mortem analysis [65]; demonstrating changed post-operative myelination. In clinical terms, if shunting results in the cease of ventricular enlargement, it is referred to as arrested or compensated hydrocephalus. Whether pathologic changes actually stop post-operatively remains a point of contention. Observational studies show long-term neuropsychiatric disorder and benefit following shunting in young adults and adults with previous “arrested” hydrocephalus [66-69]. In light of such findings, increased effort has been on objectively identifying patients who will benefit from repeat shunting despite apparent clinical stability [70-72]. Especially challenging in this clinical situation has been the lack of an adequate animal model. Although perinatal hydrocephalus has been studied 8 weeks after treatment of H-Tx rats [73-75], its applicability to human subjects, who may harbor subtle organic disease for years, is questionable.

Cerebrospinal Fluid (CSF)

Surgical insertion of shunts for draining CSF from the ventricles into the peritoneum for absorption by the vasculature is the current primary method for clinically managing hydrocephalus; shunts, however, become obstructed and eventually have to be replaced [7]. Generally, the CSF functions to cushion the brain in the cranium, and acts as a medium for the transport away of waste products and the diffusion of trophic and autoregulatory factors to the parenchyma [76-77]. 80% of the CSF is produced by ependymal cells of the choroid plexus, with the remainder comprised of end-products of cerebral metabolism [78] and flow through the blood-brain barrier [79]. CSF drains to the subarachnoid space through the foramen of Magendie and the foramina of Luschka, where it is predominantly absorbed by arachnoid granulations into the venous sinuses. Removal of CSF is also achieved through drainage into nasal lymph compartments [80], but clinical significance has not been established.

Impendence of normal CSF flow or defective CSF production causes hydrocephalus (see Fig. **1**), which may alter normal CSF function and lead to physiologic, structural, and neurobehavioral changes. Early neuropathological and ultra-sonographic studies in humans have suggested that ventricular dilation following IVH was due to initial plugging of arachnoid villi followed by the development of obliterative arachnoiditis, while meningeal

fibrosis and subependymal gliosis could cause outflow obstruction in the posterior fossa [49, 81]. This model has been widely accepted; however, a more recent model using nuclear and magnetic resonance imaging has suggested that major CSF resorption occurs through brain capillaries [82]. In this proposed model, CSF crosses the ependyma and the blood-brain barrier of local microvessels into the venous system, where any factor impeding this process could lead to hydrocephalus.

Enhanced extracellular matrix (ECM) deposition has thus been implicated in the pathogenesis of PHVD and may work to impair CSF resorption. Furthermore, some hypothesize that inflammation changes of the choroid plexus and ependymal lining of the ventricles will result in both increased production of abnormal protein-rich CSF, and the impedance of trans-ependymal CSF migration. Demonstrated by colocalized nuclear factor-KB (NF-KB) signaling and abnormal serum-derived IgG uptake by barrier cells; associating abnormal blood–brain barrier permeability with inflammation [83].

Periventricular Leukomalacia (PVL)

In the work by Cherian's group, newborn rats who developed hydrocephalus had a 48% mean reduction in the thickness of the corpus callosum and a 31% mean reduction of the frontal cortex [84]. Immunohistochemistry techniques yielded further pathologic changes in white matter [84]. Although basic pathologic changes have been described from human samples, morphologic alterations noted in the rat model should be confirmed in human disease. In very premature infants, magnetic resonance imaging (MRI) has shown that cortical surface area and complexity are decreased when compared to infants born around term [85].

Subsequent MRI studies have found that brain changes persist into adolescence, with decreases in whole brain volume, cortical gray matter and hippocampal volume noted [86]. Similarly, premature infants with periventricular leukomalacia (PVL) exhibit both reduced cortical grey matter and total myelinated white matter at term [87], although other studies have suggested that those with PVL and NBH experience an accelerated growth of grey matter structures postnatally [88]. As a disease of prematurity, similar findings in PHVD can be expected. Further studies of postconditioning modalities (such as the phosphatidylinositol-3-kinase/Akt [89-90] neuroprotective pathway), may prove to up-regulate regenerative pathways in order to mitigate these known losses in white matter, following neonatal brain hemorrhage.

Intracranial Pressure (ICP)

Findings in both animal models and humans have suggested that increased intracranial pressure and acute ventricular distension are important pathologic features of PHVD. For example, in the newborn rat model, during injection of blood or CSF into the lateral ventricles, intracranial pressure was raised approximately 8-times its normal level [84], which may reflect the raised intracranial pressure observed in premature infants developing PHVD [91] as discussed above. In regards to ventricular expansion, it has been previously shown in one study that 40% of adults treated for severe primary IVH develop hydrocephalus requiring shunting [92], while in VLBW infants, the severity of IVH was the

major predictor of short term adverse outcomes, including the development of PHVD [8]. In light of the fact that blood and CSF produce ventricular dilatation similarly in the rat model [84], acute elevation of intracranial pressure, not blood composition, is likely particularly important in the pathogenesis of PHVD.

Premature infants with PHVD have CSF pressures three-fold higher (9.1 mm Hg) than control patients [91]. In the same study, CSF pressures continued to be elevated, but less than two-fold, in “arrested” cases where ventricular dilatation was stable or reversing. At 15 mm Hg, blood flow through major cerebral vessels can be halted during diastole, which is restored when intracranial pressure is reduced to 6 mm Hg [29]. In addition, deep white matter vessel density is transiently decreased in preterm gestation [44]. Combined, these factors give periventricular white matter high susceptibility to ischemic-hypoxic injury. Periventricular axons therefore appear to be the primary target of ventricular expansion, with axonal degeneration and other neuronal distortions demonstrated that may occur independent of ischemia [34-35, 38, 57, 93-94]

Shunting is accompanied by both expected and unexpected outcomes, and, in addition, some pathologic changes that occur prior to shunting are likely not reversible. Much focus has been placed on early interventions, including quickly identifying patients that will most benefit from shunting. Other therapies involving early fibrinolytic therapy were investigated in animals [95-98], and in humans [46]. White *et al* have proposed a new treatment method of drainage, irrigation and fibrinolytic therapy (DRIFT). Studied in human neonates, DRIFT aims to remove cytokine and iron-containing blood products from early hydrocephalic brains [99]. The breakdown of clot facilitates the irrigation of blood from the ventricular system. A reduction of CSF concentrations of transforming growth factor-beta (TGF-β) may be one beneficial outcome of such therapies. Other interventions that block the release or action of TGF-β may be found effective; however, such treatments must aim to avoid the unintended cerebral damage demonstrated in TGF-β1 knockout mice [100]. Prematurity remains a common occurrence with strong pathologic associations, including IVH and PHVD. Animal models, particularly newborn rat models of these diseases, can be used effectively in pre-clinical investigations of pathogenesis, pathophysiology, and treatment of IVH and its complications, as is further elaborated in this review.

NEUROVASCULAR UNIT

Blood-Brain Barrier (BBB)

Dr. Ballabh’s group has collected much information regarding the structural and molecular characteristics of each individual blood-brain barrier component [101-106]. Much of the data was obtained through samples from post-mortem fetus and premature infants. According to their findings, in prematurity, IVH is most typically an extension of GMH, and cortical or white matter bleeding is far less common, together suggesting that germinal matrix vasculature has relative fragility in comparison to other areas in the developing brain. In all brain regions, the blood-brain barrier is similarly comprised of endothelial tight junctions, basal lamina, associated pericytes, and perivascular coverage by astrocyte end-feet. Although these components work in conjunction in the normal blood-brain barrier, it is

possible that a dysfunction in any of these pieces would result in increased susceptibility to hemorrhage.

Endothelial tight junctions are comprised of three major integral membrane proteins claudin, occludin and junction adhesion molecules and cytoplasmic accessory proteins that include ZO1, ZO2, ZO3, and cingulin [31]. These strengthen cell-to-cell adhesion, and thus enhance structural integrity of the vessel, and, in the brain, limit paracellular flow of substrates; forming the selectivity of the blood-brain barrier [107]. Ballabh's group hypothesized there would be a differential presence of these proteins in the forebrain (using Western blot analysis and other immunohistochemical techniques); however comparable expressions of claudin, occludin, and junction adhesion molecules were shown between cortex, white matter and germinal matrix endothelial cells as a function of gestational age [102]. Thereby it has been discussed that deficiencies of tight junction proteins were unlikely responsible for enhanced germinal matrix fragility; however, further study of molecular signaling pathways involved in endothelial tight junction formation may yield useful information in future neonatal studies [107].

Through analysis of post-mortem fetus and premature infants, Ballabh *et al* have demonstrated that, throughout human gestation (between 16-40 weeks), vessel density and cross-sectional area increased in all three studied brain regions: germinal matrix, white matter, and cortical grey matter [101]. Interregional comparison also showed that those same vascular parameters were greatest in the germinal matrix throughout gestation. Cross-sectional imaging of the germinal matrix showed vessels to be round in shape in comparison to the flat vessels of grey and white matter regions. This has been described as evidence of vessel immaturity [108]. Both study findings have suggested that high vascularity with morphologic immaturity, although useful in providing blood flow to areas of high metabolic demand, likely increases the susceptibility of the germinal matrix to hemorrhage.

In application, experimental studies using adult animals have implicated Src family kinases (SFKs) in the modulation of N-methyl-d-aspartate (NMDA) receptors involved with neurovascular cell death following brain bleeding [through excitatory and mitogenic signal transductions] and these play a dual role in both the early stage-acute endothelial tight junction disruption; and also BBB-recovery over subsequent weeks following the brain hemorrhage [109]. However, such a mechanism has yet to be investigated in a corresponding neonatal study.

Angiogenesis

The germinal matrix is a highly vascularized region of increased angiogenesis and endothelial turnover, and physiologic hypoxia may be their trigger in this brain region. Hypoxia is an important trigger for pro-angiogenic factors [110-112], and as noted, VEGF and angiopoeitin-2 levels are greater in the germinal matrix compared to cortical and white matter regions [106]. In the rabbits, premature pups euthanized 2 hours postnatally showed more intense staining of Hypoxyprobe (immunolabeled in tissue exhibiting low P02, often used in tumor studies), in the germinal matrix than in other forebrain regions, suggesting relative hypoxia [2].

As such, using post-mortem human samples and premature rabbit pup models, Ballabh's group has shown VEGF and angiopoietin-2 expression to be higher in the germinal matrix when compared to forebrain grey and white matter regions [106]. In the same study, premature infants at hours after birth had greater endothelial proliferation compared to those at mean postnatal day 7. This suggests that angiogenic rate decreases within days in the postnatal period.

Two angiogenic inhibitors, the COX-2 inhibitor, celecoxib, and the VEFGR-2 inhibitor, ZD6474 were then studied in the premature rabbit pup model, with prenatal celecoxib treatment resulting in decreased angiopoietin-2 and VEGF expression, and decreased germinal matrix endothelial proliferation [106]. Both celecoxib and ZD6474 were effective in decreasing the incidence of glycerol-induced NBH [106]. These angiogenic inhibitors have been similarly used to significantly enhance pericyte coverage and decrease blood-vessel area and vascular density in the germinal matrix [105].

Ways to utilize angiogenic inhibitors such as celecoxib in order to promote blood-brain barrier integrity while avoiding tissue hypoxia are thus being explored. The concern has been that by stunting angiogenesis, CBF (cerebral blood flow) would not meet the metabolic demand of the germinal matrix. However, cancer studies have demonstrated that specific low-dose concentrations of some antiangiogenic agents function to improve tumor vessel morphology and function, as well as tissue oxygenation [113].

Accordingly, other tumor studies have shown that VEGFR2 inhibition increases expression of angiopoietin-1 to enhance pericyte coverage, and is involved in activating metalloproteinases to degrade pathologically thick basal lamina [114-115]. Further investigation into antiangiogenic therapies is deserved. Short courses of current inhibitors at low doses, or novel usage of other modulators [116-121], including the study of balancing matrix metalloproteinases (MMP) [122-123] and TIMP (tissue inhibitors of metalloproteinases) [124-125], together may help promote vascular stability, while limiting germinal matrix devascularization.

Extracellular Matrix (ECM)

The ECM basal lamina is comprised of fibronectin, laminin, collagen, heparin sulfate proteoglycan and perlacan molecules [126-127]; and elimination of fibronectin, laminin, collagen IV or perlacan genes in knockout mice have shown the importance of the basal lamina in angiogenesis, vessel stability [128-130], and thus in extension (for GMH/IVH). For example, levels of propeptide of type I procollagen increased in the CSF of PHVD premature neonates when compared to those with hydrocephalus associated with congenital malformation [131]; reflecting increased local type I collagen synthesis and turnover, related to the neuropathological (ECM) fibrotic changes found within arachnoid and meningeal tissues.

Laminin, collagen V and other important basal lamina proteins, have also been studied for their role in GMH/IVH. Ment *et al.* used the newborn beagle pup model to explore if the decreasing risk of GMH/IVH with increased postnatal age was related to germinal matrix vasculature maturation. Immunohistochemical evaluation revealed increased staining for

laminin and collagen V in the germinal matrix on postnatal day 4 compared with postnatal day 1 [132]. A second study from this group demonstrated increased germinal matrix staining for laminin and collagen V in postnatal indomethacin-treated animals [133]. Together, the studies suggest that sufficient laminin and collagen V deposition in the extracellular matrix may stabilize the basal lamina of the germinal matrix. Although this is physiologically accomplished with postnatal aging, indomethacin and other interventions may be useful in preventing GMH/IVH in neonates. Other forms of collagen appear less significant in relation to neonatal brain hemorrhage. Collagen I, II, and IV concentrations in the germinal matrix showed no deficiency relative to cortical and white matter vessels [134]. Regardless, the role of basement membrane integrity in NBH is likely to be further investigated.

Fibronectin, an extracellular glycoprotein that binds both integrins and other extracellular matrix components, functions in cell movement, cell-cell adhesion, and cytoskelatal arrangement [135]. Polymerization of fibronectin is important for further cell growth, contractility, and strengthening of the extracellular matrix [136-137]. In post-mortem samples, Xu *et al* demonstrated significantly lower levels of fibronectin in the germinal matrix of both human fetuses and premature infants in comparison to cortical and white matter regions [104]. In comparison, the presence of a1, a4 and a5 laminin, a1 collagen and collagen IV, and perlacan was not significantly different. Knockout mice models with inactive fibronectin gene produced fatal neural development and vessels with variable deformity [128]. Fibronectin studies have thus been interpreted as evidence that insufficient levels of basal lamina fibronectin may contribute to germinal matrix propensity to hemorrhage. Low-dose prenatal betamethasone therapy is associated with increased expression of fibronectin [104], and as in GFAP studies, supports the role of corticosteroids in preventing NBH. In addition to glucocorticoids, new approaches to fibronectin up-regulation in the germinal matrix should be considered. Increasing expression of Transforming growth factor (TGF) may be one novel approach. In rat models, iatrogenic elevations in TGF increased fibronectin expression [138]. Similar to fibronectin, TGF levels are lower than those seen in other brain regions. The clinical efficacy of increasing TGF has not been explored. Although higher levels may promote basal lamina strengthening through increased fibronectin expression, TGF has diverse targets and functions, which may limit its clinical specificity.

Transforming Growth Factor Beta

Alterations in TGF-β concentrations in the CSF may play a role in the pathogenesis of PVHD. As a family of signaling proteins, TFG-β proteins are involved in regulating a variety of molecular pathways, including cell proliferation and differentiation, immunity, inflammation cascades, and tissue repair [139-153]. They appear in both animals and humans, and both systemically and in the central nervous system (CNS) [139-152]. TGF-β is an important mediator in collagen formation that is capable of rapid induction of angiogenesis, collagen formation and fibrosis [139]. Although this cytokine family plays mostly physiologic (i.e. *homeostatic*) roles, TGF-β also is involved in the development of diseases of pathologic collagen and ECM deposition, as in glomerulonephritis [140] or liver

cirrhosis [141]. These molecules are therefore appropriately studied in both humans and experimentally in animal models.

Both animal models and humans have been used to demonstrate the role of TGF-β in PVHD. Experimentally, non-communicating hydrocephalus was induced in mice following injection of human recombinant TGF-β into the subarachnoid space [142], while transgenic mice who over express TGF-β from glial cells developed severe ventricular dilatation with observed seizures and motor dysfunction, as well as upregulation of ECM proteins laminin and fibronectin [143]. In humans, high concentrations of TGF-β1 have been demonstrated in CSF studies of adults with hydrocephalus following subarachnoid hemorrhage compared to non-hemorrhagic hydrocephalus patients [144], where two elevation spikes in TGF-β1 were appreciated: early on from known release from hemorrhaged platelets, and a delayed spike likely reflecting exogenous upregulation. Similarly, elevated levels of TGF-β1 and –β2 have been shown in the CSF of premature infants with PHVD [145].

The rodent model has been used extensively to relate CNS injury to TGF-β expression. For example, TGF-β is up-regulated in response to ischemic cerebral insult [146-147]. Its expression is also enhanced following penetrating brain lesion, and is thought to mediate formation of a glial scar observed at the site of injury [148]. These models therefore suggest that cerebral injury, including NBH, is capable of releasing high levels of TGF-β into the CSF, an alteration that has been implicated in the pathogenesis of PHVD in both mice models [143, 149] and clinical studies [145, 150]. Pathogenetic studies, whether done in animal models or humans, are particularly important, as they are often the first step in developing sound therapeutic interventions.

The rat model of PHVD has also been used to study the role of TGF-β [151-152]. In these studies by Cherian and Love *et al*, in contrast to the brains of normal 21-day old rats, those who received intraventricular blood or CSF-infusion showed significantly increased expression of TGF-β isoforms. Using immunohistochemistry, staining was prominently found for TGF-β1 in the ependyma, periventricular white matter, and deep cortical neuropil, TGF-β2 was present in neuronal cell bodies and periventricular oligodendrocytes, and TGF-β3 stained in oligodendrocytes and microglia. Although TGF-β1 and –β2 were elevated in rats injected with blood or CSF-infusion regardless if they developed ventricular dilatation, levels of these isoforms were highest in hydrocephalic animals [152]. The immunolabeling of intracellular phosphorylated p44/42 MAP kinases, modulators of TGF-β effects, rose similarly to TGF-β1 and –β2, as did ECM deposition of fibronectin, laminin and vitronectin proteins [152].

Astrocytes

Perivascular coverage is provided by close association with astrocyte end-feet that surround the cerebral vessels. End-feet contribute to the structural stability of the vessel and are major components to the blood-brain barrier. Glial fibrillary acidic protein (GFAP) is an intermediate filament astroglial marker thought to be important in maintaining mechanical strength and shape to astrocytes. In post-mortem analysis, El-Khoury's group has demonstrated that GFAP+ astrocyte end-feet increased as a function of gestational age in both the cortex and white matter between 19 - 40 weeks, but perivascular expression of

GFAP+ end-feet was decreased in the germinal matrix relative to the cortex and white matter from 23-34 weeks [103]. This discrepancy may indicate decreased cytoskeletal stability, resulting in increased vulnerability of the germinal matrix to hemorrhage. GFAP+ astrocytes first appear in the spinal cord at 9 weeks of gestation, and are then present in the ependyma from the 14^{th}-19^{th} weeks; while their expression has been described in germinal eminence cells at 17 weeks [154-156]. They are present early in gestation, and are therefore exposed to perinatal therapies. *In vitro* studies have shown that GFAP expression significantly increased in the presence of hydrocortisone [157], potentially explaining the efficacy of prenatal corticosteroids in reducing the incidence (or severity) of NBH. The above studies regarding astrocyte end-feet support the idea that they play an important role in allowing or preventing GMH.

On the other hand, ‘astrogliosis’ is an *abnormal* increase in the number of astrocytes in the recovery period following brain hemorrhage [60, 158]. This is postulated to involve molecular mechanisms with both beneficial and detrimental end-outcome effects [159]. The functional role of this process after neonatal hemorrhagic brain injury thus raises the prospect of therapeutically targeting this glial -cell response in future study, as this is to date poorly defined perinatally.

Pericytes

Pericytes are cellular constituents of the blood-brain barrier that surround endothelial cells of small vessels in the brain. As part of the neurovascular unit, they function in endothelial tight junction formation, blood-brain barrier differentiation, microvascular vasoactivity, structural stability of the vessel, and in angiogenesis [160]. Pericytes appear to control angiogenesis at many stages, including both initiation and maturation [161]. Early in angiogenesis, they regulate proliferation and migration of endothelial cells. Later, pericytes closely associate with the new vessel and contribute to endothelial cell differentiation, maturation and extracellular matrix deposition [162].

Pericyte recruitment and functions are regulated by four major ligand-receptor systems: TGF-B-TGFR-B, PDGF-B-PDFGR-B, angiopoietin-Tie, and sphingosine-1-phosphate-S1P1 [162]. Ligand or receptor null mice failed to recruit pericytes to endothelial cells, resulting in microaneurysms of the microvasculature, with propensity to rupture [163-164]. In post-mortem infant and rabbit pup models, Braun’s group found less pericyte coverage and pericyte density in the germinal matrix compared to grey or white matter regions [105]. The relative lack of pericytes in the germinal matrix suggests it may be a factor in GMH/IVH. The authors further investigated the molecular basis of lower levels of pericytes in the germinal matrix of human fetuses, preterm infants, and preterm rabbit pups. Ligand-receptor expression studies demonstrated lower TGF-B1 in the germinal matrix than in the cortex and white matter. Levels of PDGF-B, PDGFRB, angiopoietin-1 and its receptor Tie were not significantly different among the brain regions, while S1P1 and N-cadherin expressions were higher in the germinal matrix compared to cortex and white matter [105]. The authors suggest low levels of TGF-B1 may promote endothelial proliferation, while high levels of S1P1 and N-cadherin are likely involved in vascular maturation; however both these characteristics are important in germinal matrix angiogenesis. TGF-B1, an important

regulator, promotes neurovascular stability through mesenchymal differentiation into pericytes, synthesis of extracellular matrix, and organization of pericytes around the endothelium [165]. Hence, low expression of TGF-B1 may be related to the decreased pericyte density and perivascular coverage in the germinal matrix, and may further contribute to GMH.

CEREBROVASCULATURE

Hemostasis

In conjunction with known fragility of the germinal matrix, it is tempting to hypothesize that disorders in hemostasis have a role in the disease. The relative contribution of coagulation factors in preventing or causing (in the case of deficiency) GMH/IVH, however, is not completely understood. For example, thrombocytopenia has been linked to IVH [166-167]. Further, in preterm neonates, fibrinolysis in the CSF may be inefficient in breaking blood clots impeding CSF flow, as decreased plasminogen and increased plasminogen activator inhibitor have been demonstrated in post-IVH CSF studies [168-169]. This is a potentially reversible abnormality, with CSF infusion of fibrinolytics having been explored [46, 169]. However, it is unlikely that connective tissue deposition induced by the blood clot can be effectively reversed or removed.

In a study of premature neonates with known intracranial hemorrhage, marked decreases in platelets, fibrinogen, and factor XIII activity were reported [170]. In the same study, those treated at 6 hours after birth with factor XIII concentrate had a significantly lower incidence of IVH. Since coagulation and inflammatory pathways appear interrelated in the development of IVH, various co-genotypes (of IL-1β, IL-4, IL-6, IL-10, and TNF-α), have been investigated as potential predictors of both IVH risk and severity [171-173]. In these studies, Harding's group found an association between the CC genotype of IL-6 and higher incidence of significant intracranial hemorrhage and poorer clinical outcomes, while Gopel *et al* failed to confirm those results.

Currently, these remain preliminary findings, but there is continued interest in finding risk modifiers in GMH/IVH. Other alterations in hemostatic components are thus likely present; for example, hemostatic differences have been noted in preterm infants as compared to those born at full gestation [174-176]; and warrant continued investigation.

Cerebral Venous Pressure (CVP)

A recent multi-hospital observational study of neonatal intensive care units found that among VLBW infants, there was borderline association between severe NBH and hypotension, while there was no association with hypertension [177]. Previous investigations have also found data supporting a relationship between hypotension and NBH [178-180]. In contrast, other research teams demonstrated no association between the two factors [181-183]. This is of clinical importance considering that CVP increases in mechanical ventilation, positive pressure ventilation, pneumothorax, and likely many other conditions.

In regards to CVP, elevated pressures are postulated to increase risk of NBH in prematurity[184]. Post-mortem microscopic analysis of preterm neonates found the majority of germinal matrix hemorrhages to stem from venous sources, although the sample size was small [27]. Hypotension and hypertension have a variety of congenital, physiologic and iatrogenic causes in premature neonates [185]. However, with a possible prevalence of 24%-45%, hypotension is a much more common disorder in prematurity [177]. A mechanism of disease may be related to changes in cerebral blood flow (CBF), where elevated CVP leads to reduction in cerebral perfusion pressure (CPP). CPP, which is normally dependent on the gradient between MAP and intracranial pressure (ICP, CP = MAP – ICP), may be alternately determined by CVP if CVP is higher than ICP. Autoregulatory ranges of neonatal brains are thus poorly defined, as compared with adult or pediatric populations [186]; justifying further study.

Cerebrovascular: Cerebral Blood Flow (CBF)

In the acute phase of disease, much importance is placed on the role altered cerebral blood flow (CBF) has on pathogenesis in hydrocephalus, increased intraventricular pressure, and ischemia of periventricular microvasculature [187-189]. Accordingly, in animal models, reduced capillary number, density and vessel diameter have all been demonstrated in local white matter [190-192]; following hydrocephalus. Regional CBF, assessed in humans through xenon clearance, Doppler techniques, and spectroscopy, is also decreased in hydrocephalic human brains [193-195]. A reduction in regional CBF has been associated with a number of metabolic changes: increased glucose consumption in the cat model [61], increased production of reactive oxygen species (ROS) and lipid peroxidation in H-Tx rats [196], and activation of proteolytic enzymes capable of axon degradation in kaolin-injected rat models [197]. Likewise, CSF assays from hydrocephalic humans demonstrate likely disturbance in metabolism and neurotransmission [198], as well as increases in oxidative stress [199]. Of note, similar abnormalities and processes are implicated in hydrocephalus, stroke and traumatic brain injury, which may relate to shared pathogenic factors. Lastly, specific to hydrocephalus, shunting results in normalization of local CBF that has been linked to improved outcomes [200-202]; however, others have suggested that this may not account for clinical improvement seen in the long-term [193].

On postnatal day 1, Perlman *et al* studied CBF velocity using Doppler ultrasonography in very low birth-weight (VLBW, <1500 g) premature infants who required mechanical ventilation secondary to respiratory distress syndrome. At 12 hours of age, two CBF patterns emerged: 1) stable, where peak and trough systolic and diastolic blood flow velocities were relatively consistent; and 2) fluctuating, where blood flow velocities were varied. Flow velocities reflected simultaneously-recorded blood pressures. IVH developed in 21/23 infants with the fluctuating pattern, most within 24 H of birth, and in 7/27 neonates with a stable pattern [188]. Similar results were demonstrated in infants with gestational ages <34 weeks, regardless of respiratory status [203]. In a subsequent study by Perlman's group, significantly less IVH and grade III IVH developed following pancuronium-induced paralysis [189]. Muscle paralysis was thought to stabilize a fluctuating CBF velocity pattern by eliminating dyssynchrony between infant and mechanical ventilations. Accordingly, variability in CBF velocities in ventilator-dependent infants has been demonstrated to

improve with synchronous respiration [204]. Hence, fluctuating CBF velocity was seen as a preventable cause of IVH. While paralytic agents tend to be avoided clinically (in premature ventilator-dependent infants) out of concern for adverse effects with extended use; synchrony promoting modes of ventilation (between infant and machine) can be widely employed. These include assist control and synchronized intermittent mandatory ventilation. Of note, serum hyperosmolarity may also contribute to IVH through alteration of CBF, although investigators have argued for and against this hypothesis [205-207].

Despite a consensus not being reached, it is plausible that rapid infusion of large quantities of hypertonic sodium bicarbonate, as used in neonatal resuscitation, may lead to high PaCO2 and subsequent cerebral vasodilatation. Rapid increases or fluctuations in CBF may thus increase the propensity of the germinal matrix to hemorrhage, and should be avoided. Finally, fluctuating CBF is also associated with hypotension, hypercapnia, patent ductus arteriosus and clinical restlessness [203, 208-209], all preventable or treatable risks that may aid in preventing IVH in the premature.

Emerging clinical modalities include investigations using sonothrombolysis (e.g. therapeutic ultrasound) with-or-without adjuvant micro-bubbles, as a means to more rapidly remove any impedance of normal blood circulation, are a possible approach in the brain (to salvage damaged tissue); and to achieve better hematoma mass reduction following neonatal hemorrhagic stroke [210].

Autoregulation

Two predominant regulatory responses constitute cerebral autoregulation: myogenic responses to intravascular pressure, and functional hyperemia via neurogenic responses. Through these processes, stable and adequate CBF to the brain is achieved [211]. On a cellular level, autoregulation occurs through the innate ability of pericytes and smooth muscle cells surrounding cerebral vessels to constrict and relax in response to intravascular pressure changes. The molecular pathway begins with triggering of stretch-activated Ca^{++} channels, allowing the influx of calcium and subsequent activation of phospholipase A2 [212]. Consequently, arachidonic acids are released from cell membrane phospholipids, which are in turn metabolized to 20-hydroxyeicosatetraenoic acids (20-HETEs) by P450 enzymes. 20-HETEs function to inhibit Ca^{++}-dependent K^{+} channels, sequentially leading to smooth muscle cell depolarization and contraction. The resulting vasoconstriction counteracts hypertension-induced increases in CBF.

Lack of cerebrovascular autoregulation, or pressure-passivity, indicates the inability of the vasculature to keep CBF constant despite variations in mean arterial pressure (MAP). CBF has been assessed by xenon clearance, as well as by cerebral oxygenation studies that include Doppler techniques, near-infrared spectroscopy (NIRS), and spatially resolved spectroscopy (SRS) [181, 213-215]. Pressure passivity is subsequently determined by factoring both CBF and MAP. A lack of cerebrovascular autoregulation in prematurity was thought to contribute to the development of NBH. An early study using xenon clearance in premature infants on mechanical ventilation showed decreased pressure-flow autoregulation and vasoreactivity to changes in PaCO2 in those subsequently developing severe intracranial

hemorrhage [213]. In contrast, pressure-flow autoregulation was preserved in patients without hemorrhage.

Using near-infrared spectroscopy (NIRS; in a more recent study of similar patients), found those with greater difference between intravascular oxygenation and MAP (indicating impaired autoregulation) had a higher incidence of either severe GMH/IVH, periventricular leukomalacia (PVL); or both [216]. Further suggesting pressure-passivity relates to cerebrovascular disease. In contrast to previous xenon and Doppler ultrasonography techniques, researchers have strongly favored continued use of NIRS in the evaluation of autoregulation because of the ability to record continuously [217].

Results that do not support an association between pressure-passivity and NBH have also been found. A relatively large and recent study using continuous NIRS on VLBW infants reported pressure-passivity was significantly related to low gestational age and birth weight, but was not associated to NBH incidence [181]. Similarly, a group using SRS (related to NIRS) demonstrated impaired cerebral autoregulation present in clinically sick preterm infants predicted subsequent mortality, but did not relate to the development of NBH [215]. Together, these studies suggest impaired cerebrovascular autoregulation is a phenomena more common to sick, premature and ventilated infants, but without any clear association with NBH. Further investigation should employ NIRS, SRS or other methods of continuous recordings for more useful results.

Functional Hyperemia

Functional hyperemia is achieved through a complex neurogenic regulatory response aimed at matching CBF to metabolic demand. The entire neurovascular unit appears involved; however, their coordination has not been entirely elucidated. On a molecular level, it is thought that a cascade initiated by activation of synaptic glutamate receptors results in the production of vasoactive agents [218]. Specifically, nitric oxide and adenosine are considered to have primary roles in the genesis of functional hyperemia, which, along with CO_2, H^+, arachidonic acid metabolites and cytokines, are all associated with increased CBF [211, 219].

In the case of adenosine, smooth muscle relaxation and subsequent vasodilatation occur through cAMP-pathway activation of K_{ATP} and K_{Ca} channels [220]. Moreover, recent studies in the mouse model have further implicated COX-1 and COX-2 as being important regulators of functional hyperemia by causing vasodilatation and elevations in CBF [221-222]. In contrast, indomethacin, commonly used in neonates to close a patent ductus arteriosus, was demonstrated to reduce CBF in a sheep model [223]. Taken together, as impaired cerebral autoregulation is linked to brain bleeds in premature infants, further such study of the molecular basis may yield effective preventative therapies in future preclinical and clinical trials [224].

Interstitial Flow

Separate from alterations in CBF, changes in extracellular fluid flow and composition may contribute to cellular dysfunction. Physiologic *waste* products that fail to cross the blood-

brain barrier into the systemic venous system must filter through the interstitial space and in to the CSF [76]. In the normal cerebrum, this flow occurs at 0.1-0.3 μl/min/g of brain tissue [225], but is thought to be impeded in hydrocephalus. In rodent models of hydrocephalus, the extracellular compartment volume in grey matter is reduced [226-227], extracellular fluid movement is diminished [228-229], and CSF composition changes as metabolic byproducts and other neuromodulators accumulate [198]. In humans, elevated biomarkers that result from increased CSF protein and *waste* concentrations are being investigated in the non-invasive diagnosis of chronic hydrocephalus [230]. Even slight alterations in waste product concentration and factors in neurotransmission may significantly impact glial and neuronal function.

MECHANISM

Free Radicals

Free radicals can exacerbate white matter injury in PHVD [231-232]. The pathogenesis of increased oxidative stress in PHVD may primarily relate to IVH [233-234]. During hemorrhage, a large quantity of iron is released into the CSF. Non-protein-bound iron is elevated in preterm infants with PHVD [232], and likely reflects iron in excess of the total iron-binding capacity of the CSF. Via the Fenton reaction, free iron mediates the production of hydroxyl radicals that potentially damage periventricular white matter [235]. In rat models of congenital hydrocephalus, increased reactive oxygen species and lipid peroxidation have been demonstrated [196], while human CSF studies have shown similar findings in premature neonates with white matter injury [231] and with hydrocephalus [199].

Cell loss immediately adjacent to the bleed may be mediated in part by the toxicities of extracellular hemoglobin (Hb) and thrombin [236-237] (and correspondingly responsive to free-radical scavengers like hydrogen [238-239] or melatonin [240-245]). However, at *low* concentrations, ‘*offending*’ proteins may *precondition* tolerance to hemin and iron; to decrease peri-hematomal injury through heme oxygenase (HO)-1 and iron binding protein modulation [246], e.g. transcription factor Nrf2 (Nuclear factor-like 2) [247]. Study of such mechanisms could help find strategies to further protect against periventricular erythrocyte lysis-related damage [248-249].

Oxidative Stress

Oxidative stress may also increase secondary to ischemia-reperfusion injuries in periventricular white matter, while hyperbaric-oxygen (HBO) therapy may have protective effects [250]. Hypoxanthine, a purine metabolite, is a reliable marker for hypoxia, and has been shown to be elevated in preterm PHVD infants [251]. Under normal conditions, xanthine dehydrogenase uses NAD+ as final electron acceptor to oxidize hypoxanthine and xanthine to uric acid. However, in ischemic tissue, xanthine dehydrogenase is converted to xanthine oxidase, which uses oxygen as the final electron acceptor, resulting in the generation of free radicals [252-254]. Xanthine oxidase persists with reperfusion, causing continued oxidative damage with purine metabolism. Oligodendrocyte precursors, highly present in the periventricular germinal zones, appear especially vulnerable to hypoxia-

ischemia and oxidative stress in human studies of periventricular leukomalacia (PVL) [255-257].

Inflammation

Leukocyte (white blood cell) trafficking in the acute phase following experimental brain hemorrhage in adult rodents is a molecular target that may ameliorate cerebral inflammation [258-259]. Specifically, it has been shown that blood-derived monocyte populations (inflammatory macrophages and dendritic cells) travel to the brain in the 12 hours following brain bleeding, and this response out-numbers neutrophil migration [260]. Further study nonetheless will need to determine the significance of these findings and any role of these cells after neonatal brain injury [261]; as this pathophysiological process may differ from what is reported in the adult literature.

Specifically, the inflammatory response is related to white matter injury in VLBW infants [262], and has been demonstrated to be strong and prolonged in preterm infants with PHVD (i.e. *hydrocephalus*). In corresponding CSF studies, pro-inflammatory cytokines tumor necrosis factor-α, interleukin-1β (IL-1β), IL-6, IL-8, and interferon-γ were significantly elevated and were associated with increased risk of subsequent white matter injury and poorer neurologic outcomes [263]. Increased inflammatory response with elevations in pro-inflammatory cytokines [264] appears important in the pathogenesis of PVL (i.e. white-matter loss) [265-266], and clinical evidence supports a similar role in the development of white matter disease in PHVD. In extension, recent therapeutic approaches using adult animals may one day prove useful in neonates [264] and vice-versa. Notably, proteasome inhibition using *PS-519* was found to attenuate rodent brain inflammation, and related edema, through perihematomal modulation of nuclear factor-KB [267]. This intervention reduced expression of inflammatory astroglial iNOS; and improved functional recovery following the brain injury.

NEUROPATHOLOGY

Monoamine Neurotransmission

Abnormalities in monoamine neurotransmission systems are associated with hydrocephalus [34]. In animal models, monoamine neurotransmitter concentrations are decreased [268-269]; while reductions in cholinergic and dopaminergic neurons in particular brain regions have also been demonstrated [270-271]. Much of the literature regarding neurotransmitters is related to the association between hydrocephalus and Parkinsonism's, rarely akinetic mutism, and other movement disorders [272-275].

Experimentally in rats, hydrocephalus resulted in mechanical distortion and functional injuries of cholinergic and GABAergic neurons in the neostriatum and dopaminergic neurons in the substantia nigra [276-277], with improvement following shunt placement [278]. Likewise, in human positron emission tomography studies, functionally repressed dopamine receptors (D2 receptors) in the nigrostiatal system have been linked to gait disturbances in NPH [279]. Post shunting, upregulation of D2 receptors was correlated to clinical improvement [280]. Considering that D2 receptor hypoactivity in the dorsal

putamen may be able to predict the severity of gait disturbance in idiopathic NPH [279], there is potential to find additional biomarkers with clinical significance.

While periventricular axons appear to be the primary target of ventricular expansion with hydrocephalus, non-axonal architectural changes are also observed. Damage and functional impairment are not limited to periventricular tissue, as biopsy and post-mortem human samples in chronic hydrocephalus demonstrate degenerative changes that extend beyond this region [281]. Thus abnormalities in neuronal conduction pathways likely results from both peri-hematomal morphologic changes with distal alterations of synaptic transmission.

Endocrine

The hypothalamic-pituitary axis (HPA) is exposed to ventricular expansion in the third ventricle. Hypothalamic changes related to hydrocephalus are not extensively established. However, initial gross and microscopic findings in the HPA of hydrocephalic humans have been described, with noted changes including an enlarged infundibular recess and a shortened infundibular stalk [282-284], although clinical significance has not been determined. Endocrine abnormalities, however, are associated with hydrocephalus. Pituitary hormone secretion appears affected. In shunted humans, myelomeningocele and hydrocephalus have been related to growth hormone deficiency, higher basal FSH and LH (and GnRH), precocious puberty, and amenorrhea [285-287]. However there is often an improvement of the reproductive cycle, following shunting [286]. Following experimental hydrocephalus in rats, increased hypothalamic GnRH was also observed [288].

Experimentally, angiotensin II receptor content is increased in third ventricle circumventricular organ systems [289], while alterations in the catecholaminergic system have been described [269, 290]. The exact pathogenesis in HPA dysfunction has not been clearly demonstrated, but it potentially parallels gross and cellular mechanisms evident in periventricular white matter disease. Therefore, continued use of neonatal animal models will be beneficial to better outline the role of these molecules in preterm neonates, as recent findings supporting therapeutic modulation of Arginine vasopressin (AVP; also known as vasopressin, or antidiuretic-hormone) a neurohypophysial hormone found in most mammals - may differ from experimental adult models of brain hemorrhage [291-293].

Synaptogenesis

Non-axonal architectural changes in the neuron have been demonstrated in hydrocephalus models. In kittens, visual cortex neurons are smaller, cortical neuron somata are disoriented [294], hippocampal synaptic contacts are decreased [295], and dendritic deformity in the cortex is apparent with electron microscopy [296]. Morphology did not normalize after shunting [296]. In rats, cortical dendrites were decreased in length, displayed fewer, shorter branches [297-298], and had frequent varicosities of the dendritic shaft [297]. In contrast, cellular columns and serotonergic innervations in the somatosensory cortex were preserved, suggesting that some basic cytoarchitecture is unaffected by hydrocephalus [299]. Although evidence of cortical neuropil degeneration is observed in H-Tx rats, early shunting may prevent these changes [300].

Synaptic morphology and function has also been experimentally described. In rat models, synaptophysin, a presynaptic vesicle protein, showed decay or decrease after 4 weeks in hydrocephalus [301-304], while synaptophysin staining in the hippocampus of H-Tx rats showed possible resilience of synaptogenesis [305]. Findings in animal models should be correlated with human studies. Electron microscopies of human samples from hydrocephalic brains have shown evidence of synaptic degeneration, clumping of synaptic vesicles, and glial abnormalities in association with the synapse [306-307]. Models of chronic hydrocephalus and biopsies from chronic hydrocephalus patients can more clearly define long-term characteristics of synaptogenesis. Of note, upregulation of neurotrophins, including growth-associated protein and nerve growth factor, has been demonstrated in rat models [308-311] and may indicate important axonal protection and synaptic remodeling.

Visual System

In regards to sensory abnormalities, the visual system is the most extensively studied. Hydrocephalus can cause pathology at a number of points along this pathway. Increased intracranial pressure and subsequent papilledema can damage the retina and optic nerve [312-313]. Ventricular expansion can cause morphologic alterations to geniculocortical pathways [314], while cortical and subcortical pathways can become ischemic if posterior circulation is significantly compressed. As briefly mentioned before, the integrity of visual pathways can be evaluated through the use of visual evoked potentials, which has been done in animal models [315] and in humans [316-318]. Parinaud's syndrome, an upward gaze palsy that is seen in midbrain dysfunction, has been suggested to indicate shunt malfunction [319-320]. It is potentially caused by functional impairment of the midbrain associated with transtentorial pressure differences [320] or by structural distortion of the tectum by suprapineal recess (part of ventricular system) dilation [321], and may be a combination of multiple factors.

Periventricular Axon Degeneration

The primary pathologic change to the neuron from ventricular expansion in hydrocephalus is periventricular axon degeneration [35, 57, 93-94], while neuron cell death is rarely observed, regardless of the severity of hydrocephalus [94, 322]. However, neuronal cell death has been observed in the thalamus of H-Tx rats, which has been attributed to retrograde degeneration and apoptosis of the cell body following axonal damage [323]. In the periventricular white matter of the hydrocephalic brain, the primary sites of axonal injury occur in the limbic system, particularly the fimbria-fornix pathway and the corpus callosum [324-327]. A study of callosal fibers in kaolin-induced hydrocephalic rats suggests a subpopulation of axons may be particularly vulnerable [328]. However, as demonstrated in both experimental and human studies, all periventricular white matter, including long corticospinal tracts and deeper layers, are susceptible to injury [34, 62, 329]. Accordingly, in kaolin-induced hydrocephalic cats, midbrain, thalamic, and cortical axonal tracings were decreased, but shunt therapy restored labeling in some, but not all, regions [330]. In the dog model, cytoskeletal damage of neurons was most significant in periventricular white matter and showed incomplete normalization following shunting [331]. Although much of the pathology discussed is largely attributable to increased intraventricular pressure and ventricular enlargement secondary to hydrocephalus, the contribution from possible

underlying neurologic disease is difficult to ascertain. For example, prematurity is associated with multi-system abnormalities, while post-hemorrhagic hydrocephalus occurs with local injury and exposes the parenchyma to irritating blood components.

ANIMAL MODEL

Pathophysiology

Previous works have studied the immediate pathophysiology of cellular damage and long-term consequences of germinal matrix hemorrhage/intraventricular hemorrhage. For example, cellular proliferation in the rodent germinal matrix is significantly decreased following hemorrhagic insult [30]. Chronic neurologic dysfunction may be partially explained if progenitor cells are damaged. Pro-inflammatory states have also been postulated to contribute to brain injury. In human neonates, intrauterine infections are associated with preterm birth, intraventricular hemorrhage, and cerebral palsy [332]. Similarly, inflammation and brain damage in mouse models increase with immune pre-activation by the endotoxin lipopolysaccharide [333]. Neonatal mice show increased cerebral injury in the presence of higher levels of serum thrombin and plasmin, suggesting that proteolysis may additionally play a pathogenic role [334]. Regarding long-term complications of germinal matrix hemorrhage/intraventricular hemorrhage, developmental delay and chronic behavioral deficits have been demonstrated in neonatal rat periventricular hemorrhage models [335]. Associated with intraventricular hemorrhage, hydrocephalus has been experimentally induced in rat models by blood injection into bilateral ventricles [29, 84]. On a molecular level, alpha V integrin-null mice develop spontaneous intracerebral hemorrhage in midgestation, hypothesized to be secondary to poor endothelial/pericyte association with surrounding cerebral parenchyma [336]. The continued use of knockout mouse models promises to further detail mechanisms of disease.

Neurological Dysfunction

Neuronal function depends on effective neurotransmission, structural integrity, working support cells, and intact regulatory mechanisms [337]. Any point of abnormality can ultimately lead to neurologic disorder. Clinically, global and regional abnormalities in neural activity associated with hydrocephalus can be demonstrated on electroencephalogram [338-339]. The integrity of particular conduction pathways in hydrocephalus has been investigated using sensory and motor-evoked potentials. Dysfunctional changes in the pyramidal tract, callosal, and corticospinal fibers have been demonstrated in humans [340-341], while visual cortex, motor cortex, and thalamo-cortical pathways have been shown in animal models [315, 342-344]. Using kaolin-induced hydrocephalic rats, pyramidal cells in the hippocampus showed attenuation of long-term potentiation of population spikes, a finding suggestive of abnormal postsynaptic integration [345]. In cats, single cell recordings from visual cortex cells demonstrated reduced responsiveness [346]. Performance-testing has been used to describe larger functional abnormalities related to hydrocephalus.

Experimentally, memory and learning difficulties have been shown in animal models [347-349] and in humans [350-352], with interest in potential reversibility with shunting.

Such cognitive impairments have been related to abnormalities in the limbic system. In rats, septohippocampal cholinergic neurons are decreased [353], while in humans; limbic fiber aberrances were more common in myelomeningocele and Chiari II malformations [354]. Pathologic location may also relate hydrocephalus-type. Limbic and frontal dysfunction are implicated in aqueductal stenosis, while, in normal pressure hydrocephalus (NPH), cognitive deficits may be more attributable to abnormalities in prefrontal structures [355]. We determined memory deficits and spatial learning using the cognitive assessments outlined by Morris *et al* [356]. Juvenile rats with NBH injury had increased hyperactivity in the open field (path length) as well as diminished working memory (T-maze) than control groups [357].

Rapid changes in rat brain development occur during the first 14 days of life [358-359]. Early reflex locomotor assessments conducted by using grip traction, righting-reflex, and negative geotropism tests, are amongst the first developmental motor milestones for neonatal rats [360-362]. Thus, early cerebrovascular injury [363], such as GMH, could disrupt early brain development, resulting in delayed acquirement of basic neurobehavioral skills. In humans, delayed early developmental functions in premature infants have been strongly associated with reduced neuromotor function as they age [18]. Furthermore, deficits in posture, balance, gait, and motor learning have been similarly described in hydrocephalic animals [364-365] and humans (both adult and pediatric populations) [366-370]. We found that during the first 3 days following collagenase-induced neonatal brain hemorrhage in rats [357], significant sensorimotor deficits were observed in injured neonates when compared to sham (needle trauma only), which corroborates with a rabbit model of spontaneous pre-term brain bleeds and the clinical presentation [234]. We also observed losses in body weight 1 day following the brain bleed injury, similar to weight changes in P7 rat pups in a related model of cerebral hypoxia-ischemia [371-372]. This timeline differed, however, from a rodent direct blood-injection model, which had significant neurobehavior deficits observed between 1-2 weeks following injury [17, 335]. This free-hand needle insertion method may have caused unintended traumatic brain injury, and this may help explain the observed differences in timing of neurobehavior deficits between the two models [30].

Translational Studies

The use of animal models is necessary for a variety of reasons, including the complexity of human subjects and the need for controlled experimental environments to assess potential therapeutics, and the study of injury progression [373-377]. This has been modeled by either changing systemic hemodynamic properties (serum glycerol, blood pressure, circulating blood volume, oxygenation levels, or osmolarity) or direct, needle injection of blood into the ventricle in several animal models including mouse, rat, rabbit, dog, pig, and sheep ([234, 378-379]; see Table **1** for summary). In prematurely born rabbits (27-30 days gestation), spontaneous intraventricular hemorrhage was induced by creating intracranial hypotension using intraperitoneally injected glycerol [380]. Ventricular distension upon the blood flow patterns in neighboring brain tissues was studied in newborn dog brains by direct blood injection [381]. Physiological factors that lead to a greater predisposition to GMH have been evaluated extensively in dog models [378]. There is an interesting neonatal hypoxia-ischemia model using mice that secondarily develops spontaneous bleeding at superficial

foci [382]; however that pathophysiology is different compared with what occurs in human preterm infant brain hemorrhage [2]. While early experimental neonatal brain hemorrhage models relied on the spontaneous development of IVH in preterm subjects [383-384], current models produce IVH through two major means: 1) direct injection of autologous blood into the ventricles or 2) induction of IVH through the alteration of physiologic conditions that increase susceptibility to IVH, for example hypotension, increased intracranial pressure or hypercarbia [385-387].

Available animal models, however, are each limited in the ability to individually model neuropathology, etiology, and clinical outcomes following neonatal brain bleeds [17, 29, 84, 335, 388]. Hemodynamic modification has confounding factors such as hypertensive, hypercarbic, hyperosomotic, hypoxic, or hypervolemic states. Direct blood infusion, in addition to the inherent disadvantage of causing needle trauma to the surrounding tissue, does not mimic a spontaneous bleed. Further, the specialized expertise required to rear and care for prematurely delivered large mammals is very expensive. On the other hand, rodent brain injury models are relatively inexpensive to reproduce, use, maintain, and the developmental aspects are well documented [360].

Compared with pig and dog models, the newborn rat has greater neurodevelopmental similarities to preterm humans at 24-26 weeks, since neurogenesis is mostly complete [389] and the germinal matrix is present in both species. In addition, the germinal matrix has been studied extensively in rats [390-392], and long-term behavioral developments are well documented [360, 393]. In early studies, post-hemorrhagic hydrocephalus (PHVD) was not observed following injection of blood into mouse periventricular tissue [30]. However, a later neonatal rat model was outlined by Cherian *et al*, where ventricular dilatation was demonstrated following injection of citrated rat blood or artificial CSF (aCSF) into the ventricles [84]. Thereafter, ventricular expansion was produced after injection of blood and thrombin into the lateral ventricles of adult pigs [95]; and with injection of pre-clotted blood into the lateral ventricles of adult dogs [96-98]. Of note, unlike Cherian's group, these models used adult animals and studied ventricular clot lysis; thus applicability to PHVD of prematurity was questionable.

Collagenase

Previously, we described a neonatal brain hemorrhage model using stereotaxically injected collagenase into the germinal-matrix of neonatal rats [357]. The rats exhibited grade III-IV brain bleeds, as the hematoma spread into the ventricles, similar as to what was delineated by clinical imaging studies in premature human infants ([4]; animal model illustrated in Fig. **1**). Analogous to intraventricular hemorrhage in human premature infants, this model ruptured blood vessels within the germinal-matrix, breaks the ependymal, and fills the ventricles with blood [380]. In addition, the progressive and spontaneous escalation of focal bleeding and rebleeding, transmural pressure, and blood-vessel rupture in this model, which all raise intracranial pressure to severe levels during the first few days of neonatal life, are comparable to GMH-intraventricular hemorrhage of human premature infants [380, 394]. Clinically, elevated transmural pressures across intracerebral blood vessel walls are caused

by diuretic administration, bicarbonate infusions, and high pulmonary-ventilator pressure [2].

Compared with prior animal models that used free-hand injections [335, 395], with ultrasound or MRI monitoring in a select few [30]; our model used a commercially-available, standardized, neonatal stereotaxic frame with a Hamilton syringe in order to minimize needle trauma to the brain parenchyma. We induced the brain bleed by injecting collagenase into the ganglionic eminence as this creates a standardized, spontaneous rupture that bleeds into the lateral ventricles [396-398]. This modeled the consequential conditions including regional brain swelling (edema), fibrogenesis, gliosis, motor /cognitive deficits, altered brain/body growth, delays of neurodevelopment, ventriculomegaly, brain atrophy, increased hemoglobin / thrombin, and a strong inflammation response. The slow intraventricular bleeding rate in the collagenase-induced rat neonatal brain bleed model had fewer confounding factors like related trauma, infarction, rapidly increased intracerebral pressure (ICP), as compared to models using rapid intraventricular infusions of relatively large blood volumes [84, 95, 335, 388]. Fortunately, rodent neurobehavioral and histopathological responses to brain injuries are well documented [397-401]; in addition to rodent models being less labor intensive, expensive, and having a much lower mortality rate, with survival into adulthood, compared with models using rabbits, piglets, or beagles [84, 234, 379, 388, 402].

In limitation, the collagenase approach may exaggerate the inflammatory response [403]. Indeed, a strong inflammatory response may account for the observed increase in ventricular dilation in the collagenase model when compared to direct blood injection, which requires twice the hemorrhagic volume to induce comparable ventricular dilation in only 65% of the pups [84]. Also, the effects of anti-thrombin drugs and iron-chelators need to be evaluated independently when assessing neurobehavioral and hydrocephalus development. Therefore the effects of iron, thrombin, hemoglobin, and deactivated collagenase is needed [404].

Moreover, our NBH model has a very low mortality rate for the high-grade of brain bleed injury produced; which is very different from the 30-50% mortality rate in humans with similar severity [405]. Furthermore, the mechanism behind CSF drainage impairment needs investigation; even though it is widely believed that blood and coagulation products disrupt arachnoid villi function. Additionally, it will be important to ascertain the effects of drugs on blood in the ventricles or on brain tissue; even though blood within the ventricles is a causative factor for hydrocephalus development; and future modalities such as MRI may help further clarify these associations (as partially illustrated in the Fig. **1**).

SUMMARY

Neonatal brain hemorrhage is a devastating neurological disease of prematurity, and is in need of further therapeutic interventions. In this review, we discussed the latest pathophysiological findings; most specifically in the context of hydrocephalus. This pathological outcome can be studied from several perspectives, including: post-hemorrhagic ventricular dilatation (PHVD), increased cerebrospinal fluid (CSF) accumulation, and dangerously elevated intracranial pressures (ICP).

The neurovascular unit was explored and reported from several different perspectives. These included the blood-brain barrier (BBB) itself, changes in angiogenesis and related factors, the extracellular matrix (ECM), and molecules therein. Of note: TGF-β (transforming growth factor-beta) has been implicated by many different investigators, to be involved in both the recovery and increased brain injury mechanisms, and thus may likely emerge as a key molecular target in future studies. Finally, the role of other neurovascular cells: specifically astrocytes and pericytes were described in the context of pre-term neonatal brain bleeds.

Current advancements of hemostasis and hemostatic factors, and the role of brain vascular components, including changes in cerebral venous pressure (CVP) tone, cerebral blood flow (CBF) regulation, independent cerebrovascular autoregulation, functional hyperemia consequences, and, lastly, interstitial flow were discussed. Several non-novel mechanisms of brain injury were also investigated (i.e. free radicals, hypoxic-ischemic stress, and inflammation). In this context, the neuropathology following neonatal brain hemorrhage was characterized- and included pathological periventricular leukomalacia, monamine neurotransmission deficits, endocrine deficiencies, long-term synaptogenesis problems, effects on the visual system (i.e. eye-sight), and periventricular axon degeneration.

Finally, several animal models are summarized in terms of their given pathophysiology and translational insights into human disease; specifically, long-term neurological, cognitive, and sensorimotor dysfunctions as essential mimics of human disease. We also presented the potential strengths and limitations of our collagenase rodent model, the developmental stage, and appropriateness for further translational studies [406].

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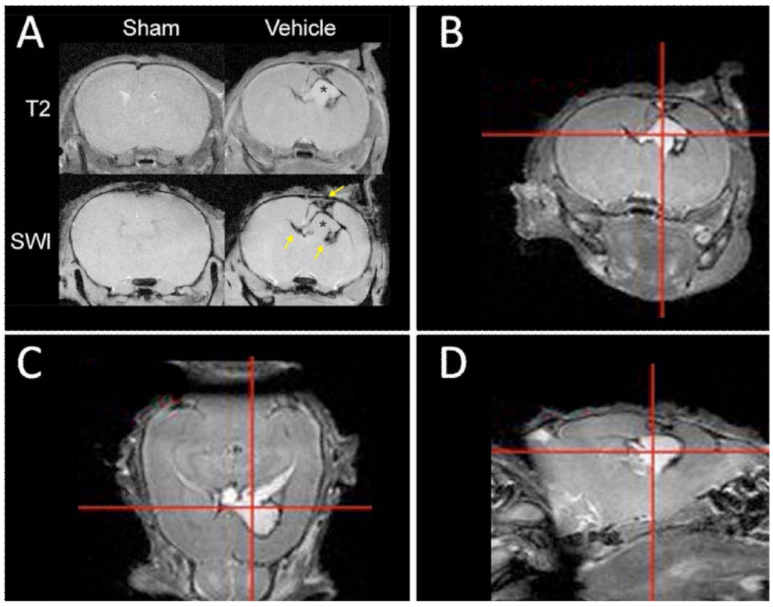

Fig. (1). CSF accumulation and ventriculomegaly 7 days after neonatal brain hemorrhage induction depicted by imaging

Magnetic resonance imaging (MRI) was used to evaluate injury progression in sham and vehicle P14 rat pups 7 days after NBH induction. These images suggest hydrocephalus development commences as early as 1 week following NBH induction. **(A)** T2-weighted MRI (top row) depicts CSF accumulation (hyperintense T2-signal marked with an asterisk) and ventriculomegaly. Susceptibility weighted imaging SWI (bottom row) depicts clots within the periventricular region (hypointense signal marked with arrows). Sham animals did not have any visible brain injury. T2-weighted MRI depicting **(B)** coronal, **(C)** axial and **(D)** sagittal cross-sections of NBH animal depicting CSF accumulation, ventriculomegaly, and minor midline shift.

Table 1

Comparison of Neonatal Brain Hemorrhage (NBH) Animal Models.

Species	NBH Induction Method	Developmental Ages Comparable to Pre-term Humans	Advantages	Disadvantages
Rodents [29-30, 84, 333-335, 357]	Injection of autologous blood or collagenase into the periventricular region	Newborns comparable to 24-26 week human gestational age, 7 day-old rats comparable to 32 week human gestational age	Availability of knockout strains, well-documented neonatal brain development, germinal matrix in postnatal age, and inexpensive	Substantial anatomical and physiological differences with humans
Rabbits [380, 384, 407-414]	Intraperitoneal injection of glycerol to induce intracranial hypotension, sodium bicarbonate hyperosmolality, or furosemide diuresis	28 days gestation or 3-4 days before term are most comparable to pre-term humans	Some postnatal brain development features similar to fetal humans, such as blood vessel immaturity in germinal matrix	Inconsistent and diffuse hemorrhage development
Pigs [415-424]	Intraventricular autologous blood injection	Studies performed in newborn pigs, not very comparable to humans	Good for studying pathogenesis of brain injury in neonates	Brain is developmentally mature
Sheep [385, 425-431]	Asphyxia with arterial and venous hypertension in exteriorized sheep fetuses	58 to 85 days gestation comparable to 26-30 week preterm humans	Vasculature of germinal layer is similar to humans	Brain is developmentally mature at birth, inconsistent hemorrhage development, sheep fetuses must remain unbilically attached their mothers, and sheep have carotid rete mirables
Cats [432]	hypernatremia induced by intraperitoneal sodium injection	Studies performed in 6+ week old kittens, not very comparable to humans	Well documented neonatal neuronal development	Poor documentation on kitten germinal matrix and hemorrhage sites in prior studies
Dogs [132, 378-379, 383, 386, 433-450]	Induced hypertension, hypotension, or hypercarbia at 12-48 hours post-birth in beagles, or asphyxiation of beagles at 6 days before term	Substantial germinal matrix layer at term that is comparable to pre-term humans	Large size makes physiological observations easy, many well documented studies related to neonatal brain hemorrhage	Inconsistent hemorrhage development, limited long-term neurofunctional studies, and dog brains contain a carotid rete mirables
Primates [451-456]	Prematurely delivered baboons at 125-days gestation spontaneously develop hemorrhages	Baboons at 100 days gestation comparable to 24-week human gestation age	Most comparable to human development, spontaneous NBH development	Very expensive