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Neonatal posthemorrhagic hydrocephalus from prematurity: pathophysiology and current treatment concepts

A review

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Object. Preterm infants are at risk for perinatal complications, including germinal matrix–intraventricular hemorrhage (IVH) and subsequent posthemorrhagic hydrocephalus (PHH). This review summarizes the current understanding of the epidemiology, pathophysiology, management, and outcomes of IVH and PHH in preterm infants.

Methods. The MEDLINE database was systematically searched using terms related to IVH, PHH, and relevant neurosurgical procedures to identify publications in the English medical literature. To complement information from the systematic search, pertinent articles were selected from the references of articles identified in the initial search.

Results. This review summarizes the current knowledge regarding the epidemiology and pathophysiology of IVH and PHH, primarily using evidence-based studies. Advances in obstetrics and neonatology over the past few decades have contributed to a marked improvement in the survival of preterm infants, and neurological morbidity is also starting to decrease. The incidence of IVH is declining, and the incidence of PHH will likely follow. Currently, approximately 15% of preterm infants who suffer severe IVH will require permanent CSF diversion. The clinical presentation and surgical management of symptomatic PHH with temporary ventricular reservoirs (ventricular access devices) and ventriculosubgaleal shunts and permanent ventriculoperitoneal shunts are discussed. Preterm infants who develop PHH that requires surgical treatment remain at high risk for other related neurological problems, including cerebral palsy, epilepsy, and cognitive and behavioral delay. This review highlights numerous opportunities for further study to improve the care of these children.

Conclusions. A better grasp of the pathophysiology of IVH is beginning to impact the incidence of IVH and PHH. Neonatologists conduct rigorous Class I and II studies to advance the outcomes of preterm infants. The need for well-designed multicenter trials is essential because of the declining incidence of IVH and PHH, variations in referral patterns, and neonatal ICU and neurosurgical management. Well-designed multicenter trials will eventually produce evidence to enable neurosurgeons to provide their smallest, most vulnerable patients with the best practices to minimize perioperative complications and permanent shunt dependence, and most importantly, optimize long-term neurodevelopmental outcomes.

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Key Words • **germinal matrix–intraventricular hemorrhage** • **hydrocephalus** • **preterm infant** • **subgaleal shunt** • **ventricular reservoir** • **ventriculoperitoneal shunt**

Neonatal neurosurgical care for preterm infants has lifelong consequences, and the medical care of these infants is rapidly evolving. The 15-year rise in the proportion of infants born preterm in the US finally appears to have peaked, and in 2008, the most recent year for which data are available, it decreased to 12.1%.[67] Germinal matrix–intraventricular hemorrhage, the most commonly diagnosed brain lesion in preterm infants, tends to occur in the sickest preterm infants and often is only one of several comorbidities of prematurity. Approximately 15%–20% of infants who weigh less than 1500 g at birth will develop IVH.[25] A subset of infants with IVH develop posthemorrhagic ventricular dilation (PHVD), which may be due to hydrocephalus ex vacuo from encephalomalacia or symptomatic progressive PHH with increased ICP. Currently, infants with PHH are treated with progressively invasive

Abbreviations used in this paper: AHW = anterior horn width; cPVL = cystic periventricular leukomalacia; EGA = estimated gestational age; EPO = erythropoietin; ETV = endoscopic third ventriculostomy; ICP = intracranial pressure; IL = interleukin; IVH = germinal matrix–intraventricular hemorrhage; LP = lumbar puncture; MDI = Bayley Mental Developmental Index; NICU = neonatal ICU; $paCO_2$ = partial pressure of CO_2; PDI = Bayley Psychomotor Developmental Index; PHH = posthemorrhagic hydrocephalus; PHVD = posthemorrhagic ventricular dilation; PVHI = periventricular hemorrhagic infarction; PVL = periventricular leukomalacia; rEPO = recombinant EPO; rtPA = recombinant tissue plasminogen activator; TGF = transforming growth factor; VP = ventriculoperitoneal; VSG = ventriculosubgaleal.

This article contains some figures that are displayed in color online but in black and white in the print edition.

measures, ranging from serial lumbar punctures to temporary shunts to permanent CSF diversion with VP shunts. At each stage, a subset of infants with transient hydrocephalus will have spontaneous resolution of symptoms, such that only a small percentage of those who initially suffer IVH will eventually require permanent CSF diversion. As time progresses, with further improvements in perinatal care and the incidence of IVH declining further, it is likely that fewer infants will ultimately need neurosurgical intervention. Expertise in this area will continue to be essential, however, because hydrocephalus from preterm IVH can be quite challenging to manage. Children with shunts from prematurity are more likely to require shunt revisions and to develop slit-ventricle syndrome, loculated hydrocephalus, and shunt infections than children with hydrocephalus from other causes.

This review primarily focuses on the recent literature. Significant progress has been made to reduce neonatal mortality, and more recently, neurological complications of prematurity.[119] For example, the incidence of cerebral palsy in children at 2.5 years' corrected age who were born at a gestational age of less than 34 weeks has decreased about 3-fold from the early 1990s to the early 2000s.[108] While the majority of the decrease in cerebral palsy is likely due to the 93% reduction in cystic periventricular leukomalacia (cPVL), severe IVH remains an independent risk factor for cerebral palsy.[108] Neonatologists made several practice changes in the past decade that have impacted the incidence of IVH and PHH. Similarly, pediatric neurosurgery has made significant progress in the past 5 years in decreasing perioperative complications, particularly surgical-site infections. Although it is likely that fewer preterm infants will suffer IVH in the future, the prevention, treatment, and outcomes of IVH in preterm infants remain challenging.[94,119] Well-designed multicenter trials are essential to recruiting enough patients within an epoch of neonatology advances to identify significant differences and to discount institution-specific referral patterns and practices. Prevention, neuroprotection, and neurorepair are likely to form the cornerstone of effective new initiatives for IVH and PHH, as for head and spinal cord trauma.

Methods

For this review, the following terms were searched in the National Library of Medicine's MEDLINE database for English-language articles: preterm intraventricular hemorrhage, preterm infant hydrocephalus, preterm ventricular reservoir, subgaleal shunt, and preterm ventriculoperitoneal shunt. Additional relevant articles were identified from references found through the initial search. Relevant articles were evaluated and summarized.

Results

Terminology

Preterm infants are infants born before 37 weeks' EGA (Table 1). Gestational age is estimated based on the pregnancy and the infant's developmental characteristics and is expressed as completed weeks.[29] In general, infants born earlier in gestation and with lower birth weights have a higher risk of perinatal problems, including IVH. Germinal matrix–intraventricular hemorrhage is diagnosed by cranial ultrasound performed at bedside. The most commonly used scale to describe the severity of the IVH is the Papile grading system,[79] which has undergone slight modifications over time.[27,115] Grade I IVH is restricted to the subependymal parenchyma or minimally involves the ventricle (< 10% of the ventricle), Grade II extends into the ventricle but does not expand or occupy more than 50% of the ventricle, and Grade III involves more than 50% of the ventricle and often distends it (Fig. 1). The former classification of Grade IV refers to extensive IVH with parenchymal involvement, likely due to terminal venous occlusion with venous infarction and subsequent secondary hemorrhage, and is now termed periventricular hemorrhagic infarction (PVHI).[27,115] About one-third of infants with IVH develop posthemorrhagic ventricular dilation (PHVD),[23] defined as ventricular enlargement above the 97th percentile for EGA.[55]

Cystic periventricular leukomalacia, a separate entity from IVH, is also observed in preterm infants and is diagnosed by ultrasonography and MRI.[27] Intraventricular hemorrhage and cPVL often occur in combination and probably share partially overlapping pathophysiological mechanisms. In support of the concept that IVH Grade III and PVHI describe separate entities with differing pathophysiological mechanisms, a retrospective study of risk factors for IVH and cPVL found different associations between IVH Grade III, PVHI, and cPVL.[53] Cranial ultrasound examinations performed in preterm infants (EGA < 30 weeks and weight < 1500 g) showed that 43% of the infants with cPVL also had IVH, whereas only 13% of the infants with IVH also had cPVL.[53] The number of infants with both cPVL and IVH was higher than the number with either condition alone, leading the authors to conclude that PVHI is likely different in etiology from IVH Grades I–III and that the etiology of cPVL plus IVH is different from that of cPVL alone.[53] Defining the exact overlap between IVH and especially diffuse white matter damage, the most common current form of white matter injury, awaits long-term outcome analyses that include the results of term-equivalent MRI and genetic analyses.

In addition to being vulnerable to IVH and PVL, preterm infants are vulnerable to other CNS injuries that impact their prognosis. Cerebellar hemorrhage occurs with or without supratentorial IVH and/or PVL and has been associated with poor long-term outcomes.[58] Although cranial ultrasonography reliably detects IVH within the lateral ventricle and severe PVL, more subtle abnormalities that can impact outcomes can be difficult to detect with ultrasound.[27] For example, MRI detected cerebellar hemorrhage in 10% of all preterm infants studied, but ultrasound detected only 23% of the lesions detected on MRI.[102] On long-term follow-up, children with cerebellar hemorrhage had a 5-fold increased risk of abnormal findings on neurological examination compared with children without neonatal cerebellar hemorrhage.[102] Preterm infants with severe IVH were also found to have diminished cerebellar volume compared with infants without

TABLE 1: Definitions of common terms used in neonatology*

Category & Term	Abbreviation	Definition or Description
prematurity		
term infant		born at ≥37 wks' gestation
preterm		born at <37 wks' gestation
late preterm		born at 34–36 & 6/7 wks' gestation
gestational age		
estimated gestational age	EGA	based on pregnancy & infant's developmental characteristics at birth; expressed as completed wks (example: baby born at 32 wks 5 days has an EGA of 32 wks)
small for gestational age	SGA	birth weight <10th percentile for EGA
intrauterine growth restriction	IUGR	subgroup of SGA infants who are underweight due to placental insufficiency
corrected age		chronological age minus (40 − EGA in wks) (example: 3-mo-old baby born at 32 wks has a corrected age of 1 mo)
birth weight		
normal		weight >2500 g at birth
low birth weight	LBW	weight 1500–2499 g at birth
very low birth weight	VLBW	weight <1500 g at birth
extremely low birth weight	ELBW	weight <1000 g at birth
cranial ultrasonographic abnormalities		
intraventricular hemorrhage	IVH	germinal matrix hemorrhage that extends to the lateral ventricle
Grade I IVH†		IVH that extends from the germinal matrix to the lateral ventricle, but involves <10% of the ventricle
Grade II IVH†		IVH that occupies <50% of the lateral ventricle & does not expand the ventricle
Grade III IVH†		IVH that occupies >50% of the lateral ventricle & often expands the ventricle
posthemorrhagic venous infarction	PHVI	IVH that extends into the surrounding parenchyma, formerly classified as Grade IV IVH†
ventriculomegaly	PHVD	posthemorrhagic ventricular dilation above the 97th percentile for EGA
periventricular leukomalacia	PVL	white matter lesion observed in one-third of infants w/ severe IVH
cystic periventricular leukomalacia	cPVL	severe white matter damage that causes visible cysts

* Based on Engle.[29]
† Papile grading system.

IVH.[101] Infants who suffer lobar cerebellar hemorrhage can develop lateral ventricular dilation without associated lateral ventricle IVH.[26] Cranial ultrasonography allows safe management of IVH and PHH for fragile infants, but likely underidentifies brain abnormalities such as diffuse white matter injury and cerebellar injury that can markedly impact neurodevelopmental outcomes. Neurological prognosis based on term-equivalent MRI is likely to be much more reliable than cranial ultrasonography.[27]

Epidemiology

Perinatal outcomes have improved over the past decade. The outcomes for more than 9500 extremely preterm infants (EGA ≤ 28 weeks and weight ≤ 1500 g) who were born between 2003 and 2007 and whose cases are documented in the registry of the National Institutes of Health's National Institute of Child Health and Human Development Neonatal Research Network provide a current multicenter snapshot.[100] Survival to discharge increased with gestational age and was 92% for infants born at 28 weeks. Overall, 16% of the infants had severe IVH.[100] The percentage of infants with IVH Grade I remained fairly constant as gestational age increased from 22 to 28 weeks. In contrast, the percentage with higher IVH grade (II–IV) increased as gestational age decreased.[100] For example, PVHI was found in 30% of infants born at 22 weeks, and the incidence decreased 10-fold to 3% in infants born at 28 weeks. In the total group of infants, only 2% had ventriculomegaly without IVH.[100] Cranial ultrasonography detected PVL in addition to IVH Grade III in 5% of infants and PVL and PVHI in 16% of infants.[100]

The care of preterm infants and their perinatal difficulties, including the incidence of IVH, reflects in part the population and resources for maternal and child health care. Geographic region, decade of study, referral pattern, imaging modality (cranial ultrasonography or MRI), gestational age, and birth weight all affect reported outcomes.[10,63,75,88,89] Comparison among various reports is challenging because parameters often do not match between studies. A multicenter report from the 1990s showed that, among preterm survivors (< 1500 g) with IVH, approximately half had no ventricular dilation, approximately 25% had nonprogressive PHVD, and the remaining 25% had progressive PHH.[74] Of those with progressive PHH, 60% had arrest of the PHH spontaneously or with lumbar punctures (15% of the total with IVH), and the remaining 40% (10% of the total with IVH) required a permanent shunt.[74] In a study of neonates spanning 1989–2005, the distribution of

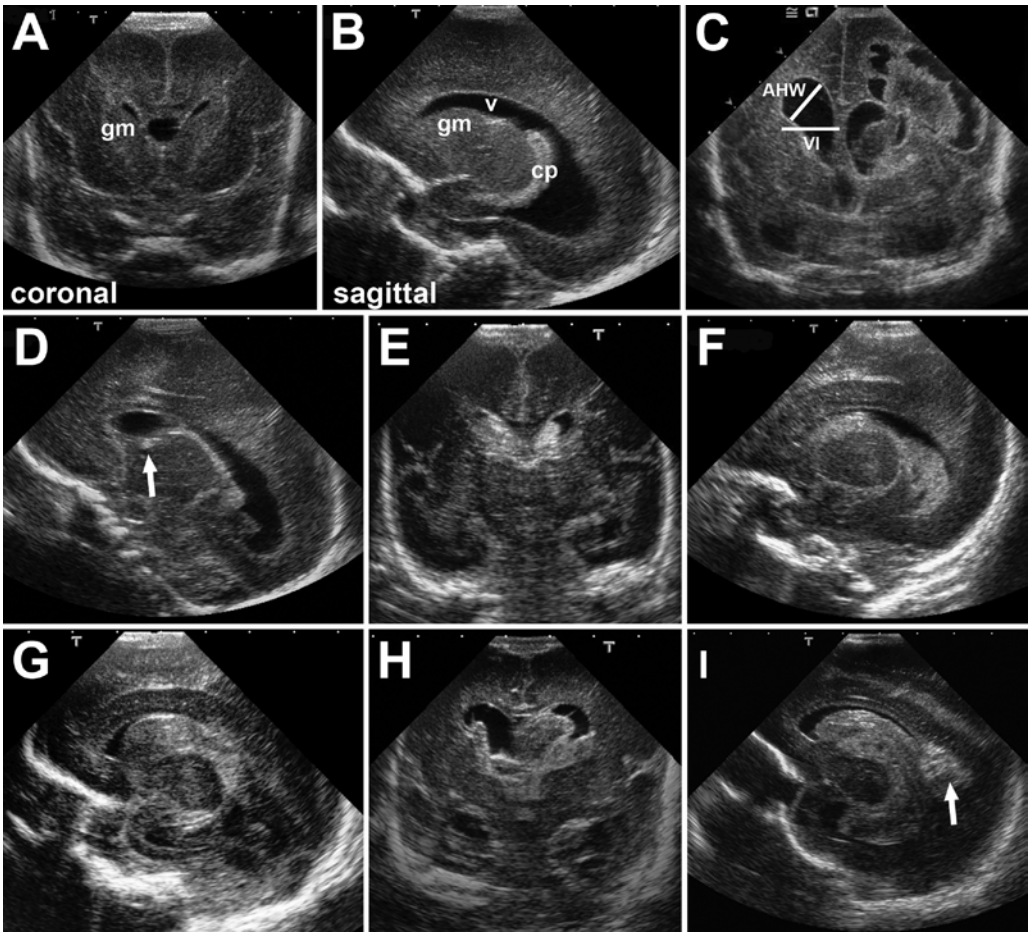

Fig. 1. Ultrasound images. Cranial ultrasonography is routinely used to evaluate preterm newborns because it provides adequate information to inform patient management without requiring transportation of critically ill infants. **A and B:** Coronal and sagittal images showing normal ultrasonographic findings, including no sign of hemorrhage in the germinal matrix (gm), nondistended ventricles (v), and the choroid plexus (cp). The coronal plane is best to determine the presence or absence of IVH (including germinal matrix hemorrhage), whereas the sagittal plane is best for determining the extent of hemorrhage, and thus the IVH grade.[116] **C:** Coronal ultrasound image illustrating the 2 most commonly used measurements to describe ventricular dilation in preterm infants. The Levene ventricular index (VI) is measured from the falx to the lateral extent of the anterior frontal horn[54] (shown in the right frontal horn). The AHW, measured in the same coronal plane, may be a more reliable early indicator of increased ICP.[16,97] The patient also had PVHI on the left. **D:** Sagittal image of a small Grade I IVH *(arrow)*. Grade I involves less than 10% of the lateral ventricle.[116] **E and F:** Coronal and sagittal images showing a bilateral Grade II IVH, which occupies more than 10% but less than 50% of the lateral ventricle. **G:** Sagittal image demonstrating a Grade III IVH that involves more than 50% of the lateral ventricle. Grade III IVH typically distends the ventricle and causes ventriculomegaly. **H:** Coronal image showing a Grade III IVH in the right lateral ventricle and PVHI (formerly termed Grade IV IVH) on the left. **I:** Sagittal image of the PVHI (Grade IV IVH) demonstrating extension of the IVH into the parenchyma *(arrow)*.

IVH severity was 48% Grade I, 18% Grade II, 15% Grade III, and 19% PVHI.[111] For the total IVH group, the mortality rate was 20%, PHH developed in 22% of patients, and 9% required a permanent shunt.[111] For the subgroup of patients with severe IVH, the mortality rate was 44%, hydrocephalus developed in 60%, and 25% required a permanent shunt.[111] By comparison, a recent report spanning 1999–2008 found 29% of infants (< 40 weeks and < 1500 g) with severe IVH developed symptomatic PHH requiring surgical intervention, and 21% required insertion of a permanent shunt.[57] Given the differences due to study populations and reporting methods, based on the literature, approximately 10% of preterm infants with any IVH and 20% of infants with severe IVH will require a permanent shunt. This approximation from the literature is similar to our experience at Rainbow Babies and Children's Hospital, where 15% of very preterm infants with severe IVH during 1997–2008 required a permanent VP shunt.

Currently, some variation in the rate of development of symptomatic PHVD exists in NICUs across the US. For example, a stable incidence of PHH requiring treatment during the past decade was recently reported.[57] By contrast, at our institution, despite a stable number of high-risk preterm infants admitted to the NICU, the number of infants who have required surgical intervention for PHH has dropped 3-fold over the past decade. The numerous genetic and environmental factors, when added to variations in NICU referral and practice patterns, make achieving a consistent reduction in the incidence of IVH and subsequent symptomatic PHH a complex challenge.[71]

Pathophysiology of Germinal Matrix Hemorrhage and Posthemorrhagic Infarction

Preterm infants are quite vulnerable to cerebrovascular injury due to a unique constellation of pathophysiological factors.[24] The following mechanisms have been proposed and investigated, but are not yet proven (Fig. 2).[24] Preterm newborns can have difficulty maintaining an adequate cerebral perfusion pressure. As the newborn adjusts to extrauterine life, it is prone to hypotension and low cardiac output, especially in the 1st day of life.[24] About 24%–40% of infants who weigh less than 1000 g at birth experience hypotension.[30] Endotracheal intubation with positive pressure ventilation increases central venous pressure, which when combined with episodes of hypotension, can lead to episodic poor cerebral perfusion. In support of the hypotension hypothesis, a retrospective analysis of preterm infants (birth weight < 1500 g) with hypotension and a matched normotensive control group found that hypotension was associated with IVH, as well as PVL and long-term neurological disability.[52] Other authors have proposed that a hypoperfusion-reperfusion pattern is more of a culprit than direct hypotension or low cardiac output.[24] In addition, intrinsic cerebral vasoreactivity and autoregulatory mechanisms are poorly developed in the immature brain. The autoregulation pressure range is narrower and lower with decreasing gestational age.[24] It is not clear whether only sick early preterm infants have impaired autoregulation or whether healthy early preterm infants also have immature autoregulation.[27] It can be quite difficult to detect clinical deterioration associated with IVH in sick newborns. Thus, serial surveillance cranial ultrasound examinations are obtained to detect and follow the progression and resolution of IVH.

In addition to the reduced reserve between cerebral blood flow and the ischemic injury threshold, other anatomical factors likely contribute to IVH in preterm infants, including incomplete arterial ingrowth into the deep white matter and a fragile germinal matrix vasculature that is more vulnerable to hypoperfusion and fluctuations in perfusion pressure.[25] Arteries grow in from the pial surface, and the long deep penetrating arteries are the last to reach their targets in deep white matter.[24] Similarly, the muscularis layer in cerebral vessels follows a maturation pattern of maturing first out near the pia and later in the deep vessels in the white matter. Thus, the white matter vessels are last to develop the cerebrovascular resistance necessary for autoregulation.[24]

The germinal matrix, a transient neural cell proliferative zone with poorly developed vasculature near the caudothalamic groove, involutes in the third trimester.[24] The combination of 1) the residual proliferative zone with its fragile vessels, and 2) the lack of cerebrovascular re-

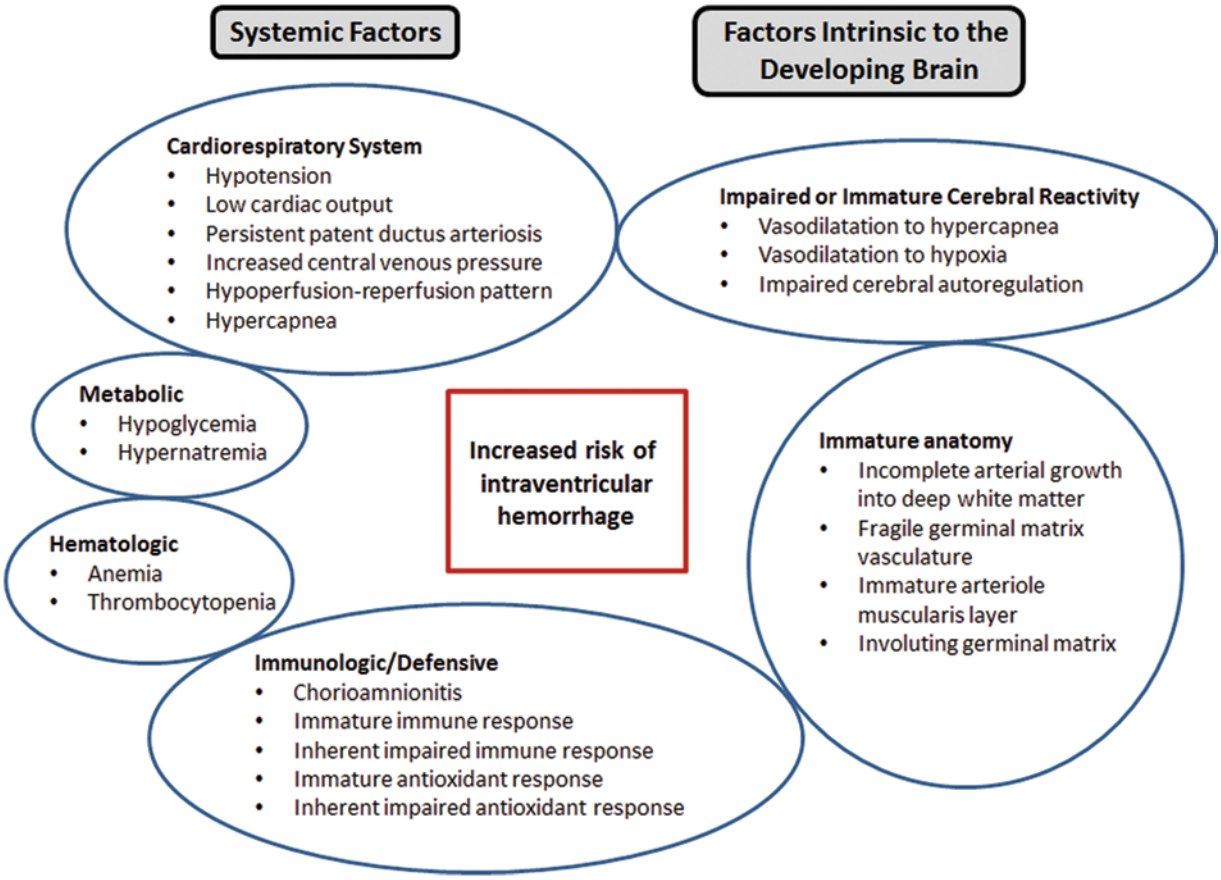

Fig. 2. Diagram illustrating the numerous systemic and intrinsic CNS factors that likely combine to increase the risk of a preterm infant suffering an IVH. Many of the factors are interrelated with each other and are also interrelated with other comorbidities of prematurity.

sistance leaves the region particularly prone to hemorrhage.[24] The inability to obtain accurate direct measurements of cerebral hemodynamics in preterm infants and the lack of correlation between systemic parameters, such as systemic arterial blood pressure, and cerebral perfusion have made investigations in this field challenging.[25] Also, the type and degree of hemodynamic insult that produces injury in the preterm infant brain are not well characterized.[25] A recent study that correlated umbilical artery mean arterial pressure and the results of near infrared spectroscopy in preterm infants (EGA < 30 weeks and weight < 1500 g) from less than 12 hours after birth through 5 days after birth with neonatal outcomes found that infants with poor cerebral pressure autoregulation were more likely to suffer IVH.[77] Clarification of the mechanisms involved in the pathogenesis of IVH awaits both the necessary techniques to accurately measure critical parameters in fragile newborns and well-designed studies to distinguish the impact of various parameters.

Prenatal clinical risk factors contribute to the risk of IVH and poor neurodevelopmental outcomes (Table 2). Histological signs of chorioamnionitis (maternal neutrophil infiltration of the chorion and amnion) with fetal involvement (umbilical vasculitis) are associated with a higher risk of IVH, based on the findings of several single-institution studies,[9,66,73,97] as well as a recent meta-analysis.[93] Analysis of pooled data suggests that clinical signs of chorioamnionitis increase the risk of cerebral palsy by 140%, and histological signs increase the risk by 80%.[93] Chorioamnionitis is more likely with early gestational age, and in a recent multicenter study, the incidence rate ranged from 70% at 22 weeks to 34% at 28 weeks.[100] Ureaplasma species, small gram-positive *Mycoplasma*, are the most common bacteria involved.[114] How chorioamnionitis leads to an increased occurrence of IVH is not yet fully understood.[66] Several reports have implicated the proinflammatory cytokine IL-6. In a recent study examining the association of neonatal outcomes and maternal serum obtained prospectively in a cohort at risk for preterm delivery, elevated maternal serum IL-6 levels were associated with preterm IVH, even after adjusting for EGA at delivery.[98] Also, IL-6 mediates monocyte infiltration. A subset of placentas with chorioamnionitis have monocyte infiltration instead of neutrophil infiltration, and monocyte infiltration is associated with an increased risk of IVH and infant mortality, compared with neutrophil infiltration.[62] Elevated IL-6 expression was found in placentas with chorioamnionitis, compared with controls.[62] Prior studies had suggested an association between the IL-6–174CC genotype and the risk of IVH, but a large study of preterm infants (weight < 1500 g) showed no correlation between IL-6 genotypes and an increased risk of severe IVH, PVL, need for CSF diversion, or mortality.[36] Other mutations or cytokines may be involved.[72] In support of the hypothesis that an inherent altered inflammatory response predisposes a subset of preterm infants to complications such as IVH, serum and monocyte responses to inflammation in former preterm children with cerebral palsy who were preterm infants were found to be much more pathological than those in a control group without cerebral palsy matched for gestational age.[61]

TABLE 2: Factors that influence the risk of IVH in preterm infants

Clinical characteristics associated w/ IVH
chorioamnionitis[9,62,71,92,96]
arterial hypotension[105]
hypercarbia[24,110]
large base excess[110]
low regional cerebral tissue oxygenation[111]
high fractional tissue oxygen extraction[111]
patent ductus arteriosus[36]
hypernatremia[5]
hypoglycemia[113]
thrombocytopenia[84]
anemia[113]
Biomarkers associated w/ IVH
elevated non–protein bound iron level[79]
elevated total hydroperoxide level[79]
elevated advanced oxidation protein product level[79]
elevated IL-1β level[90]
elevated IL-18 level[90]
decreased chemokine CC ligand 18 level[44]
elevated cord blood EPO level[10]
Clinical characteristics & biomarkers not associated w/ IVH
specific IL-6 genotypes[34]
anti-angiogenic molecule 2-methoxyestradiol[4]
mean platelet vol[21]

Hemodynamic instability in the first 3 days of life likely contributes to the risk of IVH. A case-control study of preterm infants (EGA ≤ 32 weeks and weight < 1500 g) with severe IVH showed that low birth weight and arterial hypotension were associated with IVH Grade III and that hypercapnia ($paCO_2$ > 55 mm Hg) and a large base excess were associated with PVHI.[112] Permissive hypercapnia (tolerating $paCO_2$ 45–55 mm Hg) has been used to decrease the complications of intubation and positive pressure ventilation, including high tidal volumes, increased central venous pressure, and barotrauma. Although sick preterm infants may have an impaired vasoactive response to elevated levels of $paCO_2$,[24] the vasodilation induced by hypercapnia may contribute to IVH,[25] and its use remains controversial. Cerebrovascular reactivity to oxygen likely also plays a role, but does not seem as vulnerable to maturation as the reactivity to CO_2.[24] Another case-control study found that preterm infants with IVH had lower regional cerebral tissue oxygenation and higher fractional tissue oxygen extraction during the first 2 weeks after birth, independent of IVH grade.[113] Persistent patent ductus arteriosus is also associated with an increased risk of IVH, necrotizing enterocolitis, and mortality.[38] While these studies emphasize the role of pressure-passive circulation, acidosis, and impaired cerebral perfusion in preterm infants who suffer IVH, they also support the use of interventions to minimize clinical instability in the early postpartum period.

Because hypernatremia is associated with an increased risk of IVH in term infants, the association of sodium intake and IVH in preterm infants was recently

evaluated in a single-institution retrospective study.[5] High sodium intake was an independent risk factor for preterm IVH.[5] Hypoglycemia has also been implicated, but its role as a risk factor is not yet proven.[115]

Thrombocytopenia is common among preterm infants. A recent retrospective study found that platelet counts less than 150,000/ml were associated with increased mortality, IVH, and gram-negative infections at 7 days.[85] In contrast, mean platelet volume is not associated with IVH.[22] A decrease in hemoglobin may result in compensatory increased cerebral blood flow, which may challenge the fragile germinal matrix vasculature.[115]

Biomarkers. Biomarkers are being sought to predict which preterm infants are most at risk for IVH. Identification of infants at risk would improve prognostication and allow novel interventions to be targeted to the most vulnerable populations. Cord blood oxidative stress biomarkers may prove useful. Cord blood was prospectively collected from infants (EGA < 32 weeks and weight < 2500 g) and analyzed for markers of free-radical–related diseases.[81] Free-radical diseases are associated with excess levels of toxic reactive oxygen species, and several of the complications of prematurity, including IVH, PVL, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotizing enterocolitis, are attributed in part to impaired or immature antioxidant mechanisms.[81,116] As hemosiderin breaks down, free (non–protein bound) iron is released. High non–protein bound iron, total hydroperoxide, and advanced oxidation protein product levels were associated with increased risk of free-radical diseases, including IVH.[81] Another recent study found a direct association between IVH and cord blood erythropoietin levels.[10] Cord blood levels of the antiangiogenic molecule 2-methoxyestradiol were assayed, but no correlation was found with the risk of IVH or PHH.[4]

Several studies have examined associations between altered immunoprotein levels and IVH. Elevated levels of IL-1β and IL-18 were found in preterm infants with PHH compared with the levels in controls.[91] Interferon-γ levels were elevated in infants with both PHH and cPVL.[91] Additional studies with larger cohorts are needed to determine whether proinflammatory cytokines mediate specific aspects of CNS injury or whether elevated levels are consistent indicators of injury. In a recent prospective cohort study (involving infants with an EGA < 32 weeks), low cord blood levels of the chemokine CCL18 (C-C motif ligand 18) predicted the risk of IVH, and the receptor for CCL18 was found in the region susceptible to IVH, suggesting a biological role.[46] Further studies are necessary to determine whether CCL18 binding in the periventricular cells drives local events precipitating IVH.

Neonatal Interventions. As the current treatment of IVH and one of its primary complications, symptomatic PHH, with temporary and permanent shunts remains suboptimal, several neonatal interventions have been studied in preterm infants in an attempt to reduce the risk of neonatal mortality, IVH, and subsequent poor neurodevelopmental outcome (Table 3). Some interventions reduce the incidence of IVH but have not yet been shown to improve long-term neurodevelopmental outcomes. Antenatal corticosteroids have been the most effective measure thus far to reduce the incidence of IVH, PVL, and other comorbidities of prematurity, but a recent meta-analysis found that they have not yet been proven to restore neurodevelopmental outcomes.[8] Antenatal steroids enhance the microstructural maturation of the choroid plexus in a mouse model, which may explain one mechanism of steroid reduction of IVH.[61] Cesarean delivery was an independent predictor of decreased risk of developing IVH, along with birth weight greater than 800 g, gestational age 27–28 weeks, and antenatal steroids in a single-institution retrospective study.[22] Prophylactic intravenous indomethacin significantly reduced the risk of severe IVH, but did not affect the risk of severe neurological disability or morbidity in a recent meta-analysis.[32] A retrospective comparative study of efficacy and safety of indomethacin and ibuprofen found no difference in efficacy for patent ductus arteriosus treatment or the risk or grade of IVH, although ibuprofen had fewer other associated complications (renal failure, thrombocytopenia, and hyponatremia) than indomethacin.[60] Etamsylate (formerly ethamsylate), a synthetic hemostatic agent, improves platelet adhesion via P-selectin and restores capillary resistance.[35] A meta-analysis of etamsylate showed that, although there was no difference in neonatal mortality or neurodevelopmental outcome at 2 years, there was a decrease in IVH at 31 and 35 weeks' EGA, without the identification of adverse effects.[44] Currently, antenatal corticosteroid administration has shown the most effective reduction in the IVH incidence.

Several neonatal interventions have been investigated but have not reduced the occurrence of IVH in preterm infants. For example, in term infants, inhaled nitrous oxide is effective for hypoxic respiratory failure. For preterm infants, however, no association between inhaled nitrous oxide and IVH or neurodevelopmental outcomes was found.[6] Genetic analysis of blood from 124 African-American preterm infants found that a mutation of the endothelial nitrous oxide synthase gene (mutant allele –786C) was a significant risk factor for respiratory distress syndrome, bronchopulmonary dysplasia, and IVH.[109]

TABLE 3: Neonatal interventions that influence the risk of IVH

Interventions that decrease risk of IVH
antenatal corticosteroid treatment[8]
cesarean delivery[21]
prophylactic intravenous indomethacin treatment[30]
prophylactic ibuprofen treatment[58]
etamsylate treatment[42]
Interventions w/ no impact on IVH
nitrous oxide treatment[6]
phenobarbital treatment[120]
prophylactic synthetic surfactant treatment[94]
early (<8 days) postnatal corticosteroid treatment[35]
Interventions that increase risk of IVH
red blood cell transfusion[3]
rapid vol expansion[113]
intraventricular streptokinase treatment[119,123]

Because this study did not include infants with IVH without respiratory difficulties, the mutation's impact on IVH alone cannot be determined. Phenobarbital had also been proposed as a treatment to stabilize neonatal blood pressure and minimize damage from free radicals, but a meta-analysis found that phenobarbital was not beneficial in reducing the incidence of IVH.[123] Similarly, a recent meta-analysis confirmed that prophylactic synthetic surfactant improves clinical outcome by decreasing the risk of pneumothorax, pulmonary interstitial edema, and mortality, but does not decrease the risk of IVH.[95] Currently, the use of continuous positive airway pressure instead of intubation and less prophylactic surfactant are being studied in an effort to decrease the development of bronchopulmonary dysplasia and its negative consequences on neurodevelopment.[100] A recent meta-analysis of early (< 8 days) postnatal corticosteroid treatment found that it did not decrease the risk of IVH, PVL, or mortality.[37] In fact, trials with neurodevelopmental outcomes at 2 years' corrected age suggested that there is likely an increased risk of poor neurodevelopmental outcomes with postnatal treatment, especially with dexamethasone.[37]

Some interventions to treat other problems of prematurity also increase the likelihood of IVH. For example, red blood cell transfusions have also been shown to be an independent risk factor for IVH. Preterm infants who had normal findings on an initial cranial ultrasound examination and then received a red blood cell transfusion were much more likely to develop severe IVH in a retrospective comparison of controls who continued to have normal cranial ultrasonographic findings.[3] Rapid volume expansion may also contribute to IVH.[115]

Pathophysiology of PHH

Hydrocephalus due to IVH in preterm infants has been attributed to fibrosis of arachnoid granulations, meningeal fibrosis, and subependymal gliosis, which combine to impair CSF resorption.[19] Microscopic arachnoid villi are present in preterm infants; arachnoid granulations are not yet mature.[115] The molecular pathogenesis of PHH is not yet fully understood.[119] One hypothesis is that TGF-β2 in the CSF stimulates deposition of extracellular matrix proteins in the neuropil and perivascular spaces, which impairs CSF resorption.[18,94] In support of this hypothesis, one study found a correlation between abnormal levels of TGF-β2 and extracellular matrix proteins (chondroitin sulfate proteoglycan) and the development of symptomatic PHH in preterm infants (in contrast to preterm infants without PHH).[20] In an animal model of IVH, drugs that inhibit TGF-β2 were ineffective in controlling hydrocephalus.[2] In another human study of biomarkers specifically implicated in impaired CSF absorption, the levels of TGF-β1 and aminoterminal propeptide of Type I collagen (PC1NP) were studied in neonates with symptomatic PHH, hydrocephalus from open spina bifida, and aqueductal stenosis.[40] Infants with PHH had significantly higher levels of both markers,[40] consistent with impaired absorption due to arachnoid granulation fibrosis. An earlier study found elevated levels of vascular endothelial growth factor in CSF from infants with PHH, compared with controls, but no difference in CSF TGF-β1 levels.[41] Further work is needed to determine which molecules promote the altered physiology of PHH and which are bystander markers.

White matter damage secondary to PVHI is likely exacerbated by compression and ischemia from increased ICP of symptomatic PHH. Neural progenitor cells have been found in the CSF of preterm infants with symptomatic PHH but not in the CSF of control infants.[51] The IVH may stimulate recovery mechanisms that induce neural progenitor proliferation, or these neural cells may be shed secondarily into the distended ventricular system.

For infants with IVH Grade III or posthemorrhagic venous infarction, the severity of IVH may not correlate with the likelihood of developing symptomatic hydrocephalus. In a relatively recent comparison of neurodevelopmental outcomes for preterm infants (≤ 34 weeks' EGA) with IVH Grade III or PVHI, 76% of infants with IVH Grade III developed PHVD compared with only 53% of infants with PVHI.[12] More infants with Grade III IVH also became symptomatic from the ventricular dilation.[12]

Clinical Presentation

The clinical presentation of IVH in preterm infants typically follows 1 of 3 patterns: catastrophic, saltatory, or clinically silent.[115] Catastrophic deterioration over minutes to hours mimics in many ways the rapid neurological demise observed in older patients with large intracranial hemorrhages. Aggressive neurosurgical intervention is rarely considered in these infants as they have a grave prognosis. The saltatory course evolves over hours to days, sometimes in a stuttering pattern, and involves decreased alertness and activity, hypotonia, abnormally tight popliteal angle, abnormal eye movements, and respiratory difficulties.[115] Many IVHs are clinically silent, which supports the use of surveillance cranial ultrasonography. An unexplained decline in the hematocrit may suggest that an IVH has occurred.[115]

The clinical presentation of symptomatic PHH in preterm infants is generally similar to that of symptomatic hydrocephalus in term neonates, with allowances for the preterm infant's relative immaturity. Orbitofrontal head circumference, fontanel fullness, and the splaying of sutures all show limited reliability when studied as measures among numerous practitioners of varied skill levels, but these clinical signs can be reliable when used by trained and experienced practitioners to asses progressive ventricular dilation in the same infant. Progressive splaying of the sagittal suture width is perhaps the most reliable indication of increased pressure. A subset of infants will show other signs of increased ICP, such as apnea, bradycardia, lethargy, and decreased activity. These signs are nonspecific and frequent discussions with the neonatology team are essential to provide optimal management.

Imaging

Cranial ultrasonography is used to diagnosis IVH and PHVD in preterm infants. Ultrasonography can be safely performed at the bedside and avoids the risks associated with transporting critically ill and medically unstable infants for MRI. The Levene ventricular index

is the horizontal measurement from the midline falx to the lateral aspect of the anterior horn of the lateral ventricle in the coronal plane obtained at the level of the third ventricle/foramen of Monro (Fig. 1C).[15,27] As a guideline, the ventricular index 97th percentile + 4 mm curve, a curve that has been used as a threshold for intervention for PHVD, increases from 14 to 15 to 16 mm at 27, 31, and 33 weeks' EGA, respectively.[119] Because an increase in the ventricular index may be a relatively late sign of increased ICP, some prefer to use the anterior horn width (AHW), which may more accurately reflect early expansion of the ventricles.[15] A normal AHW is less than 3 mm, with the 95th percentile curve reaching 2 mm at 36 weeks and 3 mm at 40 weeks.[96] The implications of AHW between 3 and 5 mm is not clear, but an AHW greater than 6 mm is generally considered abnormal.[15,96] Sex does not impact ventricular measurements significantly, and ventricular asymmetry is an anatomical variant.[15] In some infants with perhaps the forme fruste of colpocephaly, the occipital horn dilates first; it is not yet established whether occipital horn enlargement is a reliable indicator of increased ICP.[15] An alternative suggestion to define PHVD by ultrasonography is the combination of an AHW greater than 4 mm, a thalamooccipital dimension greater than 26 mm, and a third ventricle width greater than 3 mm.[119] The interrater reliability for the last 2 measurements is not well established.[15] While the ultrasonographic measurements are useful for the identification of a PHVD, clinical decisions about surgical intervention are typically based on a combination of history, physical examination, and ultrasonographic findings.

Infants who suffer IVH are at risk for other structural abnormalities in addition to PHH, and MRI can be informative once the infant is stable enough for transport. Cranial US has limited potential to predict neurodevelopment outcomes compared with MRI. The predictive ability of near-infrared spectroscopy techniques has been investigated to identify infants with IVH on cranial ultrasonography,[77] but this technique has not been widely adopted yet. Most infants are followed with serial ultrasound examination until near term, and those infants at risk for deficits undergo MRI near term equivalent. Computed tomography is rarely used in sick preterm infants except to assess and make clinical decisions regarding acutely evolving intracranial pathological conditions such as an acute subdural or intraparenchymal hematoma. With additional experience and standardization, amplitude-integrated electroencephalography will likely provide a functional supplement to the identification of CNS abnormalities in preterm infants on MRI.[49,104]

Temporary Treatment Options for Symptomatic PHH

Clinical findings and serial imaging with cranial ultrasonography are useful tools to determine whether PHVD has transformed into symptomatic hydrocephalus. Serial cranial ultrasonography can also provide useful information, but the determination of symptomatic hydrocephalus versus ventricular dilation due to hydrocephalus ex vacuo is typically made on the basis of clinical symptoms and signs in combination with imaging. Previously, the ultrasonographic threshold for intervention was an increase in the ventricular index above Levene's 97th percentile for EGA + 4 mm.[23] If interventions are initiated, then the combination of physical examination and serial ultrasonography can be used to follow the stabilization or reduction in the ventricular size.

Nonsurgical Treatment. A subset of preterm infants with PHH likely develop only transient symptomatic hydrocephalus and require CSF diversion only for several days to weeks. Although oral medications are effectively used as a temporizing measure in older children and adults with CSF disorders such as idiopathic intracranial hypertension (pseudotumor cerebri),[99] a randomized trial from the 1990s demonstrated that the addition of acetazolamide and furosemide to standard therapy for preterm infants with IVH did not decrease the need for permanent shunt insertion and increased the likelihood of death and neurological morbidity at 1 year of age.[48,122] Thus, no medications are currently recommended to treat symptomatic PHH.

Serial LPs are often adequate to treat the transient period of hydrocephalus if the lumbar subarachnoid space communicates with the ventricular system.[119] A retrospective study showed that early intervention with serial LPs (with "early" defined as before the ventricular index crossed Levene's 97th percentile + 4 mm line) reduced the need for surgical intervention.[23] In that study, hydrocephalus stabilized without any surgical intervention in about one-quarter of all of the infants. Among infants who had early intervention with serial LPs, only 29% required temporary surgical intervention, and only 16% eventually required permanent shunt insertion. In contrast, 62% of infants who had late intervention (defined as after significant ventricular dilation, a ventricular index above 97th percentile + 4 mm) required insertion of a permanent shunt.[23] At our institution, we have found similar efficacy for serial LPs, with surgical intervention required in only half of the infants who had symptomatic hydrocephalus from severe IVH and were treated with LPs. Daily LPs can be used if necessary to stabilize the head circumference, and usually up to 10 ml of CSF is removed per LP. The multicenter randomized controlled Early Versus Late Ventricular Intervention Study (ELVIS) is currently enrolling patients to determine whether the timing of intervention for ventricular dilation improves neurodevelopmental outcomes or decreases shunt dependence.[82,119]

In general, ventricular puncture should be reserved for treating infants in extremis, because it has been associated with the increased development of CSF infection and loculated hydrocephalus.[118] Intraventricular injection of streptokinase was investigated but was not found to be better than standard therapy to decrease mortality or shunt dependence.[124,128] A Phase I trial of intraventricular tissue plasminogen activator followed by ventricular irrigation showed that fewer infants required permanent shunt insertion in comparison with historical controls;[125] however, a subsequent randomized trial failed to demonstrate a benefit in early results, and more infants treated with the novel regimen appeared to suffer secondary IVH.[120]

Temporary Surgical Treatment. In some infants it is not possible to remove adequate CSF via serial LPs to

maintain a stable clinical picture, and those infants often require surgical treatment (Fig. 3). Experience with early insertion of permanent shunts and their high rate of infection, occlusion, and skin breakdown led to the current practice of temporary shunt placement to postpone permanent shunt insertion.[105,119] A retrospective study compared the outcomes for preterm infants with PHH who underwent ventricular reservoir insertion or initial permanent VP shunt insertion.[126] Despite undergoing permanent shunt insertion at an older age and larger weight, the infants who underwent initial VP shunt insertion required twice as many revisions at a mean follow-up of 3 years compared with those infants who had a temporary shunt prior to a permanent shunt.[126] Delayed insertion potentially allows the blood products in CSF (from the IVH) to dissipate and allows the infant to gain weight and mature.[119] Clinical judgment determines for each infant the risk and benefit ratio of the potential damage during the neonatal period due to inadequately treated elevated ICP, the perioperative risks of surgery (such as infection), and the potential risks associated with a permanent VP shunt. In this respect, the neurosurgical team has a unique perspective, because few other specialists involved in neonatal care appreciate the lifelong potential risks of shunt dependency, especially in a child with hydrocephalus secondary to preterm PHH.

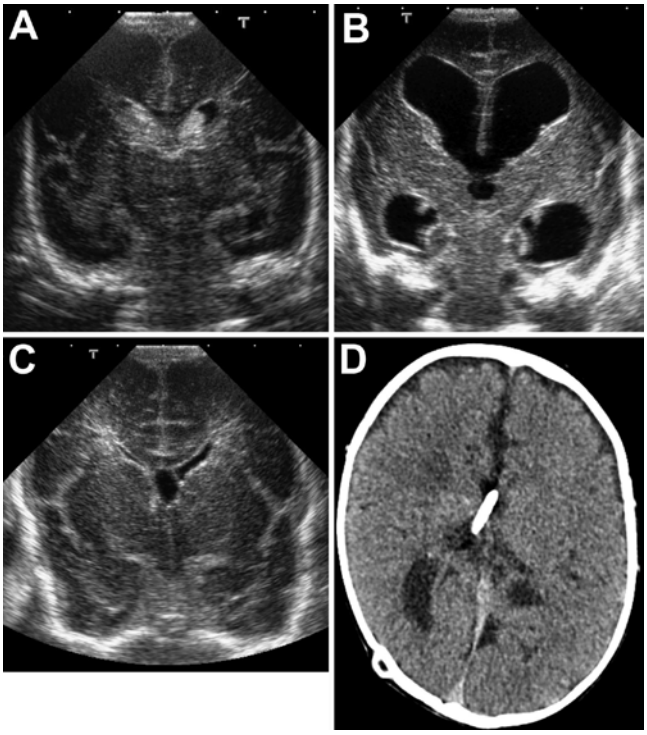

Fig. 3. Typical imaging findings for a preterm infant who suffered IVH as a newborn and subsequently developed symptomatic hydrocephalus that required a temporary left frontal subgaleal shunt and eventually a right occipital permanent VP shunt. **A–C:** Ultrasound images. An IVH Grade II was identified on surveillance cranial ultrasound study within a few days of birth at 26 weeks' EGA (A). After 1 month, ventricular dilation developed and coincided with the onset of physical signs of increased ICP (B). (A study performed after insertion of a VSG shunt showed decompression of the ventricles (C). **D:** Axial CT scan obtained at 2 years of age. After the neonatal course, this patient required 1 shunt revision for proximal occlusion in 5 years.

Preterm infants have a higher risk of developing a postoperative infection after intervention for hydrocephalus than term infants.[17] Even with the best efforts to prevent infection, preterm infants are at high risk of having shunt hardware infected by hematogenous spread. Neonatal meningitis, defined by bacteria cultured from CSF, has been associated in several neonatal outcome studies with significant decline in performance at 2 years of age.[1] Thus, the threshold for surgical intervention for each infant should be determined on an individualized basis. Our practice has been to insert a temporary shunt soon after the infant has demonstrated convincing clinical symptoms and signs of elevated ICP corroborated by serial imaging studies, after failure of an attempt at management with serial LPs, and, if possible, after any active systemic infections have been treated. Clinical signs of symptomatic hydrocephalus include a rapidly enlarging head circumference (> 2 cm in < 7 days), increased splaying of the cranial sutures, a full tense fontanel, and worsening of apnea and bradycardia episodes, lethargy, and feeding intolerance (if the infant is being fed enterally).

The goal of placing a temporary shunt is to delay insertion of a permanent shunt, if it will be needed, until the infant is older and has better nutrition and immunity. The 2 primary methods of temporary CSF diversion are the ventricular reservoir and the VSG shunt. The merits and disadvantages of each device will be discussed in detail below. The ventricular reservoir is a ventricular catheter capped by a low-profile reservoir. The reservoir is tapped through the scalp on a regular basis to remove CSF and maintain a stable clinical condition. The VSG shunt utilizes the same construct as a ventricular reservoir, with a 3- to 5-cm piece of shunt tubing attached to the reservoir outlet. The CSF is directed by the tubing to a contralateral subgaleal scalp pocket where it collects and is slowly reabsorbed. Both techniques can be used until the symptomatic hydrocephalus dissipates after several weeks or until it becomes evident that permanent CSF diversion will be necessary. We do not routinely remove temporary shunts that appear to be no longer needed.

Placement of a ventricular reservoir and placement of a VSG shunt are performed with similar surgical techniques. Preterm infants are quite vulnerable as surgical candidates, and extra attention should be paid to maintaining body temperature and protecting the skin. Each institution has age-dependent guidelines for skin preparation agents, and infants with an EGA of less than 48 weeks may have specific restrictions.

Ventricular Reservoirs. The ventricular reservoir, also termed a ventricular access device, was first reported as a treatment for preterm infant PHH by McComb in 1983.[70] In another report from the 1980s, ventricular reservoirs were implanted in 20 preterm infants at a mean age of 31 days.[11] Twenty percent of the infants died, and 10% developed perioperative infections. A permanent shunt was required in 75% of the survivors. Of those who had a shunt inserted, most required a revision within 2 years.[11] In a large retrospective series of cases from the 1990s in which ventricu-

lar reservoirs were placed, the total revision rate was 20%, and the infection rate was 8%.[43] Of the 133 survivors, 88% required permanent shunt insertion.[43]

Numerous series have reported on the infection rate associated with serial ventricular reservoir taps, and the infection rate has declined over time.[14] One recent study demonstrated that no infections occurred in 29 infants who underwent 681 taps performed by the neonatology team, even though 45% of the infants suffered late-onset sepsis with positive blood cultures.[50] The development of a specially trained team may produce the lowest infection rates, as well as a more reliable schedule of tapping than relying on physicians.[13] In institutions where both techniques of temporary diversion have been used, ventricular reservoirs have not had a higher infection rate.[57] Depending on the amount of CSF removed, and the infant's other fluid requirements, fluid replacement for the removed CSF may be needed.

Reservoir taps are typically performed to minimize clinical signs of increased ICP, with the frequency varying from twice daily to twice weekly. A study performed to quantify the impact of tapping on ICP and cerebral blood flow velocity found that significant improvement in cerebral blood flow velocity only occurred if the pre-tap ICP was greater than 6 cm H_2O and the post-tap ICP was less than 7 cm H_2O.[64] The amount and frequency of tapping is tailored for each infant to optimize ICP control. In a study that supported this concept, ICP monitors were placed simultaneously with ventricular reservoirs, and the ICP was monitored for 7 days while CSF was removed daily. Significant changes in ICP were noted after daily taps, suggesting that there could be significant fluctuations in ICP associated with taps.[7] Doppler ultrasound assessments of cerebral blood flow before and after CSF removal from reservoirs showed consecutive improvement in cerebral perfusion with serial taps.[107]

Ventriculosubgaleal Shunts. The VSG shunt was described in the modern era in 1977.[80] The theoretical advantage of the shunt is that it allows continuous CSF diversion, and thus sustained relief of elevated ICP, rather than the intermittent diversion provided by ventricular reservoir taps. Although no long-term neurodevelopmental outcome studies have yet demonstrated that the VSG shunt provides better results, the concept is attractive. No study has evaluated ICP or cerebral perfusion using Doppler ultrasound in infants with VSG shunts.

Several retrospective reports have described the natural history of VSG shunts. In a study of 17 infants with VSG shunts, no infections occurred, and the mean length of time to conversion to a permanent shunt was 56 days.[47] Conversion to a permanent shunt was performed in 82% of infants in that study. Although in a report of 22 infants treated with a VSG shunt for IVH in the 1990s, there were no VSG shunt infections,[34] other centers have experienced infections rates ranging up to 6%.[106] The family must be prepared for the subgaleal fluid collection that forms in the scalp. This pocket will resolve once the hydrocephalus resolves or if the shunt is converted to a permanent VP shunt (Table 4). We do not routinely replace the VSG shunt at a specified age or weight, but wait for the temporary shunt to fail and the infant to become symptomatic prior to placing the permanent VP shunt. This allows the infant to mature and grow as much as possible before permanent shunt placement. Additionally, the persistence of symptomatic hydrocephalus at the time of temporary shunt failure demonstrates to the family and the health care team that the permanent shunt was required, a concept that becomes important later when the child experiences shunt malfunctions and other shunt-related complications.

Comparison of Outcomes for Temporary Neonatal Shunts. No study performed in the US has rigorously examined long-term neurodevelopmental or shunt outcomes after temporary shunt placement. There have been several retrospective reports from single institutions, and one from multiple institutions, that describe perioperative complications and the need for conversion to a permanent shunt.[54,57] A recent retrospective study reported the use of both devices at a single institution; the choice of device was based on the surgeon's preference.[57] The mean age of the infants at the time of surgery was similar in the 2 treatment groups. Shunt infection; revision; early and late mortality rates; and permanent shunt insertion, revision, and infection rates were not significantly different between the 2 types of temporary shunts.[57] Another current study through the HCRN (Hydrocephalus Clinical Research Network), the SOPHH (Shunting Outcomes in Post-Hemorrhagic Hydrocephalus) trial, is a prospective trial to standardize PHH management prior to a planned HCRN trial to compare early and late outcomes for VSG shunts and ventricular reservoirs (J. Wellons, personal communication, 2011). The lifetime risks and potential complications of permanent shunt insertion cannot be underestimated. No studies have examined long-term neurodevelopmental outcomes of both devices in a rigorous manner. This will require a multiinstitutional study with a large number of patients, especially given the variation in referral and practice patterns and the numerous comorbidities that also affect developmental outcomes in this population. The other factors that impact neurodevelopmental outcomes, such as gestational age, birth weight, sex, and neonatal comorbidities of bronchopulmonary dysplasia, necrotizing enterocolitis, and sepsis, likely play a much greater role in determining neurodevelopmental outcome than the type of temporary shunt used.

Permanent Surgical Treatment

Many of the infants who require a temporary shunt will not need permanent shunt placement. Interventions to decrease the likelihood of needing permanent CSF diversion have been studied, but none have been proven effective. In the 1990s, intraventricular urokinase administration was investigated, but all patients eventually required a permanent shunt.[39] More recently, a combination of ventricular drainage, irrigation, and fibrinolytic therapy with rtPA in a randomized trial (DRIFT) did not decrease the need for a permanent shunt, and there was perhaps a tendency for more secondary hemorrhage.[120] The investigators have since modified this protocol to use only ventricular lavage without rtPA,[82] although some

TABLE 4: Expected clinical findings in infants with a VSG shunt

Parameter	Shunt Status		
	Functioning	Malfunctioning	Inactive (no longer required)
fontanel	flat, soft	tense, full	flat, soft
cranial sutures	not splayed	splayed	not splayed
subgaleal fluid pocket	full, even tense	not full	resorbed
head circumference	reasonable curve	crossing percentiles	reasonable curve
general condition	content, eating & sleeping well	irritable, sleeping & spitting up more, more apnea & bradycardia	content, eating & sleeping well

have argued that tPA decreases the burden of blood products that likely cause brain damage and PHH.[119]

The timing of insertion of a permanent shunt has also been investigated. The general recommendation has been to insert the permanent shunt once the infant reaches about 2.5 kg and is infection free and the CSF protein has decreased to less than 1.5 g/L.[119] A recent retrospective report from a single institution found no correlation between CSF protein or glucose levels or cell counts and infection and early shunt survival.[33]

Ventriculoperitoneal Shunts. Ventriculoperitoneal shunts are the current primary mode of permanent CSF diversion for infants with PHH. For infants without adequate peritoneal reabsorption, options include continuing the use of a temporary shunt or placement of a ventriculoatrial or ventriculopleural shunt. Because of the lifelong consequences of shunt-dependent hydrocephalus in this population, significant efforts to avoid placing a permanent shunt are indicated.[105,119] For infants who underwent shunt insertion prior to 1 year of age, 40% of whom had preterm PHH, 45% required shunt revision within 9 months.[92]

One of the main issues with permanent shunt insertion in this population is infection. The relatively high rate of infection may be due to an immature immune system, or preterm infants who are prone to IVH and PVL may have an inherent impaired inflammatory response.[59] Delaying the insertion of the permanent shunt until the infant is older and larger may decrease the risk of infection.[105] The immune system matures and the skin integrity and nutrition improve rapidly in the 1st few months. In a recent single-institution retrospective study of preterm infants with PHH (EGA < 37 weeks and weight < 1500 g), permanent shunts were inserted at a mean gestational age of 43 weeks and mean weight of 2.9 kg.[33] Primary shunt failure occurred within 3 months in 12.6% of cases. Shunt infection occurred in 13.8% of the preterm infants, compared with 8.5% of the overall shunt-treated population at the authors' institution.[33] Some authors have advocated the use of antibiotic-impregnated shunt tubing,[92] while others have shown a marked reduction in shunt infections using a strict infection reduction protocol.[84]

Endoscopic Third Ventriculostomy. Endoscopic third ventriculostomy offers an excellent alternative to a shunt in selected patients with obstructive hydrocephalus; however, ETV alone has not been reliably effective for preterm infants with PHH. A single-institution study found ETV was effective for aqueductal stenosis in young infants (77% success rate), but failed to show efficacy (14% success rate) in preterm infants with communicating hydrocephalus secondary to IVH.[28] A recent pilot study of that ETV combined with choroid plexus coagulation showed promise for avoiding placement of a permanent shunt in a selected subset of infants.[117]

Neurodevelopmental Outcome and Comorbidities

Perinatal mortality has improved markedly over the past few decades due to improvements in obstetrics and neonatology.[127] In an early 1980s series, only 35% of the infants survived 3–5 years, and only 29% of survivors were without major impairment.[70] In another 1980s study of preterm infants who underwent ventricular reservoir insertion, 70% survived and underwent neurodevelopmental assessments at 2 years, with 36% labeled as "normal," 36% labeled as having "mild delay," and 28% labeled as having "significant delay."[11] In a study from the 1990s, IVH severity was the primary determinant of cognition, motor function, and risk of epilepsy in term survivors, and the most important determinants of long-term survival were IVH grade and multiple (> 5) shunt revisions.[56] Improvements in neonatal care largely accounted for the progress over the past 2 decades in preterm infant survival and improved neurodevelopment.

Pediatric neurosurgical trials for PHH emerged in the 2000s. A multicenter randomized trial of drainage, irrigation and fibrinolytic therapy with rtPA (DRIFT) was initially halted because the early results showed no decrease in the need for a permanent shunt and a trend for increased risk of secondary hemorrhage.[120] The developmental outcomes analysis at 2 years showed that the DRIFT treatment group had a significantly lower rate of death and severe disability (54%), defined as a Bayley Mental Developmental Index (MDI) lower than 55, than the standard treatment group (71%).[121] No difference in outcomes was found when an MDI less than 70, the more common threshold of disability, was used.[121] The group is continuing to test the ventricular lavage intervention without rtPA.[82,119] These studies, as well as the multicenter trials currently enrolling patients or in planning stages in the US, will provide insight into the neurosurgical interventions that will best optimize long-term neurodevelopmental and shunt outcomes.

The risk of chronic neurological deficits persists despite appropriate intervention for PHH, an important concept to review with families, as they need to distinguish the benefits and limitations of hydrocephalus treatment

from other neurological problems related to prematurity. A large retrospective study found that children who developed PHH had poorer functional outcomes at a mean follow-up of 5 years, regardless of whether surgical intervention was required or not.[111] A multicenter study evaluating the outcomes at 2 years for preterm infants (< 28 weeks) with cranial ultrasonographic abnormalities found that poor outcomes (Bayley II MDI or PDI < 70) were associated with ventriculomegaly and echolucencies from white matter damage.[78] Another study of preterm infants (born at an EGA of < 31 weeks and weight < 1500 g) showed that ventricular dilation impacted neurodevelopmental outcomes at 2 years only when additional brain pathology, such as cPVL or IVH, was present.[68] In that report, 69% of the children with ventricular dilation and severe impairment did not have a VP shunt.[68] A relatively recent comparison of neurodevelopmental outcomes for infants (≤ 34 weeks' EGA) with IVH Grade III or PVHI found that, although infants with IVH Grade III were more likely to develop ventricular dilation and become symptomatic from hydrocephalus than infants with PVHI, the diagnosis of cerebral palsy by 2 years' corrected age was much higher among infants with PVHI (49%) than infants with Grade III IVH (7%).[12]

Some have suggested that infants who develop PHH have a greater burden of neurological deficits overall. In a recent study comparing outcomes (up to 36 months' corrected age) for patients who suffered unilateral PVHI versus bilateral PVHI as preterm infants, 64% of those who had unilateral PVHI had an MDI greater than 70 and no or mild cerebral palsy, and 43% had a PDI greater than 70; in contrast, only 7% of those who had bilateral PVHI had an MDI greater than 70 or PDI greater than 70, and only 12% had no or mild cerebral palsy.[65] Children who had unilateral PVHI and a VP shunt were more likely to have moderate or severe cerebral palsy (58%), visual impairment (37%), and seizures (37%) than those without a shunt (cerebral palsy 24%, visual impairment 6%, seizures 0%).[65] Although the overall rate of neurological morbidity is starting to improve for preterm infants,[100] not all subpopulations have followed this trend. In a recent multicenter retrospective analysis, infants born at less than 25 weeks' EGA during 1999–2001 and 2002–2004 did not show any change in significant neurodevelopmental outcomes (IVH Grade III, PVHI, cPVL, or need for shunt insertion) evaluated at 2 years after birth.[42] Infants who suffer IVH are also at risk for persistent cognitive and behavioral difficulties. In a recent case-control study of 65 adolescents who weighed less than 1500 g at birth, IVH increased the risk for attention deficit disorders.[45] Magnetic resonance imaging in preterm infants with isolated IVH without PHH, PVHI, cPVL, or PHVD revealed a significant loss of cortical gray matter volume associated with uncomplicated IVH.[110] The burden of neurological deficits in addition to PHH emphasizes the need for large multicenter trials to examine the impact of neurosurgical interventions on neurodevelopmental outcomes.

Interventions to Improve Neurodevelopmental Outcomes. The past decade has shown that improved neonatal treatment of preterm infants can decrease the incidence of perinatal complications, including IVH. The rates of cerebral palsy and severe hearing and visual impairment appear to be declining, but many infants are still prone to long-term cognitive and behavioral difficulties.[87] Trials of neuroprotective strategies with developmental outcomes are beginning to appear. Promising pharmacological agents include caffeine[90] and EPO.[16,76] Although caffeine has shown neurodevelopmental benefit for infants who receive it for apnea of prematurity, the mechanism underlying this benefit is not yet clearly defined. Erythropoietin, a pluripotent cytokine that regulates the survival and differentiation of neural cells, is currently used to treat anemia of prematurity in low doses. Animal studies have shown that exogenous EPO delivered systemically in the neonatal period after a prenatal injury can minimize damage and produce sustained functional improvement in adulthood.[69] In an animal model of intrauterine inflammation, rEPO reduced histological signs of brain damage.[86] No early adverse effects were identified in a trial of high-dose rEPO administered to preterm infants within 48 hours of birth.[31] In a single-center study, rEPO administered during the first 6 weeks of life (cumulative dose 3750 U/kg) was associated with higher MDI scores in preterm infants (EGA ≤ 30 weeks and weight < 1500 g) evaluated at 1 year.[16] At 10–13 years of age, children who suffered IVH as infants (weight < 1000 g) and received rEPO for anemia during the 1st week of life were more likely to score in the normal range on intelligence testing (52%, mean IQ score 90) than those who did not receive rEPO (6%, mean IQ score 67).[76] No significant difference was found for those without IVH.

Stem cells, with their potential to differentiate into various cell types and their self-renewability, also hold promise to enhance repair. The use of stem cells reprogrammed (dedifferentiated) from adult embryonic somatic cells, termed induced pluripotent stem cells, avoids the ethical controversies and genetic variability of embryonic stem cells. Either induced pluripotent stem cells or umbilical cord cells can be induced to differentiate into specific neural cell populations. Recent studies of neurorepair in animal models suggest that the role of stem cells may be to decrease inflammation, normalize the local environment, and release neurotrophic factors, rather than to directly replace lost neural cell populations.[21,83,129] Use of an infant's own umbilical cord stem cells to supplement neurorepair after an insult is a promising arena of research. For example, $CD133^+$ endothelial progenitor cells harvested from umbilical cord blood reduced hypoxia-induced damage to the developing CNS in an in vitro animal model.[103] Thus, a preterm infant's umbilical cord blood could potentially be collected at birth, and if concern for CNS damage arose in the perinatal period, specific stem cell populations could be amplified, and modified stem cells could be reinfused intravenously to target the damaged cerebral areas.

Conclusions

The outlook for our smallest patients has markedly improved over the past few decades. With improved prenatal and neonatal care, fewer preterm infants are likely to suffer IVH and other devastating neurological insults

as newborns. Despite these advances, a small subset of infants will continue to develop PHH and require neurosurgical intervention. Current and future well-designed multicenter prospective neurosurgical trials will allow neurosurgeons to provide these vulnerable patients with optimal management throughout their lives.

Disclosure

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