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Preterm Hemorrhagic Brain Injury

Recent Advances on Evaluation and Management



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KEYWORDS

• Hydrocephalus • Intraventricular hemorrhage • Newborn • Preterm • Treatment
• Neurodevelopmental outcome

KEY POINTS

- The incidence of germinal matrix hemorrhage-intraventricular hemorrhage (GMH-IVH) increases with decreasing gestational age and is more likely to affect preterm infants born less than 32 weeks' gestation.
- Cranial ultrasonography (cUS) is the preferred neuroimaging modality to assess GMH-IVH and to detect related complications with high sensitivity in preterm infants.
- Timely interventions with close cUS monitoring for post-hemorrhagic ventricular dilatation is crucial to prevent adverse neurodevelopmental outcomes.

INTRODUCTION

Preterm germinal matrix hemorrhage and intraventricular hemorrhage (GMH-IVH) are common complications of prematurity affecting up to 45% of infants born extremely preterm.¹ The risk of GMH-IVH increases with decreasing gestational age and is more likely to affect preterm infants born less than 32 weeks' gestation.² GMH-IVH generally occurs soon after birth, with 50% of the hemorrhages occurring within 1 day, and 90% within 3 days after birth, although antenatal and later postnatal presentations are possible.³ GMH-IVH can present unilaterally or bilaterally and is classified

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Abbreviations	
AAP	American Academy of Pediatrics
AHW	anterior horn width
BDNF	brain-derived neurotropic factor
CPS	Canadian Pediatric Society
CSF	cerebrospinal fluid
DRIFT	drainage, irrigation, and fibrinolytic therapy
GMH-IVH	germinal matrix hemorrhage and intraventricular hemorrhage
MSC	mesenchymal stem cell
NEL	neuroendoscopic lavage
PHVD	posthemorrhagic ventricular dilatation
PVHI	periventricular hemorrhagic infarction
TOD	thalamo-occipital distance
VI	ventricular index
VP	ventriculoperitoneal

based on the extent of hemorrhage and coexisting acute ventricular dilatation. The most commonly used classification systems for grading GMH-IVH have been proposed by Papile and Volpe.^{4,5} In a recent Canadian consensus article,⁶ GMH-IVH was classified based on the Volpe classification: grade I is hemorrhage within the germinal matrix, grade II is hemorrhage within the lateral ventricles without dilatation of the ventricle, grade III is hemorrhage in the lateral ventricles occupying more than greater than 50% of the ventricles causing acute ventricular dilatation, and periventricular hemorrhagic infarction (PVHI) is an ipsilateral hemorrhagic infarction in the periventricular white matter secondary to GMH-IVH. In this review, we discuss the pathophysiology, risk factors, evaluation, management, and neurodevelopmental outcome trajectories of GMH-IVH and its complications. We focus on evaluation and management of GMH-IVH and posthemorrhagic ventricular dilatation (PHVD) and highlight best practices based on recent studies. Emerging therapies for PHVD are also reviewed.

HEMORRHAGIC BRAIN INJURY AND ASSOCIATED CONDITIONS

GMH-IVH can lead to further complications including PVHI, PHVD, and brain dysmaturation.³ PVHI was previously thought to be an extension of GMH-IVH; however, it is now widely accepted that the white matter injury in PVHI results from impaired venous drainage following GMH-IVH, which leads to ischemia and hemorrhagic infarction.⁷ Gestational age is an important risk factor for PVHI, as it occurs more commonly in preterm infants born at earlier gestations.⁸ PVHI is usually unilateral and tends to occur more frequently with ipsilateral high-grade GMH-IVH.⁹ The white matter injury can range from a focal to extensive lesion in the frontal, parietal, temporal, or occipital regions.^{9,10} PHVD is progressive dilatation of the ventricles secondary to GMH-IVH. The presence of blood in the ventricles can impair cerebrospinal fluid (CSF) flow and absorption, leading to obstruction and ventricular dilatation. Hypersecretion of CSF from the choroid plexus also contributes to PHVD.¹¹ PHVD is seen in up to 25% of infants with GMH-IVH and is more common with high-grade GMH-IVH.¹² Similar to PVHI, PHVD is also more likely to occur in infants born at earlier gestational ages.¹³ Brain dysmaturation refers to abnormalities in brain growth and development with or without brain injury.¹⁴ These brain changes include reduced cortical, gray and white matter volumes, ex vacuo ventriculomegaly, and abnormal white matter maturation, which are commonly seen in preterm infants on term-equivalent age scans.¹⁴

Perinatal risk factors for GMH-IVH include maternal hypertension, chorioamnionitis, and vaginal delivery with prolonged labor.^{15–18} Infants who were outborn, or transferred

to a tertiary center have higher rates of GMH-IVH compared with inborn infants.^{19,20} Antenatal corticosteroids have been shown to be protective against GMH-IVH.^{21,22} Similarly, delayed cord clamping is associated with a lower risk of GMH-IVH.²³ Among neonatal risk factors, lower gestational age has consistently been found to be associated with a greater risk for GMH-IVH.^{2,24} Several studies have found that rapid fluctuations in blood pressure and low oxygen saturation can increase the risk of GMH-IVH.^{25–27} While resuscitation efforts and admission to the neonatal intensive care unit (NICU) are lifesaving for preterm infants, increased number of intubation attempts and both high-frequency oscillatory and conventional ventilation are associated with increased rates of GMH-IVH.^{28–30} Routine everyday features of the NICU such as procedural pain, loud noise, frequent handling, non-midline head positioning, lumbar punctures, frequent suctioning, and rapid fluid boluses can also increase the risk of GMH-IVH.^{15,31,32}

ASSESSMENT

The Indispensable Role of Cranial Ultrasonography

GMH-IVH is typically clinically silent but may also present with sudden or progressive clinical deterioration.³ Given that GMH-IVH can present without clinical signs, routine neuroimaging of preterm infants is required. Cranial ultrasonography (cUS) is the preferred neuroimaging modality to assess the presence, severity, and timing of GMH-IVH and to detect related complications with high sensitivity in preterm infants. There are several advantages of using cUS, including accessibility, portability, and the lack of ionizing radiation. Assessment of GMH-IVH with cUS should include views from the anterior fontanelle and supplemental acoustic windows. Based on the extent of hemorrhage, and the presence or absence of acute ventricular dilatation, GMH-IVH can be graded on a scale of I to III.⁶ PVHI, which is noted separately, may present as a globular or fan-shaped echogenic lesion, ipsilateral to the side of GMH-IVH.³ The natural evolution of PVHI involves the formation of a single large porencephalic or multiple small cysts, which are easily seen with cUS.^{3,10} PHVD once detected, requires serial cUS at least weekly to monitor progression.³³

Considering that the majority of GMH-IVH occurs within the first 3 days after birth, the first cUS should be performed in the first week. There are several published guidelines for the timing of cUS in preterm infants.^{33,34} Guidelines published by the Canadian Pediatric Society (CPS) recommend that very preterm infants born less than 32 weeks' gestation should have initial imaging 4 to 7 days after birth, and repeat imaging 4 to 6 weeks after birth.³³ The same protocol should be considered for preterm infants born between 32 weeks and 36 weeks with risk factors. The CPS guidelines also state that a routine cUS at term-equivalent age should be performed for neonates born before 26 weeks' gestation. The CPS guidelines are similar to the American Academy of Pediatrics (AAP) guidelines, which also recommend the first cUS within 7 days after birth, and repeat imaging at 4 to 6 weeks in infants born less than 30 weeks.³⁴ A recent expert opinion paper by Inder and colleagues recommended more frequent cUS scans for very preterm infants, with scans on day 1 (optional), 3, 7, 14, 28, every other week until 34 weeks postmenstrual age, and a final scan at term-equivalent age or discharge.³⁵ Outside of these guidelines, additional cUS should be performed for any preterm infant with altered level of consciousness, neurologic signs, or clinical deterioration.

The Supportive Role of Brain Magnetic Resonance Imaging

Brain MRI can be helpful in assessing GMH-IVH, parenchymal brain injury, and PHVD. The advantages of MRI include the high spatial resolution allowing for detailed

assessment of the brain parenchyma and lack of ionizing radiation. T1-weighted and T2-weighted images are ideal for assessing intracranial hemorrhage and parenchymal lesions (Fig. 1). Susceptibility-weighted imaging sequences can detect subtle areas of hemorrhage, particularly for grade I GMH-IVH or hemorrhage in less typical locations. Currently, there are no guidelines recommending routine brain MRI for preterm infants. However, a term-equivalent age brain MRI should be considered for preterm infants with abnormalities detected on cUS, greater burden of risk factors and for more detailed neuroprognostication. A review by Inder and colleagues described the importance of a term-equivalent age brain MRI in detecting less overt signs of preterm brain injury, or brain dysmaturation which may be seen following GMH-IVH.³⁵ The authors also suggest a brain MRI at term-equivalent age for preterm infants born less than 28 weeks or less than 1000 g, and for those born 28 to 32 weeks with risk factors or abnormal cUS findings.³⁵ Considering the diagnostic and prognostic capabilities of brain MRI, we strongly recommend considering brain MRI at term-equivalent age for the extremely preterm population.

MANAGEMENT

Updates on Monitoring and Management of Posthemorrhagic Ventricular Dilatation

Despite preventative strategies,^{15,36} GMH-IVH will continue to occur in a substantial proportion of preterm infants and can progress to PHVD. Ventricular size monitoring is important in infants with PHVD and can be done with serial cUS (see Fig. 1). Ventricular index (VI) and anterior horn width (AHW) have been studied, and normal ranges for preterm infants across postmenstrual age have been published.^{37–39} Measuring the occipital horn, or the thalamo-occipital distance (TOD), in the sagittal plane is also suggested as there can be a discrepancy between the enlargement of the anterior

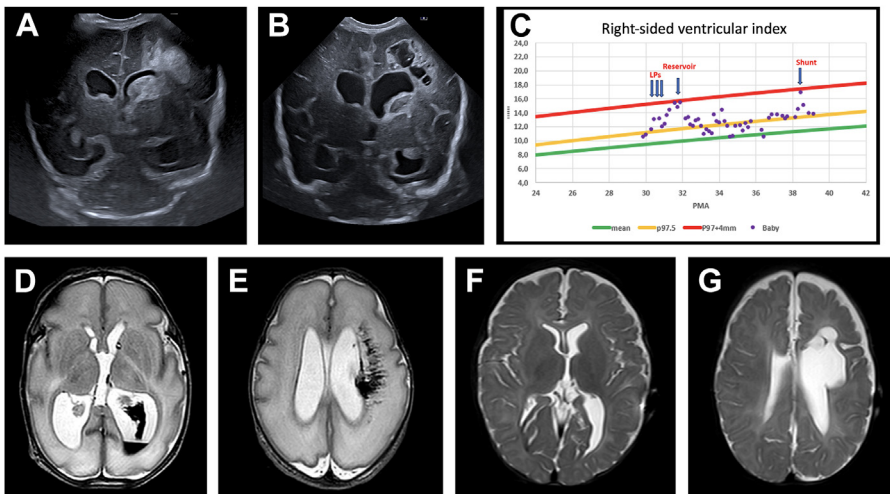


Fig. 1. (A) Coronal cUS scan of a preterm infant who was born at 29^{1/7} weeks' gestation and scanned on postnatal day 3 presenting with left-sided grade III GMH-IVH and PVHI. (B) The same infant at postnatal 5 weeks shows cystic changes in the left periventricular white matter area. (C) The chart shows measurements of the right ventricle and the timing of interventions for PHVD. (D, E) Early brain MRI (T2 sequence) on day 6 demonstrating left-sided grade III GMH-IVH and PVHI. (F, G) MRI (fast T2 sequence) at 6 months corrected age with expected evolution of PHVD into a porencephalic cyst.

and posterior horn. Alternative ventricular measurements are described (eg, frontal occipital horn ratio and frontal temporal horn ratio),⁴⁰ however, AHW and VI are the preferred measurements for monitoring PHVD.⁴¹ PHVD is defined as the persistence of acute ventricular dilatation with VI greater than 2 standard deviations or greater than 97th percentile, and/or AHW greater than 6 mm.^{37,38} When ventricular size exceeds these cut-offs, patients should be closely monitored with serial cUS for progression. A framework for monitoring PHVD describes 3 risk categories, green, yellow, and red, with each category having radiological and clinical criteria and management recommendations.⁴²

There is an ongoing debate about the best time to intervene for progressive PHVD, with many centers waiting for clinical symptoms (rapid increase in head circumference, bulging fontanelle, split sutures, apnea, bradycardia) to occur, while others prefer early intervention, based on an increase in the ventricular measurements, as documented with serial cUS. Medical management for PHVD using acetazolamide and furosemide is not recommended as it is associated with increased mortality.^{43,44} Although the drainage, irrigation, and fibrinolytic therapy (DRIFT) method demonstrated sustained cognitive benefits to 10 years of age in preterm infants with PHVD, it also increased the rate of secondary hemorrhages and is an invasive technique.^{44,45} Today, PHVD-related interventions typically begin with lumbar punctures to decompress the ventricles followed by temporizing interventions such as insertion and taps from a ventricular reservoir or insertion of a ventriculo-subgaleal shunt.^{42,46} In patients with ventricular reservoirs, CSF can be aspirated once or twice a day beginning with 10 mL/kg with an aim to reduce the VI over the next 7 to 10 days to within the normal range.⁴⁷ When infants with a ventricular reservoir reach 2000 to 2500 g, CSF removal can be held for a few days as a challenge. If ventricular indices increase during the challenge, then insertion of a ventriculoperitoneal (VP)-shunt should be considered.⁴⁷ The (Early versus Late Ventricular Intervention [ELVIS]) study demonstrated that early interventions based on cUS measurements reduced the VP-shunt rate to a range of 20% to 25%, compared with 40% to 60% reported in previous literature.⁴⁸ Complications of VP-shunts include obstruction, shunt malfunction, and infection,⁴⁹ therefore, earlier interventions should be implemented to avoid VP-shunt insertion.

Recently, the Children's Hospitals Network Consortium reported significant inter-center variation in the rate of intervention reflecting variability in care and referral patterns.⁴⁶ Considerable variability was also reported in the management of PHVD among Canadian centers and between Canadian and European practices.⁵⁰ There is accumulating evidence supporting the benefits of earlier interventions for PHVD.^{51–53} A multicenter retrospective observational study by Leijser and colleagues compared early intervention for PHVD based on ventricular measurements to late intervention based on clinical signs of increased intracranial pressure. In this study, preterm infants who received early intervention for PHVD had better neurodevelopmental outcomes at 18 to 24 months than those who received late intervention.⁵³ Among the preterm infants in the early intervention group, those who required a VP-shunt had similar cognitive and motor outcomes as those who did not require a VP-shunt. In contrast, among infants who received late intervention, those who required a VP-shunt had worse cognitive and motor outcomes than infants without a shunt.

The recent randomized controlled ELVIS trial also studied the timing of PHVD interventions.^{48,52} In this study, 126 preterm infants with progressive PHVD were prospectively recruited into a low-threshold for intervention (VI >97th percentile and AHW >6 mm and/or TOD >25 mm) or high-threshold intervention (VI >97th percentile + 4 mm and AHW >10 mm). In both groups, interventions were based on cUS

measurements and initiated in asymptomatic infants, to reduce ventricular size to less than 97th percentile. Although no difference in the VP-shunt rate was observed between groups, the need for VP-shunt placement in both groups was the lowest reported in the literature (19% and 23% in the low-threshold and high-threshold groups, respectively). In a nested substudy of the ELVIS trial, the high-threshold group had greater ventricular volumes and more brain injury compared with the low-threshold group, further demonstrating the benefits of early intervention.⁵² A follow-up study of the same cohort at 2 years of age found that low-threshold intervention was associated with lower odds of death and neurodevelopmental impairment in the post hoc analysis.⁵¹ In their meta-analysis, Lai and colleagues examined a cohort of 2533 infants with PHVD to assess if variability in the type and timing of temporizing neurosurgical interventions influenced patient outcomes.⁴⁹ They found that delaying temporary neurosurgical interventions was associated with an increased likelihood of progressing to VP-shunt placement and moderate-to-severe neurodevelopmental impairment.

The advantages of early intervention in PHVD may be due to the reduction of pressure on the surrounding brain tissue or decreased inflammation and neurotoxicity.^{54–57} Isaacs and colleagues showed that PHVD was associated with diffuse white matter injury, including axonal and myelin injury, cellular infiltration, and inflammation.⁵⁴ Diffusion tensor imaging studies have found that PHVD was associated with abnormal white matter microstructure in the periventricular, parietal, and occipital white matter.^{55,56} Similarly, lower fractional anisotropy values have been reported in the corpus callosum of infants with PHVD, which was in turn associated with cognitive and motor scores at 2 years.⁵⁷

Emerging Therapies for Posthemorrhagic Ventricular Dilatation

The search for additional PHVD management strategies is ongoing, with groups investigating the role of alternative neurosurgical techniques and the use of stem cells. Neuroendoscopic lavage (NEL) for PHVD has been studied, which involves using an endoscope to evacuate blood clots and irrigate the ventricles.^{58–60} NEL can be performed once or serially to remove blood products from the ventricles, reduce inflammation, and prevent ventricular dilatation. One retrospective cohort study of 46 preterm infants with PHVD found that NEL was associated with smaller ventricular size and improved neurodevelopmental outcomes.⁵⁸ In terms of adverse effects, CSF infection was seen in 20%, leaks in 13%, and secondary hemorrhage in 7% of infants. The mortality rate was 7%, however, death was not related to NEL or postoperative complications. In a retrospective cohort study, 26 preterm infants who underwent NEL and endoscopic third ventriculostomy had a decreased need for VP-shunt.⁵⁹ Similarly, a second retrospective cohort study of 60 preterm infants found that NEL was associated with lower rates of VP-shunts relative to traditional neurosurgical approaches.⁶⁰ A recent consensus guideline has been proposed by a group of neurosurgeons to standardize the indications and procedures of NEL for PHVD.⁶¹ In these guidelines, preterm infants can be considered for NEL if they are born preterm (<37 weeks) and have PHVD greater than 97th percentile + 4 mm. These guidelines state that there are no clear indications of repeat NEL, but it may be considered in cases with high clot burden or if repeat operation is required for temporizing device dysfunction.⁶¹ An international multicenter prospective cohort study (Treatment of Posthemorrhagic Hydrocephalus [TROPHY]) evaluating surgical treatments, including NEL for the management of PHVD, is ongoing.⁶² The first results of TROPHY reported that of 110 patients treated surgically for PHVD, 43% received NEL, and centers implementing NEL had lower rates of external ventricular drains.⁶³ A randomized

controlled trial in the United Kingdom examining outcomes of reservoir insertion compared with NEL (Endoscopic Lavage After Intraventricular Hemorrhage in Neonates [ENLIVEN] study) is actively enrolling participants and will provide further insight into the role of NEL in PHVD.

Stem cell therapy for PHVD has been investigated in preclinical studies and a phase-1 human study.^{64,65} In a study by Ahn and colleagues intraventricular transplantation of human umbilical cord mesenchymal stem cells (MSCs) was found to attenuate PHVD and brain injury in newborn rats.⁶⁴ The underlying mechanism may relate to the reduction of inflammation and/or neuroprotective effects of MSC-secreted brain-derived neurotrophic factor (BDNF).⁶⁶ A separate study by Ahn and colleagues⁶⁵ showed that MSC with intact BDNF function was associated with decreased neuronal death in vitro (newborn rat cortical cells), and reduced brain injury and progression of PHVD in vivo (newborn rats) compared with BDNF knockouts. The same group performed the first phase-1 clinical trial examining the safety and feasibility of intraventricular MSC transplantation in preterm infants with PHVD.⁶⁷ In this study, 9 preterm infants received incremental doses of MSC, which was well tolerated with no serious adverse effects or death. The same group also finished enrollment for a phase-2 study, but the results are pending. Further randomized controlled trials are needed to better understand the risks, benefits, and efficacy of stem cell therapy.

NEURODEVELOPMENTAL OUTCOME TRAJECTORIES

Despite advances in the detection and management of GMH-IVH, it is associated with an increased risk for mortality, neurodevelopmental delays, and disability.^{68–70} Mortality rate ranges between 10% and 50%, which is more commonly seen with high-grade GMH-IVH in the presence of PVHI and PHVD.^{2,13} Mortality rates are also higher in preterm infants with GMH-IVH born at earlier gestational age or lower birth weight (<750 g).³ It should be noted that the high mortality rate reported in some studies may be attributed to redirection of care practices often in the context of multi-system involvement or comorbidities.⁹

GMH-IVH is associated with adverse neurodevelopmental outcomes including motor delays and impairment, cerebral palsy, cognitive and behavioral concerns, neurosensory impairments, and epilepsy.^{69,71} Outcomes will vary based on the grade of GMH-IVH, site and extent of parenchymal involvement, concurrent PHVD, and additional clinical factors.^{69–73} PHVD is associated with neurodevelopmental impairments with infants requiring VP-shunts being at greatest risk for poor neurodevelopmental outcomes.⁷⁴ Timing of intervention for PHVD matters and better outcomes are consistently reported with early intervention.^{51,53,75} Of note, approximately 1 in 3 newborns with PHVD may experience spontaneous resolution, and this subset of newborns will have lower rates of neurodevelopmental impairments.⁷⁶ It has also been shown that extremely preterm infants who survive to 10 years of age after PHVD have on average lower health-related quality of life than their peers in self-care, mobility, cognition, and dexterity domains.⁷⁷ In PVHI, there is parenchymal brain injury which may disrupt the descending motor tracts resulting in more severe motor impairment. Cerebral palsy, mostly unilateral spastic cerebral palsy, is seen in a higher proportion of children with PVHI.^{9,51} Increasing size and severity of PVHI and involvement of the PLIC and trigone are associated with worse motor outcomes.^{9,78} The presence of PLIC diffusion restriction on MRI, within a week of PVHI onset can help with early prediction of motor impairment. Other regions that can be affected in PVHI include frontal, temporal, and occipital lobes, which can lead to cognitive and language delays, visual impairments and social-emotional and behavioral difficulties.^{75,79,80}

SUMMARY

GMH-IVH is a leading cause of brain injury and neurodevelopmental disability in children born preterm. cUS is the preferred modality for the diagnosis and evaluation of GMH-IVH, and an initial scan should be performed in the first days of life. Subsequent timing of cUS can be determined based on gestational age, risk factors, and the presence of previous cUS abnormalities. The management of GMH-IVH begins with preventative strategies aimed at modifiable risk factors. Once hemorrhage is detected, serial cUS is required to monitor for progression, and earlier intervention for PHVD based on ventricular measurements is recommended. PHVD interventions should begin with lumbar punctures and temporizing interventions before proceeding to VP-shunt insertion, which will be required in a subset of the affected infants. There are ongoing studies examining new therapies for PHVD including alternative neurosurgical techniques and stem cell therapy. Neurodevelopmental outcomes of GMH-IVH will vary based on grade, location, extent, the presence of PHVD, PVHI, and additional clinical risk factors.

Best Practices

- cUS is the preferred neuroimaging modality to screen for GMH-IVH and monitor related complications.
- Prevention of GMH-IVH includes targeting modifiable perinatal and neonatal risk factors that can alter cerebral blood flow and intracranial pressure.
- Management of GMH-IVH involves serial cUS to monitor progression and enable early intervention for PHVD (based on ventricular measurements and prior to the emergence of clinical signs) with lumbar punctures, ventricular access device insertions, and eventually ventriculoperitoneal shunts.

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