Core Concepts: Intraventricular Hemorrhage
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Core Concepts: Intraventricular Hemorrhage

Andrew Whitelaw, MD, FRCPCH*

Abstract
The very preterm infant is uniquely vulnerable to bleeding into the cerebral ventricles because of the numerous but unsupported blood vessels in the subependymal germinal matrix and unstable blood pressure and flow resulting from preterm delivery and respiratory distress. Approximately 25% of infants whose birthweights are 500 to 1,500 g have some intraventricular hemorrhage (IVH). Even a small IVH is associated with an increased risk of disability. A large IVH is sometimes complicated by hemorrhagic parenchymal infarction (also known as grade 4 IVH), which is believed to arise when venous occlusion from hematoma impairs perfusion in periventricular white matter. Large unilateral infarctions are usually associated with contralateral hemiparesis, but cognitive function may be less impaired. Prenatal glucocorticoid therapy reduces IVH by nearly 50% in randomized trials. Postnatal indomethacin reduces IVH, but reduced disability has not been consistently documented.

Objectives After completing this article, readers should be able to:

1. Discuss the epidemiologic risk factors, mechanisms, diagnosis, and prognosis of intraventricular hemorrhage (IVH) and parenchymal hemorrhagic infarction.
2. Review therapeutic interventions and evidence from trials.

Anatomy and Pathophysiology of IVH
Bleeding in and around the cerebral ventricles is one of the most serious complications of being born too early. In contrast, such bleeding is rare in babies born at term, even if severely ill. The reasons for the preterm infant’s unique vulnerability are partly anatomic and partly pathophysiologic. The site of bleeding is usually from the subependymal germinal matrix (Fig. 1). The bleeding may continue, rupture the ependymal lining, and fill and distend the ventricular system (Fig. 2).

The germinal matrix actively produces new brain cells that migrate outward. Earlier in pregnancy, the germinal matrix produces neurons that migrate toward the cortex. At 23 to 32 weeks’ gestation, the germinal matrix produces glial cells, especially oligodendroglia, which lay down myelin sheaths. The production of new cells requires increased quantities of substrate and energy and, therefore, a rich blood supply (Fig. 3). (1) However, by the time the fetus reaches term, the job of producing new cells is largely complete, and a rich blood supply to the germinal matrix is not needed. The immature vascular network in the germinal matrix does not have the protective structure of capillaries that are designed to last for 80 years. Ballabh (2) recently demonstrated that germinal matrix blood vessels have a paucity of pericytes, the cells that encircle the endothelium. In addition, the basal lamina is immature and glial fibrillary acidic protein in the feet of the ensheathing astrocytes is deficient. The risk period for IVH is the first 3 days following birth, after which the germinal matrix vessels become more robust. Ment and associates (3) investigated the beagle pup model of IVH and showed that collagen V and laminin, two important extracellular matrix proteins, increase markedly between postnatal days 1 and 4.

The anatomic vulnerability in the first 3 postnatal days is compounded by physiologic instability after preterm birth. The sick preterm infant has a very limited ability to autoregulate cerebral blood flow. Many different complications of preterm birth may result in fluctuating cerebral blood flow, increased cerebral blood flow, increased cerebral venous

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pressure, or decreased cerebral blood flow followed by reperfusion. The combination of unstable pressure and flow in the cerebral circulation and the poorly supportive but plentiful blood vessels near the center of the brain accounts for the unique vulnerability to IVH of the preterm infant in the period after birth.

Clinical Signs
In a prospective study of structured neurologic examinations and cranial ultrasonography in 100 infants, Dubowitz and colleagues (4) found that impaired visual tracking, an abnormally tight popliteal angle, and roving eye movements correlated strongly with the presence of IVH. Hypotonia and reduced spontaneous movement also correlated with IVH. However, few neonatologists have the time or the expertise to conduct structured neurologic examinations, and for practical purposes, clinical diagnosis of IVH in a small, sick, ventilated preterm infant is difficult. It is common for an infant to have significant IVH without the nurses and medical staff noticing clinical signs. Continuous electroencephalography (EEG) may reveal that IVH with parenchymal infarction is often accompanied by electrical seizures. A large IVH produces a substantial reduction in hemoglobin concentrations.
Diagnosis
Because clinical diagnosis of IVH is difficult, diagnosis is dependent on neuroimaging. The initial classification and grading system were developed by Papile’s group (5) using computed tomography scan, but the same scheme has been applied to cranial ultrasonography and is very widely used:

- Grade 1 IVH refers to hemorrhage that is subependymal and confined to the germinal matrix (Fig. 4).
- Grade 2 IVH refers to hemorrhage that is definitely in the lumen of a lateral ventricle, but the amount of blood is not sufficient to distend the ventricle (Fig. 5).
- Grade 3 IVH refers to hemorrhage within the lumen of the lateral ventricle(s) associated with dilation of the ventricle in Papile’s classification. (5) This definition can make it difficult to distinguish between a small IVH with a large ventricle distended by cerebrospinal fluid and a large IVH that is sufficiently bulky to distend the ventricle with blood alone. This distinction has been clarified by Volpe, who has defined grade 3 IVH as “IVH >50% of ventricular area on parasagittal view, usually distending the lateral ventricle” (Fig. 6). (6)
- Grade 4 IVH refers to the combination of blood within the lateral ventricle and an echogenic area, often fan-shaped, in the periventricular tissue that is in apparent continuity with the intraventricular blood (Fig. 7). In the early days of cranial ultrasonography, this was referred to as “extension of IVH,” but its true nature is parenchymal infarction that has become hemorrhagic.

Epidemiology
During the 1980s, when cranial ultrasonography allowed universal imaging of entire populations, epidemiologic risk factors for IVH were identified:

- Short gestation (7)
- Male sex (7)
- Respiratory distress syndrome (7) and its complications: hypercapnea, (7) pneumothorax, (8) fluctuating arterial blood pressure, (9) and early hypotension and reperfusion (10)(11)

Condition at birth, as reflected in Apgar scores and acid-base balance, is associated with IVH in some, but not all, studies, as is hypothermia, which probably reflects prolonged resuscitation in the delivery room. Thrombocytopenia and coagulopathy are not believed to be causative in usual cases of IVH. (12)

Approximately 90% of IVH is apparent by 7 days of age, with 78% evident by 72 hours of age. (13) A small proportion of IVH is visible on scans performed immediately after birth, and some of these antenatal hemorrhages are associated with prenatal alloimmune thrombocytopenia (14) or congenital deficiency of a clotting factor. (15)

Incidence
When cranial ultrasonography was introduced in the early 1980s, IVH was very common in infants whose birthweights were less than 1,500 g; an incidence of 50% was common. Since that time, the incidence has de-
creased substantially. In 1998, Sheth (16) reported that IVH was found in about 30% of infants whose birthweights were less than 1,000 g. Among those whose birthweights were 1,000 to 1,500 g, only 15% developed IVH. Among the developing IVH, 40% were grade 1, 25% were grade 2, 20% were grade 3, and 15% were grade 4. These figures are similar to those in our region.

**Prognosis**

In the past, small hemorrhages (ie, grade 1 or 2 IVH) were believed not to increase the risk of disability significantly over and above the background risk associated with gestational age and birthweight. However, current evidence suggests that even a small IVH increases the risk of disability. Patra and associates (17) (Table) showed that among infants whose birthweights were less than 1,000 g, cerebral palsy, low Mental Development Index, and total neurodevelopmental impairment were higher in infants who had grades 1 and 2 IVH compared with those who had no IVH.

Sherlock and colleagues (18) showed an increase in cerebral palsy to 24% in extremely low-birthweight infants who had grade 2 IVH compared with 6% in infants of similar birthweight who had no IVH.

<table>
<thead>
<tr>
<th>Normal Ultrasonographic Findings</th>
<th>Grade I to II IVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N 258</td>
<td>104</td>
</tr>
<tr>
<td>Mental Developmental Index (MDI)</td>
<td></td>
</tr>
<tr>
<td>MDI &lt;70</td>
<td>25%</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>5%</td>
</tr>
<tr>
<td>Neurologic impairment</td>
<td>28%</td>
</tr>
</tbody>
</table>

*362 infants who weighed <1,000 g at birth and were seen at 20 months of age
In a survey of studies of large IVH without parenchymal infarction (grade 3 IVH), Volpe estimated that 50% of survivors had definite neurologic consequences. Futagi and coworkers (19) found that 23% of survivors of grade 3 IVH developed cerebral palsy compared with 17% of those who had grade 2 IVH and 7% of those who had grade 1 IVH.

Parenchymal Hemorrhagic Infarction (PHI) (Grade 4 IVH)

Anatomy and Pathophysiology
The venous drainage of the periventricular white matter is shown in Figure 8A. The veins from the periventricular white matter drain blood into the terminal vein, which runs through the germinal matrix. A hematoma in the germinal matrix, therefore, can partially or completely occlude the venous drainage and increase venous pressure. When combined with hypotension or hypoxemia, this circumstance can contribute to infarction, which is localized to the area with venous obstruction (Fig. 8B). The increased venous pressure subsequently contributes to secondary bleeding into the infarction. This hypothetical mechanism is based on the anatomy and on PHI being usually unilateral on the side of a large germinal matrix hemorrhage. The concept is also supported by evidence of PHI appearing after IVH and color Doppler ultrasonography showing absent flow in the terminal vein in the presence of germinal matrix hemorrhage. (20)

Progression
Figure 9 illustrates the progression from fresh, uniformly echodense PHI to echolucent porencephalic cyst communicating with the lateral ventricle. If the clinician obtains scans every day after PHI first appears, it is our experience that 6 days is the earliest that echolucency (liquefaction) is visible.

Prognosis
The risk of subsequent disability relates to the size and location of the parenchymal injury. Lesions measuring less than 1 cm in dimension may not be associated with subsequent cerebral palsy, particularly if they are located in the frontoparietal area. When extensive unilateral infarction involves the frontal, parietal, and occipital areas, major motor deficits (eg, spastic hemiplegia or asymmetric quadriplegia) are found in more than 80% of cases. Cognitive outcome is more variable. Some children who have large unilateral injury have cognitive function within the normal range. If the unilateral infarction is large enough to produce midline shift, the disability is increased further. Extensive bilateral parenchymal lesions...
are associated with 100% severe motor and cognitive disability. (21)

**Prenatal Preventive Interventions**

Administration of glucocorticoid before preterm delivery is highly effective in preventing subsequent IVH, particularly if 24 hours has passed between the start of treatment and delivery. The most commonly used regimen is a total dose of 24 mg betamethasone divided over 24 hours. In meta-analysis, the relative risk of IVH is 0.55. (22) Much of the benefit may be due to the induction of surfactant and prevention of respiratory distress syndrome, but there may some brain protection from neonatal blood pressure being maintained at a higher and more stable level after corticosteroid administration.

Observational evidence suggests that in utero transfer and cesarean section reduce the risk of IVH, but this could be due to selection introducing bias. Antenatal phenobarbital, (23) vitamin K, (24) and magnesium sulfate (25) have been evaluated but have not shown consistent evidence of protection.

**Postnatal Preventive Interventions**

Indomethacin has been tested in 19 controlled trials. The two biggest trials are important and interesting because they were of high quality and gave opposite conclusions. Ment and associates (26) randomized 431 infants to receive 0.1 mg/kg per day for 3 days or placebo. Total IVH was reduced from 18% to 12% and grade 4 IVH was reduced from 4.5% to 0.5%. The reduction in IVH was significant in boys but not in girls. At 36 months of age, there was no overall difference in cerebral palsy, but there was a cognitive benefit in boys. (27) In a cohort magnetic resonance imaging study, Miller and colleagues (28) concluded that indomethacin treatment was associated with decreased white matter injury.

Schmidt and associates (29) randomized 1,203 infants whose birthweights were less than 1,000 g to receive 0.1 mg/kg per day for 3 days. Severe IVH (grade 3 or 4) was reduced from 13% to 9%, but there was no difference in neurodevelopmental impairments at 18 months. There was evidence of an adverse effect of indomethacin in girls and no significant benefit at 18 months in boys. (30) Indomethacin may reduce IVH by reducing cerebral blood flow, cyclooxygenase activity, and free radical generation or by accelerating physical maturation of microvessels in the germinal matrix.

In randomized clinical trials, volume-targeted ventilation resulted in significant reductions in severe (grade 3 and 4) IVH, with a relative risk of 0.32 and number needed to treat of 6. (31)

**Immediate Treatment after IVH**

Consequences of a large IVH, such as hypotension, shock, anemia, and acidosis, have not been subjected to randomized trial, but the basic principles of circulatory support apply, with appropriate use of volume, blood products, and inotropes. If abnormal movements of the limbs, mouth, or eyes are seen, continuous monitoring of EEG or amplitude-integrated EEG is indicated because diagnosing seizures without EEG is difficult. Although conclusive evidence of improved outcome is lacking, we treat subtle clinical seizures confirmed by EEG.
American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Know the risk factors for development, proposed mechanisms, clinical and laboratory features, and diagnosis of PIVH (periventricular-intraventricular hemorrhage).
- Know the proposed prevention strategies, evolution, early complications, management, and long-term consequences of PIVH.

References
NeoReviews Quiz

13. Bleeding in and around the cerebral ventricles is one of the most serious complications of preterm birth. Of the following, the most likely cause of periventricular-intraventricular hemorrhage (PIVH) in preterm infants is:
   A. Disseminated intravascular coagulopathy.
   B. Germinal matrix vulnerability.
   C. Neonatal sepsis.
   D. Perinatal trauma.
   E. Systemic hypertension.

14. Although clinical symptoms and signs, such as a substantial drop in hemoglobin concentration, seizures, and hypotonia, may be suggestive, the definitive diagnosis and grading of PIVH is based on neuroimaging. Of the following, based on the Papille grading system, PIVH confined to the lumen of the cerebral lateral ventricle without causing its distension is most consistent with:
   A. Grade 0 PIVH.
   B. Grade 1 PIVH.
   C. Grade 2 PIVH.
   D. Grade 3 PIVH.
   E. Grade 4 PIVH.

15. Serial cranial ultrasonography of populations of preterm infants has allowed determination of the timing of occurrence of PIVH. Of the following, most cases of PIVH manifest at:
   A. Birth.
   B. 0 to 72 hours of age.
   C. 3 to 7 days of age.
   D. 8 to 14 days of age.
   E. 15 to 28 days of age.

16. Several antenatal and peripartal interventions have been examined for their effects on prevention of PIVH in preterm infants. Of the following, the single most effective intervention in decreasing the risk of PIVH in preterm infants is:
   A. Antenatal glucocorticosteroid.
   B. Antenatal phenobarbital.
   C. Cesarean section delivery.
   D. Magnesium sulfate.
   E. Vitamin K.
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