9 Preterm Brain Injury

The two most common forms of brain injury noted in preterm neonates are intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL).[1] These lesions are more common in the smallest and most premature neonates and contribute significantly to mortality, morbidity during hospital stay, and long-term neurodevelopmental impairment. The overall incidence of IVH among VLBW neonates is 20-25% but two thirds of them are of mild to moderate severity (grade 1-2). Severe forms of hemorrhage (grade 3 and periventricular hemorrhagic infarction [PVHI]), although rare, have higher incidence among extremely preterm neonates. About 25% of neonates with birth weight between 501 and 750 g and 14% between 751 and 1000 g develop severe forms of hemorrhage.[2]

Intraventricular hemorrhage (IVH)

The site of IVH in preterm neonates is the fragile capillary network of the germinal matrix, which is located between the caudate and thalamic nuclei at the level of or slightly posterior to the foramen of Munro. The germinal matrix is a highly vascularized structure that also serves as the area of origination of neuronal and glial precursors. It begins to involute after 34 weeks of gestation which explains why IVH occurs predominantly in very preterm neonates.

Grades and diagnosis

Grade I refers to hemorrhage confined to the subependymal-germinal matrix with no blood clot in the ventricular lumen while grade II is hemorrhage occupying 10-50% of the lateral ventricles without any ventricular enlargement. Grade III is hemorrhage occupying >50% of the lateral ventricle and associated with ventriculomegaly. Grade IV hemorrhage is a separate notation in Volpe's classification called periventricular hemorrhagic infarction; which isIVH associated with ipsilateral parenchymal hemorrhage.[3]

Ultrasonography is the primary imaging modality for the screening and diagnosis of IVH and parenchymal hemorrhage in neonates because of the ideal acoustic window offered by the anterior fontanelle, easy and quick image acquisition at the bedside, and lack of radiation hazard.

Clinical presentation

There are three presentations of IVH- clinically silent, saltatory and catastrophic, of which the most common is clinically silent presentation. The preterm neonate is often asymptomatic and the only clinical sign may be an unexplained fall in hematocrit. In the saltatory presentation, the symptoms evolve over days to weeks and may present with lethargy, apnea, tone abnormalities and tight popliteal angle on examination. The most striking but the least common is the catastrophic presentation, with rapid evolution over hours. It manifests with severe apnea, seizures, altered sensorium, decorticate or decerebrate posturing, hypotension and even death. Because most neonates with IVH are asymptomatic, screening is mandatory in high-risk neonates (see 'Protocol on cranial ultrasound'). Generally, all neonates at high risk for IVH (gestational age <32 weeks or birth weight <1500 g) should undergo screening. More mature preterm infants (32-34 wks) should also be screened if they experience a turbulent postnatal course (shock requiring inotropes, unexplained anemia, or severe RDS requiring mechanical ventilation).

Consequences of IVH

The hemorrhage into the lateral ventricle spreads throughout the ventricular system and into the subarachnoid space where it can trigger obliterative arachnoiditis. The CSF flow can be impaired both inside the ventricles (at the aqueduct of Sylvius) and outside it (at the arachnoid granulations). The consequences of IVH are three-fold (in the temporal order of occurrence):

1. Damage to germinal matrix and thereby injury to the glial and neuronal precursors
2. Periventricular hemorrhagic infarction (PVHI):noted in 15% of all IVH among VLBW neonates, denotes a

parenchymal lesion occurring on the same side as severe IVH. PVHI is actually a venous infarct due to obstruction of the terminal vein by the large IVH (often grade III).

3. Post hemorrhagic hydrocephalus (PHH): Obstruction to the flow of CSF due to particulate matter in the hemorrhage leads to acute ventriculomegaly while progressive dilatation is secondary to obstructive arachidonitis. The rapidity and severity of ventriculomegaly is related to the size of IVH.

Progression of IVH

Approximately half of all IVH occur on day 1 of life, an additional 25% on day 2, and another 15% on day 3 of life. Hence a single scan on 3-4th day of life is likely to detect about 90% of all hemorrhages. However, in neonates with birth weight between 500 and 750 g, two thirds of IVH occur on day 1 and it may be reasonable to perform the first scan on day 1 itself. One third of hemorrhages increase in size and the maximum size is usually attained 3 -5 days after the onset of hemorrhage. Hence serial ultrasounds are needed to follow the progression of bleed. Even when the initial ultrasounds are normal, it is necessary to repeat scan at around 3 weeks of postnatal age followed by another one closer to 36 weeks' PMA to detect cystic lesions of PVL or ventriculomegaly. Although cranial ultrasounds have a sensitivity of 100% and specificity of 91% for detecting hemorrhages larger than 5 mm, it has limited sensitivity (50%) and specificity (87%) for the diagnosis of PVL.[4]

Complications of IVH

1. PVHI: The most common sequelae of PVHI is a large porencephalic cyst at the site of the lesion. This lesion is particularly common in preterm neonates with birth weight <750 g, and it accounts for most of the morbidity attributable to IVH. It is usually a single large cyst, often unilateral, on the same side as the large IVH and communicating with the lateral ventricle. In one third of cases, PVHI can be bilateral - the lesion is often asymmetric depending on the size of IVH on the same side. In contrast to PVHI, periventricular leukomalacia (PVL) is due to ischemia of periventricular

white matter, is non-hemorrhagic, and results in multiple small or large cysts symmetrically distributed in periventricular area.

2. Post hemorrhagic hydrocephalus (PHH): Among all VLBW neonates with IVH, approximately 25% develop ventricular dilatation or hydrocephalus[5]. The exact incidence of PHH depends on the severity of IVH; the incidence being 4% with grade 1 IVH, 12% with grade 2 IVH, and 70% with severe grades.[5] The injury to the periventricular white matter accompanying hydrocephalus is due to excessive pressure and distortion of nerve fiber tracts, free radical injury, and inflammation from iron and cytokines.

Management of IVH

The focus should be on preventing IVH in the first place (discussed below). During acute phase, ensure airway patency, breathing and circulation. Maintain blood pressure in normal range, avoid hypercarbia, acidosis, hypoxia, rapid fluid boluses, pneumothorax, and seizures. Serial ultrasounds should be done to monitor progress of IVH and the development of complications.

Clinical monitoring in a neonate after IVH includes biweekly or alternate day measurement of occipito-frontal circumference (OFC) and monitoring for clinical signs and symptoms of raised intracranial pressure (ICP). Serial ultrasounds are mandatory to monitor the progression of severe IVH and to measure the size of lateral ventricles because the classical signs of raised ICP and head enlargement are delayed for days to weeks after the onset of ventriculomegaly (Table 9.1).With a large IVH, there is a greater likelihood of rapid ventricular enlargement within days and need for intervention.

Table 9.1: Criteria for diagnosis of hydrocephalus following IVH

Excessive head growth • Normal head growth between 26 to 32 weeks' gestation is approximately 1 mm/day and between 32 to 40 weeks is 0.7 mm/ day. • A **persistent increase of >2mm/day** should raise the suspicion of hydrocephalus. • It is recommended to measure head circumference on alternate days: increments of >4 mm in 2 days or >14 mm/week is labeled as hydrocephalus
Signs and symptoms of raised ICP Bulging fontanelle, splayed sutures, symptoms like lethargy, poor feeding, vomiting. Neurological signs include changes in muscle tone, down set eyes and seizures

Cranial ultrasound
• 2D ultrasound to measure ventricular sizes; Levene's index provides guidance on intervention for various gestational ages
• Doppler ultrasound of anterior or middle cerebral artery to measure resistive index **(RI)**
  • RI > 0.85 suggests raised intracranial pressure
  • RI = 1 (absent diastolic flow - impaired perfusion)

Levene's index is measured from the falxto the lateral wall of the body of the ventricle.[6] Reference ranges have been published according to gestational ages and measurement exceeding 4 mm above the 97th centile for ventricular index ('action line') indicates the need for therapeutic intervention. There is no role of ICP measurement in the management of PHH as progressive ventricular dilatation and head enlargement occurs first before an increase in CSF pressure.

Management of PHH

Among infants with PHH, spontaneous arrest of ventriculomegaly without any treatment occurs in one third; the remaining two-thirds require intervention (serial lumbar punctures in 14%, surgical treatment with insertion of a ventricular reservoir or ventriculo-peritoneal shunt in 34%, while 18% die).[5] The available interventions include temporary measures like serial lumbar punctures (LP), repeated aspiration of CSF through a ventricular access device, and permanent insertion of a ventriculo-peritoneal (VP) shunt. Use of diuretic agents like acetazolamide and furosemide to decrease CSF

production is associated with a higher risk of neurological complications, morbidity, and mortality, and hence is not recommended.[7]

While the optimal time for CSF tap is not clear, we follow a combination of clinical and objective evidence of ventriculomegaly to decide when to do therapeutic LP. Presence of two or more of the following features is taken as indication for performing therapeutic CSF tap:

- Head circumference increase >14 mm/ week or >2mm/ day for ***2 weeks***
- Ventriculomegaly: Levene index greater than 'action line' (>97thcentile +4mm)
- Features of raised ICP like bulging fontanelle, splayed sutures or neurological signs (lethargy, poor feeding, tone abnormalities or seizures)
- Resistive index >0.85 on Doppler of intracranial vessels

Serial LP is effective only if communication exists between lateral ventricles and lumbar subarachnoid space. A minimum of 10 mL/kg of CSF and maximum of 20 mL/kg needs to be removed. The rate of removal should not be faster than 1 mL/kg/min to avoid complications like apnea, bradycardia and desaturation.[8] If LP is not successful in removing CSF or if the hydrocephalus is obstructive, ventricular tap is required. Ventricular puncture is, however, associated higher risk of CSF infection and development of loculated hydrocephalus.

Therapeutic LP produces an immediate improvement in symptoms of raised ICP but if symptoms persist or recur, a repeat LP can be performed based on the criteria described above. However, routine use of serial LP is not recommended.[9] When the need for CSF removal exceeds 2 lumbar punctures or more than one ventricular tap, surgical placement of a ventricular access device (VAD) or ventriculo-subgaleal (VSG) shunt should be considered. Due to high rate of primary shunt failure (17% within 3 months of insertion)[10]and shunt infections (15.5%), VAD or VSG is often the first choice rather than a ventriculo-peritoneal shunt in infants.[11]

CSF tapping from the ventricular reservoir (ventriculo-subgaleal shunts are self-draining) can continue as long as the following criteria are met - normal head growth and CSF protein < 150 mg/dL and free of infection. Once these criteria are met and the infant has reached at least 2.5 kg weight, one can temporarily stop the reservoir taps and monitor head size. Approximately half of the infants respond to temporary surgical measures and may not need a permanent VP shunt placement. However, if the head growth is excessive despite these measures and the above criteria are met VP shunt insertion is planned. The interval between VAD insertion and the decision to do VP shunt may be 4 weeks or more. Shunt infection and shunt malfunction are the two important complications that require monitoring after shunt insertion.

Outcome and prognosis of IVH

The severity of IVH is the major predictor of adverse short-term outcome (mortality and need for surgery). While the risk of mortality is only 4% with grade 3 IVH, almost 75% neonates with a parenchymal hemorrhage or grade 4 IVH die. The risk of neuromotor and cognitive impairment is more related to the presence of parenchymal hemorrhage than the presence or management of hydrocephalus.[12] Motor deficits and abnormal DQ occurred in 54% and 8%, respectively among neonates with grade 3 hemorrhage, while the same were 100% and 78%, respectively with PVHI.

Periventricular leukomalacia

Periventricular Leukomalacia (PVL) refers to focal and diffuse white matter injury (WMI) that occurs in the periventricular region of the brain.[1]The focal component involves loss of all cellular elements (premyelinating oligodendrocyte, axons and inter-neurons) deep in periventricular white matter. The injury evolves over several weeks into small macroscopic cystic lesions readily visualized by cranial ultrasound (cystic PVL) or as multiple micro-cystic lesions that evolve into glial scars and not readily seen by neuro-imaging (non-cystic PVL). Cystic PVL (c-PVL) is rare in the current era and the majority of cases (up to 70% of preterm neonates) are constituted by non-cystic and diffuse PVL.

c-PVL, classified according to the grading system of deVries *et al*[13] generally takess 4 weeks to appear and sometimes disappear altogether leaving behind only ventriculomegaly. In diffuse PVL (d-PVL), the main target of injury is premyelinating oligodendrocyte that finally results in impaired myelination in various regions of the brain including cerebral white matter, thalamus, basal ganglia, cerebral cortex, brainstem, and cerebellum. Diffuse PVL is recognized in MRI as signal abnormalities, disturbances in diffusion parameters (diffusion tensor imaging) and decreased volume of neuronal structures (volumetric MRI) as early as at term equivalent age (40 weeks' PMA).

The risk factors of PVL include prematurity, multiple pregnancy (monochorionic twins), chorioamnionitis, intrauterine growth restriction, fetal distress, hypotension period, hypocarbia, sepsis, and use of postnatal corticosteroids. The pathogenesis is mediated through an interplay between hypoxia, ischemia and inflammation of the oligodendrocyte progenitor cells present in the periventricular area of infants born at 23 to 32 weeks of gestation.

The clinical correlate of cystic PVL is spastic diplegia, while non-cystic PVL and diffuse PVL correlate with the cognitive, attention, and behavioral deficits observed later in childhood. Among VLBW infants, 5% to 10% develop cerebral palsyand 25% to 50% develop significant cognitive and behavioral deficits. Given that cranial ultrasound lacks sensitivity to diagnose diffuse white matter injury and structured evaluation using MRI at term equivalent age (40 weeks' PMA) predicts neurodevelopmental outcome in childhood[14], there has been an increase in use of MRI in preterm neonates before discharge. However, MRI cannot be recommended as a routine diagnostic or prognostic tool for evaluating all high-risk neonates at present.[15]

Prevention of preterm brain injury

Table 9.2 enlists the evidence based interventions[16] for preventing preterm brain injury.

Table 9.2: Potential strategies to decrease risk of brain injury in preterm infants[16]

Period	Intervention
Antenatal	• Prevent preterm delivery • Regionalization of care: Lesser odds of mortality if delivery occurs in well-equipped centers compared with less specialist centers • *In-utero* transfer: Transport of preterm neonates after birth (the first 48 hours of life) is associated with increased rates of severe IVH; ideal strategy is to transfer the pregnant woman • Antenatal steroids: Reduces IVH (all grades) by 46% • Antenatal magnesium sulfate in women at risk of preterm birth < 32 weeks' gestation decreases the risk of severe and moderate CP and the incidence of gross motor dysfunction. • Antibiotics for PPROM: Prolongs pregnancy, decreases EONS by 30%, fewer abnormal cranial ultrasound scans by 20%.
Postnatal	• Delayed cord clamping: *Early benefits* - hemodynamic stability, less inotropes, less need for blood transfusion; *Later benefits* - improved motor function at 18–22 months. • Caffeine for apnea of prematurity: CAP trial showed that caffeine in the first 10 days decreased the incidence of CP and cognitive impairment at 18–21 months in at-risk LBW infants • Indomethacin prophylaxis: Significantly reduces the incidence of severe IVH but no difference in developmental outcomes at 18-24 months was noted. *We do not use indomethacin prophylaxis.*. • Ventilator strategies: o Volume targeted ventilation produces a significant reduction in hypocarbia compared with pressure-limited ventilation. This translates into 30% reduction in the combined outcome of PVL or grades 34 IVH. o Synchronized mechanical ventilation o Early surfactant administration o Minimizing complications like pneumothorax o Minimize mean airway pressure, extremes of $PaCO_2$ o Minimize use of postnatal steroids • Prevent late onset sepsis, NEC and postnatal growth restriction

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