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Intracranial Hemorrhage in the Newborn

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1. Introduction

Intracranial hemorrhage (ICH) is a major source of neonatal morbidity and mortality. In full-term infants, it most often occurs during labor as the result of mechanical factors; however, in the pre-term infants it can occur even prior to labor or as late as the second week of life usually as a result of hemodynamic instability. Besides etiology, the location of hemorrhage, clinical presentation and neurological outcome also differs in the term and preterm infants. It is important for the radiologists to provide an accurate anatomic description of the compartment(s) confining the hemorrhage, as correct location may be an indicator to the underlying cause and provide a roadmap to the neurosurgeons if intervention is required. The knowledge of the anatomic compartments is vital for interpreting the imaging findings in case of ICH and formulating a differential diagnosis. Cranial ultrasound is often used as the first imaging modality for newborns. CT is the preferred diagnostic study for evaluation of acute intracranial hemorrhage. MRI is indicated when subarachnoid bleed or posterior fossa hemorrhage is suspected. Prevention of ICH is a subject of great interest in premature newborns. Prenatal prophylaxis and improved obstetric and neonatal care in general markedly reduces the stress to premature fetus and neonate.

2. Etiopathogenesis

Intracranial hemorrhage (ICH) is perhaps the most dramatic manifestation inherited in the birth process. The etiology of ICH differs according to the gestational age of the infant and the site of hemorrhage.

Of all types of ICHs, germinal matrix-intraventricular hemorrhage (GM-IVH) by far is the most common and distinctive pathology in premature infants. The pathogenesis of GM-IVH is multifactorial. It involves a combination of vascular-anatomic immaturity and complex hemodynamic factors. The role of inflammatory and genetic factors is currently under investigation. Germinal matrix (GM) is a highly vascular structure and the source of developing brain cells (neuronal and glial cells). The tissue surrounds the fetal ventricular system and gradually involutes to reside over the body of the caudate between 24 and 28 weeks of gestation, at the level of head of caudate nucleus in the caudothalamic groove between 28 and 34 weeks of gestation, and finally completely regresses and converts into normal cerebral parenchyma by the 36th week of gestation. The capillary network of germinal matrix is composed of high-caliber, thin-walled (deficient in muscularis layer) and immature fragile vessels predisposed to rupture. Furthermore, GM lies within an arterial end zone, and is directly connected to the deep galenic venous system, thereby exposing it to insults of arterial ischemic-reperfusion and to venous congestion.[1,2,3] The rupture hemorrhage of the vulnerable GM requires the coexistence of several intrinsic and extrinsic hemodynamic factors. Premature infants are believed to have impaired cerebral pressure autoregulation (a major intrinsic factor) that renders these infants susceptible to both cerebral hypoperfusion and ischemia at the border zone GM vessels and hence the rupture of fragile germinal matrix vessels. In term infants, a well developed cerebral pressure autoregulation mechanism maintains a relatively constant cerebral blood flow (CBF) across a range of cerebral perfusion pressures.[4] Various extrinsic hemodynamic factors that potentially interfere with the integrity of the vulnerable GM include low CBF (hypotensive events and frank perinatal asphyxia), high CBF (hypertension, bolus fluid infusion, hypercarbia and low hematocrit), fluctuating CBF, and factors causing increased cerebral venous pressure (respiratory distress syndrome, positive pressure ventilation, pneumothorax, or pulmonary hemorrhage).[1,2] Immature deep galenic system, in a preterm infant, which is prone to venous congestion and stasis is another major factor responsible for development of GM-IVH and its complications. Immature cerebral venous system has several vulnerabilities because (i) development of cerebral venous system occurs late in relation to that of the arteries, (ii) there is sequential remodeling and considerable individual variation in the pattern and size of different veins entering the internal cerebral veins, (iii) immature veins have high caliber and thin wall, they branch parallel to the ventricle, hence tend to collapse, (iv) because of relative paucity of superficial cortical veins between 24 and 28 weeks of gestation, most of the cerebral venous drainage is dependent on the deep galenic system that drains GM and most of the white matter, and (v) the periventricular veins, particularly the terminal (thalamostriate) vein, which is the main vein draining the white matter passes directly through the GM and takes a U-turn to join the internal cerebral vein.[1,2]

In term newborns ICH is relatively uncommon and has a different etiology. ICH in term neonates may be subarachnoid, subdural, intraventricular, parenchymal or epidural in location. In clinical practice, hemorrhage involving multiple compartments is not unusual.[5] Both subdural and subarachnoid hemorrhage in a term newborn is associated with birth trauma either from forceps delivery/vacuum extraction or unassisted vaginal delivery. Vertical moulding of skull causes stretching and tearing of blood vessels of tentorium, falx and dura

to produce SDH, while tearing of bridging blood vessels or dural sinuses causes SAH.[5,6] Intraparenchymal hemorrhage (intracerebral or cerebellar) is less frequent than subdural and subarachnoid hemorrhage in term newborns. Intraparenchymal bleeding in the full term newborn may occur as a result of birth asphyxia, instrumental delivery, infection, primary clotting abnormality or congenital vascular abnormality.[7] The incidence of intraventricular hemorrhage (IVH) in term newborns (4.6%) compared to preterm newborn (50%) is very low, probably due to greater maturity of the brain at term. In the term newborn, intraventricular hemorrhage commonly originate from choroid plexus (cryptic hemangioma) or as an extension of the thalamic hemorrhage or subependymal GM bleed.[8] Epidural hemorrhage is rare in term newborn because the middle meningeal artery, which is not yet encased within the bone, moves freely away from displacements of the skull. Epidural hemorrhage, however, may occur in the newborn, in absence of skull fracture, during a difficult forceps extraction when an external forceps causes the outer layer of dura to detach from the inner table of skull. [9]

Several risk factors have been reported in term newborns with ICH. Maternal risk factors causing ICH in the first neonatal week includes usage of drugs (such as aspirin, cocaine), pregnancy-induced hypertension, placental abruption, placental alloimmunization and autoimmune disorders. Major perinatal risk factor are birth trauma, low Apgar score, resuscitation at birth, thrombocytopenia, breastfed infants who received no vitamin K, inherited coagulopathy, disseminated intravascular coagulopathy, increased cerebral venous pressure, prolonged labor, unassisted vaginal delivery, forceps delivery, suction cup, and cesarean-section (sometimes).[10]

3. Clinical presentation

GM-IVH in premature infant is typically diagnosed during the first week of life, 50% on the first day and 90% within the first 4 days. GM-IVH is usually subependymal and asymptomatic, diagnosed by routine screening cranial ultrasound (CUS) in 25-50% of premature infants less than 1,500 gm birth weight and less than 32 weeks' gestation. Clinically symptomatic cases with large hemorrhage and its complication may present with various degree of altered consciousness, cardiorespiratory deterioration, unexplained drop in hematocrit, acidosis, blood glucose alteration, inappropriate antidiuretic hormone secretion, severe apnea or neonatal seizure, bulging fontanelles, abnormal eye movement or alignment, abnormal pupillary response, and abnormal neuromotor examination (hypotonia, decreased motility, tight popliteal angle). [1,3]

The pattern of hemorrhage also differs from GM hemorrhage common in preterm newborns in having a later onset between the 4th and 10th days after birth. Neurologic manifestations like neonatal seizure, decreased level of consciousness, increased intracranial pressure are the most common presentations of ICH in term newborns. The newborn's history, maternal and family history and perinatal risk factors may suggest the diagnosis of ICH.[5]

4. Role of neuroimaging

4.1. Germinal Matrix-Intraventricular Hemorrhage (GM-IVH) in preterm infants

For years neonatal cranial ultrasound (CUS) has been the key diagnostic tool for GM-IVH in premature infants due to its widespread availability, relative low cost, direct bedside scanning and high resolution to detect GM-IVH. CUS is nearly as accurate as CT but much less stressful for an ill premature infant. Diagnostic screening with CUS is recommended in all premature infants (less than 1,500 gm birth weight and less than 32 weeks' gestation) during the second week of life (after which further bleeding is uncommon) or earlier if clinical conditions indicate. [11] Doppler ultrasound can also be used for the imaging and flow velocity measurements of the terminal vein. [12] CT had been used in the original studies to grade the GM-IVH, however, it is no longer recommended for diagnostic purpose due to the adverse effect produce by ionizing radiation on immature brain. MRI is superior to CUS and CT for detection of associated white matter (WM) abnormalities and for identifying hemorrhages particularly small petechial hemorrhage, subacute to chronic hemorrhage and for extracerebral or posterior fossa hemorrhage. [13] The severity of GM-IVH has been evaluated by Papile [14] and Volpe's [15] grading system. When bleeding is confined to the subependymal region, it is classified as grade I; grade II is extension of hemorrhage into non distended lateral ventricle(s) where blood fills less than 50% of the ventricular diameter; in grade III, extensive intraventricular hemorrhage fills greater than 50% of the ventricular diameter leading to hydrocephalus; whereas, grade IV is periventricular hemorrhagic infarction (PVHI). [14,15] Most cases have grade I or grade II intraventricular hemorrhage and do not show late sequelae. [16,17] Infants with grade III or IV hemorrhage have high incidence of neurologic sequelae (approx. 30% will have severe cerebral palsy or mental retardation). [18,19]

Once GM-IVH is diagnosed, follow-up CUS examinations are necessary to determine its complications like periventricular hemorrhagic infarction (PVHI) and post-hemorrhagic hydrocephalus (PHH) and associated cerebellar hemorrhagic injury (CHI), periventricular leukomalacia (PVL), and SAH. [1,4]

Periventricular hemorrhagic infarction (PVHI), classified as grade IV GM-IVH, is a complication of GM-IVH. As previously thought, it is not due to rupture of ependymal lining and extension of intraventricular hemorrhage into the periventricular white matter; rather it occurs due to compression of the terminal vein by GM-IVH resulting in impaired venous drainage and congestion of the medullary veins, which in turn leads to hypoxia-ischemia, infarction and finally hemorrhagic transformation in the periventricular white matter. [20] PVHI can be associated with all grades of GM-IVH (grade I-III) and may be unilateral (65-75% cases) or bilateral (symmetrical or asymmetrical). The severity of PVHI can be graded based on three CUS parameters: (i) extent, (ii) bilaterality, and (ii) the presence of a midline shift. [21] Decreased flow velocity and displacement of the terminal vein can be seen in surviving infants with PVHI using Doppler flow velocimetry. [22] PVHI is in the distribution of the fan-shaped periventricular medullary veins. Intravascular thrombi within the medullary veins can be demonstrated on T2-weighted MRI as linear abnormalities in the WM of centrum semiovale. [20] In living infants, venous infarction usually evolves to produce a porencephalic cyst and

rarely multiple cysts. The evolving cyst(s) are associated with the destruction of motor and associative WM axons and preoligodendrocytes. These infants have a high incidence of hemiplegia later in their life.[23] Asymmetric myelination of the posterior limb of the internal capsule on MRI at term has been suggested as an early predictor of hemiplegia in PVHI. [24]

Incidence of ventricular dilatation increases with the severity of GM-IVH. CUS is an ideal tool for monitoring ventricular dilatation in newborns with open fontanelle. Detailed imaging with MRI is usually required prior to shunt surgery and for monitoring the progression or shunt complication after closure of the fontanelle. Posthemorrhagic hydrocephalus (PHH) may be progressive (due to obstruction by blood clot or secondary inflammatory changes which interferes with CSF flow), nonprogressive (due to parenchymal loss secondary to PVHI or PVL) or a combination of the two. PHH survivors with grade III and IV GM-IVH have high risk of significant neurodevelopmental sequelae (e.g. quadriparetic cerebral palsy and/or profound mental retardation).[3,25]

A very high association (77%) has been reported between the cerebellar hemorrhagic injury (CHI) and supratentorial GM-IVH. CHI can result from cerebellar GM hemorrhage (subependymal or subpial), primary hemorrhage, ischemic hemorrhagic transformation of either arterial or venous origin, or dissection of blood through the fourth ventricle or subarachnoid spaces following massive supratentorial GM-IVH. The location of CHI could be unilateral, vermian, bilateral or a combination of these. Mastoid CUS view helps to detect CHI in 3% of premature infants. MRI detects small petechial cerebellar hemorrhages not visible on CUS. CHI may eventually lead to several types of atrophic changes. 40% of CHI survivors have global developmental (cognitive and social communication disabilities) and functional deficits (motor deficits).[3,26]

A strong association between GM-IVH and periventricular leukomalacia (PVL) has been suggested. GM-IVH and PVL may develop in parallel, the ischemic injury may injure the GM and the periventricular WM leading to both GM-IVH and PVL. The CUS markers of cystic and diffuse PVL include echolucencies, echodensities and nonprogressive ventriculomegaly.[3,27]

Subarachnoid hemorrhage (SAH) is relatively common in premature infants with GM-IVH. The true incidence of SAH is not known as it is difficult to visualize the extra-axial hemorrhage by CUS. MRI is the modality of choice to detect SAH. SAH could be one of the reasons for PHH (obstructive arachnoiditis), neonatal seizure (irritation of cerebral convexity) and cerebral/cerebellar growth impairment.[28,29]

Impaired cerebellar and supratentorial gray matter growth has been reported in GM-IVH survivors. The complicated GM-IVH (PVHI and PVL) causes impaired growth and development of the contralateral cerebellar hemisphere due to injury to specific supratentorial projections (crossed cerebellar diaschisis).[28] The uncomplicated GM-IVH (without parenchymal involvement) is associated with impaired growth of the supratentorial gray matter, probably because the GM destruction prevents the neuronal and astrocyte precursor cells from reaching their cortical destination. In addition, SAH (circulating free radical) may directly injure the cerebral cortex surface.[29]

4.2. Intracranial hemorrhage (ICH) in term newborns

Subarachnoid hemorrhage (SAH) is the most common type of hemorrhage among the symptomatic term newborns.[6] On FLAIR (fluid attenuated inversion recovery) sequence of MRI, SAH is detected as hyperattenuating fluid in the basal subarachnoid spaces or along the cerebral sulci. Extensive subarachnoid hemorrhage may be difficult to distinguish from subdural hemorrhage and the two may co-exist. [3]

Subdural hemorrhage (SDH) is the most frequent hemorrhage among asymptomatic term newborns.[5] SDH is usually infratentorial, may result from rupture of the vein of Galen, straight or transverse sinus. On imaging, SDH can be seen as a crescent-shaped hyperattenuating region conforming to the adjacent brain. Small posterior fossa SDHs are common in infants and are usually of no clinical significance; however, when large, may result in compression of the brain stem and death. Infratentorial SDH may be difficult to distinguish from transverse sinus thrombosis. The two may co-exist or a SDH may compress the sinus predisposing to thrombosis. Convexity SDH are less common than posterior fossa hemorrhage and the two may co-exist. Rupture of superficial cortical veins gives rise to convexity SDH, which may be accompanied by SAH. Convexity SDH is mainly unilateral. Large convexity hemorrhage may be associated with infarction of the brain either from arterial occlusion or impaired venous drainage. Associated parenchymal hemorrhage either due to hemorrhagic tendency or in association with infarction may also occur.[3]

Large SDH may result in impairment of CSF flow and associated ventricular dilatation or widening of the extracerebral space (external hydrocephalus). The evolution of SDH may result in the formation of a subdural effusion which may remain at the site of a previous SDH for months and may be associated with rebleeding.[3]

Parenchymal hemorrhagic lesions may co-exist with hemorrhage elsewhere in the cranium. Parenchymal hemorrhage may be focal or multifocal and of any size. Multifocal small hemorrhages may be found in term infants presenting with convulsions during the first few days of life. Thalamic hemorrhage is usually unilateral and associated with IVH. Primary thalamic hemorrhage needs to be distinguished from the bilateral thalamic abnormalities seen in HIE. The thalamic lesions in HIE are focal, usually involving the lateral thalamic nuclei and sometimes the medial nuclei, these lesions have high signal intensity on T1-weighted images and low signal intensity on T2-weighted images due to capillary proliferation in region of infarction (not due to hemorrhage). However, infants with HIE may develop large intracranial hemorrhage. Basal ganglia hemorrhage may occur as an isolated event in term newborn, sometimes it is difficult to differentiate it from a hemorrhagic infarction involving a deep branch of middle cerebral artery. Cerebellar hemorrhage may be primary, secondary to venous infarction or may complicate massive intraventricular or subarachnoid hemorrhage. The MR appearance of parenchymal hemorrhage varies with time depending on the oxidation state of hemoglobin.[30]

5. Prevention and management

5.1. GM-IVH in preterm infants

Modern practice should emphasize on (i) prevention of GM-IVH, (ii) halting its progression, and (iii) reducing its complications. Important preventive measures include (i) special obstetric care for high-risk pregnancies, (ii) treatment of bacterial vaginosis for reducing premature delivery, (iii) prevention of imminent premature labor using tocolytic agents, cesarean section delivery in selected cases, and (iv) maternal administration of magnesium sulfate. In addition, optimal ventilation and strict hemodynamic control of the premature infant are the cornerstones of preventing GM-IVH and its progression. Several postnatal pharmacological agents for prevention of GM-IVH are still under trial.[25,31,32]

PHH, a complication of GM-IVH has a very unpredictable course. 60% of the infants may undergo spontaneous resolution while 40% may require a ventriculoperitoneal shunt, the definitive treatment of progressive PHH.[25] Repeated lumbar puncture may temporarily arrest the progression of PHH, but the long-term benefit of this approach remains unknown.[3]

5.2. ICH in term newborns

The single most important primary prevention is successful accomplishment of a vaginal delivery with or without obstetric instrument. However, forceful vaginal delivery should not be attempted if either vacuum extraction or forceps delivery has failed.[33]

Medical interventions should be implemented on the very first clinical suspicion of ICH. The goal of medical therapy is to provide adequate ventilation, prevent metabolic acidosis, to keep vital organs well perfused and to control seizure activity. Sick newborns with ICH are managed in the intensive care unit. Any treatable etiological factor (e.g. sepsis, dehydration, thrombocytopenia, vitamin K deficiency or coagulopathy) should be identified and treated promptly. Most symptomatic newborns with intracranial hemorrhage do not require neurosurgical intervention. Neurosurgical intervention could, however, be lifesaving in a situation in which there is a sudden clinical deterioration primarily due to rise in intracranial pressure as a result of massive ICH and PHH.[34] The secondary prevention is to limit the extent of parenchymal injury to the brain due to neurosurgery or hematoma.[35]

6. Summary

GM-IVH and its complications have potential impact on morbidity, mortality and long-term neurodevelopmental outcome. The mechanism of GM-IVH is multifactorial and involves a combination of vascular anatomic immaturity and complex hemodynamic factors. Goals are prevention of GM-IVH, halting its progression and reducing its complications.

A strong association between traumatic deliveries especially vacuum extraction/forceps delivery and hemorrhagic lesions has been well established in term newborns. Hemorrhage

is often present at more than one site. MRI can be used to time the onset of lesions. Hemorrhage may be primary or secondary and occur within an arterial or venous infarct. Neurodevelopmental outcome varies with the site of hemorrhage and the underlying cause. In the majority of term newborns with ICH, medical therapy is the primary mode of treatment; rarely, surgical intervention may be needed in selected cases.

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