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Chapter

Germinal Matrix-Intraventricular Hemorrhage: Current Concepts and Future Direction

Sadhika Sood and Rohit Gulati

Abstract

Germinal Matrix Hemorrhage-Intraventricular hemorrhage (IVH) is a bleed of multifactorial etiology involving the highly vascular and delicate neuro-glial precursors in the developing brain. It poses a challenging complication in preterm newborns. This chapter provides a focused discussion on the current concepts in pathogenesis, management, and complications of IVH. The radiological findings at diagnosis and follow-up and the cytological features of CSF will be valuable to both frontline and diagnostic healthcare providers. The chapter also reviews the ongoing scientific development in the field. The authors believe that this chapter will be a valuable tool for all healthcare providers (students, physicians, and in nursing care) in managing this challenging condition.

Keywords: Germinal matrix hemorrhage, intraventricular hemorrhage, IVH, intracranial hemorrhage, superficial siderosis, central nervous system, cerebrospinal fluid, genetic alterations, cranial ultrasound, preterm complications, low birth weight

1. Introduction

The germinal matrix (GM) is a specialized layer of glial and neuronal precursor cells in the periventricular region of the brain with high metabolic activity, which is strongly dependent on its rich vascularity and rapid angiogenesis [1]. The dense and fragile vasculature makes GM selectively vulnerable to hemorrhage. Germinal matrix – intraventricular hemorrhage (GM-IVH) is the most common type of intracranial hemorrhage in preterm infants. A combination of increased perinatal stress, poor cerebral autoregulation, and inherent fragility of the nascent vessels in the germinal matrix increases the likelihood of the development of GM-IVH in preterm infants. Also, there is evidence of occurrence in-utero and among full-term infants, however, such cases are rare [2]. The germinal matrix disappears by 36–37 weeks of gestation (wg), so GM-IVH is more likely in preterm infants than full term.

The global incidence of GM-IVH among preterm infants ranges from 14.7% to 44.7%, with variations across gestational age groups, countries, and antenatal and neonatal care [3]. The widespread use of cranial ultrasonography since the early 1980s, increasing knowledge of risk factors, antenatal steroid usage, and improved intensive care have improved incidence, survival, and morbidity of GMH [4]. However, GMH continues to remain a significant healthcare issue in preterm infants and a recognizable cause of long-term neurological and behavioral issues in survivors.

2. Germinal matrix-intraventricular hemorrhage

2.1 Pathogenesis

Developmentally, GM is located in the ganglionic eminence of the brain and is most pronounced in the caudate nucleus. The thickness and density of GM vasculature are higher than other brain areas and begin to decrease after 24 weeks of gestation (wg) and almost disappear at 36–37 wg with increasing fetal maturity [1, 5]. A significant bleed in the highly vascular GM breaks the associated ependyma to involve the lateral cerebral ventricle constituting intraventricular hemorrhage (IVH) [6, 7]. The incidence of GMH-IVH increases with decreasing gestation age at birth in preterm infants [8–10].

The pathogenesis of GM-IVH is complex and heterogeneous. The blood-brain barrier (BBB) associated with GM vasculature is distinct from the remaining areas in the brain due to diminished: 1) pericytes, 2) fibronectin in the basal lamina, and 3) GFAP (glial fibrillary acidic protein) in astrocyte endfeet (**Figure 1**). The paucity of three essential components of the BBB leads to the altered structural integrity of GM vasculature. First, pericytes play an essential role in BBB development, especially in early angiogenesis, extracellular matrix production, and endothelial maturation [11]. The paucity of pericytes in GM is associated with diminished levels of TGF- β [12] and predisposition to hemorrhage in dilatated blood vessels in experimental models [13]. Second, fibronectin, a high molecular weight glycoprotein, is selectively deficient in the GM basement membrane [14]. Fibronectin polymerizes to provide structural integrity to blood vessels and is dependent on TGF- β for its upregulation. While other basement membrane components, including Collagen I, II, IV, laminin, and perlecan, are similar to other components in the human brain [14, 15]. Third, astrocytes provide vascular integrity by sheathing the predominance of the BBB with their GFAP rich extensions (endfeet). Autopsy studies in premature infants show decreased GFAP expressing astrocyte endfeet in GM than



Figure 1.

Diagrammatic representation of the coronal section of a preterm brain to highlight the factors contributing to the labile structure of the blood brain barrier in the germinal matrix and pathogenesis of the GM-IVH.

cerebral cortex and white matter [16]. These make the blood–brain barrier fragile and more susceptible to hemorrhage.

Microscopically the GM vasculature has been described as circular in coronal sections, compared to elongated and flat vessels in other areas of the brain, representing the immaturity of the vessels from rapid angiogenesis and high endothelial turnover [17]. In addition, immunofluorescence and electron microscopy have shown a paucity of pericytes in the GM vascular environment [12].

Finally, fluctuations in cerebral blood flow precipitate into hemorrhage in the delicate GM. In addition, defects in the hemostatic mechanisms expectantly promote hemorrhage [6, 7].

Germinal matrix cells being metabolically active precursor neuronal and glial cells in the early stages of maturation demand a specialized and rich blood supply. This requirement is met by accelerated angiogenesis dependent on high levels of vascular endothelial growth factors (VEGF) and angiopoietin-2 and low expression of TGF- β [1]. Also, the GM is in a state of relative hypoxia, a driving force for continuous angiogenesis [6, 7]. Intriguingly, this may explain the near absence of GM-IVH after over 3–5 days of birth irrespective of the duration of gestation. Likely, higher oxygenation following birth inhibits rapid angiogenesis. Thus, a labile combination of metabolically active immature/precursor cells with a rich but "structurally weak" vasculature provided a high-risk background for bleeding, especially with high-velocity cerebral blood flow.

Among many factors associated with alteration in cerebral blood flow, severe respiratory distress syndrome, patent ductus arteriosus, high central venous, and hypercarbia are most prominent. While autoregulation maintains constant cerebral blood flow, this mechanism is impaired in premature infants with lower birth weight. Thus, changes in blood volume or pressure are more likely to affect cerebral circulation. Interestingly, the results of studies directly comparing impaired auto-regulation with GMH-IVH have been mixed [18–20] and provide an opportunity for further research in this direction. As seen in pneumothorax and mechanical ventilation (on high mean airway pressure mode), high central venous pressure stands out as a solid contender to contribute to IVH. This is also concordant with the venous nature of GM-IVH [21]. Interestingly, mechanical ventilation in synchronized and intermittent mandatory mode prevents higher velocity/turbulence of cerebral blood than fixed frequency/pressure modes.

Significant other risk factors affecting include prolonged labor, maternal chorioamnionitis, early-onset sepsis, development of respiratory distress, recurrent tracheal suctioning (supportive care especially during mechanical ventilation), and hypoxia. While most of these factors impact cerebral blood flow, infectious and hypoxic etiologies alter the GM microvasculature. The role of hypotension and rapid sodium bicarbonate infusion in the causation of IVH are inconclusive.

2.2 Diagnosis

Clinical manifestations of GM-IVH include asymptomatic to subtle alterations in consciousness, limb and eye movement, and changes in muscular tone following IVH. Further, severe cases may be associated with cardiorespiratory distress and progression to seizures, hypotonia, or decerebrate posturing [22].

Cranial ultrasound (CUS) remains the most practical and well-utilized approach for diagnosing and monitoring GM-IVH evolution. Newer ultrasound devices with high-frequency transducers allow for enhanced evaluation. Epidemiologically, surviving infants born preterm at 24 weeks have a higher incidence (10–25%) of high-grade GM-IVH (grade 3–4) as compared to preterm infants born after 28 weeks (<5%) [8–10]. Almost half the cases of postnatal GM-IVH present on the first day of life, with nearly ~90% presenting within the first 72 hours. As discussed in pathogenesis, increased oxygenation after birth likely stabilizes the GM-BBB and makes infants almost resistant to GM-IVH after the first week of life irrespective of gestational age [23]. Therefore, regular CUS schedules have been recommended based on the gestational age at birth and when otherwise clinically indicated [24].

Traditionally, GM-IVH had been graded into four categories based on the extent of hemorrhage beginning in the venule that drains into the subependymal collector veins: grade-1 representing subependymal hemorrhage; grade-2 with limited (filling <50% of normal-sized ventricles) IVH; and grade-3 with extensive IVH. Grade-4 was defined as IVH with parenchymal extension [25]. However, the latter was better identified as parenchymal venous infarction (PVI), though parenchymal extension does also rarely occurs [26]. Interestingly, PVI may occur in all, including lower grades (1 and 2) of GM-IVH [22]. Since PVI is associated with long-term complications and risk of mortality (based on location and extent), a three-stage grading with an additional description of PVI has been recommended [22, 24] (**Figure 2**). In addition, early GMH may alter local neuronal and glial precursors with neurological consequences, description of location of bleed in addition to grade is suggested.

On CUS, grade 1 GMH is subependymal, hyperechoic, and globular. Evaluation in both coronal and sagittal planes helps distinguish a small GMH from choroid plexus on an initial diagnostic scan. Also, echogenicity at the caudothalamic groove (usual site for GMH) in the late neonatal period likely represents hyperechoic germinolysis and not late GMH [27]. Distinguishing pure subependymal bleed from IVH may be challenging on CUS. Indirect signs of hyperechoic ependymal changes, which usually occur 2 to 4 weeks after IVH, and insonation through mastoid fontanelle are helpful in this distinction [24] and aid prognostication and counseling.



eurUS.brain: GMH/IVH: GMH origin and grading

Figure 2.

GMH/IVH: Origin and grading. GMH starts in a venule that drains into lateral subependymal collector veins; it extends into white matter by virtue of venous compression and infarction; bottom row: T2-weighted MRI of GMH with limited IVH and limited venous infarct. (Derived from Parodi et al. [24]).

Clot changes overtime should also be recorded. A subacute clot or clot remnants early after birth may represent an antenatal hemorrhage.

PVI typically is identified as a triangular echo density in the periventricular white matter adjacent to the GMH. The infarct may not touch the GMH initially and may or may extend into the GMH depending on severity. Infarcts eventually evolve into cavitary lesions, and porencephaly ensues in 1–2 months [24]. This cavitation is asymmetric, unilateral, and permanent in contrast to cysts of periventricular leukomalacia (symmetric, bilateral, and transient) [22].

A quarter of infants with GM-IVH develop posthemorrhagic ventricular dilatation (PHVD) due to imbalanced production and resorption of CSF. This dilatation occurs a few days to weeks after IVH and is followed by subsequent regression [28]. PHVD is more common in higher grades but can occur in all cases with IVH. Thus, serial CUS is recommended in IVH cases until term-equivalent age. While a subset of cases resolves spontaneously, balancing the complications of compression versus those of surgical management (tapping, shunt) remains a challenge [29]. PVHD, as expected, is associated with a poor neurological outcome in the long term.

2.3 Genetic factors in GM-IVH

Thrombophilic genotype is frequently associated with a subset of severe GM-IVH patients with atypical clinical presentation. The atypical presentation includes periventricular hemorrhagic infarction presenting within 6 hours of birth or after four days of birth, in the absence of secondary inciting factors like sepsis. Factor V Leiden mutation was the most common genetic alteration, frequently with mothers being carriers. Prothrombin mutations and polymorphism of the *MTHFR* gene were also reported [30]. Previous studies have shown an association of a thrombophilic profile with early grade 1–2 GMH [31, 32]. Polymorphism of TNF- α has been associated with an increased risk of GMH-IVH [33]. Of interest, the same study showed an association of polymorphism in TGF- β with a fatal outcome but not with IVH.

Mutations of the *COL4A1* gene, coding for type IV collagen α -chain-1, have rarely been reported in a subset of preterm IVH [30, 34]. A pair of dizygotic twins showed a heterozygous duplication at exon 4 of the highly conserved and ubiquitous *COL4A1*. Interestingly, the mother and maternal grandmother of the twins were heterozygous carriers and were asymptomatic. Also, the study evaluated 39 other cases of preterm IVH and detected no mutations in *COL4A1*, indicating its rarity [34]. Previous studies have revealed no alteration in type IV collagen components in the basement membrane in GM [14, 15].

Experimental models have shown tropomyosin receptor kinase B (TrkB) to influence the inflammatory status in the microenvironment following GMH by influencing the phosphatidylinositol-3-kinases (PI3K)/protein kinase B (Akt)/ forkhead box protein O1 (FoxO1) pathway [35].

Overall, genetic alteration in components of vascular structure, coagulation mechanism, and inflammatory pathways have been described in a subset of GM-IVH. The authors believe that recent progress in inflammation and growing knowledge of inflammasome complex may be employed towards further research in this direction.

2.4 Prevention

Our understanding of IVH due to a structurally labile and immature vasculature in the germinal matrix and alterations in cerebral blood flow in premature infants forms the focus of most strategies to prevent GM-IVH. In principle, delay of preterm birth relies on decreasing GM vascular density with advanced gestational age. Moreover, high postnatal oxygen levels in the infant mediate the stabilization of the GM blood vasculature and ensure freedom from IVH in 3–5 days after birth, highlighting the critical importance of timeliness in management and prevention.

2.4.1 Specific strategies for prevention

Steroids (glucocorticoids) like dexamethasone and betamethasone are administered to pregnant women in premature labor under 34 wg. Glucocorticoids cause a selective inhibition of blood vessels in the GM- BBB that lack adequate pericyte coverage, inhibit angiogenesis, and subsequently stabilize vasculature [12, 14, 36]. In addition, prenatal corticosteroid assists in development lungs surfactant and protect against respiratory distress syndrome. The latter effect also prevents turbulent cerebral blood flow. Prenatal corticosteroid usage is one of the rare factors that has consistently been associated with a reduction in occurrence and severity of IVH [37, 38].

Indomethacin is a non-selective cyclooxygenase (COX) inhibitor and reduces severe IVH, especially in males [39, 40]. Indomethacin is employed for closure of patent ductus arteriosus that in turn prevents altered cerebral blood flow. It also suppresses angiogenesis by COX-2 inhibition [1]. Although indomethacin can decrease IVH in the short term, its usage is not associated with reducing long-term neurological complications such as cerebral palsy, deafness, and blindness [41–43]. Hence, indomethacin has limited acceptance and is based on regional preferences.

Prenatal care and transport: It is recommended that pregnant mothers be given adequate antenatal care and those in preterm labor be transported (while pregnant) to tertiary care units better equipped to manage both mother and child. Transportation of extremely premature infants has long been associated with the increased occurrence and severe IVH [44].

It is beneficial to note that antenatal phenobarbital and magnesium, vitamin-K, and fresh frozen plasma did not influence the occurrence of IVH [45–49].

Intriguing preclinical studies show time-sensitive windows for therapeutic pharmacological targeting of the GM "weakened" BBB by altering the integrin- β 8 and TGF- β pathways [50].

2.5 Management

Currently, there is a paucity of active treatment strategies for the management of established GM-IVH. Maintaining blood pressure levels and respiratory status, with judicious use of IV fluids, blood transfusions, and respiratory support (if needed), might prevent the progression of hemorrhage. Electroencephalogram (EEG) monitoring should be done in the presence of seizures [3]. Apart from supportive treatment, emphasis is laid on the preservation of cerebral perfusion and the prevention of complications. Monitoring twice weekly with CUS for four weeks (or similar) and then weekly till term equivalent age recommended to evaluate GMH and post hemorrhage hydrocephalus (PHH).

2.5.1 Post-natal effective nursing care

Multiple trials and observational studies have focused on the relative head position of premature infants soon after birth in relation to IVH. These positional strategies focus mainly on maintaining adequate cerebral blood flow.

While previous studies on the effect on neutral head position found no significant association with the occurrence of IVH [51], these studies were also limited

by small sample size [52]. More recently, efficient, supportive nursing intervention in premature infants during the first 72 hours of birth has been associated with decreased incidence and progression of GM-IVH [53]. This four-pronged approach includes midline head position, head elevation of the incubator, and slow vascular flushing/withdrawal of blood, and sudden elevation of the legs. First, the head in midline position ensures adequate venous drainage. Head rotation impedes jugular venous outflow on the ipsilateral side and may cause congestion, relative hypoxia and eventually aid GMH [54]. Second, incubator head lift (15–30 degrees) enhances gravitational cerebral venous drainage [55]. Third, sudden elevation of legs, as in to change diapers, may result in increased venous return, increase cardiac preload, thereby altering cerebral perfusion. Finally, avoiding rapid (lasting <30 seconds) vascular flushing/blood collection can avoid a transient though significant alteration in cerebral blood flow [56]. The effect of the intervention was stronger in infants born before 27 wg [53]. While previous studies on the effect on neutral head position found no significant association with the occurrence of IVH [51], these studies were limited by small sample size [52]. A more recent meta-analysis showed the limited utility of supine midline head position for the prevention of GM-IVH. However, midline head position with an elevation of incubator head was associated with lower mortality [57]. Overall, concomitant intervention with neutral head position, the elevation of incubator head, and avoidance of sudden leg elevation and sudden vascular volumetric changes provide evidence for a better outcome.

2.6 Complications and potential treatment strategies

The survivors of severe GMH frequently develop post-hemorrhagic hydrocephalus (PHH). A subset of these cases requires surgical shunting, which is not without its complications, including infections, obstruction, and displacement [58]. In addition, the cerebroventricular dilatation causes physical pressure on the brain parenchyma and is associated with neurological impairment in the long term. Mechanism of PHH: Obstruction of the cerebral aqueduct, foramina of Luschka and Magendie, and subarachnoid outflow passages by blood clots/microthrombi may cause PHH. Historically, fibrinolytic therapy has not been successful in the management of PHH.

The tissue macrophage system responds to intracranial hemorrhage similar to other locations in the body. Red blood cells (RBCs) are phagocytosed by macrophages (erythrophages), and subsequently, hemoglobin is degraded. Iron mainly converts to coarse, irregular hemosiderin granules and porphyrin rings into bilirubin. In exceptional circumstances with closed compartments and lower oxygen tension, such as intracranial bleed, hematoidin, a crystalline, reduced biliverdin product may be formed. Post hemorrhagic components are frequently encountered on light microscopic evaluation of the cerebrospinal fluid (CSF), as early as 1–2 days after bleeding [59, 60]. In addition to the erythrophagocytosis, cellular components of the ventricular lining (ependymal cells and choroid plexus cells) and rarely, precursor germinal matrix cells (due to close proximity with disrupted ventricular lining) may be identified in CSF analysis [61–63].

Superficial siderosis (SS) is the deposition of hemosiderin in the subpial layers of CNS, resulting in sensorineural hearing loss and cerebellar ataxia in most adults cases [64]. Susceptibility weighted imaging (SWI), an MRI sequence, identified SS in the ependymal layer, brain stem, cerebellum with vermis, and Sylvian fissures. Interestingly the depth of SS correlated with the increasing grade of GM-IVH. Also, brain stem and cerebellar SS appear to relate more to IVH than cerebellar hemorrhage [65]. A review of scientific literature shows the following current trends exploring the management of GMH and prevention of complications.

2.6.1 Iron in the manifestation of PHH

Experimental models have shown the role of iron (from red blood cells) to develop brain edema and acute ventricular dilatation [66]. As proof of principle, iron chelation with deferoxamine has showed reduced long term PHH after GMH in neonatal rats [67, 68]. Another group found biliverdin reductase to enhance CD36 expression in scavenging microglia and hematoma resolution through NOS/TLR4 pathway [69]. Additionally, iron overload has been associated with increased aquaporin-4 expression [70]. However, diuretic treatment has not been found to be beneficial.

Along similar lines, "normal appearing" white matter in preterm infants with severe GM-IVH, at term equivalent age, showed paramagnetic (positive magnetic) susceptibility, likely due to diffusion of iron into the periventricular white matter [71]. This radiological finding may be employed as an innovative methodology for future research focusing on the spatial impact of iron deposition on long-term neurological consequences.

2.6.2 Role of inflammation and gliosis

Post GMH levels of pro-inflammatory markers like TNF α are elevated. In response to hemorrhage and associated tissue injury, resident microglia are activated in an inflammatory process [72–74]. Additional experimental models have shown microglial proliferation surrounding the clot with phosphorylated ERK. Minocycline and cannabinoid receptor-2 agonists have also shown promise to curb down inflammation [75]. CD200Fc inhibits inflammation following GMH likely by mediating CD200R1/Dok1 pathway [76]. IVH has been shown to cause a TLR4 and NF- $\kappa\beta$ based inflammatory pathway mediated increase in CSF production in the choroid plexus. As a proof of principle, amelioration of these mediators was associated with control of CSF production and improvement in PHH [77]. The role of M2 microglia stimulation through the PPAR γ and CD36 scavenger receptor for shortterm resolution of hematoma has also shown promising results for further clinical evaluation [78]. NT-4 controls neuroinflammation by interacting with TrkB to induces PI3K-Akt pathway and inhibits downstream FoxO1 in experimental models [35]. These results promise potential for clinical utility in the management of PHH.

Extracellular matrix (ECM), especially components fibronectin and vitronectin, are elevated post-GMH and are hypothesized to deposit (like microthrombi), potentially causing CSF obstruction [75, 79–81]. TGF-β may be induced by thrombin and promotes the production of ECM, especially TGF-β1 isoform whose levels have been elevated in studies after GMH. It's inhibition has been associated with attenuated PHH and neurological decline [75, 81]. While GFAP expression is markedly increased in experimental IVH models, umbilical cord mesenchymal stem cell infusion has been associated with a decline in GFAP expression and subsequent PHH development [82]. The role of GFAP and astrocytes in gliosis post IVH requires further attention. More recently, astrogliosis was associated with redistribution of aquaporin-4 and altered CSF dynamics. Olomoucine controlled scarring and attenuated PHH by inhibition of cyclin-dependent kinase (CDK) [83]. Secukinumab, monoclonal IgG1κ targeting IL17a, is protective against reactive astrogliosis following GMH, partly by regulating IL-17RA/(C/EBPβ)/SIRT1 pathways [84].

2.6.3 Long term complications of low grade (grade 1: 2) GM-IVH

While neurological complications in survivors of high-grade GM-IVH are well documented, the impact of low-grade IVH currently continues to be better understood. Low-grade IVH was associated with moderate to severe neurodevelopmental impairment (NDI) and without association with cerebral palsy [85]. A case-controlled retrospective study using CUS found no significant impact of low-grade GM-IVH on neurological complications of cerebral palsy and neurodevelopmental delay evaluated during 18–30 months after birth [86]. Both these studies were limited in power and in analysis by more sensitive MR-based techniques [87]. A more recent MR-based study has revealed microstructural impairment of white matter related to neurodevelopmental impairment at 24 months in early GMH [88]. Similarly, magnetic resonance with 3D pseudo-continuous arterial spin-labeling (pCASL) perfusion sequence-based study has shown consistently lower CBF in the posterior cortical and subcortical gray matter regions in preterm neonates with low grade IVH [89]. This regional susceptibility also requires correlation with long term studies. From a developmental perspective, neurological alterations are not incompatible with low-grade IVH. GMH may lead to altered myelination in the white matter since ganglionic eminence is the seat of oligodendroglial precursor cells that migrate to cerebral white matter areas to produce myelin later in the third trimester [90]. Besides, GM is involved in the development of GABAergic interneurons significant for high-level cognitive function [91].

3. Conclusion

Germinal matrix intraventricular hemorrhage is the most common intracranial hemorrhage in newborns, particularly preterm neonates. Improvements in obstetric and neonatal care have led to increased survival of preterm infants. Despite extensive research and preventive measures, the incidence of associated complications and mortality remains high. The GM is highly susceptible to hemorrhage due to a combination of delicate vasculature and fluctuations of cerebral perfusion, uncontrolled by autoregulatory mechanisms. Genetic factors and coagulation disorders may factor in if present. Obstetric and neonatal clinicians should use the available knowledge to prevent the occurrence of and progressions of hemorrhages. Therapeutic options for the management of GM-IVH are predominantly limited to supportive care and monitoring. Shunts have proven to be effective in challenging cases of PHH. Current and ongoing improvement in the molecular understanding of GM-IVH and its complications using multi-omics investigations is essential to develop biomarkers and therapeutic strategies.

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Conflict of interest

The authors declare no conflict of interest.

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