Periventricular-intraventricular hemorrhage pathogenesis

Its pathogenesis is multifactorial and relates principally to a pressure-passive cerebral circulation, fluctuations in cerebral blood flow, and derangements of coagulation and fragility of the germinal matrix microvasculature.

The metabolically active germinal matrix (GM) is susceptible to hypotension and hypoperfusion which can lead to infarction. The GM is a vulnerable watershed zone supplied by Recurrent artery of Heubner, terminal branches of the lateral striate arteries and the anterior choroidal artery.

1. postnatal hypoxia due to respiratory distress syndrome related to hyaline membrane disease, pneumothorax and/or anemia can deprive the metabolically active GM of oxygen. This ischemia to the endothelial cells lining the capillaries makes them vulnerable to infarction and then disruption

2. hypercapnia maximally dilates the thin walled vessels of the GM. If this is followed by sudden increases in perfusion the result can be rupture of the vessels

3. increased venous pressure from any cause (labor and delivery, positive pressure ventilation, stimulation, endotracheal suctioning, myocardial failure from ischemia) can result in increased venous pressure in the GM leading to hemorrhage

4. dehydration followed by rapid resuscitation with hyperosmolar solutions increases the intravascular volume by osmotically encouraging the movement of fluid from tissues into the intravascular space. With associated increases in systemic blood pressure the GM capillaries are at increased risk of rupture.

Changes in systemic and cerebral hemodynamics in preterm infants during early transitional circulation are complex and may differ between infants with or without intraventricular hemorrhage (IVH).

In total, 43 infants born at median (range) 25 + 5 (23 + 3-31) had continuous near-infrared spectroscopy (NIRS) monitoring of tissue oxygenation index (TOI) and cerebrovascular reactivity within the first 48 h of life. Measurements of left and right cardiac outputs (LVO, RVO) and patent ductus arteriosus (PDA) were collected at 6, 12, 24, and 48 h of life.

LVO increased within the first 48 h in the IVH ($P = 0.007$) and no-IVH ($P < 0.001$) groups. The pattern of change in LVO and RVO was not different between these two groups. TOI was lower in the IVH ($P < 0.001$) group. A positive correlation between TOI and LVO ($P = 0.003$) and a negative correlation between the tissue oxygen reactivity index (TOx) and LVO ($P = 0.04$) were observed at 24 h of life in the IVH group. PDA diameter was not different between IVH groups at any time interval.

Cerebral oxygenation was lower and cerebrovascular reactivity was passive to systemic blood flow at 24 h in infants who developed an IVH [1)].

It is a complex developmental disorder, with contributions from both the environment and the genome. IVH, or hemorrhage into the germinal matrix of the developing brain with secondary periventricular infarction, occurs in that critical period of time before the 32nd to 33rd wk postconception and has been attributed to changes in cerebral blood flow to the immature germinal matrix microvasculature. Emerging data suggest that genes subserving coagulation, inflammatory, and vascular pathways and their interactions with environmental triggers may influence both the incidence and severity of cerebral injury and are the subject of this review. Polymorphisms in the Factor V Leiden gene are associated with the atypical timing of IVH, suggesting an as yet unknown environmental trigger. The methylenetetrahydrofolate reductase (MTHFR) variants render neonates more vulnerable to cerebral injury in the presence of perinatal hypoxia. The present study demonstrates that the MTHFR 677C>T polymorphism and low 5-min Apgar score additively increase the risk of IVH. Finally, review of published preclinical data suggests the stressors of delivery result in hemorrhage in the presence of mutations in collagen 4A1, a major structural protein of the developing cerebral vasculature. Maternal genetics and fetal environment may also play a role [2)].

1)

Sortica da Costa C, Cardim D, Molnar Z, Kelsall W, Ng I, Czosnyka M, Smielewski P, Austin T. Changes in hemodynamics, cerebral oxygenation and cerebrovascular reactivity during the early transitional circulation in preterm infants. Pediatr Res. 2019 Apr 27. doi: 10.1038/s41390-019-0410-z. [Epub ahead of print] PubMed PMID: 31029059.

2)

Ment LR, Adén U, Lin A, Kwon SH, Choi M, Hallman M, Lifton RP, Zhang H, Bauer CR; Gene Targets for IVH Study Group. Gene-environment interactions in severe intraventricular hemorrhage of preterm neonates. Pediatr Res. 2014 Jan;75(1-2):241-50. doi: 10.1038/pr.2013.195. Epub 2013 Nov 5. Review. PubMed PMID: 24192699; PubMed Central PMCID: PMC3946468.