Pathogenesis and Prevention of Intraventricular Hemorrhage

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KEYWORDS

• Germinal matrix hemorrhage • Intraventricular hemorrhage • Astrocytes • Pericytes • Angiogenesis • Glucocorticoids • Premature infants • Indomethacin

KEY POINTS

- Pathogenesis of intraventricular hemorrhage (IVH) is ascribed to the intrinsic weakness of germinal matrix vasculature and to the fluctuation in the cerebral blood flow.
- The germinal matrix displays accelerated angiogenesis, which orchestrates formation of nascent vessels that lack pericytes, display immature basal lamina low in fibronectin, and has astrocyte end-feet coverage deficient in glial fibrillary acidic protein. These morphologic and molecular factors contribute to the fragility of the germinal matrix vasculature.
- The fluctuations in the cerebral blood flow is attributed to the cardiorespiratory and hemodynamic instability frequently associated with extremely premature infants, including hypotension, hypoxia, pneumothorax, patent ductus arteriosus, and others.
- Prenatal glucocorticoids have emerged as the most effective intervention to prevent IVH. Therapies designed to enhance the stability of the germinal matrix vasculature and reduce fluctuation of cerebral blood flow could lead to strategies that are more effective in preventing IVH.

INTRODUCTION

In the United States, about 12,000 premature infants develop intraventricular hemorrhage (IVH) every year. The incidence of moderate-to-severe IVH has remained almost stationary during the last 2 decades.[1,2] IVH is a major problem in premature infants, as a large number of them develop neurologic sequelae.[3] Approximately 50% to 75% of preterm survivors with IVH develop cerebral palsy, mental retardation, and/or hydrocephalus.[3,4] Approximately, a quarter of nondisabled survivors develop psychiatric disorders and problems with executive function.[5–7] According to the US Census Bureau and the NICHD Neonatal Research Network, more than 3600 new cases of

Source of Funding: NIH/NINDS grant RO1 NS071263.
Conflict of Interest: None.
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Clin Perinatol 41 (2014) 47–67
http://dx.doi.org/10.1016/j.clp.2013.09.007 **perinatology.theclinics.com**
0095-5108/14/$ – see front matter

mental retardation each year are children who were born premature and suffered IVH.[8,9] Hence, IVH and its resultant neurologic and psychiatric sequelae continue to be a major public health concern worldwide.

IVH typically initiates in the periventricular germinal matrix.[10] This brain region is known to developmental neurobiologists as the ganglionic eminence (Fig. 1A). The germinal matrix consists of neuronal and glial precursor cells (see Fig. 1B, C) and is most prominent on the head of caudate nucleus. The subependymal germinal matrix is highly vascular and is selectively vulnerable to hemorrhage. After 24 gestational weeks (gw), thickness of the germinal matrix decreases, and it almost disappears by 36 to 37 gw. When hemorrhage in the germinal matrix is substantial, the underlying ependyma breaks and germinal matrix hemorrhage progresses to IVH, as blood fills the lateral cerebral ventricle.

PATHOGENESIS OF IVH

Pathogenesis of IVH is multifactorial, complex, and heterogeneous. An inherent fragility of the germinal matrix vasculature sets the ground for hemorrhage, and

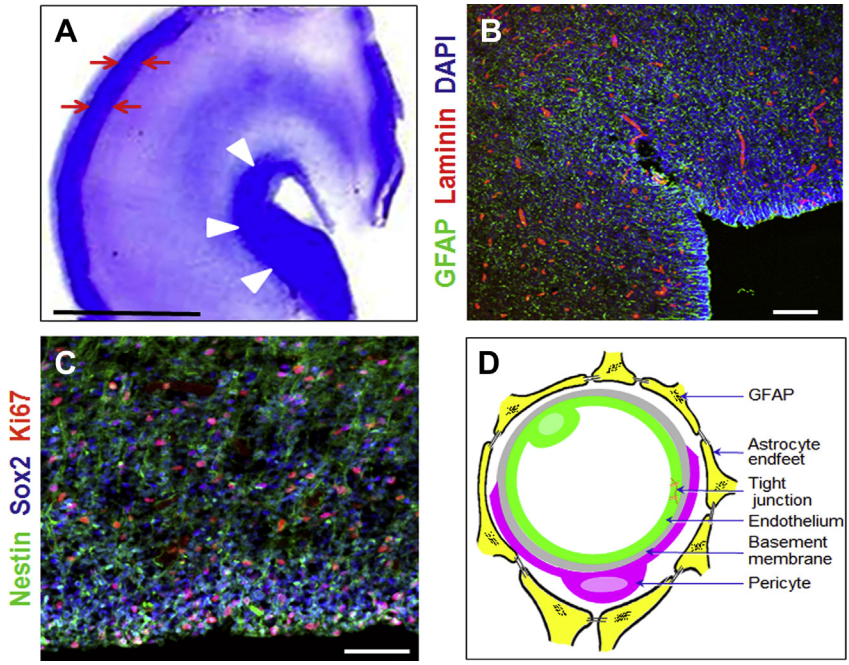

Fig. 1. Morphology of germinal matrix. (*A*) Representative cresyl violet staining of coronal section of the right-sided cerebral hemisphere of a 23-week preterm infant. Note cortical plate (*arrows*) and germinal matrix (*arrowheads*). Germinal matrix (*violet staining*) surrounds the whole ventricle, but is most conspicuous at the head of caudate nucleus. Scale bar, 0.5 cm. (*B*) Representative immunofluorescence of cryosection from germinal matrix of a 23-week premature infant labeled with DAPI (*blue*), GFAP (*green*), and laminin (*vascular marker, red*). Note germinal matrix is highly vascular (*vascular endothelium in red*) and enriched with GFAP (+) glial cells (*green*). (*C*) Coronal brain section was double labeled with nestin (*progenitor cells, green*), Sox2 (*radial glia, blue*), and Ki67 (*red, proliferation marker*). Note nestin and Sox2 positive cells are abundant in the germinal matrix. Scale bar; 100 (*B*) and 50 μm (*C*). (*D*) Schematic drawing of the blood brain barrier in cross-section showing endothelium, endothelial tight junction, basal lamina, pericyte, and astrocyte end-feet.