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Commentary

New Concepts in the Pathogenesis of Germinal Matrix Intraparenchymal Hemorrhage in Premature Infants

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In this issue of *AJNR*, Ghazi-Birry et al (1) present a detailed microscopic study of the vascular architecture of the germinal matrix in premature infants, and show that the great majority of germinal matrix hemorrhages are not arterial but venous in origin. Further, they demonstrate that tunneling of blood along perivenous spaces results in distortion, compression, and occlusion of adjacent veins. Their findings suggest that local elevations in venous pressure within the germinal matrix play a major role in the pathophysiology of this lesion. However, it would be simplistic to think that peculiarities in the vascular anatomy of the premature germinal matrix are the sole cause of its vulnerability to hemorrhage. In the next few paragraphs I will attempt to answer why the venous origin of germinal matrix hemorrhage is important, how this new finding fits with current knowledge about the developing brain, and how the brain responds to the physiologic stresses of premature birth.

Many factors have been clinically and experimentally implicated in the pathogenesis of germinal matrix hemorrhage (2). However, despite the multiplicity of potential causes, there are two interrelated phenomena that might explain the perivenous hemorrhages described by Ghazi-Birry et al. The first of these processes is hypoxic ischemia, or diminished cerebral oxygenation. Reduced oxygen delivery to the premature brain commonly occurs under a variety of circumstances, including hypoxemia, systemic hypotension, and reduced hemoglobin concentration (2, 3). There is increasing evidence that both the destructive processes and the hemodynamic consequences of hypoxic ischemia are related to excessive synaptic accumulations of excitatory amino acids such as glutamate. In addition to inducing critically sustained cell membrane depolarization and uncontrolled neuronal autolysis (3, 4), the glutamate cascade also stimulates the production of nitric oxide by induction of the enzyme nitric oxide synthase (4). This potent vasodilator can result in dramatic hyperemia in areas of injured brain. In experimental models, a 300% to 400% increase in regional cerebral blood flow has been demonstrated after direct injections of micromolar concentrations of a glutamate analogue (*N*-methyl-D-aspartate [NMDA]) (5).

There is also increasing evidence that the developing brain is particularly susceptible to excitotoxic injury. In rats, for example, brain injury related to NMDA injection is 60 times greater in the neonatal animal than the adult (6).

The second process involves alterations in cerebral hemodynamics related to extrauterine life as a sick premature infant. Many of the therapeutic maneuvers performed in caring for these infants have been associated with an increased risk of germinal matrix hemorrhage, and appear to alter intracranial venous hemodyamics significantly. Increased venous pressure has been demonstrated in infants breathing out of sequence with a mechanical ventilator, during endotracheal tube suctioning, and with high peak inspiratory pressures (2). Other factors such tension pneumothorax, exchange transfusions, rapid infusions of colloid, and myocardial injury caused by asphyxia can also have dramatic effects on venous pressure and hemodynamics (2, 7, 8).

It is likely that the combined destructive and hyperemic effects of hypoxic ischemia and therapy-related hemodynamic alterations on a vulnerable vascular bed eventually lead to germinal matrix hemorrhage in the premature infant.

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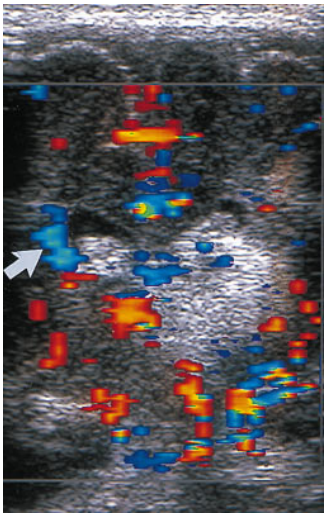

Fig 1. Coronal color Doppler image at the level of the foramen of Monro shows a patent right terminal vein (*arrow*) and a large left germinal matrix hemorrhage with no demonstrable flow in left terminal vein.

What Ghazi-Birry and colleagues contribute to this story is that the vulnerable part of the vascular bed is the small vein of the germinal matrix. This is important because the "cascade" of venous bleeding, perivenous leakage, and distortion of larger veins appears to be the same mechanism that results in larger intraparenchymal hemorrhages. Histologic studies of intraparenchymal hemorrhage and color Doppler ultrasound observations suggest that these hemorrhages are the result of venous infarction caused by obstruction of terminal veins by large germinal matrix hemorrhages (Fig 1) (9, 10).

The principal consequences of germinal matrix hemorrhage are twofold. First is the potential for progression to more serious patterns of hemorrhage and their attendant complications. Second, germinal matrix hemorrhage also appears to destroy neurons that originate in the germinal matrix and are destined to populate layers II to VI of the cerebral cortex (11). This may explain some of the complex cognitive and attentional deficits seen in between 25% and 50% of premature infants (2). Thus, the prevention of germinal matrix hemorrhage continues to be an important goal.

It is too early to tell what the specific clinical implications of this new information will have on clinical care of the sick premature infant. Nonetheless, the venous origin of germinal matrix hemorrhage represents an important new piece of the puzzle in the understanding of brain injury in this at-risk population.

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