References


Germinal matrix haemorrhage: destroying the brain’s building blocks

The most skilled stonemasons cannot construct a cathedral without an ample supply of fine granite blocks. Likewise, the human brain cannot be built properly if stocks of neuroglial progenitors (the building blocks of the brain) are depleted by injury during the critical period of progenitor cell proliferation and migration, as occurs in germinal matrix haemorrhage in prematurity.

The article by Prof. Marc Del Bigio (2011), representing the analysis of a career-spanning autopsy cohort of preterm infants with and without germinal matrix haemorrhage, he addresses a persistent clinical concern facing paediatric specialists caring for survivors of prematurity: what are the consequences of germinal matrix haemorrhage on normal brain development at the microanatomic level, and do they explain observed neurodevelopmental and neuroimaging outcome data?

As a serious complication of prematurity, germinal matrix haemorrhage and its frequent accompaniment, intraventricular haemorrhage, have been recognized in the medical literature since the turn of the last century (Corvelaire, 1903). In the period from 1940 to 1970, population studies identified the maternal, obstetric and neonatal risk factors for development of germinal matrix haemorrhage, including vaginal delivery, low birth weight, low Apgar scores, hypoxia and hypercapnea (Bassan, 2009; Ballabh, 2010). Improvements since the 1970s in neonatal intensive care have reduced the incidence of cardiorespiratory complications and increased survival following preterm delivery; however, the overall incidence of intraventricular haemorrhage in very low birth weight infants has remained static over the last two decades (Jain et al., 2009). Thus, intraventricular haemorrhage is still a significant problem affecting > 12 000 infants per year in the USA alone (Guyer et al., 1999). The extent of haemorrhage and ventricular dilatation, as detected by cranial ultrasound, continue to predict morbidity and mortality, with ultrasonographic grades III (intraventricular haemorrhage with ventricular dilatation) and IV (intraventricular haemorrhage complicated by periventricular haemorrhagic infarction) having survival rates of 40 and 67%, respectively; of those surviving, 50 and 75% ultimately develop definite neurological sequelae (Volpe, 2008). These sequelae are related to progressive post-haemorrhagic hydrocephalus and the need for shunt placement and maintenance, as well as destruction of projection and association axons traveling through the periventricular zone ipsilateral to a periventricular haemorrhagic infarction (Bassan, 2009). In addition, direct cortical injury, periventricular leukomalacia, and secondary impairment of overlying cerebral cortical development may be significant contributors to a complex constellation of destructive and development-altering influences in the sick preterm neonate (Volpe, 2009b).

Subarachnoid blood...
products are also suspected of causing secondary injury to the developing cerebellum (Bassan, 2009; Volpe, 2009a). Thus, the range of neurological deficits in these severely affected children may include motor, sensory and cognitive functions of a degree requiring life-long support.

In those survivors without ventricular dilatation and periventricular haemorrhagic infarction, neurological deficits are more subtle, but may include cognitive and attentional deficits (Bassan, 2009). These deficits are postulated to be a consequence of destruction of neuroglial precursors in the germinal zone, before their differentiation and/or migration to fulfill roles as projection neurons, interneurons or glia. Of interest is the finding on quantitative neuroimaging of a decrease in cortical grey matter volume compared to those complicated intraventricular haemorrhage had a statistically significant 16% decrease in cortical grey matter volume compared to those without intraventricular haemorrhage, leading to speculation regarding the mechanisms of haemorrhage-induced precursor cell loss (Vasilieadis et al., 2004).

The neuroanatomic and neurophysiological bases of germinal matrix vulnerability to haemorrhage are currently thought to relate to: (i) inherent fragility of the germinal matrix vasculature; (ii) disturbance in cerebral blood flow; and (iii) platelet and coagulation disorders contributing to expansion rather than initiation of haemorrhage (Ballabh et al., 2009). In that study, infants with overt white matter injury or grey matter infarcts were excluded in an attempt to detect the consequence of relatively ‘isolated’ germinal matrix haemorrhage. Of note, at term equivalent, infants with uncomplicated intraventricular haemorrhage had a statistically significant 16% decrease in cortical grey matter volume compared to those without intraventricular haemorrhage, leading to speculation regarding the mechanism of haemorrhage-induced precursor cell loss (Vasilieadis et al., 2004).

The neuroanatomic and neurophysiological bases of germinal matrix vulnerability to haemorrhage are currently thought to relate to: (i) inherent fragility of the germinal matrix vasculature; (ii) disturbance in cerebral blood flow; and (iii) platelet and coagulation disorders contributing to expansion rather than initiation of a spontaneous germinal matrix haemorrhage (Ballabh, 2010). Maternofoetal infection and inflammatory cytokine expression have also been invoked to play a role in the risk for germinal matrix haemorrhage (Bassan, 2009). Numerous studies in humans and experimental animal models have elucidated the unique characteristics of the germinal matrix zone vasculature: discontinuous glial end-feet of the blood–brain barrier (El-Khoury et al., 2006), relative lack of pericytes (Braun et al., 2007), immature basal lamina components (Xu et al., 2008), high morphometric ratio of diameter to wall thickness (Anstrom et al., 2005), angiogenic profile with rapid endothelial turnover (Ballabh et al., 2007) and developmentally regulated expression of vascular wall molecules such as alkaline phosphatase (Anstrom et al., 2002). With regard to cerebral blood flow, several key studies in the intensive care nursery have demonstrated the effect of cerebral pressure-passive circulation on the risk of haemorrhage in at least a subset of premature infants (Meek et al., 1999; Tsuji et al., 2000; O’Leary et al., 2009).

Despite the many elegant analyses of the vessels of the germinal matrix, which explain their vulnerability to the clinically observed decrease in cerebral blood flow, the fundamental ‘mechanism’ by which germinal matrix haemorrhage impacts on subsequent neurodevelopment has been the subject of limited study directly in the human brain. We know that specific blood components, such as plasma, serum, thrombin and plasmin, have toxic effects on perinatal rat subventricular zone cells, specifically in proliferation, differentiation and migration in oligodendrocyte precursor cell cultures ( Juliet et al., 2009). In addition, microglial response, including proinflammatory cytokine expression as detected in vitro, may play an important role in this phenomenon (Juliet et al., 2008). In whole animal models, unilateral autologous blood injection into the periventricular region (from which blood eventually extends into the ventricle) resulted in the suppression of cell proliferation bilaterally in the germinal matrix 8 h to 1 week post-injection (Balasubramaniam et al., 2006). Increased cell death was detected in the ipsilateral striatum and germinal matrix within 2 days, and astrocytic and microglial reaction peaked at 2 days and persisted up to 4 weeks. These studies, led by Prof. Del Bigio, laid the foundation for his current work published in this issue of Brain.

This article is of landmark significance in our understanding of the effect of localized haemorrhage on cell proliferation (suppressed), expression of cell cycle arrest transcription factor p53 (increased) and cell lineage marker expression (decreased) during the critical period in gestation in the human when cell proliferation in and migration from the germinal matrix zone occurs. While significantly increased cell death and apoptosis could not be documented by nick-end labelling and caspase-3 immunostaining, respectively, such phenomena cannot be excluded: discrepancies always exist between animal experiments, in which these techniques can be applied at 8–24 h intervals following the delivered injury, and post-mortem human studies, which are limited by lack of control over (or even exact knowledge of) these intervals. The author also contributes valuable normative data, such as germinal matrix thickness and cell proliferative indices in the second and third trimesters of human gestation, as well as the delineation, using cell lineage markers, of ventral and dorsal segmentation of the ganglionic evidence (resembling the medial-lateral division seen in experimental animals, but not fully described before in the human). The highly proliferative ventral portion of the ganglionic eminence between 15 and 34 weeks gestation, poised to transition to mature neural and glial cells destined for the cerebral cortex, basal ganglia and thalamus, represents the quarry of building blocks jeopardized by preterm birth.

Finally, work such as this directly in the human brain is essential to the translation between the bench, where animal models and tissue culture systems give mechanistic insights, and the bedside, where strategies for prevention and treatment of germinal matrix haemorrhage are desperately needed.

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