# Impaired Neurodevelopmental Outcome After Mild Germinal Matrix-Intraventricular Hemorrhage

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Germinal matrix–intraventricular hemorrhage (GMH-IVH) is a common and characteristic form of intracranial hemorrhage occurring in the premature infant.[1] The hemorrhage originates in small blood vessels in the subependymal germinal matrix (also termed the ganglionic eminence) and may disrupt the ependymal lining and extend into the lateral ventricle. Severe IVH consists of large amounts of intraventricular blood (usually termed grade 3 IVH) and may be complicated by hemorrhagic venous infarction in the periventricular white matter (often termed grade 4 IVH) or by post–hemorrhagic hydrocephalus or both. Many studies have documented increased short-term and long-term neurologic morbidity after severe IVH.[1] In this issue of *Pediatrics*, Mukerji et al[2] report the first meta-analysis of neurodevelopmental outcomes after GMH-IVH (termed periventricular/intraventricular hemorrhage in the report). Their review confirms previous data indicative of unfavorable outcomes after severe GMH-IVH but notably also reports impaired neurodevelopmental outcome after mild GMH-IVH. The findings raise 2 important questions: (1) the biological underpinning of the relationship between the severity of GMH-IVH and outcome, and (2) the extent to which the data should be used in counseling in the neonatal period.

Severe GMH-IVH (when compared with no GMH-IVH) was associated with a distinctly increased risk of the primary outcome of death or moderate-severe neurodevelopmental impairment (NDI; unadjusted odds ratio of 4.72, 95% confidence interval [CI] 4.21–5.31; adjusted odds ratio not available) and the secondary outcome of moderate to severe NDI among survivors (adjusted odds ratio of 2.44, 95% CI 1.73–3.42).[2] Because severe GMH-IVH in the meta-analysis included those with marked IVH with or without periventricular hemorrhagic infarction, it is not possible to distinguish individual outcomes for so-called grade 3 IVH and grade 4 IVH. Previous work indicates greater negative impact from grade 4 than from grade 3 IVH.[1] The anatomic substrate for the neurologic deficits with severe IVH has been reviewed elsewhere, but likely relates both to primary parenchymal destruction and to secondary disturbances of brain development, especially myelination and neuronal-axonal development.[3]

The interesting new finding of the meta-analysis of Mukerji et al[2] is the increased risk of an unfavorable outcome with mild GMH-IVH versus no hemorrhage: that is, for death or moderate-severe NDI (unadjusted odds ratio of 1.48, 95% CI 1.26–1.73; adjusted odds ratio not available) or for moderate-severe NDI among survivors (adjusted odds ratio of 1.32, 95% CI 1.09–1.77). The conclusion of increased risk with mild GMH-IVH must be qualified by awareness that only 2 to 3 studies provided usable data,[4–6] brain parenchyma was not assessed by advanced imaging modalities (MRI)

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clearly superior to ultrasonography for detection of confounding lesions, especially cerebral white matter injury, and the elevations in odds ratio were relatively small. Nevertheless, the finding of increased risk of impaired neurologic outcome with mild GMH-IVH raises important questions about the potential neurobiological basis.

Deleterious neurobiological effects of mild GMH-IVH likely involve a combination of primary destructive effects and secondary disturbances of brain development, as delineated in more detail for the neurobiological bases of cerebral white matter injury.[3] The germinal matrix (ganglionic eminence) during the developmental period of occurrence of GMH-IVH (ie, 25–32 weeks of gestation) is a principal source for proliferation of oligodendroglial precursor cells (OPCs), which later in the third trimester migrate into cerebral white matter, differentiate, and, postterm, produce cerebral myelin.[1,7,8] Loss of these myelin-producing cells could lead to impaired myelin development and neurodevelopmental outcome.

Studies of postmortem human premature brain and experimental models of GMH have shown impairment of proliferation of OPCs and their subsequent migration and differentiation.[9,10] Experimental studies suggest that these deleterious effects on OPCs are mediated by blood products, inflammatory compounds, and microglia.[10–12] Indeed, microglial activation in germinal matrix and periventricular white matter has been shown in postmortem human premature brain with GMH-IVH.[9,13]

A related possibility for a deleterious effect involves free radical–mediated effects on differentiating oligodendrocytes, and perhaps also rapidly growing axons in cerebral white matter,[14] related in part to release of nonheme iron from the hemorrhage and by the activation of microglia, as in the neurobiology of periventricular leukomalacia.[15] However, it is noteworthy that the only significant deleterious anatomic effect of mild GMH-IVH detected by MRI studies at term equivalent age involved cortical and deep gray matter development.[16,17] Interestingly, and relevant to these MRI observations, recent studies of human premature brain show that during the developmental period of 25 to 34 weeks, the germinal matrix contributes to the generation and later migration of GABAergic interneurons to cerebral cortex and to association nuclei of the thalamus, both critical for higher-level cognitive functions.[18–22] Disturbance of these latter events could have deleterious consequences for neurodevelopment.

Finally, we should address the question of the degree to which the current findings of impaired neurodevelopmental outcome after mild GMH-IVH should influence parental counseling in the neonatal period. Mukerji et al[2] indicate that their study provides "quantitative guidance to clinicians when counseling parents of infants" with mild hemorrhage. This conclusion must be qualified by recognition that the odds ratios for unfavorable outcome were relatively low, and the supportive studies did not include more rigorous neuroimaging or analysis of such critical postneonatal factors as nutrition, parenting behavior, and socioeconomic factors that may affect outcome.[23–26] Nevertheless, the interesting observations by Mukerji et al[2] do provide a valuable stimulus for future research to define more clearly in living human infants the relation between mild GMH-IVH per se and neurodevelopmental outcome.

## ABBREVIATIONS

CI: confidence interval
GMH-IVH: germinal matrix–intraventricular hemorrhage
NDI: neurodevelopmental impairment
OPC: oligodendroglial precursor cell

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