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Genes and environment in neonatal intraventricular hemorrhage

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ABSTRACT

Emerging data suggest intraventricular hemorrhage (IVH) of the preterm neonate is a complex disorder with contributions from both the environment and the genome. Environmental analyses suggest factors mediating both cerebral blood flow and angiogenesis contribute to IVH, while candidate gene studies report variants in angiogenesis, inflammation, and vascular pathways. Gene-by-environment interactions demonstrate the interaction between the environment and the genome, and a non-replicated genome-wide association study suggests that both environmental and genetic factors contribute to the risk for severe IVH in very low-birth weight preterm neonates.

Abbreviations: ANS, antenatal steroids; BW, birth weight; GA, gestational age; GWAS, genome-wide association study; IVH, intraventricular hemorrhage; NRN, neonatal research network; OR, odds ratio; QC, quality control; SNP, single nucleotide polymorphism

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Introduction

Preterm birth affects an estimated 13 million newborns worldwide annually,[1,2] and sophisticated advances in perinatal care have improved survival for the prematurely born.[3] In contrast, the incidence of neurodevelopmental handicap in the prematurely born has changed little during the last 2 decades,[4–6] mandating a more complete assessment of injury to the developing preterm brain. Intraventricular hemorrhage (IVH), or hemorrhage into the germinal matrix tissues of the developing brain with ventricular enlargement and parenchymal involvement, is one of the major causes of morbidity in the prematurely born, often resulting in cerebral palsy and cognitive handicap.[7,8] Notably, there are over 2800 new cases of mental retardation attributable to IVH in the US each year, and the lifetime care costs for these children exceed $4 billion (2010) annually.[9,10] Emerging data suggest that IVH is a complex developmental disorder with contributions from both the environment and the genome.[11]

IVH occurs during the critical period of time before 32–33 weeks gestation and has been attributed to changes in cerebral blood flow to the immature germinal matrix microvasculature.[12] Inflammation, coagulation, and vascular factors may also play a role.[8,12] Severe IVH is characterized by the acute hemorrhagic distension of the cerebral ventricular system (grade 3) and parenchymal venous infarction (grade 4). The cascade of adverse events following IVH includes destructive, inflammatory, and maturational disturbances and is characterized by white matter injury, delayed oligodendroglial maturation, loss of gamma-aminobutyric acid (GABA) interneurons, and impaired thalamo-cortical connectivity.[8] All may contribute to developmental disability.

The purpose of this report is to review both environmental and genetic data supporting the hypothesis that IVH is a complex disorder. Candidate genes, gene-by-environment interaction studies reviewed, and a recent genome-wide association study (GWAS) will be reported.

The etiology of IVH is multifactorial

Multiple sources of data support the hypothesis that, similar to most other morbidities in preterm neonates,[13,14] the etiology of IVH is multifactorial. Maternal transport and antenatal steroid (ANS) administration for fetal lung maturation and improved resuscitation techniques have become standard of care for women in preterm labor and premature infants worldwide,[15–18] but the incidence of severe IVH has remained 12–15% for the past 10–15 years.[15,19–23] In addition, both gender and twin studies support the hypothesis that IVH is a complex disorder. Preterm males are more likely than females to experience IVH,[24] and data from a twin study suggests that environmental and familial factors contributed 43% of risk for IVH.[25] Furthermore, although the incidence of IVH is inversely related to gestational age (GA), the risk period for IVH is independent of this key variable, suggesting that either the transition to extra-uterine life and/or the environmental variables to which the neonates are exposed contribute to injury to the prematurely born. Finally, recent data suggest that both candidate genes and gene-by-environment interactions may also play a role.[11,26–28]

Environmental factors and health care disparities are permissive for hemorrhage

IVH occurs against the backdrop of preterm birth in which both risk and protective factors have been well described.[15] Lower GA and birth weight (BW), male gender, white race, chorioamnionitis, Apgar <3 at 5 min, delivery room resuscitation, surfactant administration, neonatal transport, illness severity, assisted ventilation, disturbances of partial pressure of CO_2, respiratory distress syndrome, and high frequency ventilation have all been reported to increase risk for IVH, while a complete course of ANS, cesarean delivery and preeclampsia decrease the risk for IVH.[29]

Recent data suggest, however, that advances in neonatal and perinatal care and the increasing survival of extremely low-birth weight infants may have altered these associations. In addition, the recognition of the importance of health care disparities in the etiology of IVH has recently been reported. Women of African ancestry are at greater risk for preterm labor and delivery than white women, and a higher percentage of very low-birth weight infants are born to African ancestry mothers.[30–32] Further, infants of African ancestry mothers are less likely to receive surfactant or assisted ventilation,[33] and IVH-related mortality is two times higher in African ancestry neonates when compared to white preterm infants.[34] A recent large prospective analysis demonstrated that white race decreased risk for grades 2–4 IVH in preterm neonates of 500–1250 g[29]; notably, among white infants but not black neonates, multiple gestation was associated with increased risk of IVH, while higher maternal education was associated with a decreased incidence of hemorrhage. When compared to white neonates, infants of African ancestry less often received ANS exposure and required more vigorous delivery room resuscitation. For the infants of African ancestry mothers, having more than one maternal prenatal visit significantly decreased the risk for IVH, suggesting that initiating care prior to labor and delivery provides a distinct protective advantage.

Preclinical studies: Mutations in microvascular proteins confer vulnerability to IVH

The germinal matrix is a region of active angiogenesis, and IVH begins in this region. The microvessels of the germinal matrix lack the traditional components of the blood brain barrier, endothelial tight junctions, basement membrane proteins, glial endfeet and perivascular pericytes.[12] IVH is thought to be a critical period disorder, and previous work has suggested that it is the developmental stage of the germinal matrix microvessels that are permissive to hemorrhage.[35]

Preclinical data suggest, however, that variants in one or more microvascular proteins confer vulnerability to the environmental factors discussed above. As a clinically-relevant model, mice with mutations in the basement