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Review

Perinatal biomarkers in prematurity: Early identification of neurologic injury

Maria Andrikopoulou[a], Ahmad Almalki[a], Azadeh Farzin[b], Christina N. Cordeiro[a], Michael V. Johnston[c], Irina Burd[a,c,d,*]

[a] Integrated Research Center for Fetal Medicine, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[b] Division of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, United States
[c] Department of Neuroscience, Kennedy Krieger Institute, Baltimore, MD, United States
[d] Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, United States

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ABSTRACT

Over the past few decades, biomarkers have become increasingly utilized as non-invasive tools in the early diagnosis and management of various clinical conditions. In perinatal medicine, the improved survival of extremely premature infants who are at high risk for adverse neurologic outcomes has increased the demand for the discovery of biomarkers in detecting and predicting the prognosis of infants with neonatal brain injury. By enabling the clinician to recognize potential brain damage early, biomarkers could allow clinicians to intervene at the early stages of disease, and to monitor the efficacy of those interventions. This review will first examine the potential perinatal biomarkers for neurologic complications of prematurity, specifically, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and posthemorrhagic hydrocephalus (PHH). It will also evaluate knowledge gained from animal models regarding the pathogenesis of perinatal brain injury in prematurity.

Contents

1. Preterm birth and neurologic sequealae

The rate of preterm birth rate (<37 weeks) in the United States is one of the highest in the developed world, with a staggering incidence of 11.7%, with greater than 500,000 premature infants born each year (Hamilton et al., 2013). Although improved neonatal intensive care and technological advances have allowed for increased survival of extremely premature infants, preterm birth accounts for over 75% of perinatal mortality and greater than 50% of perinatal and long-term morbidity (Berghella, 2010).

The most common forms of central nervous system (CNS) injury in preterm infants are intraventricular hemorrhage (IVH), posthemorrhagic hydrocephalus (PHH) and periventricular leukomalacia (PVL). In extremely low birth weight infants weighing 500–999 g, IVH occurs in about 45% of neonates (Wilson-Costello et al., 2005),

* Corresponding author at: Integrated Research Center for Fetal Medicine, Department of Gynecology and Obstetrics, Johns Hopkins University Hospital, Phipps 228, 600 North Wolfe Street, Baltimore, MD 21287, United States. Tel.: +1410-955-8496.
E-mail address: iburd@jhmi.edu (I. Burd).

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while PVL occurs in 3–4% of infants who weigh less than 1500 g and 4–10% of those born prior to 33 weeks of gestation (Rezaie and Dean, 2002). PVL it is considered the major cause of cerebral palsy (Bass, 2011). Other long-term medical disabilities associated with preterm birth include cognitive dysfunction, blindness and impaired vision, hearing loss, and disorders of psychological development, behavior and emotion (Sutton and Darmstadt, 2013).

The high incidence of neurological injuries among preterm infants highlights the need for the discovery of biomarkers for the early detection of preterm infants at increased risk for poor neurologic outcomes, in order to allow for the implementation of early neuroprotective and postnatal treatment interventions.

Biomarkers have gained scientific and clinical value in the practice of medicine. In the past few decades, advances in genomics, proteomics, and molecular pathology have generated many candidate biomarkers with potential clinical utility in every field of medicine (Bang et al., 2007; Keller et al., 2009; Gagnon and Ye, 2008). In perinatal medicine, the pathophysiology of preterm labor is poorly understood. This has fueled increased interest in the identification of biomarkers that can predict preterm birth, as these may allow for the identification of high-risk populations as candidates for further intervention. Such discoveries could also help to define the mechanisms leading to preterm birth. However, current knowledge on pathophysiology of preterm labor and its associated biomarkers have not yet translated into a reduction in preterm birth rates. Additionally, the use of such biomarkers in clinical practice to predict adverse outcomes such brain injury remains challenging. Interestingly, Leitner et al. (2014) have recently reported that preterm birth and fetal cortical injury may occur by divergent mechanisms. This stresses the importance of identifying biomarkers targeting the prediction of adverse outcomes such as IVH, PVL and PHH, rather than those associated preterm labor alone.

Some investigators have focused on the detection of proteins in the serum that should only be present in the CNS as possible biomarkers for neuronal injury in prematurity (Gazzolo et al., 1999, 2001a,b). Others consider the detection of serological markers such as pro-inflammatoy cytokines and enzymes in maternal and neonatal blood or cord blood as a promising tool for early diagnosis of brain damage (Heep et al., 2003; Kassal et al., 2005; Poralla et al., 2012). Additionally, different groups have used other methods so as to early predict neurologic injury, such as Apgar scores, imaging modalities or EEG abnormalities of neonates as early biomarkers (Ment et al., 2009; Woodward et al., 2006; Forsblad et al., 2007; Watanabe et al., 1999). In our review, we mainly focus on serological biomarkers for early prediction of IVH PVL and PHH as complications of prematurity.

2. Intraventricular hemorrhage

Intraventricular hemorrhage is a major complication of prematurity which is associated with long term adverse neurological outcomes. The site of origin of bleeding is generally the subependymal germinal matrix, which is located between the caudate nucleus and the thalamus at the level of the foramen of Monro (Volpe, 2001a,b). IVH occurs most frequently in infants born before 32 weeks gestation or who weigh less than 1500 g at birth, and its incidence increases with decreasing gestational age. In extremely premature infants weighing 500–999 g, IVH occurs in about 45% of neonates (Wilson-Costello et al., 2005). The etiology is multifactorial and is primarily attributed to the intrinsic vulnerability of the germinal matrix capillaries to hypoxic injury and also to impaired cerebral autoregulation. In terms of clinical presentation, intraventricular hemorrhage can be asymptomatic in up to 50% of the cases. However, acute IVH can present with altered level of consciousness, bulging fontanel and neurologic deficits (Bassan, 2009).

IVH has been modeled using several animal species to study the causative factors and evolution of brain damage (Balasubramaniam and Del Bigio, 2006). Understanding the pathogenesis of subsequent brain injury is of utmost importance if IVH is to be prevented or treated. Xue et al. (2003) developed a rodent model of IVH by injecting mice with autologous blood in the periventricular region and studied molecular and cellular processes involved in brain injury, as well as long term neurologic abnormalities and outcomes in a similar rat model (Balasubramaniam et al., 2006). Additionally, the same group showed that mouse brain injury was aggravated after injection of LPS, underlying the role of inflammation at the pathogenesis of brain injury (Xue and Del Bigio, 2005). Differently, McCarty et al. (2002) utilized mutant alpha V integrin mice which developed IVH to investigate the role of adhesion of endothelial cells in pathogenesis of the brain injury.

In rat models, post hemorrhagic hydrocephalus has been induced by the injection of blood into lateral ventricles in 7-day-old rats (Cherian et al., 2003, 2004). On the other hand, Alles et al. (2010) have used a different model of uni- or bilateral infusion of collagenase into the neonatal periventricular region of 6-day-old rats to recapitulate some aspects of human IVH. Similarly, Levik et al. (2012) have developed an instructive animal model of the neurologic consequences of IVH using stereotaxic injection of collagenase into the ganglionic eminence of newborn rats. These rats exhibited hematomal extension into the ventricles and developed both early and delayed neurobehavioral deficits.

Recently, there has been an emerging interest on the use of biomarkers to predict and early diagnose IVH in preterm neonates even before the onset of clinical presentation and permanent neurologic disability. Most biomarkers studied in prematurity related to IVH since 1998 will be reviewed.

Activin is a growth factor that belongs to the transforming growth factor-beta superfamily. It regulates a variety of biologic processes and its receptors and binding proteins are widely distributed throughout the brain (Luisi et al., 2001). Different studies that have employed models of acute brain injury have shown that activin A plays a very important role in the physiologic response to acute brain injury (Tretter et al., 1996; Lai et al., 1996; Zhang et al., 2003). Florio et al. (2006) demonstrated that activin A can be used as a useful biomarker for the early identification of infants with hypoxic–ischemic brain insults who are at high risk for IVH. In the cohort of 53 preterm neonates less than 32 weeks of gestational age, the 11 who developed IVH were noted to have higher activin levels in arterial blood samples at birth than those who did not develop IVH. Similarly, urine activin levels have been found to be higher in preterm infants with IVH as compared with controls without neurologic injury (Sannia et al., 2013). Thus, activin A constitutes a promising tool for identifying preterm infants at risk for IVH and larger prospective studies are needed to further evaluate the use of this biomarker as a predictive tool.

S100b, a member of the S100 protein family, is another biomarker well-studied in brain injury. It is synthesized by astrocytes and exhibits neurotrophic or neurotoxic activity. Gazzolo et al. (1999) investigated the role of 100b in evaluating perinatal brain distress ultimately leading to IVH in preterm infants. They reported higher concentrations of S100 in blood samples of the 24 preterm infants who developed IVH in the first 24 h. Additionally, a case control study on urine samples of S100b demonstrated higher concentrations of S100 in urine sampled from preterm infants with IVH (Gazzolo et al., 2001a,b). In a final study, this biomarker was reported to be predictive of neonatal mortality (Gazzolo et al., 2005).

Uric acid (UA) has also been studied as a potential biomarker in brain injury. It is known that the purine metabolite hypoxanthine accumulates in areas of hypoxic/ischemic injury, and as reperfusion occurs, hypoxanthine is catabolized by the enzyme xanthine