Inflammatory Biomarkers of Birth Asphyxia

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KEYWORDS

• Asphyxia • Placenta • Cytokines • GFAP • Ubiquitin

KEY POINTS

- Hypothermia is a recognized standard-of-care neuroprotective therapy for newborns with hypoxic-ischemic encephalopathy, but about 45% of infants have abnormal outcomes despite treatment.
- Biomarkers could help the bedside clinician identify responders and nonresponders to hypothermia who could benefit from added neuroprotective strategies.
- The author's observations suggest an important role of the placenta through inflammatory mechanisms to the severity of the hypoxic-asphyxial insult and therapeutic responses following hypothermia therapy.
- Using a serum panel of inflammatory and neuronal biomarkers, rather than a single biomarker, seems the most promising once validated in large cohorts.

INTRODUCTION

Perinatal asphyxia remains a frequent cause of cerebral palsy, mental retardation, learning disability, epilepsy, and death.[1] The worldwide burden is 4 million newborns every year, of which one million die and an additional million have significant disabilities.[2,3] Neonatal brain injury is recognized by a distinctive clinical encephalopathy that evolves from hyperexcitability to lethargy and stupor during the first 3 days of life.[4,5] Large trials have shown that hypothermia therapy results in a significant reduction in death or disability with a relative risk of 0.76 (confidence interval [CI] 0.65–0.89).[6–12] Hypothermia is the current standard of care for hypoxic neonatal encephalopathy (NE). However, 45% of cooled newborns have significant disabilities at 12 to 18 months of age,[13] when tested by the Bayley Scales of Infant and Toddler Development gold standard neurodevelopmental tools.

Because hypothermia does not protect all affected neonates from neurocognitive delay and mental retardation, adjuvant therapies are being sought; but the real

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challenge is to define which neonates will need these therapies shortly after birth. Despite the complex pathophysiology related to the uncertain timing, severity, and patterns of the fetal insult,[14] neonates with NE are currently viewed dichotomously[15]: those who do, or do not, qualify for cooling. Hypothermia is offered uniformly in a one-size-fits-all strategy based on the early neurologic examination, which has a limited predictive value, and the striking heterogeneity between the moderate and severe groups.[6–12] Infants with mild NE are not currently cooled, yet 20% to 30% may have abnormal outcomes.[16] Amplitude electroencephalogram[17] is a good physiologic marker of neuronal integrity, but its predictive values are attenuated during hypothermia.[18,19] Although brain MRI is considered the best short-term marker of early childhood outcome,[20–23] the sensitivity improves beyond the first week of life. An ideal biomarker would be measured in real time and directly reflect the neurovascular unit function[23] linking it to outcomes.[24–26] Such a biomarker would enhance the ability to stratify the insult severity by identifying neonates with mild NE who might benefit from hypothermia and those with moderate-severe NE who need added interventions to improve outcomes. The quest for such biomarkers is still mostly research based. This review covers promising biomarkers of injury to the neurovascular unit during hypothermia therapy including (1) biomarkers of placental inflammation, (2) neuronal biomarkers, as well as (3) general inflammatory cytokines in the serum.

PLACENTAL INFLAMMATORY BIOMARKERS

The placenta mediates interactions between mother and fetus throughout gestation and provides a historical record of maternal and fetal interactions. Its fetal composition makes it an ideal storyteller of perinatal distress. In 1955, Eastman and De Leon first described the association of intrapartum infection and cerebral palsy (CP). Over the years, there has been growing evidence to support an association between placental inflammation, elevated cytokines and CP.[27–29] A multitude of elegant animal studies have shown a variable response of the developing brain to inflammation, depending on the critical timing of exposure.[30,31] When administered either 72 hours before or 6 hours after the insult, lipopolysaccharide (LPS) resulted in increased hypoxic-ischemic (HI) injury, in contrast to a reduced injury when administered 24 hours before the insult.[30] Therapeutic hypothermia was not neuroprotective in another LPS-sensitized unilateral strokelike HI brain injury model in newborn rats.[31] In a recent clinical study, postnatal sepsis was associated with increased watershed evidence of brain injury, whereas reports of isolated prenatal maternal chorioamnionitis were associated with lower incidence of MRI abnormalities in newborns with encephalopathy.[32]

The placental milieu can have various influences on outcomes, as well as the extent of responses to therapies, depending on the severity and timing of the inflammatory sensitization. The author and colleagues recently reported findings of a large cohort that included all 120 neonates born with a gestational age of 36 weeks or greater and a birth weight greater than 1800 g who were admitted to the neonatal intensive care unit at Parkland Hospital from January 2006 through November 2011 with evidence of perinatal acidosis and NE.[33] As it was routine practice for all placentas associated with specific maternal-fetal complications of pregnancy and need for presence of the neonatal resuscitation team to be sent to pathology, placentas from all the infants during the study time period were examined. Gross and histologic examinations were reported according to the 2005 Redline classification.[34] Major pathology was identified to include (1) intervillous fibrin deposition/retroplacental hemorrhage/infarction involving 20% of placental volume; (2) fetal vascular thrombo-occlusive disease with greater than 1 focus of avascular villi/thrombotic vasculopathy; (3)