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Serum Biomarkers of Brain Injury: A Call for Collaboration

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Advances in the care of infants with birth asphyxia (e.g., whole body hypothermia) have had substantial impact on improving mortality and morbidity.¹ Yet many children still suffer significant debilitation as assessed by disability-adjusted life-years.² In many cases, a complete understanding of the neurodevelopmental consequences may not be evident for years. Consequently, clinicians and families urgently need an accurate diagnostic tool that allows for early detection of neurologic injury, stratification by severity of injury, and prognostication of long term outcome. Serum biomarkers are validated and critical components of care pathways for myocardial infarction and other diseases, but none exist for pediatric brain injury.³

Prior work published by Massaro and colleagues explored serum S100b and NSE concentrations, markers of astrocyte and neuron injury, respectively, in 83 neonates with birth asphyxia who met standard criteria for therapeutic hypothermia from birth through 72 hours. They found that serum biomarkers performed well in classifying *early* outcomes including death, poor neurological outcome, and brain MRI lesions.⁴ In this issue of *Pediatric Critical Care Medicine*, they performed neurodevelopmental outcomes in the same cohort at 15–18 months using the Bayley Scales of Infant Development-II. Controlling for important covariates including maternal education level and socioeconomic background they found that this relationship persisted - increased serum S100B and NSE levels (measured at 0, 12, 24, and 72 hr) were associated with adverse cognitive and motor outcomes at 15 mos.⁵

Despite statistical significance, area under the curve results in single center biomarker studies consistently demonstrate the notion that no single biomarker can be used alone with perfect accuracy. Therefore, the question remains: What is (are) the most ideal biomarker(s) for these tasks? Other candidate serum biomarkers showing promise after acute brain injury include the neuronal Ubiquitin Carboxy-terminal Hydrolase L1 (UCH-L1) and astrocyte marker Glial Fibrillary Acidic Protein (GFAP).⁶ However, accuracy may be greatly improved when used in combination with other serum, clinical, and imaging biomarkers.⁷

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Matters important to consider in the neonatal population include safety (limiting the amount of blood and number of blood draws necessary for the assay), need for a cost-effective and rapid point of care assay, and biomarker-specific considerations such as hemolysis (NSE), long bone fractures and developmental gradation (S100b).^{8,9}

This study strengthens the growing body of evidence that serum biomarkers of brain injury, including S100B and NSE, deserve further study for clinical and prospective research utility.^{10–14} Another neonatal population at increased risk of neurological disability from hypoxia-ischemia – infants with congenital heart disease – may benefit from serum biomarker development as over half of all survivors of congenital heart disease will suffer a morbidity, most commonly neurodevelopmental.¹⁵ Both serum NSE and S100B are increased in neonates with complex congenital heart disease (CHD) following cardiopulmonary bypass surgery but there are no studies linking them with long term neurodevelopmental outcomes to date.^{16–22} There is also radiographic evidence that the brain injuries seen in both premature neonates and neonates with CHD are similar (periventricular leukomalacia).²³ They also share similarities in types of neurodevelopmental deficits found in school age children (cognitive disability in executive function and school readiness).^{24,25} Although the timing and actual insult are not exact, we suggest that there are enough similarities between these two at risk neonatal populations to benefit from a larger collaborative effort – combining resources and infrastructure for neurodevelopmental follow-up would be a win-win towards incremental improvement in long-term neurodevelopmental outcomes.

In summary, we strongly support the authors' call for the validation of promising serum biomarkers of brain injury to assess their diagnostic, theragnostic, and therapeutic properties in neonates with birth asphyxia and extend that call to include other pediatric diseases involving global hypoxia-ischemia.

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