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Minding the Brain

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Infants with congenital heart disease (CHD) are at increased risk of pre-operative and acquired brain disease and subsequent long-lasting disability, especially if surgery involves cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA)^{1,2}. Brain lesion types commonly include congenital cortical folding disorders, focal and global hypoxic-ischemic insults, and white matter degeneration^{3–7}. Identification of new brain disease early is imperative but can be clinically difficult to detect, especially in infants where the Glasgow Coma Scale (GCS) score is insensitive⁸. New injury often presents clinically with altered mental status or seizures (which may also be non-convulsive). Diagnostic tools such as brain ultrasound and computed tomography (CT) often miss early ischemic lesions and magnetic resonance imaging (MRI) typically requires lengthy transport of a critically ill patient outside the ICU. Serum brain biomarkers have potential to be a useful tool for early detection of brain insults, leading to neuroprotective interventions and prevention of evolution into more severe disease. Serum S100b and neuron specific enolase (NSE) show promise in a preliminary study in infants with CHD, but interpretation is hindered by the fact that normal S100b concentrations change during early development and NSE increases during hemolysis, which commonly occurs on bypass^{9,10}.

In this issue, Jain et al performed a prospective, single center study using serial (preoperative, 6, 24, 48, 72, 96 h) serum measurements of alpha II-spectrin breakdown products (SBDPs) 120 kD and 150 kD in neonates with CHD¹¹. Alpha II-spectrin is a protein located in brain and non-central nervous system (CNS) tissue and functions in cell cytoskeleton maintenance¹². Cleavage of calpains occurs after cellular insults, producing specific patterns of alpha II-spectrin breakdown products (SBDPs) depending on the type of cleavage enzyme¹².

The primary outcome demonstrated that neither SBDP was increased in children receiving closed heart surgery (CHS). However, unlike the previously demonstrated predominance of fragments associated with necrosis in experimental models of stroke and cardiopulmonary bypass, both 120 kD (apoptosis-associated) and 150 kD (necrosis-associated) fragments were increased in children after open heart surgery (OHS) (cardiopulmonary bypass ± deep hypothermia), peaking at 24 and 6 hours postoperatively, respectively¹². The young brain is particularly vulnerable to apoptosis during development¹³. The 120 kD fragment decreased over time and did not return to baseline by the 96 h timepoint while the 150 kD fragment peaked in bimodal fashion, perhaps representing early and delayed cell death occurrence or

in parallel with secondary brain insults such as seizures or low cardiac output (not reported in this study).

Limitations acknowledged by study authors include the small sample size and lack of control infant serum biomarker levels, the latter especially important since children with preoperative brain lesions on imaging were enrolled. Additionally, modality and timing of brain imaging was variable and unprotocolized and origin of SBDP's, although primarily found in brain tissue, can be found elsewhere in the body. Additionally, in a study of pediatric TBI, serum levels of the SBDP 145 kD fragment were increased after moderate and severe TBI but not mild TBI¹⁴. This paper lacks long term outcomes and standardized brain imaging so it was not possible to compare serum SBDP levels by severity of brain disease. Interestingly, patients in the CHS group frequently had lesions present on brain imaging but no corresponding increase in serum SBDP concentration, but the clinical implications of these lesions were not known and could be inconsequential.

Finally, a single test or clinical variable is rarely accurate alone to guide clinical decision-making. Validation of serum brain biomarkers as accurate surrogates for clinically-relevant outcomes (including testing for covariates such as CPB and DHCA), would help further development into bedside point-of-care tests and potentially integrate into perioperative neuromonitoring protocol for early detection of brain insults. Furthermore, testing in this study required very little blood (50 uL), important in this population.

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