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Prognostic MRS in Neonatal Encephalopathy: Closer to generalizability

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In the current issue of Pediatric Research, Barta et al.[1] present ^{1}H MRS data of deep gray matter acquired from infants suffering hypoxic ischemic encephalopathy (HIE) across the first two weeks of life in the manuscript entitled “Predictive performance and metabolite dynamics of proton MR spectroscopy in neonatal hypoxic-ischemic encephalopathy.” Metabolites N-acetyl-aspartate (NAA), creatine (Cr) and myo Inositol (mI) were quantified in the first two weeks of life, and the NAA/Cr and mI/NAA ratios were calculated to determine whether these ratios are useful predictors of outcome at 18–26 months of age. Infants were treated with therapeutic hypothermia. The utility of a reliable predictor of outcome using MRS is high, increasing efficiency of clinical trials, since it is non-invasive and can predict long-term outcomes across a range of post-injury intervals. However, differences in brain region(s) analyzed, gestational age, postnatal age at the time of data acquisition, and technical details surrounding data acquisition have made establishment of a reliable prognostic indicator across studies elusive.

HIE is a multi-phase brain injury characterized by acute and protracted metabolic dysregulation in brain. Acute loss of oxygen and blood flow disrupts mitochondrial function, depleting both ATP and phosphocreatine, reducing supply of phosphates that normally provide metabolic support for basic cellular functions[2,3]. Loss of blood flow and hypoxia cause the end product of anaerobic metabolism, lactate, to accumulate as it cannot be catabolized or cleared by blood flow[4]. This acute spike in lactate can be quickly cleared during resuscitation and typically resolves to normal levels within hours, but persistently high cerebral lactate can occur over the initial days of life, and is very likely to indicate severe injury and poor outcome[5]. In cases of moderate to severe HIE that involve injury of the basal ganglia or thalamus, local cerebral lactate levels remains elevated for days to weeks[5,6]. NAA is synthesized from acetyl-CoA in neuronal mitochondria, and in the healthy developing brain, NAA gradually increases (reviewed in[4,7]). When NAA remains low after developmental brain injury, outcomes are typically poor[8]. The Lac/NAA ratio in a piglet model of HIE was strongly positively correlated with cell death and microglial activation in the basal ganglia and thalamus in the first 48 hours after injury[9]. Whether this ratio remains predictive at later timepoints and in different manifestations of injury (e.g., watershed regions) is unclear, but provides an important insight into the potential mechanistic resolution of MRS and specific metabolite ratios. mI is very high in early

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development, decreasing with both gestational and postnatal age[7,10]. mI is an osmolyte and a precursor for lipid synthesis from inositol, regulating membrane dynamics[11]. Barta et al.[1] found that both the NAA/Cr and mI/NAA ratios can predict outcomes when data are acquired within the first 14 days of life. In infants that exhibit good outcome, gestational age also contributes to these metabolite ratios, similar to healthy newborn infants, where the NAA/Cr ratio increases, while the mI/NAA ratio decreases as development progresses[10]. No such relationship was evident in those facing a poor outcome. Both NAA and Cr are higher in infants born at later gestational ages, but lower than levels observed in the adult[10]. The authors conclude that when HIE is less severe, the typical developmental progression of these ratios can be observed, while more severe injury disrupts this developmental progression.

The ratio of NAA/Cr is not always a clear predictor of outcome in HIE[12]. Shibasaki et al. did not find prognostic value in the NAA/Cr ratio at early postnatal ages (within the first 96 hours of life) or after the first week of life[12]. However, together, Barta et al. and Shibasaki et al. clearly demonstrate that the level of NAA, is a predictive measure[1,12]. Infants exhibiting favorable outcome either maintain or increase NAA levels during the first 2 weeks of life, and exhibit higher absolute levels almost invariably compared to infants with poor outcomes[12]. Similarly, higher NAA/Cr ratios reported by Barta et al. are associated with better outcomes[1]. Shibasaki et al. report absolute values of total Cr, and again, infants exhibiting favorable outcomes have higher Cr levels and maintain them across the first two weeks of life or show a small decrease, while infants exhibiting poor outcomes exhibit lower levels, and are more likely to exhibit precipitous drops in Cr levels[12]. Poor outcomes anticipated by NAA/Cr ratios are likely due to a drop in NAA, and not an increase in Cr, as infants with poor outcome exhibit drops in both NAA and Cr[12]. Dysregulation of mitochondrial function and energy reserve, indicated by NAA and Cr respectively, can yield variable ratios. However, when MRS is performed around 7 days of life, absolute concentration of thalamic NAA accurately predicted adverse outcomes at follow up around 2 years of age in infants exhibiting encephalopathy with near perfect accuracy[13]. Thus, when possible, quantitative measure of NAA is prognostically very powerful.

When absolute concentrations cannot be acquired due to technical issues, factors like gestational age might provide insight into prognosis, as supported by Barta et al.[1]. Patterns of metabolites rather than a single metabolite or single metabolite ratio will likely be further refined as the search for prognostic indicators continues, particularly after the acute phase of injury, when lactate is a reliable indicator that metabolism has been disturbed. Barta et al. make this point using conventional proton MRS within the first 96 hours of birth in infants exhibiting indications of HIE[14]. In infants with favorable outcome, the mI/NAA ratio was lower, as was the mI/Cr ratio, while NAA/Cr was higher[14]. This likely reflects a more normal progression of brain development, characterized by a decrease in mI and increase in NAA in postnatal development. Use of ratios is valuable, and allows inclusion of more data across sites. Consideration of patterns of ratios with attention to observed changes in the healthy brain as well as differences between favorable and poor outcome across reports can inform judgements on prognosis and facilitate clinical trials. Understanding how variables such as gestational age influence metabolite patterns can further hone expectations, as indications of normal development can be age-matched in subpopulations of infants

suffering with HIE. When patterns of ratios or absolute values do not reflect increasing NAA, decreasing lactate and stable Cr, development is likely severely impaired.

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