TITLE: **Very Early MRI During Therapeutic Hypothermia to Measure Severity of Brain Injury in Neonates with Hypoxic-Ischemic Encephalopathy**

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BACKGROUND:
Despite therapeutic hypothermia (TH), half of all neonates with hypoxic-ischemic encephalopathy (HIE) still die or suffer severe neurologic sequelae. The secondary energy failure (SEF) is the most vulnerable period for brain injury and its severity correlates with degree of impairment. The SEF begins 8-16 hours post insult and peaks at 24-48 hours. A quantitative, early method of measuring brain viability and injury severity is needed to guide application of adjuvant neuroprotective agents. Magnetic resonance H^1-spectroscopy (MRS) measures concentrations of cerebral metabolites to elucidate derangements in aerobic metabolism. MR diffusion weighted imaging (DWI) reveals microstructural alterations by quantifying the magnitude of extracellular water molecule diffusivity (apparent diffusion coefficient, ADC) and uniformity of diffusion along neuronal paths (fractional anisotropy, FA). MRI T_2-related underspin tagging (TRUST) directly measures venous oxygen content to determine the cerebral metabolic rate of oxygen ($CMR0_2$) and oxygen extraction fraction (OEF) and has never been applied to neonates with HIE.

OBJECTIVE:
To assess severity of brain injury in neonates with moderate-to-severe HIE by early measurement of derangements in cerebral energy metabolites, oxygen metabolism and microstructure with MRI during the SEF (18-24 hours TH).

METHODS:
Neonates ≥ 36 weeks' gestation with moderate-to-severe HIE were prospectively enrolled and treated with TH for 72 hours. MRI with MRS, DWI and TRUST was obtained at 18-24 hours of active TH and at 5-6 days of life (post-TH). T-test was used to compare metabolite concentrations, OEF, $CMR0_2$, ADC and FA in patients with moderate vs severe HIE.

RESULTS:
9 neonates have been enrolled: 4 with severe and 5 with moderate HIE. During TH, neonates with severe HIE had increased concentrations of basal ganglia glutamate (0.63 vs 0.35 ± 0.03, p=0.02), increased inositol (1.27 ± 0.12 vs 0.87 ± 0.15, p=0.007), decreased glycerylphosphorylcholine [GPC] (0.28 ± 0.05 vs 0.36 ± 0.02, p=0.01), decreased GPC + phosphatidylcholine [PCh] (0.3 ± 0.05 vs 0.36 ± 0.02, p=0.01), decreased N-acetylaspartate [NAA] + N-acetyl-aspartyl-glutamate [NAAG] (0.83 ± 0.04 vs 0.93 ± 0.06, p=0.049) and decreased white matter GPC + PCh (0.35 ± 0.13 vs 0.50 ± 0.04, p=0.05) and NAA (0.57 vs 0.75 ± 0.06, p=0.046). Neonates with severe HIE had lower ADC and FA values in the thalamus, white matter, midbrain, cerebellum and limbic system ($p<0.001$ for all areas) compared to those with moderate HIE. CBF during TH was similar in neonates with moderate vs severe HIE. Neonates with severe HIE had decreased OEF (p=0.04) and decreased $CMR0_2$ (p=0.03) compared to neonates with moderate HIE.

CONCLUSIONS:
Preliminary data suggest neonates with severe HIE have decreased energy substrate concentrations, metabolic markers of mitochondrial activity, ADC, FA OEF and $CMR0_2$ values during TH vs those with moderate HIE. These findings suggest severe neuronal dysfunction and cytotoxic cerebral edema and could be used for early identification (18-24 hr of TH) of neonates at greatest risk for poor outcome to receive adjuvant neuroprotective therapies.