Prognostic Significance of Combined Diffusion Weighted Imaging and Magnetic Resonance Spectroscopy in Neonates with Hypoxic Ischemic Injury

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Introduction: Hypoxic-ischemic injury (HII) continues to be a major cause of perinatal mortality and morbidity [1]. Because the prognosis for any given baby is uncertain, reliable prognostic indicators are needed. The goal of magnetic resonance imaging (MRI) in HII lies in early detection, which could potentially influence therapy and predict outcomes. MR Spectroscopy (MRS) and diffusion weighted imaging (DWI) have emerged as potential biomarkers for outcome. The purpose of this study was to evaluate combined ADC and MRS measurements retrospectively for prediction of outcome in neonates after HII.

Methods: A retrospective database search (2002-2009) identified 17 neonates (mean gestational age (GA): 39.1 weeks) who had HII based on Sarnat & Sarnat criteria. Patients were studied at 1.5T (GE Signa, Waukasha, WI) within 5 days of life. Newborns with evidence of congenital malformations, suspected inherited metabolic disorder and evidence of intracranial infection were excluded. None of the patients received hypothermic therapy. Single voxel ^{1}H-MRS (TR/TE=1500/144ms, NA=128) was performed in 8 cm^3 regions including the basal ganglia (BG), the white matter semiovale (WM) and the occipital parietal cortex (OC). Absolute concentrations of choline (Cho), creatine (Cr), N-Acetylaspartate (NAA), lactate (Lac) and glutamine/glutamate (Glx) were obtained using the LCModel software package using the unsuppressed water peak as reference. DWI was performed at b=1000 s/mm^2 with 6 gradient directions. ADC ROIs were placed to match the MRS voxel. A receiver operating characteristic (ROC) statistical analysis was conducted to determine the predictive value of the MRS and ADC measurements relative to survival as well as favorable outcome. (Areas under the ROC curve [AUC] that exceeded 70% are highlighted in bold.) Patients were classified into favorable outcome (no, mild and moderate developmental delay) and unfavorable outcome (severe developmental delay and death). Spearman Rank analysis was used to determine the relationship between ADC and spectroscopic markers.

Results: Of the 17 term neonates 8 died before discharge from the hospital. ROC analysis revealed an association between pour outcome and low ADC values in the basal ganglia, but not in the white matter semiovale and occipital cortex. Furthermore, low concentrations of Cho, Cr and NAA in the basal ganglia were also associated with poor outcome. On the other hand, these spectroscopic markers did not distinguish between the two groups when measured in OC or WM. Elevated Glx in the BG and OC was predictive of poor outcome. Interestingly, lactate levels were similar in both groups and did not predict mortality (Table 1).

Table 1: ROC analysis against survival (AUC)

Measurement	Basal Ganglia	Occ. Cortex	White Matter
ADC	**0.86**	0.50	0.58
Cho	**0.75**	0.46	0.57
Cr	**0.76**	0.55	0.64
NAA	**0.76**	0.49	0.55
Lac	0.52	0.58	0.59
Glx	**0.87**	**0.75**	0.60

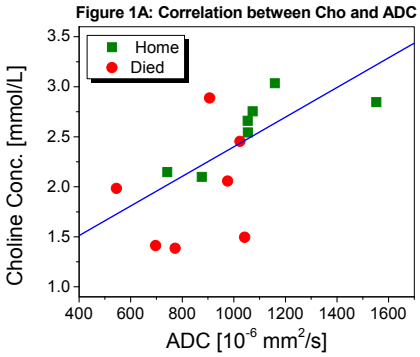
Table 2: ROC analysis against favorable outcome (AUC)

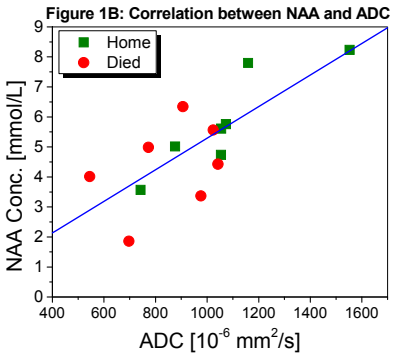
Measurement	Basal Ganglia
ADC	**0.83**
Cho	**0.73**
Cr	**0.81**
NAA	**0.81**
Lac	0.59
Glx	0.69

ROC analysis of metabolite ratios using creatine as denominator as well as NAA as a denominator did not yield highly predictive values except Glx/Cr in the BG (AUC=0.80).

Spearman Rank analysis between ADC and spectroscopic markers revealed significant correlations between ADC and choline (p=0.005, Rρ=0.71) as well as ADC and NAA (p=0.003, Rρ=0.73) (Figure 1A and 1B, respectively).

Upon further separation into favorable outcome (no, mild and moderate developmental delay (8 patients) versus unfavorable outcome (severe developmental delay and death, 9 patients) high ADC values and high NAA and Cr concentrations in the BG were found to be the best predictors for favorable outcome (Table 2).





Discussion: These results support prior studies reporting that low ADC values and low concentrations of NAA and Cho in the BG correlate with poor outcome [2,3]. Our study focuses on the first 5 days of life as the maximal decrease in ADC levels have been observed approximately 1-2 days after the hypoxic ischemic insult, followed by a pseudo normalization starting approximately 6 days after the insult. The timing of the MRI exam is important; not only ADC increases shortly after the insult but also both Glx rapidly decrease within the first week of life after HII (data not shown).

Absolute metabolic concentrations yielded a better prognosis for the outcome compared to metabolic ratios. Lower Cr concentrations in the basal ganglia were associated with poor outcome consistent with decreased energy stores. Creatine is often used as reference standard; however, creatine may not be such an ideal denominator for the assessment of neonates with HII. Interestingly, higher choline levels were predictive of better outcome and correlated with ADC values, possibly indicating sparing of glial cells. Our study confirms elevated Glx concentrations in patients with poor prognostic outcome likely due to pathological processes in which nerve cells are damaged and killed by excessive stimulation of glutamate [4].

Lactate and lactate ratios, a metabolic marker of anaerobic glycolysis, have reported by some to be an early indicator of the severity of brain injury [5,6,7,8]. Our study cannot confirm lactate as prognostic marker in neonatal HII. The lack of correlation of lactate and outcome is likely due to early reperfusion. Reperfusion can shift cell death processes from immediate necrosis to delayed necrosis or apoptosis. Lactate consumption, especially in the context of seizure activity may also affect lactate levels.

References: [1] Rutherford et al. Neuropediatrics 1995; 26:183. [2] Boichot et al. Radiology 2006 Jun;239:839. [3] Boichot et al. Magn Reson Imaging 2011;29:194. [4] Zhu et al. Transl Res. 2008;152:115. [5] Khong et al. J Child Neurol 2004;19:872. [6] Da Silva et al. Pediatr Neurol 2006;34:360. [7] Zarifi et al Radiology 2002;225:859. [8] Kadri et al. J Perinatol 200;23:181.