Predicting Clinical Outcome in Perinatal Asphyxia by MRI and MRS

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Introduction
Perinatal hypoxic-ischemia may result in hypoxic-ischemic encephalopathy (HIE) and neonatal brain injury leading to cerebral palsy, mental retardation and epilepsy (1). The identification of neonates at risk for brain injury who might benefit from intervention is currently based on non-objective indices (2). In addition, prevention of neonatal brain injury due to perinatal hypoxic-ischemia has not been well established and is still under intense investigation. The present study was undertaken to correlate MR/MRS and DWI with clinical evaluation in infants with perinatal asphyxia at risk for adverse outcome.

Methods
Twenty-six full-term infants of gestational age 38-40 weeks were clinically diagnosed with hypoxic-ischemic encephalopathy due to perinatal hypoxia-ischemia and were graded according to Sarnat and Sarnat (3). Infants with congenital malformations, inherited metabolic disorders and infection were excluded from the study. The initial MR studies were performed from 7 hours to tenth day of life. Eight patients had at least one follow-up MR study from day of life six to 12 months. All infants were clinically reevaluated for neurodevelopmental progress from the age of four months until the age of 23 months. Clinical outcome was classified as normal, abnormal and fatal. Abnormal was the outcome when an abnormality was present at the neurodevelopmental examination.

Conventional MRI and water-suppressed localized proton MRS were performed on a 1.5 T clinical MR scanner. DWI was performed using a line-scan diffusion-weighted imaging method (4). Proton MRS was performed using either a single-voxel technique and/or a multivoxel long-echo (echo time [TE] = 144 ms) Point RESolved Spatial Selection (PRESS) method. Other typical parameters for single-voxel were: TR = 1500 ms; 192 averages; 2500x1250 SW; 1048 complex data points. For multivoxel, other parameters were: TR= 1000 ms; 16x16x1 phase encoding steps; 160 mm FOV. The volume of interest was selected within the basal ganglia, and in certain cases the white matter (periventricular or subcortical). Proton MRS added approximately 4 minutes to the MRI exam. The total exam did not exceed 40 minutes. Metabolites of biological significance such as N-acetylaspartate (NAA), choline-containing compounds (Cho), total creatine (tCr), and lactate may be detected by this technique.

The Kolmogorov-Smirnov goodness-of-fit test indicated that Lac/Cho, NAA/Cho, and ADC values followed a normal (Gaussian-shaped) distribution. Therefore, the Pearson product-moment correlation coefficient (r) and linear regression analysis were used to evaluate relationships. Logistic regression was performed to examine whether each metabolite was predictive of clinical outcome. The likelihood ratio test was used to assess the significance of each metabolite. Statistical analysis was conducted using the LOGISTIC procedure in the SAS software package version 6.12 (SAS Institute, Cary, NC). A two-tailed p < 0.05 was considered statistically significant.

Results
Figure 1, shows MR images and proton MR spectra on day 1 and 2 of life of a full-term male infant with HIE, who presented with perinatal depression after suspected placental abruption, persistent seizures and metabolic acidosis (Apgar scores 8 and 9 at 1 and 5 minutes). The T2 weighted images showed hyperintensity in dorsal pons (day 1) and in basal ganglia, thalami hypomascibi and cerebellum (day 2). Multivoxel MRS on day 1 revealed accumulated lactate within basal ganglia. On day of life 2, single voxel MR spectra detected high levels of lactate again and the patient expired the same day.

NAA/Cho was measured in 26 patients, ADC in 25 patients, and Lac/Cho in 24. Some patients had more than a single measurement and therefore the total number of measurements of NAA/Cho, ADC, and Lac/Cho were 42, 38, and 32, respectively. Correlations are based on the total number of measurements across all patients. Neither Lac/Cho nor NAA/Cho were correlated with ADC (r=-0.10, p = 0.59; r = 0.14, p = 0.40). Lactate was detected in the absence of diffusion abnormalities in 5 cases. Lac/Cho correlated with Apgar score at 5 min (r = -0.50, p = 0.02) but not at 1 min (r = -0.22, p = 0.33). Lac/Cho also correlated with EEG (r = 0.45, p = 0.02) and encephalopathy grading (r = 0.72, p < 0.001). Outcome was normal in 5 infants, abnormal in 14 and fatal in 6. Multiple comparisons testing using the Kruskal Wallis test followed by Dunn’s method showed that Lac/Cho distinguished neonates with normal from abnormal or fatal outcome (p < 0.05 in each case). Figure 2, is a box-whisker plot and presents the median values and interquartile ranges of Lac/Cho [y axis] for the three outcome groups [x axis, fatal (F), normal (N) and abnormal (ABN) from left to right]. No significant differences were detected between the 3 groups for ADC (p = 0.82).

Discussion
Logistic regression revealed that Lac/Cho was an excellent marker for differentiating normal from adverse (abnormal or fatal) outcome (LRT = 13.56, p < 0.001). ADC was not predictive in differentiating between normal and adverse outcome (p = 0.91). Our experience suggests that MRS derived biochemical markers are useful in the evaluation of HIE and in identification of neonates at high risk for HIE and who are most likely to benefit from intervention.

References

Figure 1

Figure 2