Significance of Lactate in Patients with a Central Pattern of Hypoxic Ischemic Injury on DWI within the First 3 Days of Life

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Introduction: Hypoxia-ischemic injury (HII) continues to be a major cause of perinatal mortality and morbidity. The goal of contemporary MR imaging in HII brain injury lies in early detection which could potentially influence therapy and predict outcomes. MR Spectroscopy (MRS) and Diffusion imaging have emerged as the key MR techniques in the assessment of such injury. In particular, increased lactate (Lac), a metabolic marker of anaerobic glycolysis in the lentiform nucleus has reported by some to be an early indicator of the severity of brain injury [Khong J Child Neurol. 2004, da Silva Pediatr Neurol. 2006, Zarifi Radiology. 2002, Kadri J Perinatol. 2003]. In this pilot study, our objective was to determine, if the absence of lactate predicts good outcomes in patients demonstrating a central pattern of hypoxic ischemic injury on DWI within the first 3 days of life and to compare the location and extent of changes on DWI with lactate on MRS.

Methods: A retrospective database search (2001-2005) identified 8 neonates (4 males, mean gestational age (GA): 37.9 weeks) who had decreased diffusion in the ventrolateral (VL) thalamus within 3 days of birth (Group I) and had suspected HII (based on Sarnat&Sarnat criteria). Patients were studied at 1.5T (GE Signa, Waukasha, WI). Single voxel ^{1}H-MRS (TR/TE=1500/144ms, NA=128) was performed in 8 cm^3 regions including the lentiform and VL thalamus. Lac/NAA, Lac/Cr and NAA/Cr ratios were obtained using LCModel. DWI was performed at b=1000 s/mm^2 with 6 gradient directions. Free ROI's were drawn in each region of visually involved areas of decreased diffusion [vermis, VL thalamus, basal ganglia, dorsal brain stem, posterior limb of the internal capsule (PLIC) or cortex]. Each region with decreased diffusion on quantitative ADC maps was assigned a score of 1 and added up to determine the extent of changes on DWI in each patient. An equal number of neonates (5 males, mean GA: 38.5 weeks) with normal MRI in the first 3 days of life were included as a control group for calculating the normal ADC values in the above regions (Group II). Unpaired t tests were performed for comparing ADC values in the different regions. A chi square test was performed to look for association between lactate and outcome and ANOVA for extent of changes on DWI with lactate on MRS. Pearson product moment correlation was used to determine the relationship between ADC and spectroscopic markers.

Results: Five of the 8 patients in group I died and 3 had abnormal neurological outcomes at 2 years (Table 1). Two that died had no lactate on MRS but had extensive areas of decreased diffusion in the dorsal brainstem, vermis, corticospinal tract and cortex. The largest Lac concentrations were observed in patient 2, 3, 5 and 6 of which three survived. The mean ADC values were significantly decreased ($p<0.05$) in the dorsal brainstem, dorsal midbrain, ventrolateral thalamus, basal ganglia, PLIC, and the perirolandic cortex when comparing group I and II. DWI abnormalities were observed in vermis (50%), dorsal brain stem (50%), dorsal midbrain (87.5%), ventrolateral thalamus (100%), basal ganglia (100%), PLIC (87.5%), perirolandic cortex (62.5%) and visual cortex (50%). No significant correlation was obtained between ADC values and Lac/NAA (R=0.64, p=0.08), NAA/Cr (R=0.05, p=0.89) and Lac/Cr (R =0.48, p=0.23) ratios in the basal ganglia. There was no statistical significance between presence or absence of lactate or the score on DWI and outcomes. In fact, we found nearly a positive trend between Lac/NAA and ADC values which is opposite to what had been reported in adults with acute ischemia. At 2 years of age, patient 2, with the largest lactate peak at birth, was determined to have a mitochondrial disorder.

Patient No	DWI score	Lac/Cr	NAA/Cr	Outcome
1	7	0	0.74	Died
2	6	2.27	1.5	Sev. dev. delays
3	8	1.29	1.62	Sev. dev. delays
4	5	0	1.74	Died
5	4	1.38	1.04	Mild dev. delays
6	6	1.92	1.23	Died
7	5	0.98	1.08	Died
8	8	0.97	1.23	Died

Sev. dev. Delays = Severe developmental delays

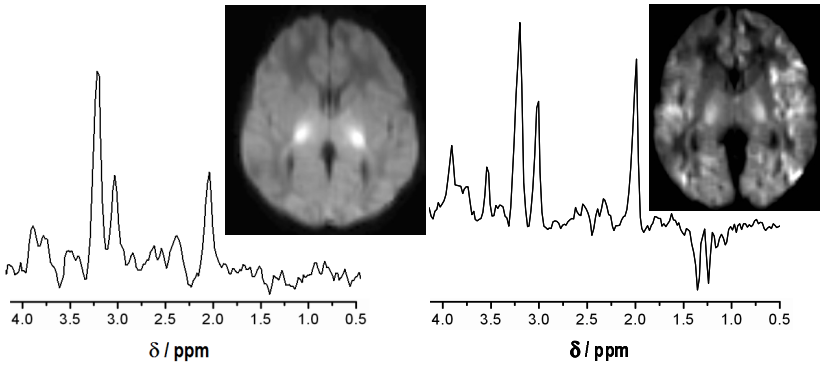

Table: Patient outcome, DWI score and MRS markers in the lentiform and VL thalamus. **Figure:** DWI and MRS from the BG on day 1 of life in patient 4 (left) and patient 2 (right). Additional peak at 1.1 ppm of 1,2-propanediol, a diluent used in phenobarbitol.

Discussion: In this pilot study, the absence of lactate in deep gray nuclei did not predict improved morbidity or mortality and lactate did not correlate with extent of DWI abnormalities or severity of ADC decrease. In adult stroke, lactate helps predict outcomes [Parsons Neurology 2000] and increasing lactate has been correlated with decreasing ADC values [Nicoli Stroke 2003, Singhal Stroke 2007], likely due to ongoing anaerobic metabolism and increasing cellular necrosis. The lack of correlation of lactate and outcome as well as lactate and ADC values in neonatal HII is likely due to early reperfusion which is expected in HII but unusual in adult stroke. 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 and ADC values. In addition, the presence of a large lactate peak should raise suspicion of an underlying metabolic disorder even if clinical criteria for Hypoxic Ischemic Encephalopathy are met. Subacute antenatal injury was unlikely in these cases as MR findings did not support this hypothesis. Thus, there is not a simple relationship between lactate and ADC or between these parameters and outcomes. In other words, neither lactate levels nor ADC values alone are likely to be good surrogate markers of neuronal health. In the context of reperfusion, the simple relationships between lactate, ADC and neuronal health no longer hold.