Comparative Prognostic Efficacy of Water ADC and Proton Spectroscopy in Newborn Infants with Perinatal Hypoxic-Ischaemic Encephalopathy

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Introduction: With the advent of neural rescue therapy there is an increasing need for early prognostic measures to aid appropriate selection of encephalopathic infants for treatment and to assess the efficacy of intervention. In experimental models we have observed a correlation between the decline in the apparent diffusion coefficient (ADC) of brain water and brain energy depletion 12-24 hours following transient hypoxia-ischaemia (HI) **(1)**. Our aim in this study was to compare the predictive values for adverse outcome of regional brain ADC and thalamic metabolite peak-area ratios obtained by proton magnetic resonance spectroscopy (1H MRS) in the early postnatal period in infants with neonatal encephalopathy (NE).

Methods: : Five healthy term infants were studied: corrected gestational age at scan (CGA) 40.7 $\pm$ 1.4 (mean $\pm$ standard deviation (SD)) weeks and postnatal age at scan (PA) was 2.2 $\pm$ 0.8 days. Fourteen term infants with NE were also studied: CGA 40.1 $\pm$ 1.6 weeks and PA 2.9 $\pm$ 1.4 days. All NE infants had a structured neurodevelopmental assessment at 1 year and were consequently divided into three outcome groups: (i) normal outcome; (ii) neuromotor signs but no functional difficulties (moderate outcome); and (iii) functional deficits as a result of their impairment or who died (severe outcome). All control infants had a normal neurological outcome at 1-year.

MR data were acquired at 2.4T (Bruker Avance). Single voxel 1H MRS data (PRESS;TE 270 ms; TR 2s; 256 echoes summed) were acquired from an 8ml cubic voxel centred on the thalami. and lactate (Lac)/N-acetylaspartate (Naa), Lac/ total creatine (Cr), Lac/ choline (Cho), Naa/Cr, Naa/Cho , and Cho/Cr peak area ratios determined using LCM software. Diffusion-weighted images were obtained using a segmented EPI sequence with automatic re-acquisition of motion corrupted segments **(2)**. The axial image slice passed through the genu and splenium of the corpus callosum so as to intersect the thalami and basal ganglia. This sequence was weighted to the trace of the diffusion tensor. Two images (b=20 and b=600) were obtained and ADC maps were computed using a two-point log-linear fit. Regions of interest (ROI) were defined on the ADC maps within the thalami and basal ganglia (deep grey matter; DGM) and within the parietal, occipital and frontal white matter (WM). Mean ADC values were calculated for each ROI. To assess differences between DGM and WM, thalamic and basal ganglia ADCs were averaged to yield a mean DGM ADC; similarly, the parietal, occipital and frontal WM ADCs were averaged giving a mean WM value. The sensitivity and specificity of ADC for an adverse outcome was calculated with moderate and severe groups combined . For this purpose, ADC was considered abnormal if outside the 95% confidence interval for control infants.

Results: Mean DGM and WM ADCs, grouped according to outcome are shown in Table 1; one infant had a moderate outcome. The sensitivities and specificities of abnormal ADC to an adverse neurodevelopmental outcome and the slopes of the regression lines for correlations between regional ADC and thalamic metabolite peak-area ratios are shown in Table 2. Significant negative correlations were observed between DGM and WM ADC and thalamic Lac/Naa , Lac/Cho, and Lac/Cr. Significant positive correlations were observed between DGM and WM ADC and thalamic Naa/Cr.

Discussion: Most infants with NE had reduced DGM ADCs compared to controls, however these were not predictive of neurological outcome. These findings suggest that DGM ADCs are sensitive to HI injury but lack specificity in predicting outcome. Our results thus confirm those found in previous DGM ADC studies **(3)**. However, reduced WM ADCs were highly specific for a severe neurodevelopmental outcome. Furthermore, if ADC in both DGM and WM ADC was abnormal this had a specificity to adverse outcome of 100%. The combined decrease in both DGM and WM ADC was thus more predictive than DGM ADC alone even though the DGM has particularly high energy-demands and vulnerability to energy failure in the full term newborn.

Reductions in both DGM and WM ADC were associated with increases in thalamic Lac/Naa, Lac/Cr and Lac/Cho. Furthermore, thalamic Naa/Cr was positively correlated with both DGM ADC and WM ADC. As the absolute concentrations of Naa and Cr both reduce following HI a fall in Naa/Cr may not fully represent the magnitude of any decrease in Naa concentration, which may reflect reduced neuronal necrosis. However, the fall in Naa/Cr may in part be due to a larger than anticipated Cr signal amplitude resulting from increased Cr T_2 due to phosphocreatine (PCr) hydrolysis (creatine has a longer T_2 than PCr). Reduced PCr would suggest impaired cerebral energy generation which may result in the observed ADC decreases. The correlation between thalamic Naa/Cr and WM ADC may be a result of widespread global damage resulting from a severe HI injury and reflecting the prognostic utility of both measures.

Outcome	N	DGM	WM
Controls	5	1.41 (0.08)	1.57 (0.20)
Normal	6	1.16 *, # (0.10)	1.55 # (0.15)
Severe	7	0.93 * (0.12)	1.11 * (0.26)

Table 1: Group mean ADC ($x10^{-3}$ mm^2 s^{-1}).

N - number of cases. * $p < 0.01$ c.f. controls
# $p < 0.01$ c.f. adverse

Region	Abnormal ADC		Pearson Product Moment – slope of regression				
	Sensitivity	Specificity	Lac/ Cr	Lac/ Cho	Lac/ Naa	Naa/ Cr	Naa/ Cho
DGM	88%	14%	-0.71 *	-0.68 *	-0.65 *	0.73 *	0.19
WM	75%	86%	-0.75 *	-0.73 *	-0.80 **	0.95 ##	0.60

Table 2: Sensitivities and specificities of abnormal early ADC to adverse outcome (moderate and severe) and slopes of regression lines for correlations between regional ADC and thalamic metabolite peak area ratios. * $p < 0.05$; ** $p < 0.01$; ## $p < 0.0001$

Refs:(1) Thornton JS, *et al*; MRM 1998; 39; 920-927. **(2)** Q Nguygen *et al*; MAGMA 2000; 11(S1); abstract 235. **(3)** Zarifi Mk *et al*; Radiology. 2002 Dec;225(3):859-70