Prediction of adverse outcome by thalamic and basal-ganglia MRI T2 relaxometry and proton MRS in infants with neonatal encephalopathy

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BACKGROUND: Perinatal cerebral hypoxia-ischaemia (HI) affects 3-5 per 1000 live births, with consequent moderate and severe neonatal encephalopathy (NE) in around 1 per 1000 live births[1]. Methods are required to predict clinical outcome for individual infants, both to inform clinical management, and to select suitable candidates for therapeutic intervention. Previous studies have demonstrated the prognostic utility of proton spectroscopy (^{1}H-MRS)[2,3] and conventional MRI[4] in this context. Our aim was to compare the predictive value for adverse outcome of thalamic and basal ganglia MRI T2 relaxometry and thalamic ^{1}H-MRS performed in the early postnatal period in infants with NE.

METHODS: 23 infants of gestational age 37-42 weeks and birth weight 2.57 ±1.36 kg (mean ± SD), with signs of acute NE as assessed by detailed structured neurological assessment, and a clinical history consistent with perinatal HI as the primary cause were studied. All MR examinations were performed within 5 days of HI. All infants had a structured neurodevelopmental assessment at 1 year and were 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 before their first birthday (severe outcome).

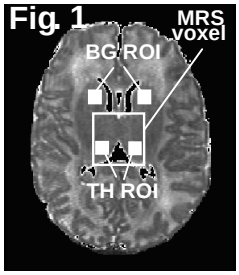
MR data were acquired at 2.4T. Standard spin-echo images (FOV 15cm; 128 x 256 acquisition matrix; 7 axial slices, slice thickness 5mm, TR 4500ms) with TE 25ms and TE 200ms were acquired separately allowing the calculation of pixel-by-pixel T2 maps assuming a monoexponential transverse-magnetisation decay. Mean MRI T2 was determined from regions of interest (ROIs) in the thalami (TH) and basal ganglia (BG) (Fig1) (Left and right ROI T2s were averaged). Single voxel ^{1}H-MRS data (PRESS; TE 270ms; TR 1730ms; 256 echoes summed) were acquired from an 8ml cubic voxel centred on the thalami, and lactate (Lac)/ N-acetylaspartate (Naa) peak-area ratios determined using LC Model software[5].

RESULTS: Relationships between MRI T2 or Lac/Naa and outcome were assessed using Pearson correlation analysis. Binary logistic regression was performed to examine the predictive value of MRI T2 or Lac/Naa in differentiating normal from adverse outcome (moderate and severe groups combined) and the model coefficients used to estimate the dependence of probability of adverse outcome upon MRI T2 or thalamic Lac/Naa.

The table gives mean MRI T2 and median Lac/Naa for each outcome group. TH and BG T2 both correlated with neurodevelopmental outcome ($r=0.594$; $p = 0.003$ and $r=0.493$; $p=0.017$ respectively), and both were significant predictors for adverse outcome (chi-sq 10.0 (1df), $p =0.002$; chi-sq 9.4 (1df), $p=0.002$; TH and BG respectively, likelihood-ratio test). Thalamic Lac/Naa also correlated with outcome score ($r = 0.707$; $p < 0.001$) and was a significant predictor of outcome (likelihood-ratio test chi-sq 19.5 (1df), $p<0.001$). The probability of membership of the combined adverse outcome group for a particular individual on the basis of TH or BG MRI T2 or Lac/Naa was calculated using the coefficients of the logistic regression models (Figure 2). Values of each measurable for which this probability exceeded 50% and 95% are listed in the table. The threshold values for 50% probability of adverse outcome were used to assign each infant to either a predicted normal or predicted adverse outcome. Comparison with the true 1yr follow-up score yielded the prognostic sensitivities and specificities given in the table.

	Outcome group (n)			$P_{adverse}$ 0.50††	$P_{adverse}$ 0.95††	Sensitivity*	Specificity*
	Normal (8)	Moderate (6)	Severe (9)				
TH T2 (ms)†	136.2 (12.2)	155.2 (12.7)	164.9 (23.5)**	> 140ms	>167 ms	87%	63%
BG T2(ms)†	149.0 (13.8)	173.8 (16.1)**	173.0 (22.5)**	> 153ms	>183 ms	80%	63%
Lac/Naa‡	0.21 (0.19-0.23)	0.33 (0.23-0.47)	1.28 (0.78-1.94)**	> 0.24	>0.31	88%	87%

†mean (sd); ‡ median (IQ range); ** $p<0.05$ vs. normal outcome group; †† value of T2 or Lac/Naa above which the predicted probability of adverse outcome exceeds 0.50 or 0.95 respectively; ***** using a threshold probability for positive classification (severe outcome) of 0.50.



DISCUSSION: The correlations between early TH and BG MRI T2 and neurodevelopmental outcome at 1 year suggest that elevated deep grey-matter MRI T2 may be associated with irreversible pathological processes in infants with NE. Both likelihood-ratio tests and the sensitivity and specificity figures, however, indicate that thalamic Lac/Naa is a more powerful predictor of outcome than TH/BG T2, and therefore that Lac/Naa may be a more specific index of cell death. Nevertheless, our results demonstrate that early TH and BG T2s are of prognostic value in infants with NE, and MRI T2 relaxometry may be a useful adjunct to investigations using other modalities, particularly in centres where ^{1}H-MRS is not available.

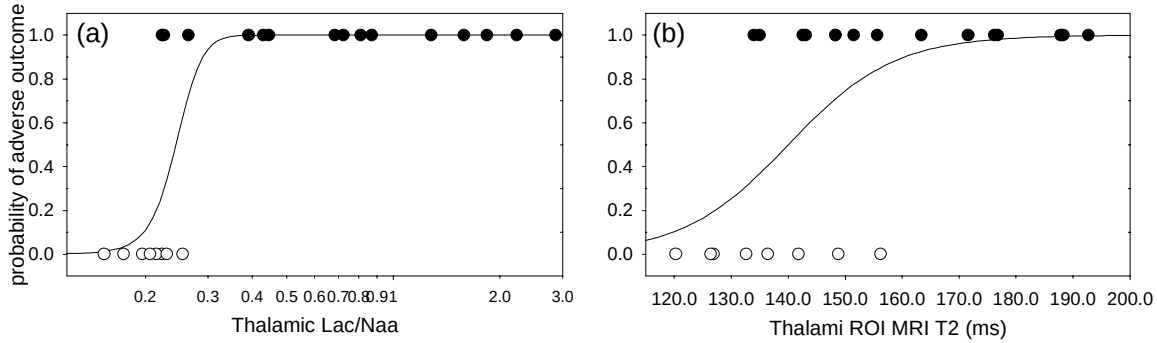


Figure 2 (a) Lac/Naa and (b) TH MRI T2 for infants classified as normal outcome (open circles) and adverse outcome (filled circles) superimposed upon plots showing the estimated dependence of probability of adverse outcome upon Lac/Naa or TH T2 (a similar curve was obtained for BG T2)

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