6383

Impaired neurodevelopmental outcome associated with increased white matter Chol/Cr in preterm infants

D. Price[1], G. S. Kendall[2], A. Bainbridge[1], S. Johnson[2], C. Hagmann[2], R. Gunny[3], X. Golay[4], E. B. Cady[1], N. J. Robertson[2], and E. De Vita[5]

[1]Medical Physics & Bio-Engineering, UCL Hospitals NHS Foundation Trust, London, London, United Kingdom, [2]Academic Neonatology, EGA UCL Institute for Women's Health, London, London, United Kingdom, [3]Neuroradiology, Great Ormond Street Hospital for Children, [4]Institute of Neurology, University College London, [5]Lysholm Department of Neuroradiology, UCL Hospitals NHS Foundation Trust, London, London, United Kingdom

Introduction: Infants born prematurely have a higher incidence of neurodevelopmental disorders. Diffuse white matter injury is the commonest MR finding in preterm infants, and has been described qualitatively as diffuse excessive high signal intensity [1], and quantitatively as increased T2 [2]; cystic white matter injury is now rare. The clinical correlate of diffuse white matter injury is currently unknown, but it is possible that this finding is related to later neurodevelopmental problems. Using localised white matter proton (1H) MRS we have previously shown that cystic white matter injury is associated with raised Lac/creatine (Cr) in the posterior periventricular white matter [3]. In adult patients with de-myelinating disease and dementia, a raised choline (Cho) and reduced N-acetyl aspartate (Naa) has been detected in the white matter [4]. A raised Cho/Cr ratio has also been shown to be associated with histological astroglyosis in experimental models (5). The metabolic signature of diffuse WM injury has not been described.
Hypothesis: Neurodevelopmental outcome in preterm infants is associated with raised Lac/Cr, Cho/Cr and reduced Naa/Cr ratios.

Methods: The local ethical committee granted approval for this study; informed parental consent was obtained. Forty preterm infants born 22-32 weeks gestation were studied at mean corrected gestational age (CGA) of 40.6±2.0 weeks. Single voxel point-resolved spectroscopy (PRESS) was performed using a Siemens Avanto 1.5 Tesla system (Erlangen, Germany). A 1.5 cm^3 voxel was manually positioned in the left PWM using previously acquired axial T2 and sagittal T1 images for guidance. Spectra were obtained using a long echo-time, water suppressed sequence (TR= 2290 ms, TE =288 ms, averages=8, 37 measurements). Data was analysed using the JMRUI spectroscopy package [6] with the metabolite ratios Naa/Cho, Naa/Cr, Cho/Cr, Lac/Cho, Lac/Cr, Lac/Naa quantified with the AMARES algorithm [7]. To date, 29 infants have reached a corrected age of 1 year of whom follow-up data were available for 24 (86%). Infants were administered the Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley III) [8] to assess cognitive, fine motor and gross motor development. Infants with scores < -1SD in each domain were classified as impaired. Statistical analysis comprised Pearson correlations and T-tests for independent samples.

Results: There was no significant association between any metabolite ratio and CGA at the time of scan (n=40). 24 babies had follow-up at 12 months corrected postnatal age. Mean cognitive (95±13) and motor (86,±13) composite scores were within the normative population range. Metabolite ratios were not significantly associated with cognitive scores at 12m corrected age. Composite motor outcome was significantly associated with tNAA/Cho (r=0.436, p=0.033), Cho/Cr (r=-0.525, p=0.008) and Lac/Cr (r=-0.414 p=0.044) ratios. When infants with and without motor impairment were compared, there were significant differences in tNaa/Cho, and Cho/Cr ratios. The difference in Lac/Cr between infants with and without composite motor impairment did not reach statistical significance (p=0.054, Table 1 and Figure 1).

	No impairment (n=14)	Impairment (n=10)	Mean Diff (95% CI)	p
NAA/Cho	0.76 (0.14)	0.64 (0.09)	-0.12 (-0.22 to -0.01)	**0.028**
NAA/Cr	1.85 (0.50)	2.28 (0.61)	0.43 (-0.04 to 0.90)	0.068
Cho/Cr	2.47 (0.67)	3.65 (1.29)	1.18 (0.34 to 2.02)	**0.008**
Lac/Cho	0.33 (0.08)	0.33 (0.09)	0.00 (-0.07 to 0.07)	0.997
Lac/Cr	0.82 (0.33)	1.23 (0.66)	0.42 (-0.01 to 0.84)	0.054
Lac/Naa	0.45 (0.17)	0.52 (0.18)	0.07 (-0.08 to 0.21)	0.368

Table 1: Metabolite ratios in infants with and without composite motor impairment at 12 months corrected age All t-tests for equal variances assumed as Levene's test for equality of variances is non-significant for all comparisons.

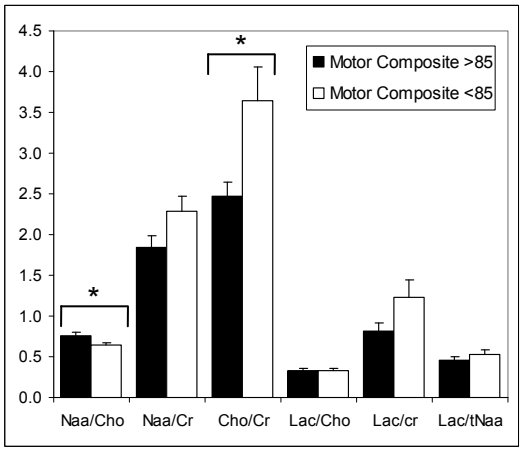

Figure 1: Metabolite ratios in babies with and without composite motor impairment at 12 months corrected gestational age

Gross and fine motor outcome were also analysed separately. There was no significant association between fine motor outcome and any of the metabolite ratios measured. Gross motor outcome at 12 months corrected age was significantly associated with Naa/Cho, Cho/Cr and Lac/Cr ratios (see Table 2).

	Fine motor (n=24)		Gross motor (n=24)	
	r	P	r	p
NAA/Cho	0.203	0.341	0.467	**0.022**
NAA/Cr	-0.258	0.224	-0.268	0.206
Cho/Cr	-0.359	0.085	-0.582	**0.011**
Lac/Cho	-0.009	0.967	-0.039	0.856
Lac/Cre	-0.292	0.167	-0.417	**0.043**
Lac/Naa	-0.145	0.498	-0.273	0.197

Table 2: Pearson Correlations: Metabolite ratios & Bayley III motor scaled scores

Discussion and Conclusions: This is the first description of a white matter proton MRS signature in infants with diffuse white matter injury that is related to motor outcome. Raised Cho/Cr and Lac/Cr, and reduced Naa/Cho were significantly associated with composite motor outcome at 12 months corrected age, and were accounted for by significant associations with gross motor development. With normal postnatal development Cho/Cr ratio falls due to myelinaton (9). Disease processes which result in membrane breakdown, lead to an increase in MR-visible choline (Moore 1998). We observed a raised Cho/Cr ratio in infants with impaired gross motor outcome; the raised choline could be attributed to delayed myelination, astrogliosis, or ongoing membrane damage. This fits with the histological hallmark of diffuse white matter injury - glial scars, failure of white matter development, prominence of activated microglia and astrocytes, and deficient myelination. The raised Lac/Cr suggests impaired oxidative phosphorylation, and the reduced Naa is in keeping with neuronal / axonal density and integrity. Further work is needed to more precisely characterise the MR metabolic signature, but this indicates Cho/Cr may be a useful surrogate biomarker of neurodevelopmental outcome in preterm infants.

References

1. Maalouf et al., 1999 J Pediatr. 135(3):351-7
2. Hagmann et al., 2009 Radiology. 252(1):209-17
3. Robertson et al., 2000 J Cereb Blood Flow Metab. 20(10):1446-56.
4. Mader et al., 2008 Eur J Radiol.;67(2):250-7
5. Kim et al., 2005 Am J Neuroradiol. 26(4):752-9.
6. Meas. Sci. Technol; 2009; 20 104035
7. J Magn Reson. 1997; Nov;129(1):35-43.
8. Bayley Scales of Infant and Toddler Development, 3rd Edition
9. Gulati et al., 2003; Indian J Pediatr. 70(4):317-25
10. Moore 1998; Pediatr Radiol. 28(11):805-14