Metabolic and Structural Correlates of Different Patterns of White Matter Injury In Preterm Infants

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Target Audience

Researchers who are interested in neonatal MR spectroscopy, neonatal brain injury, abnormal premature brain development

Purpose

Two common neuroimaging patterns of preterm white matter injury include diffuse excessive high signal intensity (DEHSI) and punctate white matter lesions (pWML). The neuropathologic-neuroimaging correlate of diffuse white matter injury associated with these patterns of injury is unknown but is likely related to oligo-axonal injury with associated thalamic-cortical abnormalities. We tested the hypothesis that different patterns of preterm white matter injury would demonstrate similar alterations in four metabolic and structural measurements: NAA/myo-inositol ([NAA]/[mI]) ratio (parietal white matter), quantitative T2 relaxation measurements (parietal white matter) , thalamic volume, and brain metric measurements.

Methods

We analyzed magnetic resonance spectroscopy (MRS) studies and structural MRI studies conducted on 108 high risk preterm infants near term equivalent age and measured: (1) the [NAA]/[mI] ratio of the parietal white matter based on absolute concentrations of short echo MRS data; (2) quantitative T2 relaxation of parietal white matter; (3) thalamic volume (manual segmentation) and (4) brain metric measurements (brain parenchyma, extra-axial space; ventricles) . These values were compared between preterm cases in relation to both the presence/absence of pWML and between different degrees of DEHSI (mild, moderate, severe) within the same dataset. Absolute concentration for each of the two metabolites (NAA and mI) was quantitated from the MRS spectra using using fully automated LCModel software (Stephen Provencher Inc., Oakville, Ontario, Canada, LCModel Version 6.1-4F). We generated a reference table for water content as a function of postconceptional age that was used for absolute quantitation of spectra in this study.

Results

PWMLs were associated with reduced [NAA]/[mI] ratio, reduced quantitative T2 signal, and reduced thalamic volume (Table 1). In contrast, only severe DEHSI was associated with reduced [NAA]/[mI] ratio ($p<0.039$) (Table 1). The abnormality in [NAA]/[mI] ratio was driven predominately by NAA compared to mI suggesting relatively more predominant detection of oligo-axonal injury compared to microglial/reactive astrocytic reaction. Brain metrics were not different within the pWML groups or the DEHSI groups.

Table 1: Comparison of metabolic and structural measurements between DEHSI and pWML groups

n	DEHSI Score	[NAA]/MI	T_2 Relaxation (msec)	Thalamic Volume (mm3)
n=28	0	.58 ± .029	204 ± 13	5626.3 ± 258
n=42	1	.50 + .023	190 + 10	5924.2 + 203
n=28	2	.495 + .029	188 + 13	6135 + .15
n=10	3	.425 + .048	235 + 21	6091 + 417
	p value	.039	.219	.540

n	pWML Score	[NAA]/MI	T2 Relaxation (msec)	Thalamic Volume (mm3)
n=78	0	.53 ± .02	189.27 ± 8	60997 ± 146
N=30	1	.47 + .03	219.19 ± 12	5458 ± 235
	P value	.045	.039	.023

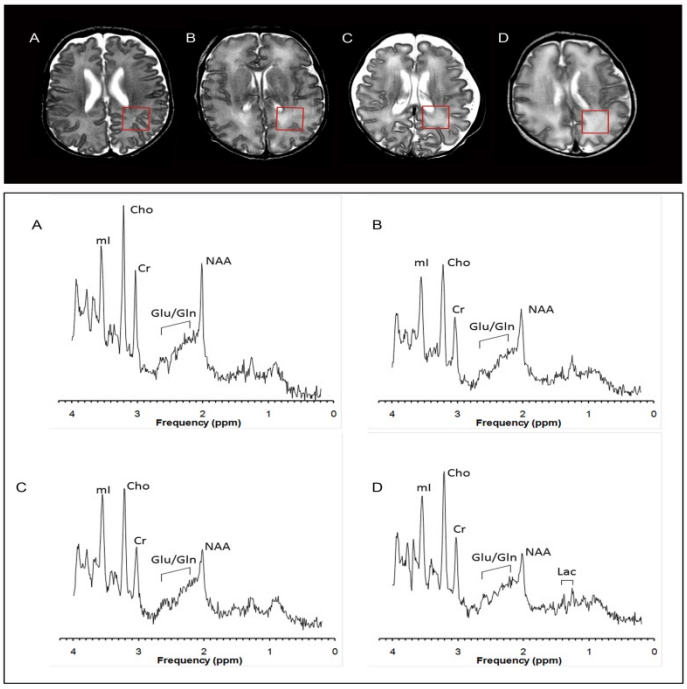

Figure 1 DEHSI examples and MRS spectra. [Top box with black background] Exemplars of cases rated as "within normal limits (wnl)" (A), mild DEHSI (B), moderate DEHSI (C) and severe DEHSI (D) showing approximate placement of 3 cm^3 MRS voxel (red square). [Bottom box with white background] MR Spectra for each of the cases above. MANCOVA was used to compare cases scores as WNL, mild, mod, severe, controlling for PCW and revealed significant between group differences for NAA/mI (p=.039).

Discussion

A major unanswered question is the "true" neuroimaging correlate of the diffuse component of white matter injury in preterm infants that may be seen in association with specific preterm white matter injury patterns including pWML and/or DEHSI. The question still remains: is DEHSI really the true correlate of diffuse white matter gliosis? Diffuse white matter preterm injury is likely to involve not only pre-oligodendrocyte injury, but also injury to axons. MRS can non-invasively measure **neuronal-axonal integrity** via the metabolite N-acetyl-aspartate NAA and **astrogliosis** via the metabolite myo-inositol. NAA is also expressed by oligodendrocyte precursor cells which are also thought to be involved in the pathogenesis of preterm white matter injury. Given that axonal density decreases and astrocytic density increases in white matter gliosis based upon neuropathologic observations, we hypothesized that the ratio of absolute concentration of NAA to myo-inositol ([NAA]/[mI]) may be a sensitive MRS marker of diffuse white matter injury . T2 relaxation measurements have also have been used by multiple investigators to assess the normal and abnormal development of preterm white matter, and may be another potential way to quantitate diffuse white matter injury [1]. Our finding suggest that diffuse injury associated with pWML is more significant that what is detected in association with DEHSI, and that the reduction in NAA (axons and pre-oligo) is responsible for the abnormality of the [NAA]/[mI] ratio compared to mI (astrogliosis).

Conclusion

PWMLs are associated with multiple metabolic and structural correlates of diffuse white matter injury compared to DEHSI in high risk preterm infants. These findings suggest that diffuse white matter injury associated with pWML not only reflects oligo-axonal injury, but also abnormalities in thalamo-cortical connectivity. Better quantitative tools and neuroimaging biomarkers assess diffuse white matter injury are needed.

Reference: Counsell et al; 2003; AJNR Am J Neuroradiol. 2003 Sep; 24(8):1654-60

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