Left-Right Hemisphere Metabolite Asymmetry in the Neonatal Brain

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Introduction Lateralization of brain function is thought to begin during intrauterine life [1]. Several Magnetic Resonance Spectroscopy (MRS) studies have reported significant hemispheric differences in metabolite levels in various regions of the child and adult brain [2,3]. This is the first study to investigate the possibility of biochemical asymmetry in the neonatal brain. The purpose of this study was to determine if left-right hemisphere metabolite asymmetry exists in the premature infant frontal white matter (WM) at a term equivalent age. Understanding early brain biochemistry provides insight into the mechanisms of cerebral lateralization and is important for planning and interpreting spectroscopic studies of the neonatal population.

Methods Brain MRS was performed on a 3.0 Tesla scanner (IMRIS, Winnipeg, Canada) using a quadrature birdcage coil (27.4 cm diameter). Eleven preterm infants were studied at a near-term age. Infants with small for gestational age birth weights, congenital infections or abnormalities, hypoxia-ischemia, metabolic abnormalities, seizures, cystic periventricular leukomalacia, unilateral intraventricular hemorrhage (IVH), and IVH with parenchymal involvement or posthemorrhagic hydrocephalus were excluded. From brain ultrasound scans, 4 infants had evidence of low-grade bilateral IVH, and 7 had no abnormality. The study population consisted of 6 males and 5 females and had a mean gestational age (GA) at birth of 28 weeks (standard deviation (SD) = 2.3) and a mean GA at scan of 36 weeks (SD = 1.1).

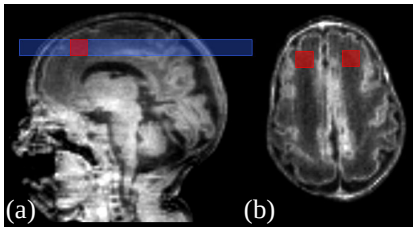

Figure 1: T1-weighted images showing MRSI slice position (a). Voxels were selected as shown in (b).

Localized proton spectra were acquired using a single-slice spin-echo spectroscopic imaging (MRSI) sequence with a slice-selective adiabatic inversion for lipid nulling (TI/TE/TR=250/135/2000ms, 160mm FOV, 13mm slice thickness, 12×12 matrix size, 2 averages, 9.5 min acquisition time). The slice was positioned axially superior to the lateral ventricles and corpus callosum in a midsagittal view (**Figure 1a**). Water suppression was performed during the inversion time using the adiabatic WASHCODE technique [4]. A T1-weighted image was acquired at the same slice position as the MRSI acquisition for anatomical correlation. One voxel within WM in each hemisphere of the frontal lobe was selected for analysis (**Figure 1**). Using a constrained Marquardt-Levenberg minimization algorithm, the unfiltered FIDs were fit in the time domain following subtraction of the residual water signal (fit using HLSVD) according to prior knowledge from *in vitro* solutions of N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), glutamate + glutamine (Glx), and myo-inositol (mI) as described previously [5]. The fitted metabolite signal amplitudes were corrected for coil load [6].

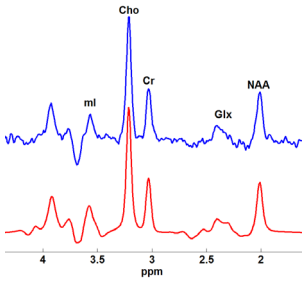

Figure 2: (top) frontal lobe white matter spectrum and (bottom) result of time-domain fitting algorithm (2-Hz filter for display)

Statistical analysis included a repeated measures MANOVA (within subjects factor = hemisphere). Post-hoc paired *t*-tests were conducted following the MANOVA. In addition, results were confirmed using the non-parametric Wilcoxon signed ranks test. All statistical analyses were carried out using the SPSS software package version 10.0.7 (SPSS Inc., Chicago, IL).

Results A sample spectrum and fit are shown in **Figure 2**. The multivariate tests showed significant within subject asymmetry ($p < 0.05$). Post-hoc paired *t*-tests revealed that NAA levels were significantly lower in the right hemisphere (~ 20%, $p < 0.01$) (**Figure 3**). In addition, the Wilcoxon signed ranks tests confirmed significant NAA asymmetry ($Z = -2.493$, $p < 0.05$). In this cohort, two infants had reversed NAA asymmetry (right > left hemisphere).

Discussion Although nominal voxels were selected to contain only WM, partial volume correction would ensure precision by correcting for potential small metabolite signal contributions from surrounding gray matter or CSF. It is possible that a portion of the asymmetry in measured NAA levels may be due to asymmetry of metabolite T2 relaxation times.

Conclusion Our finding of left-right hemisphere asymmetry of NAA levels supports the theory of early cerebral lateralization and the suggestion of inherent metabolite asymmetry. Further investigation is required to explore the possibility of (i) metabolite asymmetry in other regions of the neonatal brain and (ii) the significance of reversed metabolite asymmetry.

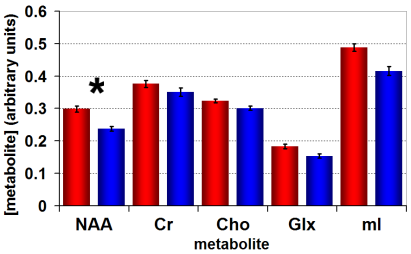

Figure 3: Mean metabolite levels (± standard error). Significant left > right hemisphere asymmetry was found for NAA (*$p < 0.01$). The left column (red) represents the left hemisphere and the right column (blue) represents the right hemisphere.

Acknowledgements

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