Altered Glutamatergic Metabolism is Associated with Punctate White Matter Lesions In Preterm Infants

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Target Audience

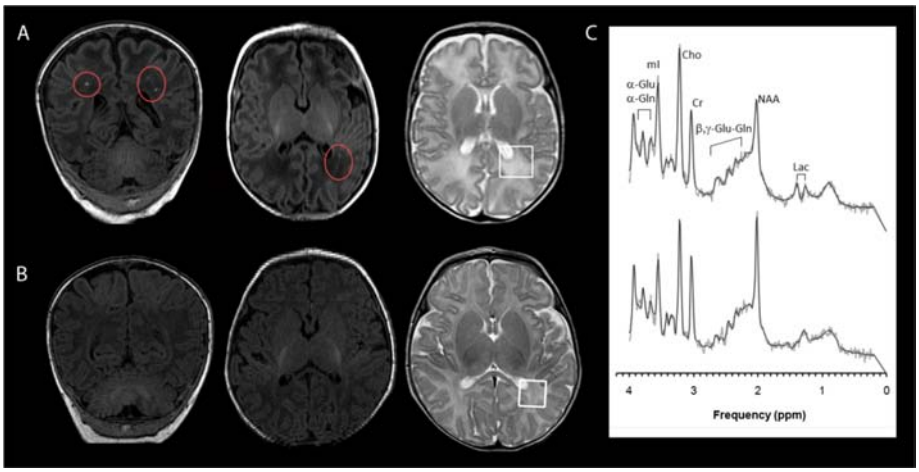
Researchers who are interested in fetal/pediatric brain injury, MR Spectroscopy or excitotoxic brain injury mechanisms.

Purpose

Preterm infants (~10% of all births) are at high risk for long-term neurodevelopmental disabilities most often resulting from white matter injury sustained during the neonatal period. Glutamate excitotoxicity is hypothesized to be a key mechanism in the pathogenesis of white matter injury[1,2]; however, there has been no *in vivo* demonstration of glutamate excitotoxicity in preterm infants. Using magnetic resonance spectroscopy (MRS), we tested the hypothesis that glutamate and glutamine, i.e., markers of glutamatergic metabolism, are altered in association with punctate white matter lesions (pWMLs) and "diffuse excessive high signal intensity" (DEHSI), the predominant patterns of preterm white matter injury.

Methods

We reviewed all neonatal MRS studies (n = 218) acquired between 2002 and 2008 at a single, tertiary care hospital, under a single, standardized imaging protocol. All available cases were included in this study provided: 1) the imaging study had been completed on an infant born before 37 weeks of age; 2) the infant was not older than 60 weeks postconceptional age (PCA; calculated as the interval between the mother's last menstrual period and birth plus post-natal age) at the time of the MRI; 3) an ^{1}H MR spectrum was acquired from a single voxel placed in the parietal white matter (standard clinical protocol at this institution on neonatal neuroimaging studies); 4) there was no evidence of cerebral abnormality other than pWMLs or DEHSI (i.e., large vessel acute or chronic infarction, parenchymal hemorrhage, infection, tumor or cerebral malformation); and 5) there was no clinical or laboratory evidence of liver failure, hyperbilirubinemia, or underlying inborn error of metabolism.



Representative MRS spectra acquired in the parietal white matter from a neonate (A) with bilateral pWMLs (circled in red) and (B) without evidence of pWMLs. MRS spectra (C-upper spectra was obtained from the 3 cm^3 parietal WM voxel outlined in white on the patient in A; lower spectra was obtained from patient in B) were processed with LCModel (Stephen Provencher Inc., Oakville, Ontario, Canada, LCModel Version 6.1-4F). Note that the lighter grey line represents the acquired spectrum while the darker black line represents the model spectrum fit by LCModel. Metabolite concentrations were corrected for the varying fractions of cerebrospinal fluid in the selected ROIs.

MRI studies were acquired under clinical indications (most often to assess brain morphology and injury following preterm birth) on a GE 1.5T (Signa LX, GE Healthcare, Milwaukee, WI) MR System using a customized neonatal transmit-receive head coil. ^{1}H spectra were acquired from a single voxel (approximately 3 cm^3) placed in the parietal white matter dorsolateral to the trigone of the lateral ventricle in the left hemisphere using a point resolved spectroscopy (PRESS) sequence with a short echo time (TE) of 35 milliseconds (ms), a repetition time (TR) of 1.5 seconds, 128 signal averages, and a total acquisition time for each spectrum of approximately five minutes, including scanner adjustments. Conventional imaging studies were acquired contemporaneously with the MRS studies and included a coronal SPGR sequence (TE= 6 ms; TR=25 ms, FOV=18 cm; matrix=256x160) or axial and sagittal T1-weighted FLAIR sequences (TE=7.4, TR=2100; TI=750; FOV=20 cm; Matrix=256x160), axial T2-weighted FSE sequence (TE=85ms, TR=5000ms, FOV=20 cm, matrix =320x160 or 256x128) and a diffusion-weighted sequence (TE=80; TR=10000; FOV=22 cm; Matrix = 128x128; slice thickness =4.5 mm, spacing 0 mm). Conventional images (T1-, T2- and DW-MRI) for all studies were independently reviewed (Figure 1) by two investigators (JLW, AP) and scored for the presence of both pWMLs (defined as punctate T1-hyperintense lesions in the periventricular and intermediate white matter) and DEHSI (defined as high signal in the cerebral white matter on T2-weighted MR images[3] and scored on a 4 point scale: 0/within normal limits, 1/mildly increased, 2/moderately increased and 3/severely increased.

Absolute concentration of glutamate (Glu), glutamine (Gln), n-acetyl-aspartate (NAA), creatine (Cr) choline (Cho) and lactate (Lac) was quantitated from the acquired spectra using LCModel software (Stephen Provencher Inc., Ontario, Canada; Ver. 6.1-4F). The basis set for LCModel included additional metabolities other than the six above. Metabolite concentrations were also corrected for varying fractions of cerebrospinal fluid and tissue water content in the ROI. Furthermore, for absolute quantitation, the signal from unsupressed water was used as an internal reference.

Results

The final sample included 108 neonates (mean gestational age at birth: 31.0 weeks ± 4.3; range 23-36 weeks) who were scanned during infancy (mean age at scan: 41.2 weeks ± 6.0; range 25.7-60.7 weeks). pWMLs were observed in 30 infants and mild, moderate or severe DEHSI was observed in 42, 28 and 10 infants, respectively. (Some infants had evidence of both WMI patterns.) Overall, there were significant differences in the concentrations of the six metabolites among preterm infants with and without pWMLs (Multivariate F [6,100] = 3.455, p = 0.004). Follow-up univerate analyses indicated that glutamine was increased by 29% in the preterm infants with pWMLs (F [1,105] = 9.688, p = 0.002) and NAA was significantly decreased by 24% (F [1,105] = 9.652, p = 0.002). In contrast, only lactate was differed among the DEHSI groups (F [3,103] = 5.569, p = 0.001), where it was elevated in the preterm infants with severe DEHSI.

Discussion

In this study, using clinically-available ^{1}H-MRS, we observed different patterns of abnormal cerebral metabolism in the parietal white matter in association with the two most predominant MRI-defined patterns of evolving WMI in preterm infants, i.e., pWMLs and DEHSI. Our results indicate, for the first time, that glutamine concentrations are abnormally elevated in association with pWMLs and support glutamate excitotoxicity in the pathogenesis of punctate white matter lesions, but not necessarily in DEHSI. Although these infants were imaged during a period of evolving injury (and not in the hyper-acute epoch), these findings indicate that MRS may be useful in not only distinguishing the pathogenesis of different patterns of WMI in neonates or other populations, but also useful for monitoring evolving injury and as an outcome measure in clinical trials assessing potential neuroprotective agents.

Conclusion

^{1}H-MRS may distinguish the underlying pathogenesis of injury in the preterm neonate and thus, may provide additional information relevant not only for prognostication but also for monitoring evolving injury and treatment response.

References: [1] Hagberg et al. Ment Retard Dev DR 2002;8:30-38. [2] Volpe et al. Int J Dev Neurosci 2011;29:423-440. [3] Maalouf et al. J Pediatr 1999;135:351-357.

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