Early proton magnetic resonance spectroscopy in newborn infants with perinatal cerebral hypoxic-ischemic injury: metabolite peak-area ratios, relaxation times, concentrations and concentration ratios.

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Background

Cerebral proton (^{1}H) magnetic resonance spectroscopy (MRS) data acquired from infants with perinatal hypoxic-ischemic (HI) injury have generally been presented as metabolite peak-area ratios, which may be T_1- and T_2-weighted, rather than absolute metabolite concentrations [1,2]. Our hypothesis was that measurement of absolute metabolite concentrations, including relaxation times, would provide further prognostic information, allow a more robust interpretation of the underlying biochemical changes associated with neonatal encephalopathy (NE) and also a more comprehensive MR description of the NE phenotype.

Methods

Seventeen infants with NE and ten healthy controls of comparable gestational age and birth weight were studied at a median (interquartile range) of 1 (1-3) and 2 (2-4) days respectively. Using a 2.4T Bruker Biospec (40 cm clear bore, 100.3 MHz) and a Helmholtz head probe (15 cm diameter and length), localised ^{1}H MR spectra were obtained from an 8 ml thalamic voxel using point resolved spectroscopy (PRESS). Peak-area ratios were measured from spectra acquired with magnetisation recovery time (TR) 1730 ms, echo time (TE) 270 ms, and 128 summed echoes. T_2s of choline-containing compounds (Cho), creatine plus phosphocreatine (Cr) and N-acetylaspartate (NAA) were calculated using spectra acquired with TE 135, 270 and 540 ms; TR 1730 ms; and the T_2 of lactate (Lac) with TE 270 and 540 ms only. Metabolite T_1s were determined by comparing spectra acquired with TE 270 ms and TR 1730 and 5000 ms. Fully-relaxed (TR 10 s) water spectra were acquired using TEs 25, 270, 540, 1000, 1500 and 2000 ms and the brain-water signal (T_2 ~ 160 ms; used as an internal concentration reference) was partitioned from that of CSF (T_2 ~1 s) by double-exponential fitting. Metabolite absolute concentrations (mmol/kg wet weight) were determined from a fully-relaxed spectrum (TE 270 ms, TR 5 s) and correcting the peak areas using the measured T_2 values and then referencing to the fully-relaxed (TR 10 s) brain-water signal from the same voxel and assuming the brain-water concentration [3]. For controls, metabolite concentrations were calculated using a mean metabolite T_2. For NE infants, the metabolite T_2 measured at each study was used. NE infants were classified into two outcome groups (normal/mild (NM) and severe/fatal (SF)) according to neurodevelopmental assessments at 1 year.

Results

Metabolite peak-area ratios, T_2 relaxation and concentration ratios are summarised in the table below (mean (SD) and median (interquartile range) as appropriate). Only measurables which showed a significant difference between any groups are presented. All metabolite peak-area ratios were significantly different for control vs SF and all except Lac/Cr for NM vs SF. Cr T_2 was very significantly raised in the SF group vs controls. In the SF group the NAA, Cho, and Cr concentrations were all reduced whereas that of Lac was increased. There were differences in NAA concentration between control, NM and SF groups. The only concentration ratio to show a difference was [Lac]/[NAA] (control vs SF). Metabolite T_1 values in the NM and SF groups were similar to control values and are not included in the table.

Variable	**Controls (C) (n=10)**	**NE group (n=17)**		***p* values**		
Peak-area ratio		**Normal/Mild (NM) (n=10)**	**Severe/Fatal (SF) (n=7)**	**C vs NM**	**C vs SF**	**NM vs SF**
Lac/Cr	0.38 (0.10)	0.41 (0.13)	0.70 (0.45-2.65)	0.61	0.04*	0.06
Lac/NAA	0.24 (0.06)	0.29 (0.09)	0.54 (0.35-2.66)	0.11	0.02*	0.03*
Lac/Cho	0.15 (0.03)	0.19 (0.05)	0.32 (0.22-1.26)	0.06	0.02*	0.04*
NAA/Cr	1.59 (0.19)	1.41 (0.28)	1.16 (0.14)	0.09	<0.001*	0.04*
NAA/Cho	0.66 (0.08)	0.67 (0.09)	0.56 (0.11)	0.73	0.04*	0.04*
T_2 relaxation (msec)						
Lac	221.8 (196.3-287.7)	242.8 (226.1-300.5)	380.5 (272.3-417.5)	0.43	0.04*	0.01*
NAA	368.9 (68.1)	383.6 (85.8)	490.6 (155.1)	0.68	0.04*	0.09
Cr	199.2 (192.4-225.3)	234.6 (212.4-254.2)	259.7 (29.6)	0.10	<0.001*	0.13
Concentration (mmol/kg wet weight)						
[Lac]	2.78 (0.83)	3.24 (1.25)	4.60 (3.20-12.08)	0.34	0.01*	0.11
[NAA]	9.21 (1.29)	7.72 (1.46)	5.24 (2.58)	0.03*	<0.001*	0.03*
[Cho]	4.39 (0.78)	3.62 (0.52)	2.60 (2.30-3.80)	0.02*	0.02*	0.14
[Cr]	10.94 (1.88)	9.07 (2.12)	7.93 (3.39)	0.05*	0.03*	0.41
Concentration ratio						
[Lac]/[NAA]	0.31 (0.12)	0.39 (0.13)	0.69 (0.38-4.12)	0.19	0.05*	0.09

* statistically significant differences

Conclusions

This study demonstrates that metabolite peak-area ratios, which may be relaxation-weighted, are more useful prognostic indicators than concentration ratios. This is because both metabolite concentrations and T_2 relaxation are pathologically modulated. The observed changes in metabolite concentrations and T_2 values also suggest that interpretation of peak-area ratios needs caution as Cr, in particular, is not a stable reference. Significant differences between outcome groups were mainly seen in metabolite peak-area ratios, metabolite T_2 values and metabolite concentrations. The only measurable that demonstrated a difference between all the groups was [NAA] - the progressive reduction in [NAA] with outcome severity suggests a relationship to neuronal density and viability. Increases in metabolite T_2 values may relate to impaired cellular energy production, failure of membrane pumps and increased intracellular water [4]. The increase in Cr T_2 may have resulted from both increased intracellular water and phosphocreatine hydrolysis leading to increased creatine, the latter having a longer T_2 than phosphocreatine. Our results suggest that the most important prognostic MRS indices in NE are metabolite peak-area ratios, NAA concentration and Cr T_2. Measurement of metabolite concentrations and relaxation values provides a more complete assessment of cerebral brain injury in NE than that provided by peak-area ratios alone.

References

[1] Penrice J, Cady EB, Lorek A, et al. Proton magnetic resonance spectroscopy of the brain in normal preterm and term infants, and early changes after perinatal hypoxia-ischaemia, *Pediatr Res* 1996;40:6-14

[2] Amess PN, Penrice J, Wylezinska M, et al. Early proton magnetic resonance spectroscopy and neonatal neurology related to neurodevelopmental outcome at 1 year in term infants after presumed hypoxic-ischaemic brain injury. *Dev Med Child Neurol* 1999;41:436-445

[3] Dobbing J, Sands J. Quantitative growth and development of human brain. *Arch Dis Child* 1973;48:757-767

[4] Cady EB, Lorek A, Penrice J, et al. Brain-metabolite transverse relaxation times in magnetic resonance spectroscopy increase as adenosine triphosphate depletes during secondary energy failure following acute hypoxia-ischaemia in the newborn piglet. *Neurosci Lett* 1994;182:201-204.