A combined brain proton MR spectroscopy and amplitude- integrated electroencephalography study in term newborns with hypoxic-ischemic encephalopathy

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Introduction.

Perinatal hypoxic ischemic encephalopathy (HIE) remains a frequent cause of neurological sequelae and death. The accurate assessment of HIE is crucial for determining the prognosis and establish an early treatment, such as brain cooling cap [1]. Low levels of N-acetyl aspartate (NAA) and high levels of lactate (Lac) measured by ^{1}H-MRS have been demonstrated a high prognostic value in newborns with HIE [2,3] and quantifiable amplitude-integrated electroencephalography (a-EEG) measures are related to the extent of cerebral injury on conventional MRI in newborns who presented HIE with or without seizures [4]. The aim of the present study was to relate the brain metabolic changes detected by ^{1}H-MRS to the a-EEG time course findings in newborns at term and to evaluate their correlation with outcome.

Methods.

Thirty-two consecutive newborns at term with a HIE encephalopathy graded by Sarnat and Sarnat [5] were recruited to undergo ^{1}H-MRS examination at 7-10 days of life, and a-EEG (CFM 5330, Olympic Biomedical, Seattle,WA) recorded within the first 6 hours of life and continued for at least 24 hrs. Tests exploring neuro-, motor-, visual and hearing functions were performed at 3, 6, 12, and 24 months of age using standardized scales. Psychomotor development was assessed using the Griffiths Mental Development Scale (GQ). Brain MR study was performed in a 1.5T GE Signa Horizon LX whole-body scanner using a quadrature birdcage head coil, monitoring the heart rate and respiratory parameters, after medication with oral chloral hydrate (50 mg/kg body weight). Single voxel ^{1}H-MRS spectra were acquired using the PRESS sequence (TE= 40ms, TR= 1500ms, number of acquisitions= 128) with CHESS water suppression. Voxels were placed in the mid-brain parietal-occipital cortex (volume=4.5 cm^3) and in the left deep grey matter (including caudate head, lentiform nucleus, and ventro-lateral thalamus (3.1-6.3 cm^3). Metabolite integrals of Lac, NAA, creatine-phosphocreatine (Cr), choline containing compounds (Cho), and myo-inositol (mI) were calculated using the fitting program LCModel [6]. In addition, unsuppressed water spectra were acquired at the same voxel locations using the same sequence, and metabolite concentrations (Lac, NAA and mI) were estimated using water as an absolute internal concentration reference. Signal of metabolites and water were not corrected for T_1 and T_2 relaxation times. However, as the reference unsuppressed water signal undergoes similar relaxation and saturation effects to metabolites, T_1 and T_2 corrections are expected to have little effect on the calculation of metabolite concentrations [7]. Metabolite ratios were compared across groups using one way ANOVA, considering $p(F) < 0.05$ as significant.

Informed consent was obtained from the parents of all subjects studied, including the control group of 10 sex- and age-matched healthy full-term neonates.

Results

26 patients underwent both ^{1}H-MRS and a-EEG; HIE was scored as grade I, mild (n= 14), grade II (n= 10) and grade III, severe (n= 2).

The follow-up at 2 years of age showed a normal motor outcome in 20 patients, a transitory hypertonia in the first year of life in 3, presenting both group a normal GQ (mean: 104) and cerebral palsy in 3 (mean GQ <85).

NAA/Cr, Lac/Cr and mI/Cr were significantly different between patients with normal and those with poor outcome at two years (data not shown).

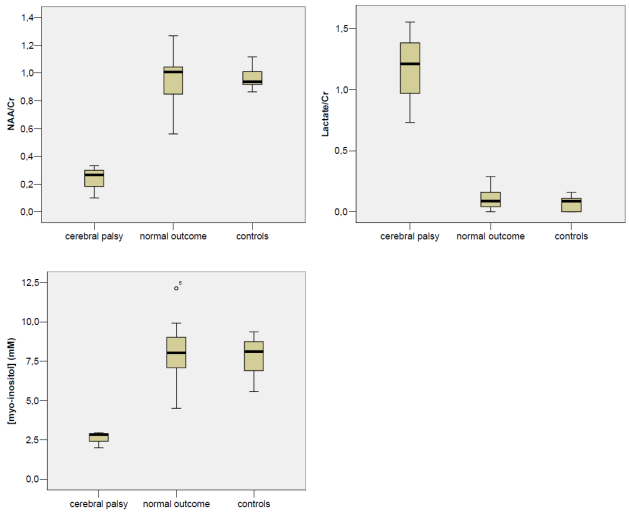
The correlations between the ^{1}H-MRS and a-EEG findings are shown in Table1. a-EEG time course during the first 24 hrs of life showed an improvement in newborns with normal ^{1}H-MRS and good outcome, and a deterioration in those with abnormal ^{1}H-MRS and poor outcome (Table1 and Figure 1).

Table 1. Relationship between ^{1}H-MRS and a-EEG findings in the HIE patients.

^{1}H-MRS	a-EEG	N patients	mean± SD	p
Left deep grey matter				
NAA/Cr	N to N	20	0.87±0.10	*<0.001*
	MA to N	3	0.76±0.07	
	MA or SA to SA	3	0.46±0.35	
Lac/Cr	N to N	20	0.08±0.06	*>0.05*
	MA to N	3	0.10±0.04	
	MA or SA to SA	3	0.14±0.23	
mI (mM)	N to N	20	5.30±0.55	*<0.001*
	MA to N	3	3.92±1.12	
	MA or SA to SA	3	3.23±1.45	
Parietal-occipital cortex				
NAA/Cr	N to N	20	0.98±0.18	*<0.001*
	MA to N	3	0.92±0.02	
	MA or SA to SA	3	0.23±0.12	
Lac/Cr	N to N	20	0.10±0.08	*<0.001*
	MA to N	3	0.14±0.08	
	MA or SA to SA	3	1.16±0.41	
mI (mM)	N to N	20	8.37±1.57	*<0.001*
	MA to N	3	7.66±0.60	
	MA or SA to SA	3	2.60±0.52	

NAA: N-acetyl aspartate; Lac: lactate, mI: myo-inositol; Cr: creatine; N: normal background pattern; MA: moderately abnormal background pattern; SA: severe abnormal background pattern.

Figure 1 Parietal-occipital cortex NAA/Cr, Lac/Cr and mI concentrations in HIE patients, divided according to motor outcome at 2 years of age, and in controls.
Each box shows the median, quartiles, and extreme values.



Conclusions

Both ^{1}H-MRS and a-EEG time course findings showed a good correlation with the severity and the outcome of cerebral hypoxic ischemic injury. These data, obtained from ^{1}H-MRS and a-EEG in non-treated infants, represent reference data for future investigations to select candidates for cool cap therapy.

References

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