Prognostic value of ^{1}H-MRS and DTI after hypothermic treatment in newborns with perinatal asphyxial encephalopathy

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Introduction

Brain cooling (BC) in term neonates with hypoxic-ischemic encephalopathy (HIE) have been shown to reduces mortality without increasing major disability in survivors[1]. Previous studies have demonstrated that brain ^{1}H-MRS and DTI provide accurate prognostic markers in non treated neonates with HIE[2,3].The aim of the study is to investigate if the early prognostic value of MRS and DTI parameters is altered by the metabolic effect of BC.

Methods

Nineteen infants (mean gestational age: 39 w) with moderate-severe HIE graded as Sarnat & Sarnat, were treated with Cool Cap Device within 6 hours of life, according to the international guidelines[1]. All patients underwent conventional brain MRI, DTI and ^{1}H-MRS examinations at 7-10 days of life. Single shot echo planar DTI was acquired in 15 noncollinear directions using a b-value of 900 s/mm^2. DTI analysis was performed using FSL software (www.fmrib.ox.ac.uk/fsl/). Study specific FA and MD templates were created in three steps: 1) affine registration of EPI T_2w images to an anatomical infant template (http://www.unicog.org/bblab/liens/index.html); 2) apply transformation to MD and FA maps to create mean templates; 3) non-linear registration to mean template. ROIs based on the final templates were created covering: supratentorial region (ST), posterior cranial fossa (PCF), genu and splenium of corpus callosum, thalamus, caudate, posterior internal capsula limb (PLIC), optic radiation (OR), lenticular nuclei (LN) (Figure) and areas from the occipital (OWM), frontal (FWM), frontoparietal WM (FPWM). ROIs were back-projected to each subject then checked and if necessary manually corrected for each patient by an experienced neuroradiologist. ^{1}H-MRS spectra were acquired using the PRESS single voxel (TE =40 ms; TR = 1500 ms; scan=128) from: (a) left deep gray matter to include caudate head, lentiform nucleus and ventro-lateral thalamus, (b) mid-brain parietal-occipital cortex, (c) fronto-parietal white matter (WM). Peak areas of N-acetylaspartate (NAA), creatine-phosphocreatine (Cr), choline-containing compounds (Cho) myo-inositol (mI), were calculated using the fitting program LCModel. Moreover the sum of lactate and lipids areas (LL, 1.4÷0.9 ppm) was calculated. Ratios of metabolites and concentrations were calculated.

MD, FA and metabolites values were compared between the group of patients with positive and negative outcome assessed by neurological standardized scales at 24 months of age ($p<0.05$). ROC curves were calculated to optimize cut-off values of MD, FA, and metabolites to discriminate patients with good/poor outcome.

Results

Five patients had a pathological (Pat_o/c) and 14 had a normal outcome (Norm_o/c).

DTI results: MD (Table 1) was significantly lower for patients with Pat_oc in the whole ST region, but not in PCF. All ROIs of deep gray matter had significantly lower ADC and also ROIs of WM except those of OWM. FA (Table 2) was neither significantly lower in PCF nor in the whole ST region. Nevertheless FA was significantly lower in neonates with Pat_oc in the FWM and FPWM and in the deep gray matter ROIs except LN.

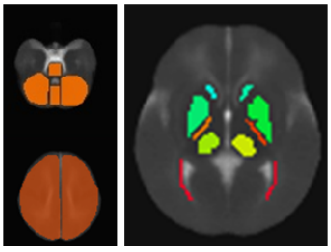

Figure. ROIs onto the mean MD template. Left top: ROI of PCF; left bottom: ROI of ST region. Right: ROIs of deep GM and WM.

Table 1

MD (mm^2/s)	Norm_o/c (10)	Pat_o/c (5)	p
ST	1.32 (0.05) 10^{-3}	1.06 (0.27)10^{-3}	**0.011**
PCF	1.21 (0.05) 10^{-3}	1.15 (0.13)10^{-3}	0.251
genu	1.34 (0.09) 10^{-3}	1.04 (0.30) 10^{-3}	**0.010**
thalamus	1.11 (0.05) 10^{-3}	0.84 (0.31) 10^{-3}	**0.015**
caudate	1.11 (0.04) 10^{-3}	0.88 (0.23) 10^{-3}	**0.015**
PLIC	1.07 (0.04) 10^{-3}	0.88 (0.23) 10^{-3}	**0.025**
OR	1.46 (0.09)10^{-3}	1.16 (0.38) 10^{-3}	**0.032**
LN	1.15 (0.90) 10^{-3}	0.91 (0.21) 10^{-3}	**0.033**
splenium	1.27 (0.08) 10^{-3}	0.96 (0.46) 10^{-3}	**0.049**
OWM	1.70 (0.10) 10^{-3}	1.39 (0.44) 10^{-3}	0.050
FWM	1.63 (0.10) 10^{-3}	1.26 (0.42) 10^{-3}	**0.016**
FPWM	1.40 (0.10) 10^{-3}	1.08 (0.31) 10^{-3}	**0.011**

Table 2

FA	Norm_o/c (10)	Pat_o/c (5)	p
ST	0.141 (0.015)	0.138 (0.018)	0.781
PCF	0.157 (0.033)	0.140 (0.015)	0.305
genu	13.0 (0.8) 10^{-4}	10.4 (3.0) 10^{-4}	**0.010**
thalamus	0.188 (0.023)	0.0141 (0.023)	**0.003**
caudate	11.1 (0.5) 10^{-4}	0.8 (0.3) 10^{-4}	**0.015**
PLIC	10.7 (0.5) 10^{-4}	0.9 (0.22)10^{-4}	**0.025**
OR	14.6 (0.9) 10^{-4}	11.6 (3.9)10^{-4}	**0.032**
LN	0.113 (0.009)	0.117 (0.024)	0.612
splenium	12.7 (0.8) 10^{-4}	9.5 (4.6) 10^{-4}	**0.049**
OWM	17.0 (1.0) 10^{-4}	13.9 (4.4) 10^{-4}	0.050
FWM	16.3 (1.0) 10^{-4}	12.6 (4.2) 10^{-4}	**0.016**
FPWM	14.0 (1.0) 10^{-4}	10.8 (0.3) 10^{-4}	**0.011**

Table 3

Basal ganglia **voxel (a)**	Norm_oc (14)	Pat_oc (5)	p
NAA/Cr-mean(SD)	0.77 (0.05)	0.63 (0.14)	0.009
NAA/Cho	2.07 (0.25)	1.4 (0.41)	0.001
mI/Cr	0.94 (0.15)	0.67 (0.24)	0.022
mI/Cho	2.57 (0.50)	1.14 (0.95)	<0.001
LL/Cr	1.83 (1.74)	12.66 (21.14)	0.017
[NAA] mM	4.35 (0.55)	2.13 (1.54)	<0.001
[mI] mM	5.29 (0.83)	2.13 (2.24)	<0.001
FPWM **voxel (c)**			
NAA/Cr	0.92 (0.07)	0.75 (0.18)	0.018
NAA/Cho	1.82 (0.15)	1.46 (0.47)	0.032
[NAA] mM	3.21 (0.35)	2.27 (0.94)	0.010
[mI] mM	5.48 (0.75)	3.60 (1.94)	0.012

^{1}H-MRS results: Significant results in voxel (a) and (c) are shown (Table 3); in voxel (b) only mI/Cr was significantly lower in neonates with Pat_o/c with respect to those with Norm_o/c. The most significant results of ^{1}H-MRS were the diminished values of NAA and mI (both in ratios and concentrations) in the basal ganglia localization.

ROC curves (not shown), calculated for the significant parameters of both MRS and DTI, have shown that a cut-off of 1.79 for basal ganglia NAA/Cho results in a AUC=0.95 with a sensitivity of 100% and a specificity of 87%, a cut off of 2.15 mM for basal ganglia [NAA] results in AUC= 0.96 with a sens=80% and spec=100%. For MD values the highest AUC (0.78) was found in FPWM (sens=60%, spec=100%) and for FA values in thalamus AUC=0.94 with sens=60% and spec=100%.

Discussion

It has previously been demonstrated that the clinical examination is not predictive of outcome in either treated or untreated HIE neonates with BC[4] while brain ^{1}H-MRS and DTI provide accurate prognostic markers in non treated neonates with HIE[2,3]. The present study indicates that BC did not change the early prognostic value of MRS and DTI, suggesting that the metabolic and microstructural evaluation in targeted brain structures using the semiautomatic analysis described here should be feasible during routine examination of HIE patients, including those treated with BC.

References

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