Combined DWI and 1H-MRS study of the brain of cirrhotic patients

C. Tonon[1], R. Lodi[1], C. Testa[1], E. Malucelli[1], D. N. Manners[1], B. Barbiroli[1]

[1]Dipartimento di Medicina Clinica e Biotecnologia Applicata, Policlinico S.Orsola-Malpighi, Università di Bologna, Bologna, Italy, Italy

Introduction

Hepatic encephalopathy (HE) is a reversible metabolic condition complicating acute liver failure or chronic end-stage liver disease. Brain oedema with increased intracranial pressure, a major complication of fulminant hepatic failure, also occur in patients with end-stage cirrhosis and adversely affect prognosis (1). Several studies point to the central role of ammonia in the development of cranial hypertension. Brain DWI showed that water apparent diffusion coefficient (ADC) is significantly increased in different brain regions of cirrhotic patients being higher in patients with higher venous ammonia levels (2). In cirrhotics, glutamine (Gln) increase and myo-inositol (mI) depletion have been implicated in brain cell swelling and altered osmoregulation, respectively. Inhibition of Gln synthesis with methionine-sulfoximine prevents the development of ammonia-induced brain oedema (3), and decreases astrocyte swelling in rats (4). The aim of this study was to investigate in cirrhotic patients the relationship between changes in brain ADC and the content of osmolytes such as Gln and mI by combining 1H-MRS and DWI.

Methods

Ten patients with viral liver cirrhosis (6 HCV and 4 HBC, 9 males, age range 44-71 years) and 12 sex- and age-matched healthy volunteers were studied in a 1.5 Tesla GE Signa Horizon LX system. Based upon Parsons-Smith criteria HE was: grade 0 in four patients, I in five and II in one. Neurological evaluation and laboratory screening including albumin, bilirubin, prothrombin time and serum venous ammonia levels were performed at the same day of MR study. Diffusion-weighted MRI was conducted using EPI. DW images (matrix= 128x128, FOV= 24 cm, slice separation= 6 mm, TE= 98.8 ms, TR= 10 s, b = 0, 300, 600, 900 mm^2/s, in 3 axes) were acquired in the axial plane. For each pixel, the ADC was calculated. Multiple brain ROIs were defined for ADC calculation (Table 1). The spatial resolution of standard DW images does not allow a reliable measurement of ADC values in the cerebral cortex as partial volume effects cannot be avoided. Therefore, in the present study cortical ROIs were not selected. Single voxel ^{1}H-MRS spectra were acquired using the PRESS sequence (TE= 40ms, TR= 1500ms, number of acquisitions=128). A 8 cm^3 voxel was placed in the mid-brain parietal-occipital cortex. Spectra were analyzed with the LCModel software package (5). The basis set used consisted of several metabolites including: N-acetyl-aspartate (NAA), N-acetyl-aspartylglutamate (NAAG), glycerophosphocholine (Gp), phosphocholine (PCho), creatine/phosphocreatine (Cr), myo-inositol (mI), glutamine (Gln), glutamate (Glu). Statistical significance, determined by Student's unpaired *t* test, was taken as $p<0.05$. Linear regression analysis was used to calculate correlation coefficients.

Results

In cirrhotic patients serum venous ammonia levels were 58±40 μM/L (range 23-156, normal range 11-35). Table 1 shows that in cirrhotic patients water ADC was significantly increased in hemispheric white matter (WM) and in deep grey matter except in the thalamus. In cirrhotics Gln/Cr was significantly increased and mI/Cr reduced. (NAA+NAAG)/Cr, (GP+PCho)/Cr and Glu/Cr were similar in patients and controls (Table 1). In cirrhotic patients Gln/Cr showed a highly significant correlation with ADC values of all brain areas (Table 2) and, among laboratory indices of liver dysfunction, only with venous ammonia ($r=0.87$, $p=0.01$). No correlation was found between mI/Cr, (NAA+NAAG)/Cr, (GP+PCho)/Cr and Glu/Cr and ADC values and laboratory variables (data not shown).

Table 1. ADC and 1H-MRS results in cirrhotic patients and controls. Data are reported as mean ± SD

ADC ($x10^{-3}$ mm^2/s)

	WM	Thalamus	Putamen	Pallidus	Caudate
Patients	0.81±0.10	0.76±0.06	0.78±0.06	0.81±0.06	0.79±0.07
Controls	0.75±0.01	0.74±0.02	0.74±0.02	0.72±0.02	0.74±0.02
p	*<0.05*	NS	*<0.01*	*<0.01*	*<0.05*

^{1}H-MRS

	(NAA+NAAG)/Cr	(GP+PCho)/Cr	mI/Cr	Gln/Cr	Glu/Cr
Patients	1.43±0.16	0.17±0.03	0.27±0.20	1.09±0.55	1.79±0.28
Controls	1.41±0.11	0.20±0.03	0.78±0.11	0.34±0.09	1.64±0.25
p	NS	NS	*<0.01*	*<0.01*	NS

Table 2. Linear regression between brain ADC and Gln/Cr in cirrhotics

Brain area	*r*	*p*
WM	0.94	0.0001
Thalamus	0.83	0.002
Putamen	0.91	0.0002
Pallidus	0.81	0.004
Caudate	0.76	0.01

Discussion

This combined DWI and 1H-MRS study showed that the increase in ADC values in cirrhotic patients is associated with an increase in Gln/Cr. Reduction of mI indicates a compensatory response to the increase in intracellular osmolarity caused by the accumulation of glutamine in astrocytes. The significant positive correlations found between brain ADC values and Gln/Cr in cirrhotic patients support the hypothesis that increased brain cell water content may be secondary to brain glutamine accumulation that has been associated with glial swelling in experimental models of hepatic encephalopathy (3,4).

References.

1. Donovan JP et al. Lancet 1998;351(9104):719-721.
2. Lodi R et al. Neurology 2004;62(5):762-766.
3. Takahashi H et al. Am. J. Physiol 1991; 261:825-829.
4. Willard-Mack CL et al. Neuroscience 1996; 71:589-599.
5. Provencher SW. MRM 1993;30:672-679.