Diffusion Tensor and Magnetization Transfer Imaging of the Brain at 3T in Patients with Cirrhosis.

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Background: Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome that affects up to 80% of patients with cirrhosis. A reversible metabolic disturbance, resulting in astrocyte swelling and low-grade cerebral edema has been suggested to be responsible, but structural integrity is thought to be preserved (1). Diffusion tensor imaging (DTI) allows a quantitative assessment of the tissue microstructure by measuring the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA). The ADC is a measure of tissue water diffusivity, reflecting the displacement of water molecules and the presence of obstacles at the cellular level. In the context of the white matter, the FA is a means of expressing the directionality of the movement of water molecules, as influenced by the orientation, density, size and shape of nerve fibres. The more structured the surrounding environment, the higher the FA, with a maximum value of 1. Magnetization transfer imaging (MT) allows the indirect measurement of bound and free water compartments in the brain and may be affected by changes in membrane fluidity, heavy metal deposition and alterations in total water content.

Methods: A total of 4 female and 10 male patients were recruited for the study of mean age 52.4 [range 38-64] yrs. All had biopsy-proven cirrhosis of the liver from a variety of underlying aetiologies. None of the patients showed signs of overt HE. Eleven of the 14 patients were assessed by computerized neuropsychometric testing (CDR battery: CDR, Reading, UK). All 4 of the female and 2 of the male patients showed signs of impairment consistent with minimal HE. An age-matched control group for the imaging study consisted of 6 female and 5 male volunteers. MT imaging was performed on 3 female patients and 4 female controls and 7 male patients and 3 male controls. DTI was performed on 4 female patients and 6 female controls and 10 male patients and 5 male controls.
All scans were acquired on a 3T Philips Intera^{TM} MR system. DTI was obtained in 32 directions of sensitization using single-shot echo planar imaging (TR 16000 ms, TE 51 ms, slice thickness 2 mm, 2 NSA, b = 1000 s/mm^2). A SENSE factor of 2 was used to reduce image distortion. Apparent diffusion coefficient and FA maps were calculated using DTI Studio version 2.1 (2). FA values were recorded from specific regions of interest (ROI) in the genu, body and splenium of the corpus callosum, anterior corona radiata (ACR) and posterior corona radiata (PCR). MT was obtained using a two-dimensional gradient-echo pulse sequence (TR 54.7 ms, TE 3.75 ms, flip angle 15 degrees, slice thickness 2mm, 1 NSA) with 20 slices positioned over the basal ganglia. MTR maps were calculated, using ImageJ® version 1.32j, with the formula MTR = MTR=1-SI_{RF}/SI_0, where SI_{RF} is the signal intensity in the image employing an off-resonance RF pulse and SI_0 the signal intensity in the initial proton density image. ROIs were drawn around the frontal white matter, head of caudate, putamen, globus pallidus and thalamus bilaterally. The significance of differences between the patient and control groups was evaluated using the two-tailed Student t-test. A level of $p< 0.05$ was accepted as statistically significant.

Results: Analysis of the female DTI data showed that the mean ADCs were significantly higher in the genu, body and splenium of the corpus callosum and in the anterior corona radiata of the patient group (Table 1). Furthermore, the mean FA was significantly lower in the genu of the corpus callosum in these patients studied with cirrhosis (Table 1). The MTR was significantly reduced in the frontal white matter of this patient group (Table 2).

Table 1. Regional Mean ADC (x10^{-3} mm^{2}s^{-1}) and Mean FA values for patients with cirrhosis of the liver. p value corresponds to t-test result.

Mean values		Controls	Patients	p value
Age (sd)		57 (5.7)	53.5 (7.3)	0.45
Genu (sd)	ADC	0.78 (0.03)	0.85 (0.02)	**0.003**
	FA	0.78 (0.01)	0.73 (0.03)	**0.02**
Splenium (sd)	ADC	0.72 (0.02)	0.79 (0.04)	**0.02**
	FA	0.83 (0.03)	0.84 (0.03)	0.82
Corpus callosum-body (sd)	ADC	0.75 (0.03)	0.83 (0.03)	**0.0098**
	FA	0.73 (0.04)	0.7 (0.04)	0.24
ACR (sd)	ADC	0.76 (0.008)	0.81 (0.05)	**0.049**
	FA	0.5 (0.03)	0.45 (0.06)	0.16
PCR (sd)	ADC	0.82 (0.04)	0.81 (0.02)	0.87
	FA	0.54 (0.03)	0.6 (0.05)	0.67

Table 2. Regional Mean MTR (%) from the basal ganglia and frontal white matter of patients with cirrhosis. p-value corresponds to t-test result

Mean values	Controls	Patients	p value
Age (sd)	53.3 (8)	51.2 (7.8)	0.6
Frontal white matter (sd)	57.7 (1.8)	55.3 (2.1)	**0.02**
Head of caudate (sd)	48.5 (2.1)	46.8 (2.1)	0.13
Putamen (sd)	48.3 (0.9)	47.4 (2)	0.28
Globus pallidus (sd)	52.7 (1.1)	49.8 (4.4)	0.11
Thalamus (sd)	53.1 (1.9)	52.9 (1.7)	0.81

Conclusions: The data from this pilot study demonstrate that ADC values are increased in specific regional white matter tracts of female patients who had HE in this cohort with biopsy-proven cirrhosis. However, the FA was only reduced in one region of the corpus callosum. When looking at the group as a whole, the mean MTR values were also decreased in the frontal white matter. These results all suggest increased mobility of water molecules within the white matter of this group of patients. These findings would be compatible with either an increase in brain water, or microstructural damage to the white matter tracts. These findings are of interest, as HE was previously thought to be entirely reversible with treatment (1). Further work should include the study of a larger cohort of patients with an attempt to correlate the imaging findings to the degree of HE and measure treatment effects with time.

References: 1) Haussinger,D et al 2000 J Hepatol.: 32: 1035-1038. **2)** Jiang and Mori, 2004. cmrm.med.jhmi.edu

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