A Pilot Investigation of Voxel Based Diffusion Tensor MRI and Cognitive Correlates in Low Grade Hepatic Encephalopathic Patients

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Introduction: Low grade hepatic encephalopathy (HE) is associated with poorer quality of life and increased work disability which is known to improve after hepatic transplantation (1). Low grade cerebral edema is considered to be responsible for the neuropsychological (NP) abnormalities in cirrhotic patients with chronic HE (2). Previous reports have discussed the anatomical and biochemical abnormalities in chronic and acute HE (3). Even though T1 weighted MRI quantifies the total brain water, it is not possible to define whether it is in the intracellular or extra-cellular compartment. Hence, a major goal of the present study was to investigate the diffusion tensor derived mean diffusivity (MD) approach to look for the minimally increased brain water contents using voxel based analysis and to correlate these changes with neuropsychological scores in patients with low grade hepatic encephalopathy.

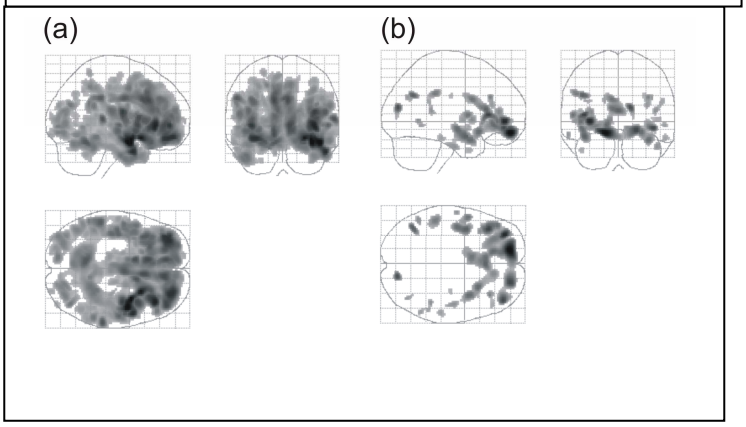
Methods: Fourteen patients (age range = 37- 66 years, mean age 53.9 years, males/females = 8/6) with cirrhosis seen at the liver transplant unit were enrolled. A control group of 15 healthy subjects (age range = 25-69 years, mean age 51.8 years, males/females = 6/9) with matching age/sex were also studied. All the patients and controls were right handed. The patients had low grade HE diagnosed on the basis of West Heaven criteria and abnormal neuropsychological tests. The diagnosis in all these patients was cirrhosis with portal hypertension on the basis of typical imaging features and or liver biopsy. In addition to dual echo PD, T2, T1 imaging, DTI was performed in all the patients and controls (4). DTI was performed using a single-shot multi-section spin-echo echo-planar pulse sequence [repetition time (TR) = 10,000 ms; echo-time (TE) = 87 ms; flip angle = 90°; averages = 3] in the axial plane, with a 128 × 128 matrix size, 230 × 230 mm^2 field of view (FOV), 2.0 mm slice thickness, 75 slices and no inter-slice gap. For each slice, diffusion gradients were applied along six independent orientations with b = 700 sec/mm^2 after the acquisition of b = 0 sec/mm^2 (b0) images. We also collected high-resolution T1-weighted images using a magnetization prepared rapid acquisition gradient-echo (MPRAGE) sequence for evaluation of brain abnormalities. Brain images of individual subjects, including T1-weighted, PD-weighted, T2-weighted, and b0 images were evaluated by an experienced radiologist for any major brain lesions before mean diffusivity (MD) and fractional anisotropy (FA) calculation. To ensure that images were acceptable for subsequent processing, b0 images were also examined for motion artifacts. We used the statistical parametric mapping package SPM5 (Wellcome Department of Cognitive Neurology, UK), DTI-Studio (v 2.4, Department of Radiology, John Hopkins University, Baltimore, MD 21205), and Matlab-based (The MathWorks Inc, Natick, MA) custom software to process images.

Results and Discussion: The areas with significant changes in MD and FA values are summarized in Table 1. Large clusters of significantly increased MD were visible in frontal gray matter, frontal white matter occipital white matter, anterior limb of the internal capsules, and parietal gray and adjoining sub cortical white matter in both cerebral hemispheres as shown in Fig. 1 (a and b). There was no any abnormality in the conventional TSE and PD weighted images in all the fourteen patients with low grade HE. The significant differences between the controls and patients were observed in Trail B, Stroop A, B, C, Block design, digit symbol and peg dominant and peg non dominant tests ($p<0.05$). The remaining battery of tests did not reach the statistical level of significance between controls and patients. The significant changes in the water content in the cortical grey matter with no significant changes in the deep gray matter was a deviation from what has been described in the published literature. The demonstration of this increased water in the cortical gray matter was highlighted due to the voxel based method of analysis which is not known to get biased by the region of interest selection on basis of prior knowledge.

Table 1. MD and FA values (Mean ± SD) in different locations.

Regions	Mean Diffusivity ($x10^{-3}$ mm^2/s)		
	Controls	Patients	p value
Left ant. cingulate cortex	0.83 ± 0.09	0.99 ± 0.1	0.003
Right ant. cingulate cortex	0.81± 0.08	0.93 ± 0.1	0.003
Left frontal white	0.75 ± 0.1	0.90 ± 0.1	0.006
Right frontal white	0.84 ± 0.01	1.04 ± 0.2	0.012
Left internal capsule	0.72 ± 0.05	0.81 ± 0.1	0.008
Right internal capsule	0.72 ± 0.04	0.82 ± 0.1	0.013
Left occipital white	0.81 ± 0.06	1.02 ± 0.1	0.00008
Right occipital white	0.82 ± 0.05	0.91 ± 0.05	0.0005
Corpus callosum	0.95 ± 0.1	1.10 ± 0.2	0.07
	Fractional Anisotropy		
Left ant. cingulate cortex	0.38 ± 0.08	0.34 ± 0.06	0.08
Right ant. cingulate cortex	0.35 ± 0.07	0.32 ± 0.06	0.2
Left frontal white	0.44 ± 0.07	0.37 ± 0.06	0.005
Right frontal white	0.40 ± 0.07	0.35 ± 0.1	0.17
Left internal capsule	0.47 ± 0.05	0.42 ± 0.07	0.037
Right internal capsule	0.46 ± 0.06	0.44 ±0.08	0.45
Left occipital white	0.43 ± 0.06	0.31 ± 0.07	0.0007
Right occipital white	0.45 ± 0.08	0.38 ± 0.04	0.006
Corpus callosum	0.55 ± 0.08	0.51 ± 0.1	0.23

Figure.1.Brain regions in 14 patients and 16 healthy controls showing significant group differences displayed in glass brain with projections across the 3D volume onto 2D axial, coronal, and sagittal views. (a) with greater MD (p = 0.01, false discovery rate correction for multiple comparison; threshold, t = 3.096). (b) with lower FA (threshold, t = 3.096).



Conclusion: The abnormal regional changes in MD correspond to those previously shown in BOLD and PET of low grade HE patients. Also, these changes correlate with the neuropsychological tests performed in this study. We conclude that voxel based approach may help in defining the more wide spread increase in extracellular low level cerebral edema in patients with low grade hepatic encephalopathy and correlates with location specific neuropsychological tests.

References

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