Diffusion tensor imaging in Patients with Acute-on-chronic liver failure

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Introduction: Acute-on-chronic liver failure (ACLF) is acute deteorioration in liver function in a previously well compensated chronic liver disease (CLD) (1). ACLF is due to acute hepatitis A or E that is a recognized trigger of hepatic decompensation in patients with CLD. The resulting ACLF is associated with considerable morbidity & mortality. Reversible cytotoxic cerebral edema (CE) in patients with FHF and reversible interstitial CE in CLD has been reported (2, 3). There are no reports of nature of CE in patients with ACLF. Previous magnetic resonance imaging (MRI) study in patients with hepatic encephalopathy (HE) has improved our understanding of basic neuroanatomical and pathophysiological alterations in patients with liver failure (3). Ranjan et al have shown significantly decreased ADC values in brain parenchyma of Fulminant hepatic failure (FHF) patients compared to control and suggested cytotoxic cell swelling in their cases (3). Diffusion tensor imaging (DTI) measures different DTI metrics; fractional anisotropy (FA) - an index of microstructural integrity of the brain white matter, mean diffusivity (MD)- an index of water movement across cell membranes and spherical anisotropy (CS)- an index of isotropic diffusion. The aim of this study was to assess CE in patients with ACLF and investigate DTI metrics (FA, MD, and CS) in patients with different grades of ACLF as compared to age/sex matched controls.

Material and Methods: 20 patients with different grades of ACLF patients (No HE & MHE = 7, Grade 2=6, Grade 3 & 4=7) (13 males, median age=46 years, range from 23-46 years) and 15 age/sex matched normal controls form the study group. Diagnosis of ACLF was made in patients with acute hepatitis A or E superimposed on chronic hepatitis. Demographic, clinical & laboratory profile were evaluated and used West Heaven criteria for the clinical grading. Informed consent was taken from the patient or their nearest kin prior to the study. The patients were treated with standard anti hepatic coma regimen. Conventional MR imaging and DTI were acquired on a 1.5 Tesla MR scanner using standard quadrature birdcage head coil. The DTI data were acquired using a single-shot echo planar dual spin-echo sequence with ramp sampling. The acquisition parameters were: TR=8sec/TE=100ms/number of slice=34-36/with contiguous 3 mm slice thickness/FOV=240mm/image matrix=256×256 (following zero-filling)/NEX=8/diffusion weighting b-factor=1000 s mm^{-2}. The data was processed using in-house developed software (based on JAVA programming language) (4). Region-of-interests (ROIs) was guided by the lesion size and it was typically 2×2 to 8×8 pixels with elliptical to rectangular shapes. ROIs were placed on anterior (ALIC) and posterior (PLIC) limb of internal capsule, periventricular white matter of frontal (FWM) and occipital (OWM) lobe, corpus callosum (CC), caudate nuclei (CN), Putamen (P), and thalamus (TH) (Fig.1). One way analysis of variance (ANOVA) was performed to compare FA, MD, and CS values in patients group and controls using statistical package for social sciences (SPSS, version 12.0, SPSS Inc, Chicago, USA). P value less then 0.05 was considered as statistically significant.

Results: All patients showed normal signal intensity on conventional T2, T1 images. Significantly decreased FA and increased CS values were observed in patient group compared to control in ALIC, PLIC, and FWM. No change in MD values was observed in patient group compared to controls (Table 1).

Table1: A summary of groups mean and standard deviation of the Fractional anisotropy (FA), Mean Diffusivity (MD) and spherical anisotropy (CS) values from the different grey and white matter regions of brain parenchyma collected from the 15 age/sex matched controls and 20 patients of different grades of acute on chronic liver failure.

FA values (mean±SD)								
Groups	**ALIC**	**PLIC**	**FWM**	**OWM**	**CC**	**CN**	**P**	**TH**
Controls	0.40±0.06	0.52±0.06	0.32±0.04	0.33±0.06	0.54±0.11	0.11±0.02	0.10±0.02	0.18±0.03
No HE & MHE	0.33±0.06	0.45±0.04	0.29±0.03	0.30±0.08	0.49±0.07	0.11±0.01	0.11±0.01	0.20±0.03
Grade 2	0.33±0.02	0.47±0.03	0.27±0.03	0.29±0.08	0.52±0.04	0.11±0.01	0.10±0.01	0.19±0.02
Grade 3 & 4	0.32±0.05	0.46±0.03	0.28±0.03	0.28±0.04	0.49±0.07	0.10±0.02	0.10±0.01	0.17±0.02
One-way ANOVA (p)	**0.00**	**0.01**	**0.02**	**0.34**	**0.42**	**0.87**	**0.63**	**0.12**
MD values×10^{-3} mm^2/s (mean±SD)								
Controls	1.08±0.07	0.99±0.08	1.08±0.10	1.11±0.09	1.13±0.10	1.11±0.05	1.05±0.06	1.08±0.09
No HE & MHE	1.09±0.06	0.96±0.02	1.05±0.06	1.06±0.05	1.15±0.07	1.10±0.07	1.04±0.03	1.06±0.03
Grade 2	1.04±0.04	0.94±0.05	1.05±0.07	1.06±0.05	1.10±0.05	1.05±0.03	1.00±0.04	1.00±0.06
Grade 3 & 4	1.05±0.03	0.94±0.04	1.03±0.07	1.08±0.04	1.14±0.07	1.05±0.04	1.02±0.05	1.05±0.04
One-way ANOVA (p)	**0.24**	**0.18**	**0.54**	**0.33**	**0.70**	**0.06**	**0.36**	**0.18**
CS values (mean±SD)								
Controls	0.68±0.04	0.56±0.06	0.72.± 0.04	0.70±0.05	0.56±0.09	0.90±0.02	0.90±0.02	0.81±0.04
No HE & MHE	0.74±0.05	0.62±0.05	0.74±0.04	0.73±0.07	0.60±0.05	0.90±0.02	0.89±0.01	0.80±0.02
Grade 2	0.74±0.03	0.62±0.05	0.75±0.04	0.74±0.07	0.58±0.05	0.90±0.02	0.90±0.02	0.81±0.03
Grade 3 & 4	0.75±0.05	0.63±0.05	0.74±0.02	0.74±0.04	0.60±0.05	0.90±0.02	0.90±0.02	0.82±0.02
One-way ANOVA (p)	**0.00**	**0.00**	**0.02**	**0.12**	**0.32**	**0.61**	**0.48**	**0.21**

ALIC, anterior limb of internal capsule; **PLIC**, posterior limb of internal capsule; **CN**, caudate nuclei; **P**, putamen; **TH**, thalamus; **FWM**, frontal white matter; **OWM**, occipital white matter; **CC**, corpus callosum.

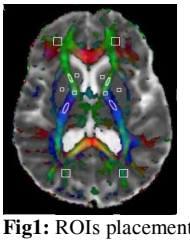

Fig1: ROIs placement on the color-coded FA map fused with MD map.

Discussion: Reversible CE in hepatic encephalopathy (HE) is well documented in literature (5). Our results of decreased FA and increased CS in ALIC, PLIC, and FWM further suggest the presence of CE in patients with ACLF. Though in our cases no significant change in MD values were observed on moving from controls to grade 3 & 4 ACLF, we observed significantly increased CS values in ALIC, PLIC, and FWM. CS is the measure of isotropic diffusion of water molecules in brain parenchyma. Zhang et al demonstrated increased no of pixels in CS=1 vertex of berycentric histogram obtained from cystic component of tumor (6), which suggests that the increased CS values reflects the increased CE. The probable explanations for the decreased FA could be due to the dilution effect of increased cerebral edema and/or microstructural changes in brain parenchyma. Increased CS values in our cases suggest that the most likely explanation of decreased FA is increased cerebral edema. No change in mean diffusivity (MD) was observed in patient group compared to controls. It appears that both cytotoxic and vasogenic edema are operative in this condition resulting in the pseudo normalization of MD. This may be explained by the pathogenesis of the disease which involves chronic and acute component of the liver failure.

References: 1. Jalan R et al. Blood Purification 2002; 20:252-261. **2.** Ranjan P et al. Metabolic Brain Diseases 2005; 20: 181-192. **3.** Kale RA et al. Hepatology 2006; 29: 698-706. **4.** Purwar A et al. Proc. Euro. Mag. Reson. Med. 2006. **5.** Jover R et al. Hepatology 2006; 43:1257-1266. **6.** Zhang S et al. Megn Reson Med 2004; 51; 140-147.