Diffusion Tensor Imaging in Patients with Fulminant Hepatic Failure

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Introduction: Fulminant hepatic failure (FHF) is acute liver failure with hepatic encephalopathy. Often it is a fatal condition, ensuring death within 8 weeks of onset of symptoms. The frequency of FHF is approximately 2000 cases per year in US and mortality rates reach more than 80 to 90% in those cases who have been in grade 4 coma for more than a few hours(1). FHF is associated with cerebral edema and raised intra cranial pressure (ICP). Till date it is not clear whether cerebral edema in FHF is predominantly cytotoxic or vasogenic. In experimental model of FHF there is evidence that both cytotoxic and vasogenic edema are operative, but the former seems to be the prominent factor (2). Magnetic resonance (MR) imaging studies have improved our understanding of basic neuroanatomical and pathophysiological alterations in patients with liver failure (3, 4). Diffusion imaging measures the relative motion of proton across cell membrane. Ranjan et al have shown significantly decreased ADC values in brain parenchyma of FHF patients compared to control and suggested cytotoxic cell swelling in their cases (5). Diffusion tensor imaging (DTI) measures different DTI metrics; mean diffusivity (MD)- an index of water movement across cell membranes, spherical anisotropy (CS)- an index of isotropic diffusion, and fractional anisotropy (FA)- an index of microstructural integrity of the brain white matter. The aim of this study was to investigate DTI metrics (FA, MD, and CS) in patients with FHF as compared to age/sex matched controls and further to see any change in DTI metrics on follow-up study.

Material and Methods: 13 patients with grade 3 & 4 FHF (10 females, median age=24 years, range 6-46 years) and 15 age/sex matched normal controls were included in our study. We used West Heaven criteria for the clinical grading and found that 2 were in stage 3 and remaining 11 were in grade 4. Informed consent was taken from their nearest kin for patients and from controls prior to the study. The patients were treated with standard anti hepatic coma regimen protocol for FHF. Seven patients had repeat MR imaging after 2 weeks of treatment. Remaining 6 patients died before follow-up study. Conventional MR imaging (T2, T1, and DWI) and DTI were acquired on a 1.5 Tesla MR scanner using standard quadrature birdcage head coil. 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) (5). Region-of-interests (ROIs) was guided by the region area and it was typically 2×2 to 8×8 pixels with elliptical to rectangular shapes. ROIs were placed on caudate nuclei (CN), Putamen (P), thalamus (TH), corpus callosum (CC), anterior (ALIC) and posterior (PLIC) limb of internal capsule, and periventricular white matter of frontal (FWM) and occipital (OWM) lobe. Student's independent t test was performed to compare FA, MD, and CS values in patients group and controls. Student's paired t-test was applied to detect the effect of treatment on FA, MD and CS values in the brain parenchyma. All the statistical analysis was performed 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. At the time of 1st study, on comparing FA, MD, and CS values from patients group with controls significantly decreased MD values were observed in all ROIs (Table 1). Significantly decreased FA values were observed in ALIC, PLIC, and FWM in patients compared with controls. Significantly increased CS values in patients were observed in ALIC, and PLIC compared to controls.
Significantly increased MD values were observed in ALIC, PLIC, P, and TH at the time of 2nd study in patient group compared to 1st study (Fig 1). No change in FA values was observed in 2nd study compared to first study. Significantly increased CS values were observed in patient group compared to controls only in CC.

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 13 patients of different grades of fulminant hepatic failure (FHF).*

Groups	FA values (mean±SD)		MD values×$10^{-3}$$mm^2$/s (mean±SD)		CS values (mean±SD)		p values
	Controls	Patients	Controls	Patients	Controls	Patients	
ALIC	0.40±0.06	0.33±0.06	1.08±0.07	0.94±0.26	0.68±0.04	0.74±0.05	p_{FA}=0.00, p_{MD}=0.01, p_{CS}=0.00
PLIC	0.52±0.07	0.45±0.06	0.99±0.08	0.87±0.24	0.56±0.06	0.63±0.05	p_{FA}=0.00, p_{MD}=0.01, p_{CS}=0.00
CN	0.11±0.02	0.12±0.04	1.11±0.06	0.96±0.26	0.90±0.02	0.89±0.04	p_{FA}=0.39, p_{MD}=0.01, p_{CS}=0.54
P	0.10±0.02	0.09±0.03	1.05±0.07	0.88±0.24	0.90±0.02	0.91±0.03	p_{FA}=0.11, p_{MD}=0.00, p_{CS}=0.10
TH	0.18±0.04	0.19±0.03	1.08±0.09	0.90±0.24	0.81±0.04	0.80±0.03	p_{FA}=0.26, p_{MD}=0.00, p_{CS}=0.20
FWM	0.32±0.05	0.29±0.05	1.08±0.10	0.97±0.27	0.72±0.04	0.73±0.04	p_{FA}=0.04, p_{MD}=0.04, p_{CS}=0.13
OWM	0.33±0.06	0.32±0.08	1.11±0.09	0.95±0.26	0.70±0.05	0.71±0.08	p_{FA}=0.65, p_{MD}=0.00, p_{CS}=0.62
CC	0.54±0.12	0.51±0.10	1.13±0.12	0.10±0.27	0.57±0.10	0.59±0.10	p_{FA}=0.22, p_{MD}=0.03, p_{CS}=0.44

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.

Discussion: Our results of decreased MD values in patient group compared to controls at the time of first study suggest predominance of cytotoxic component of cerebral edema as stated by other groups (2,6). Reversal of MD values was observed in clinically improved patients after two weeks of anti hepatic coma regimen treatment which further suggest the predominance of cytotoxic edema in these cases. FA reflects the structural integrity and geometry of axonal fibers, whereas CS reflects the isotropic diffusion. The probable explanations for the decreased FA could be due to increased cerebral edema and/or microstructural changes in brain parenchyma. Based on the literature, it appears that a relative increase in cerebral edema is a more likely explanation for a reduced FA with increased CS in ALIC, and PLIC. This is in keeping with a study by Zhang et al. (7) in patient with metastatic brain lesion in which they demonstrated the large number of voxels near the CS=1 vertex of the 2D barycentric histogram comes from tumor bearing section, reflects cystic component of tumor. We conclude that DTI metrics (FA, MD, and CS) investigates non-invasively the nature and extent of cerebral edema in FHF patients.

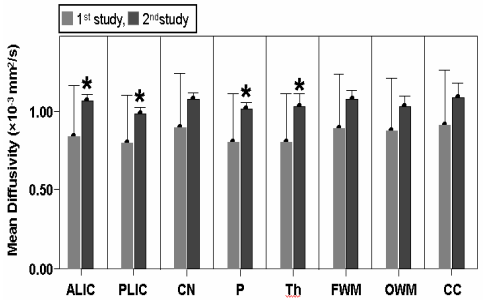

Figure1: Bar diagram shows reversal of MD values in patients following 2 weeks of anti hepatic coma regimen treatment. * denotes p values less than 0.05.

References:
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