Cerebral Diffusion Tensor Imaging (DTI) and In vivo Proton MR Spectroscopy (PMRS) in Patients with Fulminant Hepatic Failure (FHF)

R. K. Gupta[1], S. Saksena[1], V. Rai[2], V. A. Saraswat[2], R. K. Rathore[3], A. Purwar[3], M. Kumar[1], and M. A. Thomas[4]

[1]Radiodiagnosis, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [2]Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [3]Mathematics and Statistics, Indian Institute of Technology, Kanpur, Uttar Pradesh, India, [4]Radiological Sciences, David Geffen School of Medicine at UCLA, Los Angeles, United States

Introduction: Fulminant hepatic failure (FHF) is a clinical syndrome defined as severe impairment of hepatic functions in the absence of preexisting liver disease. It is often associated with coagulopathy, jaundice and multisystem organ failure[1]. Cerebral edema is a major complication in patients with FHF[2]. The neuropathology of cerebral edema in FHF is characterized by the presence of astrocyte swelling[3]. Changes in the brain osmolytes detected by the proton magnetic resonance spectroscopy (PMRS) are indirect or proxy evidence for cerebral edema. Ranjan et al[4], have reported decreased apparent diffusion coefficient in patients with FHF on diffusion weighted imaging, suggestive of predominantly cytotoxic edema. The aim of this study was to evaluate the metabolite alterations and cerebral edema in patients with FHF using *in vivo* PMRS and diffusion tensor imaging (DTI) and to look for its reversibility in survivors.

Materials and Methods: ***Subjects:*** Ten patients with FHF [5 males, median age = 24 years; 5 females, median age = 24 years (range 15-49 years)] who were clinically stable underwent imaging protocol. FHF was diagnosed in the presence of jaundice and encephalopathy with jaundice-to-encephalopathy interval being <4 weeks, and in the absence of clinical and radiological evidence of cirrhosis[5]. The etiology of FHF was acute viral hepatitis in nine (four each with hepatitis B and hepatitis E, one with hepatitis A) and one drug-induced hepatitis (antitubercular drugs). At the time of imaging, four patients were in grade III and remaining six were in grade IV encephalopathy. Five of the 10 patients, who recovered had a repeat imaging after three weeks. Ten healthy controls [4 males, median age = 26 years; 6 females, median age = 28 years (range 18-50 years)] were also included in the study. All the subject's parents gave their informed consent and the study was approved by the institutional Ethics Committee.

Image Acquisition: Imaging was performed on a 1.5-Tesla MR scanner using standard quadrature head coil. *In vivo* MR spectra were obtained by using a water suppressed localized single voxel spin echo (SE) sequence with TR / TE = 3000 ms / 35 ms. A voxel of $2 \times 2 \times 2$ cm^3 was located mainly in the right parietal region of the brain[6] in all the cases, containing part of white matter and gray matter (putamen and caudate nucleus). DTI data were acquired using a single-shot echo planar dual SE sequence with ramp sampling. The acquisition parameters were: TR=8sec/TE=100ms/number of slices=34-38/slice thickness=3mm/interslice gap=0/FOV=240mm/image matrix=256×256 (following zero-filling)/NEX=8/diffusion weighting b-factor= 1000 s mm^{-2}.

Data Processing: For evaluation and quantification of all individual spectra, the LC-Model software package (Version 6.0) was used for processing the MRS data. N-acetylaspartate (NAA), choline (Cho), glutamine (Gln), glutamine/glutamate (Glx), and myoinositol (mI) ratios were calculated with respect to creatine (Cr). The DTI data was processed and evaluated using JAVA based program[7]. Elliptical and/or rectangular region-of-interest(s) varying from 2×2 to 6×6 were placed at the level of third ventricle on right and left anterior and posterior limb of internal capsule, right and left thalamus, right and left putamen, right and left caudate nuclei, right and left periventricular white matter of frontal and occipital lobes and genu and splenium of corpus callosum for fractional anisotropy (FA) and mean diffusivity (MD) quantification in these controls as well as patients.

Results: Patients exhibited significantly increased Gln/Cr (p=0.000) and Glx/Cr (p=0.000) and reduced Cho/Cr (p=0.012) ratios compared to controls. In follow-up study, all metabolite ratios were normalized except Glx/Cr (p=0.011). Significantly decreased Cho/Cr (p=0.009) were observed in deceased patients compared to controls. In patients, significantly decreased MD and FA values were observed in most topographical locations of brain compared to controls. MD and FA values showed insignificant increase in follow-up study compared to their first study.

Discussion: In the present study, significantly increased Gln/Cr and Glx/Cr ratios in patients with FHF compared with controls have been shown to be associated with increased brain concentrations of glutamine, a finding which has been attributed to increased detoxification of ammonia by brain to glutamine via glutamine synthetase[8]. On comparing controls with follow-up study, all the metabolite ratios were normalized except that of Glx/Cr, which continued to be significantly high. This suggests that there is an incomplete detoxification of ammonia even after three weeks when the patients appear to be clinically normal. Significant decrease of Cho/Cr in deceased patients compared to controls, in comparison to the ones who survived suggests that inspite of damaged liver, it still has the capacity to synthesize enough Cho to maintain its serum level and hence Cho/Cr ratio in the brain in the survivors. Significantly decreased MD values in patients compared to controls suggest predominant cytotoxic edema. Decreased FA values could be due to the dilution effect caused by increased extracellular component of cerebral edema rather than the microstructural damage. We conclude that Cho/Cr ratio appears to be an i*n vivo* marker of prognosis in FHF. Persistence of imaging and MRS abnormalities at three weeks of the clinical recovery suggests that metabolic recovery may take longer than clinical recovery in FHF patients.

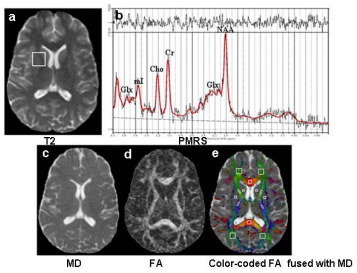

Figure 1 (a-e) A 28-year-old healthy control

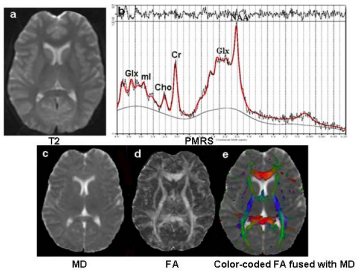

Figure 2 (a-e) Conventional magnetic resonance imaging (MRI) and DTI was performed at three days after the onset of encephalopathy in a 30-year-old woman with FHF

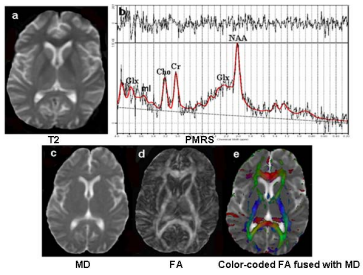

Figure 3 (a-e) Repeat MRI and DTI was performed at three weeks after the first study on the same FHF patient as in Fig. 2(a-e) after recovery from encephalopathy to look for any reversible changes on imaging

References: 1. Sass DA, et al. Liver Transpl. 2005;11:594-605.
2. Vaquero J, et al. Liver Transpl. 2005;11:1581-1589.
3. Norenberg MD. Semin. Liver Dis.1996;16:245-253.
4. Ranjan P, et al. Metab. Brain Dis. 2005;20:181-192.
5. Tandon BN, et al. J. Gastroenterol. Hepatol. 1999;**14:**403–404.
6. Thomas MA, et al. Am. J. Roentgenol 1998;171:1123-1130.
7. Purwar A, et al. Proc. Euro. Mag. Reson. Med. 2006.
8. Cooper AJ, et al. Physiol. Rev. 1987;67:440-519.