Alteration in DTI metrics and volume of the Mamillary Body in patients with Hepatic Encephalopathy secondary to non-Alcoholic Cirrhosis

R. K. Gupta[1], V. A. Saraswat[2], P. Upreti[1], R. Singh[1], J. K. Singh[3], R. Trivedi[1], S. Kumar[1], and R. K. Rathore[3]

[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

INTRODUCTION: End stage chronic liver disease is usually associated with neurological and neuropsychiatric symptoms which are quickly reversed following liver transplantation. However there are reports of persistent neurological symptoms including memory impairment and gait ataxia in alcoholic and non alcoholic cirrhotic patients following liver transplantation. Pathological changes in the brain of the patients who died of hepatic encephalopathy have been described as Alzheimer's type II astrocytosis.[1] Changes of chronic Wernicke encephalopathy like neuronal loss and gliosis have been shown in patients who died of alcoholic cirrhosis. Loss of mamillary body volume has been reported in patients with chronic alcoholism and these changes are known to correlate with severity of cognitive and memory dysfunction.[2] There are reports of low serum level of thiamine in patients with non alcoholic cirrhosis.[3,4] It is known that chronic thiamine deficiency results from its poor storage in the liver resulting in chronic Wernicke encephalopathy.[3,4] Mamillary body is associated with cognition and memory and is usually involved in thiamine deficiency. We quantified DTI metrics mainly fractional Anisotropy (FA), mean Diffusivity (MD), linear anisotropy (CL), planer anisotropy (CP), and spherical isotropy (CS) to look for any microstructural and volume changes in the mamillary body in end stage liver disease secondary to non alcoholic cirrhosis and compared these indices with healthy controls to look for any difference with an aim to establish abnormalities in the mamillary body in these patients.

MATERIALS AND METHODS: Twenty eight patients (mean age=37 years, range= 25-53 years, male=22) with end stage chronic liver disease in different grades of encephalopathy were studied. Besides patients, 25 age and sex matched healthy controls (mean age=37 years, range= 25-53 years, male=20) were also included in the study for the purpose of comparison. Acute on chronic liver failure (ACLF) was defined as clinical evidence of liver failure due to acute hepatitis superimposed on underlying liver cirrhosis. Clinical evidence of liver failure was defined as presence of ascites with high serum-to-ascites albumin gradient (SAAG) and /or hepatic encephalopathy. Acute hepatitis was defined as abrupt (within <4 weeks) rise in serum bilirubin to $\geq$ 10 mg% and / or ALT to $\geq$ 5 times of normal ($\geq$200 IU/L) and presence of detectable IgM anit-HAV or IgM anti-HEV antibodies was required to diagnose acute hepatitis A or E. Underlying liver cirrhosis was diagnosed by a combination of clinical, biochemical or ultrasonographic evidences ie. presence of high SAAG ascites, nodular or irregular liver surface, dilated splenoportal axis (PV$\geq$ 10 mm) with or without portosystemic collaterals and large esophageal varices (> grade II) in the absence of portal venous obstruction. All these patients were in grade I-IV of encephalopathy at the time of imaging.

MR imaging Protocol: Conventional MRI and DTI of all the patients were performed on a 1.5 Tesla GE MRI scanner using a standard quadrature head coil. DTI data was acquired using a single-shot echo planar dual spin echo sequence with ramp sampling. The acquisition parameters were: TR=8sec/TE=100ms/slice no.=34/slice thickness=3mm/interslice gap=0/FOV=240mm image matrix=256x256 (following zero-filling)/ NEX=8/ diffusion weighting b-factor=1000s/mm^2. The diffusion tensor encoding used was the balanced, rotationally invariant dodecahedral scheme with 10 uniformly distributed directions over the unit hemisphere. DTI data was processed by using JAVA based in-house developed DTI-toolbox.[5] **Quantification of DTI Data and volume of the mamillary body:** For calculating the DTI measures and volume of mammillary body images were zoomed four times by applying bilinear interpolation method. Region of interest (ROI) were drawn manually on the outer boundary of mammillary bodies. Number of pixels was counted automatically by implemented software inside the ROI. Total number of pixels of mammillary body in original image ware obtained as follows: Total number of pixels = Total number of pixels in zoomed image / 4×4. Volume of mammilary body was obtained by multiplying total number of pixels with pixel size and slice thickness. **Statistical analysis:** The Students' independent t-test using statistical software [statistical package for social sciences (SPSS 13.0)] was performed to compare the DTI metrics between patients and controls. p values less then 0.05 were considered as statistically significant.

RESULTS: There was no obvious abnormality detected in the mamillary bodies on conventional MRI in patients with non alcoholic cirrhosis. A significantly decreased FA and CL values with increased MD and CS values were observed in mamillary bodies of the patients compared to controls (Table 1). However there was no significant difference in the volume of the left and right mamillary bodies of the patients compared to controls.

Table 1: A summary of group mean and standard deviation of the FA, MD, CL, CP, and CS values collected from the 25 age/sex matched controls and 28 patients of different grades of acute-on-chronic liver failure (ACLF).

Groups	FA	MD (× 10^{-3} mm^2/sec)	CL	CP	CS	Volume (cc)	
						Right	Left
a. Controls (n=25)	0.18 ± 0.07	0.93 ± 0.12	0.07± 0.03	0.09± 0.06	0.82± 0.07	0.05±0.02	0.048±0.019
b. Patients (n=28)	0.14± 0.05	1.02± 0.18	0.05± 0.03	0.07± 0.03	0.85± 0.04	0.05±0.02	0.050±0.020
p values	0.01	0.01	0.03	0.14	0.04	0.95	0.79

DISCUSSION AND CONCLUSION: Our results suggest that the mamillary bodies show decreased FA and increased MD consistent with the microstructural abnormalities. Pathologically, in patients with chronic thiamine deficiency there is a loss of neurons with gliosis and the changes in DTI metrics are consistent with what have been observed in gliosis. Absence of the changes in the volume of the mamillary bodies compared to controls suggests that DTI is more sensitive for the early detection of changes due to thiamine deficiency in these patients. Our data supports the earlier studies that there is a thiamine deficiency in non alcohol induced cirrhosis which is a result of poor storage of thiamine due to hepatic dysfunction.[3,4]

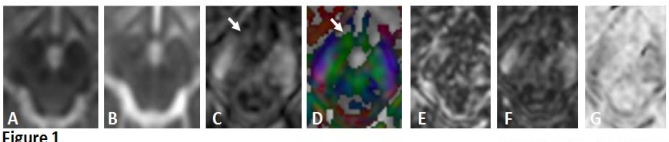

Figure 1

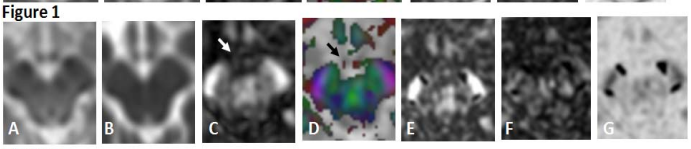

Figure 2

Figure 1(A-G): Images from 30 years old control. T2(A), MD map (B), FA map (C, arrow), FA overlaid on MD map (D, arrow), CL map (E), CL map (F), and CS (G) map shows normal distribution of signal intensity in mamillary bodies in controls.

Figure 2 (A-G): Images from 35 years old patient. Mamillary bodies appear normal on T2 (A) image. Though MD (B) map in patients appear normal, significantly increased MD values were observed in mamillary body of patients compared to controls. FA map (C, arrow) and FA map overlaid on MD (D, black arrow) map shows decreased FA values in mamillary body of patients compared to control (fig. 1C,D). Though CL (E), CP (F), and CS (G) appear normal on visually inspection, significantly decreased CL and increased CS values were observed in patients compared to controls.

REFERENCES: 1) Kril JJ, et al. *Hepatology*. 1997,26:837-841; 2) Sullivan EV, et al. *Alcohol Clin Exp Res.* 1999,23:1629-1636; 3) Onishi H, et al. *Palliat Support Care.* 2005,3:337-40; 4) Lévy S, et al. *Dig Dis Sci*. 2002,47:543-8; 5) Purwar A, et al. Proceedings of ESMRMB, September 21-23, 2006, Abstract #644.