Understanding Difference in Biochemical, Neuropsychological and Brain MR Imaging Profile of Minimal Hepatic Encephalopathy Secondary to Cirrhosis and Extrahepatic Portal Vein Obstruction

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Introduction: Minimal hepatic encephalopathy (MHE) has been well studied in cirrhosis (1). Recently, MHE has also been reported in extrahepatic portal venous obstruction (EHPVO) (2). EHPVO may be due to the partial or complete obstruction of the main portal vein with or without obstruction to its tributaries, in the absence of cirrhosis or liver malignancy (3). The term type B hepatic encephalopathy has been proposed for this condition (4). Hyperammonemia is considered the main toxin responsible for the MHE in both these group of patients. MRI studies, including MR spectroscopy, functional MRI, magnetization transfer imaging, and diffusion-weighted imaging have been well studied for understanding the pathophysiological alterations in cirrhosis induced hepatic encephalopathy (5). However no study is available comparing the biochemical and MR imaging profile in MHE in both these groups. Though hyperammonemia is common to both these groups of patients, the liver dysfunction in cirrhosis and normal liver function in EHPVO patients makes it interesting to look for the differences in biochemical and MR imaging changes if any in these patients and is likely to improve our understanding regarding its pathophysiology. With this hypothesis in mind, we compared blood ammonia, serum proinflammatory molecules, ^{1}H MR Spectroscopy and diffusion tensor imaging (DTI) metrics in both these groups of patients having MHE.

Patients and Methods: Fifty-four patients with cirrhosis (mean age 42±12 years; Child's A 39, Child's B 15, no prior HE), 31 with EHPVO (mean age 34±11years) were screened for MHE. Thirty three cirrhotic MHE and 14 EHPVO MHE with and 23 controls (mean age 25±10year, 34 men) were included for the final analysis. The study protocol was approved by the institutional ethics committee and written informed consent obtained by each individual. EHPVO was diagnosed in patients with thrombosis of portal vein, with or without thrombosis of splenic vein and superior mesenteric vein, after excluding cirrhosis or liver malignancy. Cirrhosis was diagnosed by the presence of a combination of high serum-ascites albumin gradient ascites, splenomegaly, large varices without EHPVO, irregular liver surface, portal vein ≥ 13 mm and collaterals. Liver function test, neuropsychological (NP) tests, critical flicker frequency (CFF), blood ammonia, serum proinflammatory molecules (IL-6 and TNF-α), conventional MRI, DTI and ^{1}H MR spectroscopy were recorded in all patients. DTI and ^{1}H MR spectroscopy data acquisition and processing was done as per the previously published study (6). For measurement of ammonia, blood was taken after overnight fasting, and measured by ammonia checker. Serum proinflammatory molecules were quantified by using standard ELISA method from the commercially available kits. MHE was diagnosed when≥2 of a battery of 9 NPT were abnormal (7). Abnormal CFF value was recorded at the cut off <38.6 Hz. Chi-square test was used to see the significant difference between two forms of MHE. ^{1}H MR Spectroscopy derived metabolites, DTI metrics, blood ammonia and serum proinflammatory molecules were compared by one-way analysis of variance with Bonferroni multiple comparisons post hoc analysis. For the purpose of correlation Pearson correlation coefficient was used.

Result: MHE was significantly higher in cirrhosis (33/54; 61%) than EHPVO (14/31; 45% p=0.001). CFF was abnormal more often in cirrhosis (9/54; 17%) than in EHPVO (3/31; 10%; p=0.001). Blood ammonia (p=1.0), Glx/Cr (p=0.69) and mIns/Cr (p=1.0) changes were similar in both forms of MHE, however Cho/Cr significantly decreased in cirrhotic compared to EHPVO MHE (p=0.01) (table 1). Serum proinflammatory molecules were significantly increased in both form of MHE as compared to controls, however cirrhotic MHE had significantly high serum proinflammatory molecules than EHPVO MHE (TNF-alpha, p=0.001 and IL-6, p=0.02). On DTI, both form of MHE showed significantly increased MD as compared to controls, however cirrhotic MHE showed significantly increased MD values in cingulate gyrus, genu and splenium as compared to EHPVO MHE (table 2). Significant positive correlation of proinflammatory molecules with MD values from the spectroscopy voxel was observed in cirrhotic MHE (TNF α: r=0.66, p=0.002, IL-6: r=0.544, p=0.016) as well as EHPVO MHE (TNF α: r=0.77, p=0.000, IL-6: r=0.76, p=0.000). Both form of MHE showed no significant change in FA value.

Discussion-In this study we observed increased blood ammonia, serum proinflammatory molecules, Glx/Cr and MD with decreased mIns/Cr in both form of MHE; however Cho/Cr is decreased only in cirrhotic MHE. It has been reported that increased Glx/Cr with decreased mIns/Cr and Cho/Cr are the hallmark of HE in patients with cirrhosis (8). This was reconfirmed in cirrhosis MHE, while in EHPVO MHE increased Glx/Cr, reduced mIns/Cr and normal Cho/Cr were observed. It confirms that choline depletion is related to liver dysfunction and is unrelated to MHE. Significantly increased proinflammatory molecules in both groups suggest that these are also involved in the pathogenesis of both form of MHE. Significantly higher value of proinflammatory molecules and MD in some of the brain regions of cirrhosis MHE compared to EHPVO suggests that brain water alterations are more in the former. The significant positive correlation of proinflammatory molecules with MD from the spectroscopy voxel further confirms its contribution in the development of MHE. Our study confirms that there are differences in biochemical, proinflammatory cytokines and MR profile in MHE of cirrhosis and EHPVO.

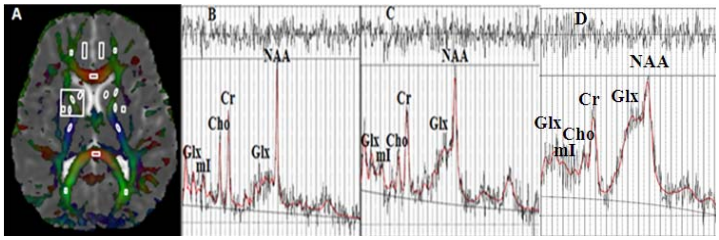

Figure1. Axial colour-coded fractional anisotropy map fused with mean diffusivity map at the level of third ventricle showing voxel placement for spectra (square on right hemisphere) and region-of-interests placement for diffusion tensor imaging measures (A). LC model processed localized proton spectra from 2×2 ×2cm voxel placed on the right parietal region of control (B), E_MHE (C) and L_MHE (D).

Group	NAA/Cr	Cho/Cr	mIns/Cr	Glx/Cr
Control	1.3±0.17	0.23±0.04	0.48±0.17	2.03±0.55
E_MHE	1.1±0.48	0.21±0.04	0.34±0.15	2.54±0.53
C_MHE	1.1±0.28	0.15±0.06	0.32±0.17	2.80±0.74
p-value	0.146	0.000	0.002	0.000

Table1: Metabolite concentrations relative to those of Cr in parietal white and gray matter in patients with E_MHE, C_MHE compared with healthy controls.

Regions	Control	EHPVOMHE	CirrhoticMHE	P value
FWM	1.0±0.03	1.04±0.03	1.04±0.04	0.002
Genu	1.1±0.05	1.0±0.05	1.1±0.06	0.000
CG	1.0±0.03	1.1±0.04	1.2±0.09	0.000
CN	1.0±0.03	1.1±0.09	1.1±0.05	0.024
ALIC	1.0±0.02	1.1±0.04	1.1±0.03	0.000
P	0.9±0.03	1.0±0.05	1.0±0.03	0.000
GP	0.9±0.03	1.0±0.05	1.0±0.03	0.013
PLIC	0.9±0.04	0.9±0.07	0.9±0.04	0.009
T	0.9±0.04	1.0±0.03	1.0±0.04	0.000
S	1.0±0.09	1.0±0.03	1.2±0.09	0.000
OWM	1.0±0.05	1.1±0.06	1.1±0.07	0.084

Table2. Showed the summary of mean diffusivity values in healthy controls and patients of EHPVO and cirrhotic with MHE by using analysis of variance (ANOVA)

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