Imaging Correlates of Neuropsychological tests in Minimal Hepatic Encephalopathy due to Extrahepatic Portal Vein Obstruction

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Introduction: Extra-hepatic portal venous obstruction (EHPVO), a common cause of portal hypertension, is defined as an obstruction of extra-hepatic portal vein with or without involvement of intra-hepatic portal, splenic or superior mesenteric veins with no evidence of liver disease or neoplasia (1). In EHPVO there is shunting of splanchnic blood directly into the systemic circulation bypassing the liver detoxification. It is generally agreed that hepatic encephalopathy (HE) occurs due to the effect of toxins on the brain, the most important being ammonia (2). Minimal hepatic encephalopathy (MHE) is a common and potentially reversible condition in patients with cirrhosis and is associated with poor quality of life, increased work disability and poor prognosis (3). MHE has been reported in patients with EHPVO, but has not been fully characterized (4). MRI studies including ^{1}H-MR spectroscopy, magnetization transfer (MT) imaging and diffusion-tensor imaging (DTI) have been used to understand cerebral alterations in patients with liver cirrhosis with HE (5) but not in patients with EHPVO. The principal aim of this study was to analyze changes in the brain metabolites and water in patients with EHPVO who develop MHE using ^{1}H-MR spectroscopy, DTI metrics and MT imaging and to correlate these changes with blood ammonia, proinflammatory cytokines and neuropsychological (NP) tests.

Material and methods: Thirty one EHPVO patients (mean age 24 ±8 year; M/F =22/9) were studied along with 23 controls (age 27±9 year; M/F=27/20) for ^{1}H-MR spectroscopy, DTI, and MRI studies. Diagnosis of EHPVO was based on consensus guidelines of Asian Pacific Association for the Study of Liver (6). MHE was diagnosed when ≥2 NP tests score differed by >2SD from age, and education-matched controls (7). All patients and controls underwent measurement of blood ammonia, ^{1}H-MR spectroscopy, MT imaging and DTI for the purpose of compairing between patients with MHE or no-MHE and controls. Conventional MRI, DTI and ^{1}H-MR spectroscopy were performed and quantified according to our earlier study (8). MT ratio were quantified as a percentage of signal loss according to the following equation: MT ratio= $100(S_0-S_S)/S_0$ in which S_0 is the mean signal intensity for a particular region obtained from the spine echo sequence without the saturation pulse and S_S is the mean signal intensity for the same region with saturation pulse. Pixel-by-pixel MTR maps were constructed from the two sets of spine-echo images. The mean value of the MT ratio within selected areas was obtained by averaging the pixel values in the regions of interest on the MTR map. In addition, coordinates of spectroscopy were co-registered with mean diffusivity (MD) maps in all subjects to measure MD and fractional anisotrophy (FA) values from this voxel to correlate these with Glx, blood ammonia, proinflammatory cytokines and neuropsychological tests. Serum cytokines IL-6 and TNF-α were measured only in 10 patients and 8 controls by using ELISA kits.

Statistical analysis: The mean and standard deviation of blood ammonia, all metabolite, MT imaging ratio and DTI metrics were compared in both patient groups and controls using one-way analysis of variance (ANOVA). A student's independent t-test was performed to compare serum proinflammatory cytokines of patients with controls. Pearson correlation coefficients were calculated to check for any correlation among blood ammonia, metabolite, MT imaging, DTI derived metrics, proinflammatory cytokines and NP tests.

Results: Twenty (64%) patients presented with variceal bleeding while eleven (36%) presented with asymptomatic splenomegaly though later was present in all patients. MHE was present in 45% (14/31) patients. Blood ammonia (normal <45 µmol/L) was elevated in all patients with EHPVO and was significantly higher in MHE compared to no-MHE (155±36 vs.117±43 µmol/L; p=0.02). On ^{1}H-MR spectroscopy, increase in Glx/Cr (p=0.03), decrease in mI/Cr (p=0.03) and no change in Cho/Cr (p=0.82) were noted in patients with MHE compared to controls (table 1). MD was significantly increased in MHE group as compared to controls in frontal white matter, occipital white matter, posterior limb of internal capsule, putamen, globus pallidus, caudate nucleus and cingulate gyrus. MT ratio values showed significant decrease in frontal white matter, genu, putamen, cingulate gyrus and posterior limb of internal capsule regions for MHE group and in putamen for no-MHE group as compared to controls, and no significant change in FA were observed in both gray and white matter in patients with MHE as compared to controls. Significantly increased serum cytokines IL-6 and TNF-α were found in patients with EHPVO as compared to controls (table 2). Significant positive correlation of proinflammatory cytokines with MD values from the spectroscopy voxel was observed in these patients (TNF-α: r=0.77, p=0.000, IL-6: r=0.76, p=0.000) as well as a significant positive correlation was noted among MD value from spectroscopy voxel with Glx (r=0.60, p=0.003) and blood ammonia (0.65, 0.003).

Discussion: Our data substantiate the central role of ammonia in the pathogenesis of EHPVO related MHE. The characteristic triad of metabolite abnormalities on cerebral ^{1}H-MR spectroscopy in adult patients with EHPVO related MHE appears to be elevation of Glx/Cr, depletion of mI/Cr and no change in Cho/Cr (4). This is unlike the ^{1}H-MR spectroscopy triad reported in cirrhosis induced MHE (5), where choline depletion is a prominent feature. Lack of change in Cho/Cr in EHPVO patients suggests that choline depletion does not play a role in the pathogenesis of MHE and normal cerebral choline level is an indicator of normal liver function in EHPVO. The pattern and differential distribution of abnormalities in MD and MT ratio findings in different brain areas among patients with MHE in EHPVO indicate that generalized, low grade cerebral edema is present in patients with EHPVO having MHE. Increased proinflammatory cytokine in these patients indicates the role of proinflammatory cytokine in the pathogenesis of MHE in these patients. Absence of liver injury in EHPVO suggests that portosystemic shunting may be responsible for increased proinflammatory cytokines induced by endotoxemia. A significant positive correlation of Glx/Cr, blood ammonia and proinflammatory cytokines with spectroscopy derived MD value indicates theses factor may contributes in the generation of cerebral edema. Correlation of MD values with trail making tests in these patients suggests that low grade cerebral edema is probably responsible of neuropsychological manifestations of EHPVO related MHE.

Groups	Glx/Cr	Cho/Cr	mI/Cr	NAA/Cr
Control (n=23)	2.03±0.56	0.23±0.04	0.48±0.17	1.27±0.17
NMHE (n=17)	2.43±0.65	0.23±0.07	0.46±0.15	1.13±0.35
MHE (n=14)	2.54±0.53	0.21±0.04	0.34±0.15	1.09±0.48
p value*	0.024	0.378	0.041	0.252

Table 1: Summary of brain metabolite ratios in healthy controls, no-MHE, and MHE, * ANOVA p- values

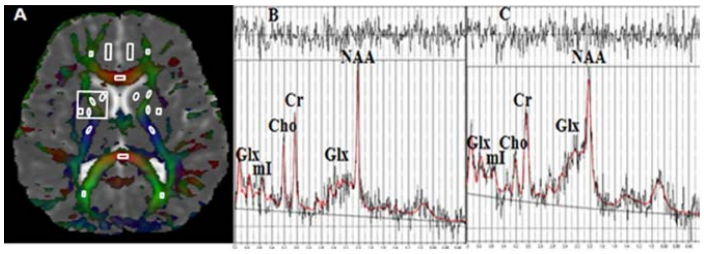

Figure 1: (A) Axial colour-coded fractional anisotropy map fused with mean diffusivity map at the level of third ventricle shows voxel placement for spectra (square on right hemisphere) and region-of-interests (ROIs) placement for DTI measures in left hemisphere. (B, C) Localized proton spectra from 2×2 ×2 cm voxel placed on the right parietal region of control and patients.

Group	Control	Patient	p value
IL-6	5.0±1.28	23±8.25	0.001
TNF	8.29±4.18	19.0±5.33	0.001

Table 2: Data were expressed as mean ± SD. Summary of mean values of IL-6 and TNF-α in control and patients with EHPVO.

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