

Proinflammatory cytokines correlates with MR imaging in patients with extrahepatic portal venous obstruction patients having minimal hepatic encephalopathy

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Introduction: Extra-hepatic portal venous obstruction (EHPVO) is defined as an obstruction of extra-hepatic portal vein with or without involvement of intrahepatic portal, splenic or superior mesenteric veins with no evidence of liver disease or neoplasia (1). Minimal hepatic encephalopathy (MHE) and hyperammonemia are seen in EHPVO patients (2). Recent studies have highlighted the role of infection and inflammation associated in pathogenesis of hepatic encephalopathy (HE) in patients with acute liver failure (ALF) [3] and cirrhosis [4]. Elevated levels of proinflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α) have been found in patients with cirrhosis [5, 6] and ALF [7]. The pathogenic mechanism of HE is not clear, however it is believed that inflammation/infection exerts synergistic effects with ammonia in causing HE. It has been reported that proinflammatory cytokines correlates with imaging parameters in patients of acute liver failure (7), however proinflammatory cytokines and its correlation with imaging are not reported in EHPVO patients. The aim of the present work was to assess the serum proinflammatory cytokines (TNF- α and IL-6) in EHPVO patients with and without MHE and their correlation with blood ammonia, ¹H-MR spectroscopy derived brain glutamine and diffusion tensor imaging (DTI) derived metrics in order to understand the pathogenesis of minimal HE in EHPVO subjects.

Material and Method: Twenty patients (12 males, mean age 16.4±7.3 year) of EHPVO and 8 controls (6 males, mean age 25.5±3.6 years) were included in this study. Diagnosis of EHPVO was based on consensus guidelines of the Asian Pacific Association for the Study of Liver [15]. Neuropsychological tests, DTI, ¹H-MR Spectroscopy, estimation of blood ammonia and proinflammatory cytokines (TNF- α and IL-6) were done in all subjects. MHE was diagnosed if patients had two or more abnormal Neuropsychological tests (2).

Statistical analysis: The mean and standard deviation of DTI derived metrics: fractional anisotropy (FA), mean diffusivity (MD), metabolite ratios, blood ammonia, IL-6 and TNF- α were calculated in both patient groups (MHE and no-MHE) and controls. One way analysis of variance (ANOVA) was done to compare FA, MD, metabolite ratios, blood ammonia, IL-6 and TNF- α between controls and patient groups. Bonferroni multiple comparison post-hoc analysis was performed among controls and different patient groups. For the purpose of correlation, Pearson correlation coefficient was computed.

Results: Proinflammatory cytokines (TNF- α and IL-6), blood ammonia, brain glutamine and MD were increased in both patient groups as compared to controls. Patients with MHE had significantly higher TNF- α , IL-6 (fig.1), blood ammonia, brain glutamine and MD signifying brain edema than controls. Blood ammonia showed significant positive correlation with TNF- α ($r=0.76$, $p<0.0001$), IL-6 ($r=0.80$, $p<0.0001$) and brain Glx ($r=0.39$, $p=0.03$). However Glx showed significant positive correlation with TNF- α ($r=0.67$, $p<0.0001$), but it did not reach at the level of significant with IL-6 ($r=0.28$, $p=0.1$). The TNF- α and IL-6 showed a significant positive correlation ($r=0.59$, $p=0.001$) with each other. Significant positive correlations of MD with IL-6 were observed in frontal white matter (FWM), cingulate gyrus (CG), caudate nucleus (CN), putamen, and spectroscopy voxel derived MD as shown in fig. 2. Similarly, TNF- α showed significant positive correlation with FWM, CG, CN, posterior limb of internal capsule (PLIC), putamen and spectroscopy voxel derived MD (fig. 3).

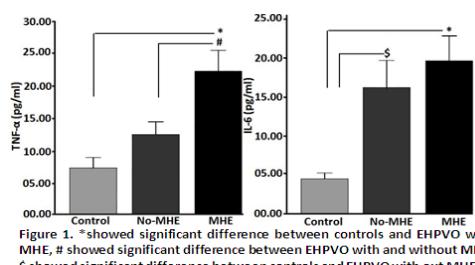


Figure 1. * showed significant difference between controls and EHPVO with MHE, # showed significant difference between EHPVO with and without MHE, \$ showed significant difference between controls and EHPVO with out MHE

Brain region	Control (a)	EHPVO Without MHE (b)	EHPVO With MHE (c)	p value
FWM	0.69±0.02	0.71±0.02	0.76±0.05	a-b=0.9, a-c=0.003, b-c=0.04
Splenium	0.70±0.02	0.74±0.05	0.74±0.04	a-b=0.1, a-c=0.1, b-c=1.0
Genu	0.72±0.02	0.75±0.04	0.77±0.05	a-b=0.6, a-c=0.1, b-c=1.0
CG	0.71±0.02	0.77±0.06	0.80±0.04	a-b=0.06, a-c=0.001, b-c=0.4
CN	0.71±0.02	0.74±0.02	0.75±0.02	a-b=0.1, a-c=0.004, b-c=0.6
ALIC	0.69±0.02	0.71±0.02	0.72±0.01	a-b=0.07, a-c=0.02, b-c=1.0
Putamen	0.65±0.02	0.69±0.02	0.71±0.02	a-b=0.04, a-c=0.000, b-c=0.1
GP	0.70±0.02	0.71±0.02	0.72±0.02	a-b=1.0, a-c=0.1, b-c=0.5
PLIC	0.64±0.03	0.65±0.02	0.70±0.04	a-b=1.0, a-c=0.01, b-c=0.06
Thalamus	0.67±0.03	0.71±0.02	0.72±0.02	a-b=0.02, a-c=0.007, b-c=1.0
OWM	0.74±0.05	0.72±0.01	0.75±0.03	a-b=1.0, a-c=1.0, b-c=0.5

Table - Mean diffusivity value in controls and extrahepatic portal vein obstruction patients with and without minimal hepatic encephalopathy

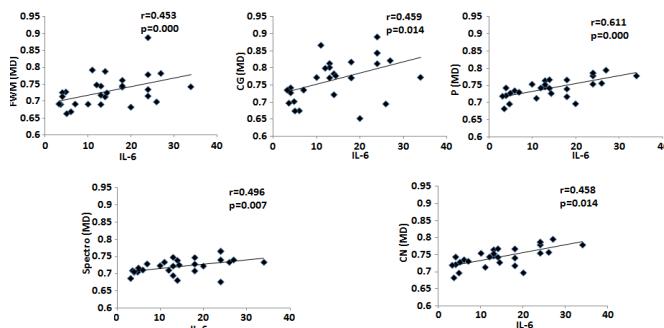


Figure 2. Correlations of serum IL-6 with mean diffusivity (MD) value quantified from different brain regions

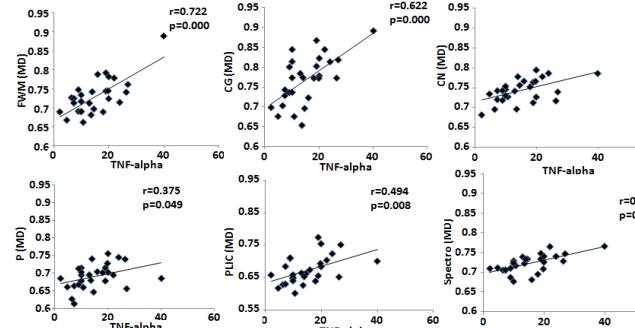


Figure 3. Correlations of serum TNF- α with mean diffusivity (MD) value quantified from different brain regions

Conclusion: This study shows that EHPVO patients with normal liver functions have higher serum proinflammatory cytokines than controls. EHPVO subjects with MHE have significantly higher TNF- α and higher though not significant IL-6 levels than patients without MHE. There is a significant positive correlation between the two proinflammatory cytokines TNF- α and IL-6, between markers of hyperammonemia i.e. blood ammonia and brain Glx. Both proinflammatory cytokines showed significant positive correlation with MD values in some brain areas. (Fig. 2 and 3). This suggests that hyperammonemia (elevated blood ammonia and brain Glx) and inflammation (elevated TNF- α and IL-6) play a role in pathogenesis of MHE in EHPVO patients as evidenced by increased MD values in various brain regions. Changes in blood ammonia, ¹H-MR spectroscopy derived metabolite and DTI derived metrics seen in EHPVO patients with MHE confirm the earlier observations that EHPVO patients with MHE have higher blood ammonia and brain Glx on ¹H-MR spectroscopy with increased MD values on DTI suggestive of cerebral edema in several brain regions as compared to EHPVO patients without MHE [8, 9]. EHPVO patients have inflammation and hyperammonemia as evident by higher blood TNF- α , IL-6, ammonia and brain glutamine levels. Significant correlation between hyperammonemia, proinflammatory cytokines and MD on diffusion tensor imaging in various brain regions suggests that both these factors play a synergistic role in pathogenesis of MHE in patients with EHPVO.

References- (1) Sarin et al. Liver International 2006; 26:512-519. (2) Goel et al. Liver Int. 2010; 30:1143-1151. (3) Shawcross et al. Metab Brain Dis 2007; 22:125-138. (4) Rolando Hepatology 2000;32: 734-739. (5) Montoliu J Clin Gastroenterol 2009;43:272-279. (6) Odeh et al Liver International 2004;24:110-116 (7) Gupta et al Metab Brain Dis. 2010 in press (8) Yadav et al J Hepatol 2010;52:348-354 (9) Srivastava J Pediatr Gastroenterol Nutr. 2010 in press.