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Evaluation of cognition, proinflammatory cytokines, and brain magnetic resonance imaging in minimal hepatic encephalopathy induced by cirrhosis and extrahepatic portal vein obstruction

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Key words cirrhosis, extrahepatic portal vein obstruction, magnetic resonance imaging, mean diffusivity, minimal hepatic encephalopathy.

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Abstract

Background and Aims: Minimal hepatic encephalopathy (MHE) is the mildest form of hepatic encephalopathy (HE) and is characterized by deficits in neurocognitive performance without any clinical symptoms of HE. In the current study, we aim to evaluate and compare the neurocognitive, biochemical, and brain magnetic resonance (MR) imaging changes between patients with cirrhotic MHE and extrahepatic portal vein obstruction (EHPVO) MHE.

Methods: Thirty-three cirrhotic and 14 EHPVO patients were diagnosed with MHE and were included in the analysis along with 24 normal healthy volunteers. All subjects underwent MR imaging including diffusion tensor imaging and proton MR spectroscopy (1H-MRS) followed by cognitive assessments, critical flicker frequency (CFF) measurements, quantification of blood ammonia, and serum proinflammatory cytokine levels.

Results: We observed abnormal neurocognitive functions and CFF measurements in both cirrhotic MHE and EHPVO MHE patients as compared with controls. Significantly increased blood ammonia, serum proinflammatory cytokines (IL-6, TNF-α) level, mean diffusivity in multiple brain sites, 1H-MRS derived glutamate/glutamine (Glx)/creatine (Cr), and significantly decreased 1H-MRS derived myo-inositol/Cr were observed in both cirrhotic MHE and EHPVO MHE compared with those of controls. Choline/Cr level was significantly decreased in cirrhotic MHE as compared with controls and EHPVO MHE.

Conclusions: Cirrhotic MHE showed more severe changes on mean diffusivity in multiple brain sites and inflammation as compared with EHPVO MHE. This study confirms that there are significant difference in neurocognitive, biochemical, and MR profile between cirrhotic MHE and EHPVO MHE, which may help to understand the pathophysiology of these two types of MHE and may contribute to improve their clinical management.

Introduction

Liver cirrhosis is a chronic disease, commonly caused by hepatitis B, hepatitis C, alcoholism, and fatty liver and associated with ascites, poor quality of life, increased work disability, and risk of infection.1–4 Consequently development of hepatic encephalopathy (HE). HE is a potentially reversible wide range of neuropsychiatric symptoms, associated with liver failures and extrahepatic portal vein obstruction (EHPVO).5–8 It is considered that increased blood ammonia and proinflammatory cytokine levels are key factors involved in pathogenesis of HE.9,10 Minimal hepatic encephalopathy (MHE) is the mildest form of HE, which represents quantifiable neuropsychological manifestations without any clinical symptoms of HE.11 MHE is frequently diagnosed in cirrhotic patients, and recently it has also been reported in EHPVO patients.6,7 EHPVO is a condition associated with an obstruction of the main portal vein with or without obstruction to its tributaries, without liver cirrhosis or malignancy.12 MHE is considered clinically relevant because of many reasons; in particular, it predicts the development of cerebral edema and overt HE.13 It is observed that hyperammonemia and inflammation are synergistically responsible for symptoms of HE in cirrhotic patients;10,14 however, in EHPVO, patients’ role of these factors are not well studied.15 It is reported that cirrhotic patients with MHE have a characteristic proton magnetic resonance spectroscopy (1H-MRS) profile such as increased glutamate/glutamine (Glx), decreased myo-inositol (mIns) and choline (Cho).16–18 and increased mean diffusivity on diffusion tensor imaging (DTI),19 whereas EHPVO patients with MHE showed increased Glx, decreased mIns and no change in Cho, while on DTI significantly increased mean
diffusivity has been observed based on region of interest analysis. Studies have shown that increased Glx, which is a detoxified derivate of ammonia in the brain generated by astrocytic cells, is characteristic of EHPVO and cirrhotic patients with MHE and may be responsible in initiating low grade cerebral edema in these patients. So far no study is available comparing the neurocognitive, biochemical, and whole brain magnetic resonance (MR) imaging profile in both form of MHE, that is, cirrhotic and EHPVO. Although hyperammonemia is common in these two groups of patients, the liver dysfunction in cirrhosis and normal liver function in EHPVO patients make it interesting to look for any differences in neurocognitive, biochemical, and brain MR imaging changes in these two patient groups, which may likely improve our understanding regarding pathophysiology of MHE in different etiologies. With this hypothesis, we compared cognitive functions, critical flicker frequency (CFF), blood ammonia, serum proinflammatory cytokines, 1H-MRS measured cerebral metabolites level, and DTI-derived brain mean diffusivity between patients with cirrhotic MHE and EHPVO MHE.

Patients and methods
Institutional Regulatory Board and Ethics Committee approved the study protocol. Patients with cirrhosis and EHPVO attending gastroenterology outpatient clinic satisfying the eligibility criteria as examined by an expert physician were prospectively enrolled in this study. Written informed consent was obtained from each patient or caregiver prior to enrollment in this study. A total of 54 patients with cirrhosis (Child’s A 39, Child’s B 15 with no prior overt HE) and 34 patients with EHPVO (no prior overt HE) were screened for MHE. Out of which, 33 cirrhotic (mean age 42 ± 12 years; 24 male, 9 female) and 14 chronic EHPVO (mean age 26 ± 10 years; 9 male, 5 female; disease duration, 6.0 ± 4.7 years) were diagnosed for MHE and included for the final analysis along with 24 healthy controls (mean age 31 ± 6.5 years; 18 male, 6 female).

Cirrhosis and EHPVO were diagnosed on the basis of suggestive clinical and imaging features with standard clinical practice guidelines. The exclusion criteria for cirrhotic patients were previous porto-systemic-shunt surgery, prior neurological or psychiatric illness, significant alcohol intake (>40 g/day) over the period of 6 months prior to imaging, ultrasonographic evidence of mass lesions in the liver suggestive of hepatocellular carcinoma, biliary obstruction, or suspected sepsis at presentation. Abdominal ultrasonography with Doppler imaging and oesophago-gastroendoscopy were performed for the diagnosis of EHPVO. The inclusion criteria for EHPVO patients were presence of obstruction of the extraparenchymal portal vein with cavernoma formation, with or without the involvements of its tributaries or branches on Doppler ultrasound and with normal liver function tests. The exclusion criteria for EHPVO patients were isolated occlusion of superior mesenteric or splenic vein or any of the following conditions such as neurologic illness, pancreatitis, malignancy, and any positive etiological marker for cirrhosis. Other exclusion criteria were history of gastrointestinal bleeding, infection, treatment with antibiotics or lactulose within the previous 6 weeks, alcoholism, drug abuse, use of psychoactive drugs, and uncorrected visual impairment.

Clinical methods. Blood sample was collected from each subject for hemogram analyses, liver function tests, prothrombin time, viral markers (hepatitis B surface antigen, anti-HCV antibody), serum ceruloplasmin, anti-nuclear, anti-liver kidney microsomal, and anti-smooth muscle antibodies.

Neuropsychological assessment. All participants performed a battery of nine Neuropsychological (NP) tests that include four trail-making tests, that is, number connection tests A and B and figure connection tests A and B, and five tests of performance subset of the modified Wechsler Adult Intelligence Scale (WAIS-P), that is, picture completion, digit symbol, picture arrangement, object assembly, and block design tests. The procedures of performing NP tests are described in detail elsewhere. Test scores were considered abnormal if subjects’ values lie beyond mean ± 2SD from norms established in healthy controls. MHE was diagnosed if ≥2 NP tests were obtained.

Measurement of critical flicker frequency. Critical flicker frequency was measured by the HEPAtonorm analyzer (Accelab GmbH, Kusterdingen, Germany). A detailed methodology is described elsewhere. The procedure was repeated eight times in each patient, and mean CFF value was measured. Mean cut-off for abnormal CFF value was considered as mean – 1SD for consistency with previous studies.

Measurement of blood ammonia levels. Ammonia levels were estimated by enzymatic-UV method (Randox Labs, UK; normal range 10–47 μmol/L) from blood sample collected after overnight fasting. Test was performed within 30 min after blood collection.

Quantification of serum proinflammatory cytokine levels. Standard enzyme linked immunosorbent assays method was used to measure serum levels of TNF-α and IL-6 using commercially available kits (R&D Systems Inc., Minneapolis, USA). Serum’s TNF-α and IL-6 measurements were performed in 11 cirrhotic MHE, 12 EHPVO MHE, and 8 controls.

Brain MR imaging. Brain MR imaging and 1H-MRS were performed on a 1.5-Tesla MR system (Signa, General Electric Medical Systems, Milwaukee, WI, USA) using a quadrature birdcage receive and transmit radio frequency head coil. Fast spin-echo T2-weighted images with repetition time (TR)/echo time (TE)/number of excitations (NEX)/slice thickness/number of slice = 6000 ms/85 ms/4/3 mm/36 and fast spin-echo T1-weighted images with TR/TE/NEX = 825 ms/9.4 ms/4/3 mm/36 were performed using 240 × 240 mm² field-of-view and image matrix of 256 × 256. These images were used to look for any structural abnormality by experienced neuroradiologist. DTI images were acquired using a single-shot echo-planar dual spin-echo sequence with ramp sampling. DTI acquisition parameters were b-factor set to 0 and 1000 s/mm², field-of-view = 240 × 240 mm², TR = 8 s, TE = 100 ms, and NEX = 8. A total of 36 axial sections were acquired with image matrix of 256 × 256 (following zero-filling) and slice thickness of 3 mm with no inter-slice gap. A balanced rotationally invariant diffusion encoding scheme with 10
uniformly distributed directions over the unit sphere was used for obtaining diffusion-weighted data. 1H-MRS was obtained by placing the voxel (2 × 2 × 2 cm³) in right basal ganglion in the brain of all subjects using a water suppressed localized single voxel point resolved spectroscopy (PRESS) with TR/TE = 3000 ms/35 ms and number of average = 64 in both patients as well as controls.25

**Mean diffusivity quantification.** For calculation of mean diffusivity maps, we used DTISTudio (v. 3.0.0, Department of Radiology, John Hopkins University, Baltimore, MD, USA), a well-established software for quantification of DTI metrics as described in detail elsewhere.25 In brief, the average noise threshold level outside the brain tissue was calculated from non-diffusion and diffusion-weighted images. Tensor was calculated using diffusion-weighted images collected from 10 directions and non-diffusion images. From the diffusion tensor, three eigenvalues (λ₁, λ₂, and λ₃) were derived by diagonalizing the diffusion tensor at each voxel. Using these eigenvalues, mean diffusivity map was constructed for individual subjects and used for voxel-based morphometry (VBM).

**Voxel-based morphometry.** Statistical parametric mapping package SPM8 (Wellcome Department of Cognitive Neurology, UK) and MatLab based (MathWorks, Natick, MA, USA) softwares were used for VBM analyses of mean diffusivity. Briefly, non-diffusion-weighted images of individual subject were normalized to the Montreal Neurological Institute (MNI) space, using a priori defined distribution of tissue probability maps, and the resulting normalization parameters were applied to the corresponding mean diffusivity maps. The normalized mean diffusivity maps were smoothed using a Gaussian filter full-width-at-half-maximum of 6 mm. The smoothed mean diffusivity maps were compared between groups using analysis of covariance (age and gender as covariates; False discovery rate (FDR), P < 0.01). Non-diffusion images were also normalized to MNI space for both patients and control subjects. Regions with significant difference in mean diffusivity values were overlaid onto non-diffusion-weighted image for structural identification.

**1H-MR spectroscopy.** Linear Combination Model software (Version 6.0; Stephen Provencher, Oakville, ON, Canada) was used for processing of 1H-MRS data.26 Metabolite ratios of N-acytethylaspartate (NAA), Cho, Glx, and mIns were quantified with respect to Cr.

**Statistical analysis**

Chi-square test was performed to observe the difference for prevalence between cirrhotic MHE and EHPVO MHE. Neurocognitive functions, CFF, blood ammonia levels, serum proinflammatory cytokine levels, and 1H-MRS derived metabolites were compared by one-way analysis of variance with Bonferroni multiple comparisons using post hoc analysis. A P-value ≤ 0.05 was considered statistically significant.

**Results**

**Etiological, clinical, and biochemical profile.** Cirrhotic MHE group consisted of patients with different etiologies [hepatitis B (n = 11), hepatitis C (n = 5), autoimmune (n = 1), cryptogenic (n = 7), alcoholic related (n = 9)]. All patients with cirrhotic MHE suffered from decompensated cirrhosis of liver, and liver function status was classified as Child’s B in 18 and Child’s A in 15 patients. In EHPVO MHE group, 10 (64%) patients presented with acute variceal bleeding while 4 (36%) with asymptomatic splenomegaly, although splenomegaly was present in all EHPVO MHE. The biochemical parameters from cirrhotic MHE and EHPVO MHE are described in Table 1.

**Cognitive functions and critical flicker frequency.** On NP tests analysis, non-significant higher prevalence of MHE was observed in cirrhotic (61%) than EHPVO (45%) patients (P = 0.12). On CFF tests analysis based on cut-off at mean – 1SD, that is, 42.4 Hz, the prevalence of MHE was significantly higher (P = 0.05) in cirrhotic (43%) than EHPVO (13%). All nine NP tests scores showed significant difference (P < 0.05) among different groups (Fig. 1). A minimum of two of the four trail-making tests were abnormal in all cirrhotic MHE and EHPVO MHE patients, and WAIS-P subset did not identify any additional MHE in both groups.

**Blood ammonia levels.** Blood ammonia levels were significantly elevated in both cirrhotic MHE and EHPVO MHE as compared with controls. No statistically significant difference in blood ammonia level was observed between cirrhotic MHE and EHPVO MHE (Table 1).

**Serum cytokine levels.** Serum’s TNF-α and IL-6 were significantly higher in cirrhotic MHE (TNF-α = 41.0 ± 20 pg/mL, P = 0.001 and IL-6 = 34 ± 19 pg/mL, P = 0.001) as well as in EHPVO MHE patients (TNF-α = 22 ± 7 pg/mL, P = 0.05 and IL-6 = 67 ± 67 pg/mL, P = 0.023) compared with controls (TNF-α = 7.2 ± 2.7 and IL-6 = 4.7 ± 1.3). Cirrhotic MHE had significantly increased proinflammatory cytokines compared with EHPVO MHE (Fig. 2).

**Mean diffusivity finding.** Brain sites with higher mean diffusivity values are summarized in Figures 3–5. Multiple brain sites including superior, mid and inferior frontal lobe, anterior prefrontal cortex, dorsolateral prefrontal cortex, inferior parietal lobe, and occipital lobe were found to have higher mean diffusivity values in cirrhotic MHE compared to EHPVO MHE.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>EHPVO MHE</th>
<th>Cirrhotic MHE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>1.8 ± 0.9</td>
<td>1.6 ± 0.9</td>
<td>0.511</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>4.1 ± .4</td>
<td>3.3 ± .9</td>
<td>0.007</td>
</tr>
<tr>
<td>AST (IU/dL)</td>
<td>44 ± 21</td>
<td>49 ± 24</td>
<td>0.512</td>
</tr>
<tr>
<td>ALT (IU/dL)</td>
<td>32 ± 13</td>
<td>45 ± 22</td>
<td>0.050</td>
</tr>
<tr>
<td>Blood ammonia (µmol/L)</td>
<td>154 ± 34</td>
<td>144 ± 35</td>
<td>0.368</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; MHE, minimal hepatic encephalopathy.
occipital lobe, anterior mid and posterior temporal lobe, insular cortices, corpus callosum, putamen, thalamus, and pons showed large clusters of significantly increased mean diffusivity values in cirrhotic MHE compared with those of the control (Fig. 3), while increased mean diffusivity clusters were observed in anterior, mid and superior frontal gyrus, superior, mid and inferior temporal gyrus, and lingual and cerebellar cortex in EHPVO MHE as compared with the control (Fig. 4). Cirrhotic MHE showed higher mean diffusivity values in cuneus, cingulate gyrus, culmen, fusiform gyrus, hippocampal and parahippocampal, and corpus callosum compared with those of EHPVO MHE (Fig. 5).

**1H-MR spectroscopy.** Significantly increased Glx/Cr and decreased mIns/Cr were observed in cirrhotic MHE as well EHPVO MHE compared with those of controls (Table 2). Cho/Cr was significantly decreased in cirrhotic MHE compared with both controls and EHPVO MHE. NAA/Cr did not show any statistically significant difference between groups (Table 2).

**Discussion**

In this study, we observed significant higher prevalence of MHE in cirrhotic than EHPVO patients based on CFF test, while the prevalence of MHE was insignificantly higher in cirrhotic than EHPVO patients using NP tests scores. In the current study, NP tests battery detected MHE in 61% cirrhotic and 45% EHPVO patients. The result in cirrhotic and EHPVO patients is consistent with previous published studies.7,22

CFF has been considered as an appropriate sensitive and reproducible method for diagnosing MHE and predicting early HE in cirrhosis and EHPVO.7,24 In this study, significantly higher MHE was observed in cirrhotic than EHPVO, which might be
due to the unexplored pathophysiological differences in these two conditions.

It is well reported that cirrhotic patients with MHE have neuropsychiatric and motor disturbance, which are associated with the changes in the brain. The key factors responsible for these changes are ammonia or its detoxified derivatives, that is, glutamine and proinflammatory cytokines. Recently, it is suggested that the same factors are responsible for neuropsychiatric and motor disturbance in EHPVO patients, too, and in due course generation of the characteristic feature of MHE.

Ammonia is known to be an important factor in the pathogenesis of HE and contributes in the development of brain edema. Hyperammonia is a main characteristic of liver failure, can be observed from cirrhotic to acute failure, and may also be detected in the absence of liver failure such as in EHPVO. It is reported that ammonia not only is directly toxic to astrocytic cell but also participates in the generation of reactive oxygen/nitrogen oxide species, which cascade the inflammatory response in HE. In the case of hyperammonia, brain astrocytes detoxify ammonia in glutamine, which increases brain glutamine level and results in low grade cerebral edema because of the higher osmotic effect of glutamine and consequently the generation of symptoms of HE.

Interstitial cerebral edema has been reported in patients with cirrhotic MHE as well as EHPVO MHE. Interstitial cerebral edema has been reported in patients with cirrhotic MHE as well as EHPVO MHE. In the current study, significantly increased mean diffusivity in multiple brain sites that include both gray and white matter from both cirrhotic MHE and EHPVO MHE as compared with controls suggests the presence of low grade cerebral edema. The possible explanation for increase in mean diffusivity could be the less restriction on intracellular water diffusion because of increased cell volume mediated by the higher intracellular glutamine level. Higher changes in mean

Figure 3  Brain sites with significantly increased mean diffusivity values in cirrhotic MHE than controls were overlaid onto single subject b0 image. Warm color represents significant t-statistic values.
diffusivity in cirrhotic MHE compared with EHPVO MHE reflect widespread low grade cerebral edema in cirrhotic MHE, which is also supported by the increased Glx/Cr level in cirrhotic MHE over EHPVO MHE.

Serum proinflammatory cytokines have been shown to increase in cirrhotic patients with and without MHE. Montoliu et al. classified MHE from no-MHE in cirrhotic patients using serum IL-6 and IL-18 levels. In the current study, significant higher proinflammatory cytokines, that is, IL-6 and TNF-α, were observed in cirrhotic MHE as well as EHPVO MHE compared with controls. Cirrhotic MHE have significantly higher proinflammatory cytokines as compared with EHPVO MHE; this may be due to the direct involvement of liver in cirrhotic MHE and may also be the possible explanation of the higher prevalence of MHE in cirrhotic patients. It has been recognized that endotoxemia is common in patients with liver failure, which is the result of uncleanness of gut-derived endotoxins such as lipopolysaccharide by the liver cells. In EHPVO patients, endotoxemia is mainly due to the porto-systemic-shunting. It is also reported that endotoxemia can increase the blood IL-6 level. Because patients with EHPVO MHE do not show any noticeable liver injury, we suggest that porto-systemic-shunting may cause endotoxemia and result in increased proinflammatory cytokines in these patients group. It has been proposed that systemic inflammatory responses induced by hyperammonemia exacerbate the neuropsychological alterations, and changes in neuropsychological functions are greater in those with higher hyperammonia and inflammation. This supports the postulation that hyperammonemia and inflammation synergistically induce cognitive deficits.
1H-MRS pattern of increased Glx/Cr along with decreased mIns/Cr and Cho/Cr is the hallmark of HE in chronic liver failure.16,17,39 Significantly increased Glx/Cr and decreased mIns/Cr with unchanged Cho/Cr are previously reported in EHPVO.7,20 Increased Glx/Cr is known to be associated with increased glutamine and glutamate concentrations in the brain that results from increased detoxification of ammonia. In the current study, we suggest that increased Glx/Cr in cirrhotic MHE is due to liver dysfunction, while in EHPVO MHE with normal liver function, it may be due to porto-systemic-shunting. No apparent change in Cho/Cr in EHPVO MHE as observed in the current study suggests no cerebral Cho depletion in EHPVO MHE and is consistent with the previous findings.7,20 Significantly decreased Cho/Cr in cirrhotic MHE was observed; however, the exact mechanism for low Cho/Cr in cirrhotic patients is not well defined. Several possible hypotheses are proposed to explain changes in brain Cho level including diminished transport of Cho,40 reduced

Table 2  Summary of brain metabolite ratios (mmol/kg) in patients with extrahepatic portal vein obstruction-MHE, cirrhotic MHE and healthy controls

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control</th>
<th>EHPVO MHE</th>
<th>Cirrhotic MHE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glx/Cr</td>
<td>2.03 ± 0.55</td>
<td>2.54 ± 0.53</td>
<td>2.80 ± 0.74</td>
</tr>
<tr>
<td></td>
<td>Cho/Cr</td>
<td>0.21 ± 0.04</td>
<td>0.23 ± 0.07</td>
<td>0.15 ± 0.06</td>
</tr>
<tr>
<td></td>
<td>mIns/Cr</td>
<td>0.48 ± 0.17</td>
<td>0.34 ± 0.15</td>
<td>0.32 ± 0.17</td>
</tr>
<tr>
<td></td>
<td>NAA/Cr</td>
<td>1.30 ± 0.17</td>
<td>1.1 ± 0.48</td>
<td>1.1 ± 0.28</td>
</tr>
</tbody>
</table>

All values are expressed as the mean ± SD. 1H-MRS peaks (Glx/Cr, Cho/Cr, mIns/Cr, NAA/Cr) are expressed as metabolite ratios with respect to Cr.

1Control versus EHPVO MHE.
2Control versus cirrhotic MHE.
3EHPVO MHE versus cirrhotic MHE.

Cho, choline; Cr, creatine; Glx, glutamine/glutamate; MHE, minimal hepatic encephalopathy; mIns, myo-inositol; NAA, N-acetylaspartate.
nutritional intake,11 and impaired cerebral metabolism as a consequence of systemic metabolic alterations resulting from liver dysfunction.12 Although in EHPVO, those who have normal liver functions together with regular uptake of Cho are able to produce adequate levels of Cho, which may justify the lack of Cho depletion in EHPVO. No significant change in Cho level indicates normal liver functions in EHPVO MHE, and it may be used as diagnostic biomarker to differentiate EHPVO MHE with cirrhotic MHE.

Conclusions

We suggest that hyperammonia, oxidative stress, and inflammation are synergistically involved in the pathogenesis of both cirrhotic MHE and EHPVO MHE. Further study on animal model with ex vivo brain analysis for the oxidative stress, inflammation, and MR imaging may provide more details on the pathogenesis of cirrhotic MHE and EHPVO MHE. Nevertheless, this study confirms that there are significant differences in neurocognitive, biochemical, and MR profile in MHE of cirrhosis and EHPVO, which may improve the clinical management of both types of MHE.

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References