Minimal hepatic encephalopathy diagnostic dilemma with insights regarding its management and impact on quality of life

Abstract

The prevalence of minimal hepatic encephalopathy (MHE) in patients with liver cirrhosis is high that varies from 20 to 80% in different studies. MHE is a subtle impairment of cognitive functions in the absence of features of OHE, which is characterized by delayed reaction time and abnormal response inhibition. Because MHE doesn’t have any recognizable clinical symptoms, the diagnosis rests on demonstration of abnormality in cognition and neurophysiological function by various tests with exclusion of concomitant neurological disorder. Various tools have been evaluated for the diagnosis of MHE. Although no single test is ideal for the diagnosis of MHE, a combination of two neuropsychological tests or psychometric hepatic encephalopathy score (PHES) battery test and/or neurophysiological test is standard for diagnosis of MHE. MHE is associated with poor quality of life, may progress to OHE and is associated with poor survival. Hence, screening all patients with cirrhosis for MHE is essential, though controversial and treatment of those patients diagnosed to have MHE has been recommended. Ammonia plays a key role in the pathogenesis of MHE, which is thought to be similar to that of OHE. Thus, ammonia-lowering agents such as lactulose are considered first line treatment for MHE. Other agents like rifaximin, L ornithine, L aspartate (LOLA) and probiotics have been found to be effective in various studies to improve cognitive and psychometric deficits, and have good safety profile.

Keywords: minimal hepatic encephalopathy, overt hepatic encephalopathy, psychometric hepatic encephalopathy score, rifaximin, L ornithine, L aspartate, ammonia

Introduction

Minimal hepatic encephalopathy (MHE) is a spectrum of disease in which patients with liver cirrhosis demonstrate cognitive impairment but have normal mental and neurological examination. MHE is a better term compared to previously recognized subclinical HE because the word subclinical itself indicates lack of clinical importance. In 1970, Zeegen et al., were the first to describe MHE. Patients with MHE show impairment in short-term memory, attention and visual perception but memory recall (or retrieval) remains intact. MHE on daily functioning

MHE impairs health related quality of life. MHE mainly affects attention and psychomotor skills. Cirrhotics with MHE reported unexpected fall and episodic HE more frequently compared to cirrhotics without MHE.

Effect of MHE on driving

Patients with MHE have defects in attention and information processing which affects driving leading to much more traffic accidents compared to normal individuals due to slow reactions, improper estimation of traffic conditions, fatigue at steering and lack of coordination. Schomerus et al., were the first to describe the impact of MHE on driving skills. Similarly Watanabe et al., & Wein et al., found that the fitness to drive a car was adversely affected by MHE on a standardized 90-minute on-road driving test.

Diagnosis of MHE

Various combinations of psychometric tests with or without neurophysiological methods are required for diagnosis of MHE in liver cirrhosis in absence of overt encephalopathy.

Neuropsychological tests

Neuropsychological testing is a commonly used test for diagnosis of MHE. These include trail making tests such as the Number Connection test A (NCT- A), Number Connection test B (NCT- B), Figure connection test (FCT A), Figure connection Test B (FCT B) and others that include the Digit Symbol test (DST) and Serial-dotting test (SDOT) (Figure 1) (Figure 2).
In NCT-A, subjects are asked to connect the circles from 1-25 which are design over the paper as quick as possible, although subjects are asked to connect numbers from 1 to 14 and letters from A to L in alternating manner in NCT-B. Individuals are given a series of double-boxes, which contain numbers in the upper part. The task is to draw a symbol pertinent to this number into the lower part of the boxes in digital symbols test. Test result is the number of boxes correctly filled within 90 seconds. In Block design test, task is to take 6-9blocks that have all white sides, all red sides and red and white sides followed by arranging them according to a pattern formed by examiner or shown on a card (Figure 3).

An electronic number connection test (eNCT) is an easier and faster method for detection of MHE. In this test individuals have to click flashed numbers 1–25 on a screen in order while being on timed. Psychometric Hepatic Encephalopathy Score (PHES) consists of 5 tests: NCT-A/B, line tracing time (LTT) and SDOT. The PHES is validated for cognitive and tests for visual-motor coordination, attention, psychomotor speed, and set shifting to detect MHE. Similarly to other psychometric tests results of PHES can be affected by age and education status of participants. Score <-4 suggest presence of MHE.
Stroop test

Stroop phenomenon is well known effect that is known since quite long in which you recognize usually color of a word but not the name of the word. Stroop effect has been widely used in psychology to measure a person’s selective attention capacity and skills, as well as their processing speed ability. Applicability for diagnosis for MHE as psychological method confirmed by Bajaj et al. Anterior attention system is responsible for modulate response inhibition and executive control which require to perform stroop test. Anterior attention system is more likely to involve in presence of MHE.

The application can be downloaded from the app store (Encephala Stroop). Two components off state and on state. Off state in which pound signs (###) shown in different colors one at a time and response given subject by touching the matching color of the stimulus to the colors. This continues until a total of 10 presentations, which are one run and the total time taken for the run as well as subject responses (off time). If the individual identify wrong color, the run stops and has to restart again. Therefore the number of runs require to make 5 correct runs also indicates the number of mistakes. Off state continue till the subject had achieved 5 correct runs. The “On” state is more challenging from a cognitive standpoint in that incongruent stimuli are presented in nine of the ten stimuli. In this portion, the individual has to correctly identify the color of the word presented which is actually the name of the color in discordant coloring, for example word “RED” is displayed in blue color and the correct response is blue, not red. Similar to the “off” state it continues the task till 5 correct runs achieve (on-time). Both off and on state require two training runs. A cut-off time of more than 190 seconds indicates presence of MHE (Figure 4).

Figure 4 Hepatonorm Analyzer for measurement of critical flicker frequency.

Neurophysiological tests

1. Electroencephalography (EEG)
   a. Standard
   b. Mean dominant

2. Evoked potentials
   a. Exogenous (auditory (BAEP), visual (VEP), Somatosensory (SSEP))
   b. Event related (P 300)
even remain stable in long-term follow-up\textsuperscript{11,32} and presence of MHE associated with increased mortality compared to those without MHE\textsuperscript{33} although it is difficult to attribute the poor outcome to the presence of MHE. Furthermore, MHE in patients with large portal- systemic shunts had a good outcome due to preserved liver function.\textsuperscript{34} Actual probability of OHE at 5 years was 56% in patients of liver cirrhosis in presence of MHE and 8% for those without MHE.\textsuperscript{32} Presence of MHE in Cirrhosis associated with shorter survival time, especially among who had high concentrations of venous ammonia after oral glutamine load.\textsuperscript{35,36}

**Epidemiology**

Prevalence of MHE in patients with cirrhosis has been detected from 22 to 74% in various studies. Diagnostic criteria used in different studies vary but most of studies used neurophysiological tests in different combinations. In a study conducted by Sharma K et al.,\textsuperscript{37} using CFF and/or two abnormal neuropsychological tests (NCT A, FCT A & DST), the prevalence of MHE was found to be 60.19%. Similarly Liu et al. has also reported prevalence of MHE in liver cirrhosis to be 60% using NCT A, NCT B and measurement of brainstem auditory evoked potentials.\textsuperscript{38} Prasad et al.,\textsuperscript{39} found the prevalence of MHE to be 67.7% based on combination of quantitative neuropsychological tests (Table 1).

Table 1 Details of important tests for diagnosis of Minimal Hepatic encephalopathy

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnoses</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Domain examined</th>
<th>Outcome prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHES (Psychometric Hepatic Encephalopathy Score)</td>
<td>Score of &lt;-4</td>
<td>Validated, gold standard</td>
<td>Lack of reference normative data in the United States</td>
<td>Attention, processing speed, response inhibition, and visuospatial awareness.</td>
<td>Score &lt; -6 predicted poor survival</td>
</tr>
<tr>
<td>Encephal App Sproop Application</td>
<td>&gt;190 seconds (on and off time)</td>
<td>Free, and can be used on a mobile platform. Has US reference data</td>
<td>Cannot be performed in red-green color-blind subjects</td>
<td>Psychomotor speed, cognitive flexibility</td>
<td>Longer times can predict OHE episodes</td>
</tr>
<tr>
<td>EEG (Electroencephalography)</td>
<td>Dependent on a neurologist's interpretation</td>
<td>Can be used on all stages of HE without learning</td>
<td>Highly variable, requires a neurologist's interpretation</td>
<td>Brain activity, mean dominant frequency</td>
<td>EEG plus MELD increases accuracy in predicting prognosis frequency</td>
</tr>
<tr>
<td>CFF (Critical flicker frequency)</td>
<td>CFF&lt;39 Hz</td>
<td>Test can be administered at bedside</td>
<td>Requires high-functioning patients and expensive equipment, needs binocular vision</td>
<td>Visual processing and discrimination, general arousal</td>
<td>Can predict OHE</td>
</tr>
<tr>
<td>Evoked potentials</td>
<td>Variable, dependent on a neurologist's interpretation</td>
<td>Sensitive without learning effects</td>
<td>High variable results, requires a neurologist's interpretation</td>
<td>Visual, auditory, and somatosensory</td>
<td>Can predict the development of OHE</td>
</tr>
</tbody>
</table>

Table 2 List of important studies for management of Minimal Hepatic encephalopathy with details

<table>
<thead>
<tr>
<th>Study</th>
<th>Tests</th>
<th>Daily doses</th>
<th>Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horsmans et al.\textsuperscript{40}</td>
<td>Psychometric tests</td>
<td>60gm lactulose</td>
<td>15days</td>
<td>Lactulose&gt; placebo</td>
</tr>
<tr>
<td>Watanbe et al.\textsuperscript{45}</td>
<td>Psychometric tests</td>
<td>45ml lactulose</td>
<td>8weeks</td>
<td>Lactulose&gt; No intervention</td>
</tr>
<tr>
<td>Dhiman et al.\textsuperscript{43}</td>
<td>Psychometric tests</td>
<td>30-60ml lactulose</td>
<td>3months</td>
<td>Lactulose&gt; No intervention</td>
</tr>
<tr>
<td>Prasad et al.\textsuperscript{49}</td>
<td>Psychometric tests</td>
<td>30-60ml lactulose</td>
<td>3months</td>
<td>Lactulose&gt; No intervention</td>
</tr>
<tr>
<td>Bajaj et al.\textsuperscript{44}</td>
<td>Psychometric tests</td>
<td>1yogurt</td>
<td>2months</td>
<td>Probiotics&gt; No intervention</td>
</tr>
</tbody>
</table>

Controversies exist regarding screening for MHE in patients with liver cirrhosis. Basis of screening is that after therapy these patients not only shown improvement in neuropsychological tests but also improve quality of life and delay onset of overt HE\textsuperscript{40} however actual benefit of screening observed for two groups of cirrhotic first patients who had increased risk of accidents and second patients with cognitive complaints.\textsuperscript{37,41} Pre-existing neurological disorders and current alcohol use affect the results of psychometric tests.\textsuperscript{42} There is no consensus regarding the timing and frequency of testing in cirrhotic, but experience has shown that it is always better to test for MHE in cirrhotic at initial visit and 6 months later if it present at time index visit (Table 2).\textsuperscript{37,39,41-43}

**Treatment**

Treatment of MHE improves psychometric performance and health related quality of life. Treatment of MHE is similar to OHE with rationale of lowering ammonia. Therapy includes lactulose, LOLA, rifaximin, probiotics and branched chain amino acids that were found to effective in reversal of MHE mainly by reduction of blood ammonia levels (Table 2).
Lactulose or lactitol are synthetic non-absorbable disaccharides that is first line of therapy for treatment of overt HE.44 Lactulose cause acidification of intestinal contents after breakage into acetic and lactic acid by intestinal flora, which converts ammonia (NH₃) into ammonium (NH₄⁺). Lactulose also has a cathartic effect increasing nitrogen excretion. Few studies enumerated in44,45 Table 2 demonstrated its efficacy in the management of MHE. Another side of coin for lactulose is that excess use of lactulose can cause severe dehydration and hyponatremia leading to worsening of HE. Hyponatremia and very high ammonia levels are predictors for failure of lactulose in MHE. Prasad et al. had shown that cirrhotic with MHE after Lactulose therapy had improvement in Health related quality of life and psychometric performance.46 A recent study showed that greater improvement in blood ammonia levels, psychometry scores, and HRQOL after lactulose, a probiotic, and LOLA therapy.47

In a study,48 response to LOLA, rifaximin, and probiotics in patients with liver cirrhosis in term of reversal of MHE compared to placebo group after 2months of therapy, pre and post treatment CFF scores and improvements in abnormal neurophysiological tests were statistically significant (P<0.05) for LOLA, rifaximin, and probiotics compared to placebo.

LOLA exerts its ammonia-lowering action not only in the liver but also in kidney, skeletal muscles and brain. Oral administration of LOLA decrease blood ammonia levels and improve psychometric performance. However it was observed that increase in ammonia once LOLA is discontinued.49 This has been attributed to a paradoxical rise in glutamine levels, which generate ammonia by the kidney and gut through the effects of glutaminolysis. Lactulose were found to be better than placebo or no intervention in reversal of MHE but effect was similar to lactulose and probiotics.46,49 In a meta-analysis,50 efficacy of LOLA tested in compare to placebo in patients with cirrhosis and analyzed that LOLA cause reversal of MHE by diminished serum ammonia levels without any adverse effect.

First non absorbable oral antibiotics were neomycin which doesn’t stand long for treatment in OHE due to significant nephro and ototoxicity in presence of liver disease. Rifaximin is a non-absorbable oral antibiotic that acts on gut and has a broad spectrum of activity that covers gram-positive, gram-negative bacteria, and anaerobes. Although rifaximin is approved for secondary prevention of OHE but data are scanty for treatment of MHE. In a study,47 rifaximin was significantly better than placebo for treatment of MHE. Rifaximin SSD IR 40mg for 24weeks has shown reduced hospitalizations rate or mortality in patients with cirrhosis and well-controlled ascites, although data is not available for MHE.51

Prebiotics, probiotics and symbiotic (probiotics and fermentable fiber) are effective in long term treatment of MHE in cirrhotic.46 Liu et al.,52 showed that manipulation of gut micro biota in patients with liver cirrhosis and MHE by symbiotic cause increase in fecal content of non–urease producing Lactobacillus species for 14days even after cessation of therapy and also showed significant reduction of blood ammonia levels after therapy. Standardization of probiotic organisms remains a question. Ornithine phenylacetate (OP)53 and glycerol phenylbutyrate (GP)54 have been used for the treatment of both OHE and secondary prevention. These appear useful in MHE although no data are available.

**Conclusion**

The prevalence of MHE is high in liver cirrhosis. Although diagnosis of MHE in cirrhotic still remains a challenge., neuro-psychometric tests remains first line for diagnosis of MHE and changes in spectral ECG and visually evoked late potential (P300) are much more sensitive. Treatment of MHE in liver cirrhosis improves not only quality of life but also psychometric performance. Double blind studies showed benefit of L-Ornithine L-aspartate, rifaximin, probiotic and lactulose over placebo for reversal of MHE in liver cirrhosis. Controversies exist regarding during duration of therapy and selection of drug for treatment of MHE.

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**Conflict of interest**

Author declares that there is no conflict of interest.
References


