Minimal Hepatic Encephalopathy
Praveen Sharma

Abstract
Minimal hepatic encephalopathy (MHE) is a condition in which patients with cirrhosis of liver that has normal mental and neurological status on standard clinical examination exhibit a number of neuropsychiatric and neurophysiological defects. Its prevalence varies up to 80% in cirrhotics. It is characterized by a specific, complex cognitive dysfunction which is independent of sleep dysfunction or problems with overall intelligence. Increasing evidence indicates that MHE is an important disorder that may seriously impair a patient's daily functioning and quality of life. Psychomotor slowing, visuomotor disabilities, attention deficits are among the few key features while fine motor performance is also impaired. MHE may predict the development of overt hepatic encephalopathy. Various tools have been evaluated for the correct diagnosis of MHE, however, in the absence of a “gold standard,” combination of test methods is recommended to most reliably diagnosed MHE. Presently, lactulose is the mainstay of treatment for MHE. However various therapies like probiotics and ornithine aspartate are under evaluation as an alternative to lactulose.

Introduction
Minimal hepatic encephalopathy (MHE) is a condition in which patients with cirrhosis of liver that has normal mental and neurological status on standard clinical examination exhibit a number of neuropsychiatric and neurophysiological defects. According to the recommendation of World Congress of Gastroenterology, MHE is a better term because the word subclinical may be mistaken as signifying lack of clinical importance(1). MHE is present in 25%-80% of cirrhotic patients without overt hepatic encephalopathy (HE). Although named “minimal”, MHE can have a far-reaching impact on quality of life, ability to function in daily life and progression to HE. This review will summarize the current status of the diagnostic methods for MHE and analyze the data that show what is clinical implication of MHE. The purpose is to help the physician who takes care of patients potentially affected by cirrhosis and MHE.

Pathogenesis of MHE
Gut-derived nitrogenous substances are universally acknowledged to play a major role in the pathogenesis of hepatic encephalopathy and pathogenesis of MHE is thought to be similar to that of overt HE. Specifically, ammonia is thought to be a critical factor in the pathogenesis. Ammonia- induced alterations in cerebral blood flow and glucose metabolism have shown that there is a significant decrease of glucose utilization of various cortical regions that correlate with the patients cognitive functions. Altered glioneuronal communication as a result of low grade astrocyte swelling is one of the terminal events in the pathogenesis of HE, similar changes have been noticed in patients with MHE and is the basis of new diagnostic tests for detecting MHE like Critical Flicker Frequency (CFF) and MR-spectroscopy.

Prevalence of MHE
Due to lack of gold standard for the diagnosis of MHE various studies have found varying prevalence of MHE. Cirrhotic patients without evidence of overt HE, 25%-80% are found to have MHE on specialized psychometric or electrophysiological studies. In western countries, the rate of MHE in several research series has been reported to be 60%-80%, again using a combination of psychometric and neuro-physiologic techniques. In Asian countries especially India reconfirmed the high prevalence of MHE.

Diagnosis of Minimal Hepatic Encephalopathy
By definition, MHE is not perceived by the physician. For this reason, the diagnosis requires the indication of tests in subjects who appear normal, but may suffer this disorder. MHE (Table 1) develops in patients with significant liver function impairment or with porto-systemic shunting. Traditionally, the diagnosis has been limited to patients with cirrhosis of the liver. In cirrhotics with good liver function (Child A) the prevalence is low (15%), while in those with advanced cirrhosis (Child B/C) half of them may be suffering from MHE.

There are many methods to assess neurological function that have been applied for the diagnosis of MHE (Table 1). By definition, any technique that demonstrates abnormalities of the central nervous system attributable to liver failure would be valid. However, traditionally the diagnosis has been limited to the presence of neurological impairment demonstrated by neuropsychological or neurophysiological tests. Psychometric and neurophysiologic methods have been the most trusted and widely used tests. Unfortunately the diagnostic approach to the assessment of MHE is not uniform various combinations of psychometric tests with or without neurophysiological methods has been used to diagnose MHE.

Commonly used psychometric tests include trailmaking tests (number and figure connection tests) and Wechsler Adult Intelligence Scale (WAIS) for verbal and performance skills. Among the various neuropsychological or psychometric tests, trailmaking tests and block design and digit symbol tests from WAIS-performance battery appear to be adequate for diagnosis of MHE. The diagnostic criteria for MHE were formally standardized as patients require a normal mental status.

Examination and a significant reduction (>2 standard deviations from appropriate normative population) in
Table 1: Tests for diagnosis of minimal hepatic encephalopathy

<table>
<thead>
<tr>
<th>Commonly used Psychometric Tests</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. WAIS – Verbal</td>
<td>Nonverbal skills (performance intelligent quotient)</td>
</tr>
<tr>
<td>2. Information</td>
<td></td>
</tr>
<tr>
<td>3. Comprehension</td>
<td></td>
</tr>
<tr>
<td>4. Arithmetic</td>
<td></td>
</tr>
<tr>
<td>5. Similarities</td>
<td></td>
</tr>
<tr>
<td>6. Digit span</td>
<td></td>
</tr>
<tr>
<td>7. Vocabulary</td>
<td></td>
</tr>
<tr>
<td>Digit symbol</td>
<td>Motor speed and accuracy, short time visual memory</td>
</tr>
<tr>
<td>Block design</td>
<td>Visual spatial motor functioning</td>
</tr>
<tr>
<td>Picture completion</td>
<td>Basic perceptual and conceptual</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>skills as assessed through visual</td>
</tr>
<tr>
<td>Object assembly</td>
<td>recognition and identification</td>
</tr>
<tr>
<td>Trail making tests</td>
<td></td>
</tr>
<tr>
<td>1. Number connection test A</td>
<td>Visuo-spatial orientation,</td>
</tr>
<tr>
<td>2. Number connection test B</td>
<td>motor speed, concentration and</td>
</tr>
<tr>
<td>3. Figure connection test A</td>
<td>Attention</td>
</tr>
<tr>
<td>4. Figure connection test B</td>
<td></td>
</tr>
<tr>
<td>Cancellation’s test</td>
<td>Preattentive visual processing</td>
</tr>
<tr>
<td>Digit span</td>
<td>Attention</td>
</tr>
<tr>
<td>Line tracing test</td>
<td>Visuo-motor co-ordination and psychomotor slowing</td>
</tr>
<tr>
<td>Serial dotting test</td>
<td>Motor speed and co-ordination</td>
</tr>
<tr>
<td>Simple reaction time to light</td>
<td>Psychomotor speed in response to light</td>
</tr>
<tr>
<td>Simple reaction time to sound</td>
<td>Psychomotor speed in response to sound</td>
</tr>
<tr>
<td>Choice reaction time to light</td>
<td>Psychomotor speed in response</td>
</tr>
<tr>
<td>Choice reaction time to sound</td>
<td>to a light or a sound stimulus when either stimulus may occur; also evaluates decision making time</td>
</tr>
</tbody>
</table>

Neurophysiological methods

1. Electroencephalogram (EEG)
   a. Standard
   b. Mean dominant frequency
2. Evoked potentials
   a. Exogenous
      i. Brainstem auditory evoked potentials (BAEP)
      ii. Visual evoked potentials (VEP)
      iii. Somatosensory evoked potentials (SSEP)
   b. Event-related potentials (P300)
      i. Visual paradigm
      ii. Auditory paradigm
3. Critical flicker frequency (CFE)

Performance of at least two of the battery of psychometric tests for a diagnosis of MHE.

Clinical Significance

Impact on Daily Activities

MHE is associated with poorer quality of life and increased work disability. Groeneweg et al.18 studied the Sickness Impact Profile (SIP) in a cohort of cirrhotics being tested for MHE (Medical Outcomes Trust, Boston, MA). The SIP consists of 136 items which questions patients about 12 sections; sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement (the last three generate a physical sub score), social interaction, alertness behavior, emotional behavior, and communication (comprising the psychosocial sub score). All scales were significantly impaired in MHE patients compared to others. A recent study by Prasad et al.18 confirmed these findings in MHE patients in all spheres apart from communication, which was similar between patients with or without MHE.

Impact on Driving Skills

MHE may increase the risk of accidents. MHE affects attention, psychomotor function and working memory, all of which are essential for safe driving. Most studies of driving ability using on-road driving tests have demonstrated that MHE patients have significant defects in reaction time, resulting in their pronouncement as unsafe drivers.20-23

Risk of Overt encephalopathy

Cirrhotic patients with MHE more frequently develop episodes of overt HE than those without MHE.5-6,11 In one study the actuarial probability of overt HE at 3 years was 56% for those with MHE and 8% for those without MHE.6 It is probable that MHE is a marker of advanced liver failure, because it is associated with shorter survival time, especially among patients with high concentrations of venous ammonia after oral glutamine load.24-26 For this reason, MHE has been proposed as an indication for liver transplantation.

When and in whom to Test for Minimal Hepatic Encephalopathy

Some authors have proposed testing all cirrhotics to identify patients with MHE.20 The basis for this proposal is that several studies have shown improvement of neuropsychological function with therapy.18,26-28 It has been suggested that therapy may improve quality of life or delay the development of an episode of hepatic encephalopathy. Due to controversy of the actual benefits of therapy, screening of all cirrhotics cannot be recommended.26 The decision to indicate a test for MHE should be individualized. It needs to be taken into consideration to what extent the diagnosis could modify the life of the patient. Aspects that should be considered include: quality of life, working performance, cognitive complaints and risk of accidents. While the benefits of therapy may be questionable, medical advice may be important, especially for two groups of cirrhotics (a) patients at risk of accidents; (b) patients with cognitive complaints or decline in work performance.18,26-28 Psychometric performance can be affected by current alcohol use, use of psychoactive drugs and pre-existing neurological disorders.29 In cirrhotics who do not fulfill these criteria, it is in the best interest of the patient to be offered testing at the initial visit regardless of their subsequent activities. There is no consensus regarding the frequency of testing, but experience has shown relative similarity in psychometric scores at 6 months intervals in the absence of acute clinical and neurological events such as development of HE.

Treatment of Minimal Hepatic Encephalopathy

Treatment of MHE improves psychometric performance and quality of life.18,26-28 Several reports, conducted as a placebo-controlled, double blind study, presented a favorable result in treating MHE. They included branched chain aminoacid, flumazenil-a benzodiazepine receptor antagonist, lactulose, lactitol, and L-ornithine-L-aspartate.20-34

Branched chain amino acids (BCAAs) were reported to improve nitrogen metabolism, blood ammonia level, and
psychomotor tests. Flumazenil, an antagonist of benzodiazepine receptor, has not been associated with established consensus on the effectiveness in MHE. L-ornithine-L-aspartate (OA) exerts its ammonia-lowering action in the kidney, skeletal muscles, brain, as well as in the liver. OA administered per orally improved number connection test, ammonia levels, and mental state. OA may be a promising therapy for patients with MHE. Treatment with lactulose is of benefit in patients with MHE. Lactulose lowers ammonia levels by alteration in gut flora, lowers colonic pH and decrease the absorption of ammonia by non-ionic diffusion. A recent consensus conference promulgated lactulose as the first choice of therapy for MHE in concordance with the previous study data and the AASLD survey. However, whether this would have any effect on development of OHE, driving capability or overall survival remains to be investigated. Since driving and psychometric impairments are highly correlated, it is reasonable to expect that driving performance would also improve after MHE therapy. However, the adherence rate of lactulose in patients with OHE is low; as could cause diarrhea and flatulence. Therefore, alternatives to lactulose have also been studied for MHE. We have shown probiotics improved psychometric function and MHE. Although probiotics are attractive options that spare the patients from the poor palatability of lactulose, difficulties in the availability and the standardization of probiotic organisms remain. Therefore, although treatment options for MHE are evolving, it is still important to test patients to offer them the available therapeutic options.

References

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