



DIAGNOSIS AND TREATMENT PROGRESS OF MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH LIVER CIRRHOSIS

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ABSTRACT

Hepatic Encephalopathy (HE) is a significant clinical issue of cirrhosis of the liver and portal hypertension that is characterized by neuropsychiatric and neurologic abnormalities. It is described as personality changes, cognitive dysfunction, and altered level of consciousness. Minimal hepatic encephalopathy (MHE) is characterized by subtle cognitive and psychomotor deficiencies and the absence of noticeable clinical signs and symptoms of HE and is documented by psychometric tests and neurophysiological tests. There is no established clinical evidence for diagnosis of MHE. The sequence of two neuropsychological tests, or psychometric tests and neurophysiological tests are regarded as standard for the diagnosis of MHE. The pathogenesis of MHE is corresponding to that of hepatic encephalopathy, and hyper-ammonia is considered to be a most important factor in the pathogenesis of HE. However, the accurate pathogenesis of MHE is still unclear. Thus, ammonia-level reducing drugs such as lactulose are established as the first-line treatment for MHE. The medications used to treat OHE have been tested in patients with MHE, particularly lactulose, rifaximin, probiotics and L-ornithine and L-aspartate (LOLA) have all been found to be beneficial and recorded the improvement in psychometric performance after treatment.

Keywords: Minimal hepatic encephalopathy, Overt hepatic encephalopathy, Psychometric tests, Lactulose, Rifaximin, L- ornithine, L- aspartate, Ammonia

INTRODUCTION

Hepatic encephalopathy (HE) is a described clinical problem of liver cirrhosis and portal hypertension that is manifested by neurologic and neuropsychiatric abnormalities. It is distinguished by personality changes, cognitive dysfunction, and altered level of consciousness [1]. Minimal hepatic encephalopathy (MHE) is recognized by subtle cognitive and psychomotor deficiencies in the absence of perceptible clinical manifestations of hepatic encephalopathy (HE) and is documented by Neuropsychological tests and Electrophysiological tests, but HE grades 1 is described by the presence of mild clinical evolutions like euphoria, anxiety, or a shortened attention span [2]. Minimal hepatic encephalopathy may have a poor impact on the quality of life, risk of road traffic accidents, and can develop to overt HE. At least two of the Neuropsychological tests such as Number Connection Test-A (NCT-A), NCT-B, Block-Design Test (BDT), and the Digit-Symbol Test (DST) should be used for the diagnosis of MHE [2]. The existing definition of MHE is built on psychometric test results that at least two psychometric tests are abnormal [3]. Treatment for MHE is intended toward the gut, due to the ammonia-genic role of the gut contents, which have been hypothesized to play apart in MHE pathogenesis. However, they stated that when a patient has obvious cognitive impairment, or deterioration of quality of life (QoL), unfit for driving, or inadequate to perform jobs that are required for manual work have high risk of HE; and the patient should be treated accordingly [4]. Minimal hepatic encephalopathy is concerned as a proportion of the wide spectrum of typical neurocognitive changes in liver cirrhosis that mostly involve the regions of attention, awareness, response inhibition, and directorial functions. Minimal Hepatic encephalopathy cases vary worldwide between 30 to 84% in cirrhotic patients [5,6]. In a study directed by Sharma K et al. [7], implementing the two atypical neuropsychological tests including (NCT A, FCT A and DST), the prevalence rate of MHE was significantly higher. Gut-derived neurotoxin ammonia generates gliopathy due to the synthesis of glutamine through Alzheimer type II astrocytes, which also synchronize cerebral blood flow by maintaining the solidarity of the blood-brain barrier; and assumed to cause brain swelling. Ammonia generates the evolution of neurosteroid leading to a positive modulatory effect on the GABA-A receptor [8]. Ammonia influences cerebral blood flow and glucose utilization of different cortical areas and causing altered glioneuronal transmission as a result of astrocyte swelling that corresponds with the patient's cognitive functions in hepatic encephalopathy. Lockwood et al. [9] Shown that increase of ammonia levels in the brain can progress encephalopathy even in the presence of normal arterial ammonia levels; which is correlating with excess diffusion of ammonia across the blood-brain barrier in MHE [10]. Numerous studies suggested that inflammation plays a significant role in ammonia as well as in producing and modulating minimal hepatic encephalopathy [11]. Studies in patients with cirrhosis have documented higher levels of pro-inflammatory cytokines like tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6. It reverses the prospect of progressing a systemic inflammatory response that changes the blood-brain barrier permeability and moreover enables the diffusion of ammonia [12].

Diagnosis of Minimal Hepatic Encephalopathy:

Various combinations of psychometric tests (NCT-A, DST) with or without neurophysiological methods are required for the diagnosis of MHE in liver cirrhosis. The clinical identification of HE can be confirmed based on the West Haven criteria (Table 1), which are effective and commonly used by health professionals; these criteria assume obvious neurological symptoms, and thus of limited appositeness in MHE [13].

Grade	Features
0	No abnormality detected
1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition
2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior Impaired performance of subtraction
3	Somnolence to semi stupor, but reactive to verbal stimuli Confusion Gross disorientation
4	Coma (unresponsive to verbal or toxic stimuli)

Table 1: West Haven criteria for semi-quantitative grading of psychological state

Psychometric tests or Neuropsychological tests:

Neuropsychological tests are widely employed in routine clinical practice for the diagnosis of MHE in cirrhotic patients. These tests such as, the Number Connection test- A (NCT- A), Number Connection test- B (NCT- B), Digit Symbol test (DST), Figure connection test- A (FCT- A), Figure connection Test- B (FCT- B) and Serial-dotting test (SDOT); which are directly measure cognitive functions that are directly related to activities of daily living.

Number connection tests(NCT):

The NCT-A, Generally, this test is shown on a sheet of paper with randomly sprinkled 25 circles numbered from 1 to 25. The patients must attach the numbers in sequence in the shortest time possible without mistakes. If an error is made, the subject must stop, correct the error, and then continue without stopping the clock. The test score is the time required to carry out the test, including the time needed to correct all errors. In the NCT-B, the numbers from 1 to 13 and the letters from A to L were comprised in circles. In this test, patient is asked to link the numbers and letters in an alternating way; which means start from 1-A-2-B-3-C and so on.

The test result is the time needed by the patient to perform the test, including error correction time. Furthermore, this test is a satisfactory to study the ability for shifting attention, besides of visuo-spatial orientation and psychomotor speed. [14, 15]. These tests are time-consuming, and their results are affected by age and educational status. However, these tests are recommended for the diagnosis of MHE [16].

Digit symbol test (DST):

The digit symbol test usually shown, on a sheet of paper with nine secured pair of digits from 1 to 9 that designated as symbols; and which are present at the top of the test sheet. The patient asked to draw or write down the symbol corresponding to the digit into the bottom part of the boxes within 90s [17].

Block design test:

This test recorded speed and accuracy. The task is to take 6-9 blocks that have all red sides, all white sides, and red-and-white sides followed by presenting them according to a pattern organized by the interviewer or represent on a card [18].

The line drawing test is the test of motor speed and accuracy. The patients have to go along with the direction of this labyrinth without crossing or touching the borderlines [19].

The circle dotting test is the easiest trial of the battery. This test also assesses the pure motor speed. The subjects are demanded to place a dot in each of the 100 circles given on the sheet after they have arranged by dotting the 20 circles at the upper part of the sheet first. The required time is the outcome of the test.

Computerized tests:

In recent time, several studies have shown that computerization of neuropsychological tests could lead to clarify and easy to administrate in the clinic within a few minutes [20].

The critical flicker frequency (CFF):

CFF test is a psycho-physiological apparatus that examines the patient's ability for the frequency at which a fused light emerges to be flickering to the observer. Earlier studies have shown depletion in its performance with aggravating cognition and improvement after therapy. Studies evaluated that its efficacy in the diagnosis of MHE is simple, reliable and accurate. CFF prognosticates the first episode of OHE in cirrhotic patients who had never experienced OHE and anticipate mortality risk [21].

The inhibitory control test (ICT):

It is a computerized test of response suppression and working. ICT demands highly functional patients. The ICT can be done using a laptop and is analyzed utilizing an automatic computerized system that remarkably improves the convenience and flexibility of using this test in the clinical circumstances. It was established that the inhibitory control test is easy to operate and has higher sensitivity/specificity for screening MHE than the standard psychometric test. Contrarily, Taneja et al. established that ICT is not as effective as the psychometric tests in diagnosing of MHE in cirrhotic patients [22].

Continuous reaction time (CRT) test:

CRT test assesses the motor reaction time by the patient press a button in response to auditory stimuli (using headphones). The most significant test result is the CRT index, which assesses the stability of the reaction times. The test result can evolve between organic and metabolic brain impairment. The test is not influenced by the patient's age, gender with no education or sickness impact [23].

Electrophysiological or Neurophysiological tests:

The electrophysiological tests have been advanced as a more objective and specific technique for the evaluation of MHE.

Electroencephalography (EEG): EEG is employed to detect the changes in cortical cerebral function over the wide spectrum of hepatic encephalopathy (HE) without patient cooperation. The quantitative data analysis including the background frequency with mean dominant frequency or spectral band analysis can be improved by the authenticity of EEG analysis.

Although, it is not that specific, but it can be affected by accompanying metabolic disturbances and drugs. The important finding on Electroencephalography (EEG) is a common reduction in wave frequency and an increase in wave amplitude. These abnormalities may be found even in cirrhotic patients without clinical signs of encephalopathy. The sensitivity of the EEG for the diagnosis of subclinical HE is limited differentiated to psychometric tests [24]. The EEG is beneficial for follow-up examinations, predominantly. Among EEG assessments, the most sensitive test is computer-assisted analysis, including the mean dominant EEG frequency and the power of a specific rhythm. Quantified-EEG has a prognostic standard for the mortality of cirrhotic patients as well as the incidence rate of minimal hepatic encephalopathy [25].

Magnetic resonance imaging and spectroscopy:

Magnetic resonance imaging (MRI) differentiated the morphological cerebrum abnormalities including mild cerebral edema, hyper-intensity of the globus pallidus, sub-cortical nuclei, and central and cortical atrophy in patients with liver cirrhosis. On T1-weighted images in the Globus pallidum region have been perceived with high-signal abnormalities in cirrhotic patients, even without a clinical evidence of HE, as there is no direct association between pallidal hyper-intensity and grade of encephalopathy. The deposition of manganese is considered the most likely demonstration of this high-signal abnormality [26]. Globus pallidal hyper-intensity on MRI is a common finding in patients with liver cirrhosis and it also appears in patients with non-cirrhotic portal hypertension. Magnetic resonance spectroscopy (MRS) shows a reduction in Myo-inositol/creatine and choline/creatine proportions in the white matter with an increase in the Glx (glutamine and glutamate) concentration in the basal ganglia in patients with MHE [27]. Diffusion tensor imaging has shown that mean diffusivity, a measure of water movement over cell membranes, is significantly greater in patients with MHE in the sections of the inner capsules, corpus callosum, caudate nuclei, and occipital white matter. After completion of three weeks of lactulose therapy, mean diffusivity values decreased significantly and there was a corresponding enhancement in Psychometric test or neuropsychological test scores in patients

with MHE [28]. Therefore, Magnetic resonance imaging methods, and the neuropsychological test is useful in the evaluation of minimal hepatic encephalopathy [27].

Treatment of Minimal Hepatic Encephalopathy:

Treatment of MHE with lactulose, probiotics, or l-ornithine-l-aspartate was found to be beneficial in decreasing abnormal tests and impede or eradicating hazardous motor car accidents [29].

Non-absorbable disaccharides:

Lactulose or lactitol are synthetic non-absorbable disaccharide; which are the first-line drugs choice for the treatment of MHE [13]. This lactulose causes acidification of intestinal contents after affliction into acetic and lactic acid by intestinal flora, which transforms ammonia (NH₃) into ammonium (NH₄⁺). Treatment strategy for MHE can be instigated with lactulose, and 30–60 mL of lactulose in two or three divided doses are required every day; so that patients can pass two to three semi-soft stools per day. However, the proper duration of treatment for MHE is nomadic, at least three studies propose that treatment may be suggested for 3–6 months. It was seen that cirrhotic patients with MHE had enhancement in health-related quality of life and psychometric conduct after lactulose therapy [30]. Lactulose and lactitol, both drugs have consequences on gut flora and are regarded as intestinal prebiotics [31].

Kale et al. [32] revealed that interstitial brain edema observed in patients with MHE rectifies following treatment for 3 weeks with lactulose in parallel with improvements in neuropsychiatric performance.

Rifaximin:

Rifaximin is a lingual administered, non-absorbable, semi-synthetic antibiotic accompanied by the broad-spectrum reaction on both Gram-positive and Gram-negative bacteria [33]. It was established that Minimal hepatic encephalopathy (MHE) patients treated with rifaximin for 8-weeks duration showed significantly better improvements in awareness and driving performance and the psychosocial dimension of the Disease Impact Profile apart from those given a placebo [34]. In recent years, a randomized controlled experiment distinguished the potency of rifaximin with lactulose in a reversal of MHE and showed improvement in HRQoL in cirrhotic patients with MHE. The study concluded that both drugs enhance HRQoL correspondingly well, in cirrhotic patients with MHE [35]. Condensed in the gut, rifaximin is expected to modulate intestinal bacteria, thereby decreasing intestinal ammonia and toxin formation [36]. In a current open-labeled trial, Bajaj et al conducted a system biologic analysis of the micro-biome and appraised cognitive alterations after treatment with rifaximin (550 mg bid) in cirrhotic patients diagnosed with MHE [37]. The preliminary studies for rifaximin illustrated its potency in the management of MHE; and advocated that treatment with rifaximin compared to lactulose is more productive in patients with MHE [38]. In a randomized double-blind placebo-controlled trial over a 6-month-duration, rifaximin (550 mg bid) minimized the risk of an episode of Overt HE with no significant adverse effects [39]. These findings were additionally by Bajaj et al in a randomized double-blind placebo-controlled trial evaluating the effect of rifaximin on driving performance [40]. Rifaximin or placebo is given twice daily for 8 weeks duration for liver cirrhosis patients diagnosed with Minimal hepatic encephalopathy.

LOLA (l-ornithine-l-aspartate):

LOLA (l-ornithine-l-aspartate) are agents that decline in blood ammonia concentration by enhancing the metabolism of ammonia to glutamine. Bai et al. evaluated eight RCTs, assessing the potency of LOLA compared to placebo in patients with liver cirrhosis. He established that treatment with LOLA reduced serum ammonia levels [41]. Studies also reported the significant benefit of LOLA used in RCTs patients with MHE that measured by psychometric tests analysis. The lingual formulation of LOLA was determined to be remarkably effective for the treatment of MHE or OHE. Recently, in a randomized trial, liver cirrhosis patients diagnosed with MHE were treated with LOLA or placebo more than 6-months-duration [42].

Prebiotics, Probiotics or Synbiotics:

Prebiotics are non-digestible food components that particularly stimulate the growth and/or action of the bacteria in the colon. Probiotics are live microbes that change the intestinal balance of the microflora. The composition of prebiotics and probiotics is called synbiotics. The meta-analysis of nine studies showed significant evidence for the potency of prebiotics, probiotics, and synbiotics in the management of MHE [43]. This consequence preserved for two weeks after cessation of supplementation; which was corresponded with a significant reduction in blood ammonia and endotoxin levels; and also improved reversal of MHE in cirrhotic patients, as the severity of the liver disease was evaluated based on the CTP classes [44]. Probiotics may represent an effective, safe, long-term therapy for MHE and maybe a substitute to lactulose.

Zinc:

Zinc, regarded as a cofactor of urea cycle enzymes, is deficient in patients with cirrhosis, particularly with malnutrition or MHE [45]. Zinc is an important key factor for the synthesis of coenzymes that mediates biogenic amine synthesis and metabolism; its deficiency also leads to neurotransmitters alteration such as γ amino-butyric acid and nor-epinephrine [46].

A recent RCT published that zinc supplementation can enhance MHE in patients with liver cirrhosis associated with significant improvement in neurophysiological tests and significantly reduced arterial ammonia levels [47].

CONCLUSION

The incidence of MHE is high in liver cirrhosis. Psychometric tests are first-line investigations for diagnosis of MHE. Treatment of MHE in liver cirrhosis not only improves the quality of life but also in psychometric and cognitive performance. The advantage of Rifaximin, L-Ornithine L-aspartate, Probiotics, and Lactulose over placebo for reversal of MHE in the liver cirrhosis. Lactulose and probiotics are safe, effective and can be used for treating MHE.

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