Minimal Hepatic Encephalopathy

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Abstract
Minimal hepatic encephalopathy (MHE) is a potentially reversible neurocognitive syndrome that consists of a series of neuropsychological disorders in patients with acute and chronic liver disease. A physical examination may or may not show evidence of neurological abnormalities. MHE is responsible for cognitive impairment, has a negative impact on quality of life of patients, essentially cirrhosis. The impossibility of detecting this neuropsychological disorder clinically has led to the use of psychometric tests for screening and diagnosis. MHE modifies the prognosis of disease, and early detection allows intervention against the risk of developing clinical hepatic encephalopathy (HE) in patients with cirrhosis which has been associated with decreased survival.

Keywords
Encephalopathy, minimal hepatic encephalopathy, liver cirrhosis.

INTRODUCTION

"Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma." (1-4) This is the definition of the American Association for the Study of Liver Diseases (AASLD) which also says that it is one of the most frequent complications of liver disease and that it substantially compromises the quality of life of patients. (5) A large number of patients with chronic liver disease develop subclinical neurocognitive syndrome which forms the basis of a series of neuropsychological disorders that significantly affect the quality of life of patients and their caregivers. MHE is a clinically undetectable condition which has no evidence of abnormality in a neurological examination. (1,2) MHE commonly causes cognitive deficits and increases the risk for development of evident HE. It requires an appropriate therapeutic approach because otherwise it is associated with low survival rates. (6)

Knowledge about MHE is key to its early detection. (7) The importance of evaluating MHE lies in predicting development of HE and its impact on quality of life of the patient. It has the potential for reducing socioeconomic impact of HE and can provide advance warning for patients and their caregivers about the disease to enable them to obtain appropriate guidance and clinical monitoring. Finally, it allows for establishment of appropriate therapeutic measures aimed at the correction of cognitive impairment and improvement in the quality of life.

DEFINITION

HE manifests through a spectrum of motor and mental disorders. According to the International Society for Hepatic Encephalopathy and Nitrogen Metabolism

(ISHEN), when HE is not clinically evident, it is called covert hepatic encephalopathy (CHE). The term includes MHE and HE grade I, according to the West Haven criteria. (4) MHE is defined as the presence of signs indicating cognitive dysfunction accompanied by the results of a psychometric or neurophysiological test that quantifies the deficit in patients with liver disease who are not disoriented and are without asterixis. (1, 4, 5) The term "minimum" essentially refers to the absence of clinical signs or clearly cognitive indications as defined within the criteria for HE.

EPIDEMIOLOGY

Thirty to forty-five percent of patients with cirrhosis develops a set of potentially reversible neurocognitive abnormalities within the spectrum of HE. (1) MHE represents the preclinical stage of the disease which is present in approximately 80% of cirrhotic patients. (8) Its prevalence varies and depends on the choice of diagnostic tests. The application of standardized testing and correction of data obtained according to age and patient level of education modifies the prevalence of MHE in patients with compensated cirrhosis to a range of 25% to 35%. Generally speaking, it is considered that the prevalence of MHE in patients with chronic liver disease is approximately 50% which suggests a need for screening of at risk patients. (1, 2) A discussion has arisen about strategy since it can be costly in relation to the diagnostic clarity offered, since results can be inconclusive, and since treatment is not always advisable.

PHYSIOPATHOLOGY

HE is the clinical expression of the harmful effect of neurotoxins in the central nervous system due to deficiencies in detoxification resulting from hepatocellular injury or from a portosystemic shunt. (9) The main neurotoxin is ammonia, which is a key intermediate product in the metabolism of proteins and nitrogen. It is produced in the digestive system, especially in the small intestine, through the activity of intestinal glutaminase. Ninety percent of the ammonium is metabolized in the liver by the urea cycle. In chronic liver disease, classically cirrhosis, other organs exercise the function of detoxification, in this case the skeletal muscle due to its ability to synthesize glutamine. Other inhibitors of neural activity such as manganese and endogenous benzodiazepines have also been described. (10)

Metabolic failure or a portosystemic shunt can promote hyperammonemia. Ammonium cross the blood brain barrier (BBB) into the central nervous system. Within the central nervous, astrocytes are the only cells capable of metabolizing glutamine. They do this by means of glutamine synthetase. The osmotic activity of glutamine promotes water displacement into the cells which causes a low degree of edema which is then compensated by the release of Myo-inositol (9). The high energy consumption implied by this process leads to oxidative stress which is accompanied by cellular dysfunction and disruption of neurotransmission especially of glutamate and γ-aminobutyric acid (GABA). (11) Recent studies in patients with cirrhosis have documented higher levels of proinflammatory cytokines (IL-6, TNF-α) than in healthy subjects. (12) This considers the possibility of developing a systemic inflammatory response that alters the BBB's permeability and allows diffusion of ammonia which precipitates and prepetuates the disease.

IMPACT

Quality of life

MHE affects domains which include complex activities such as attention, information processing and psychomotor skills. (13, 14) Basic activities like shopping and good personal hygiene remain unaffected. The influence of the disease on the daily functioning of people has been evaluated by applying the Sickness Impact Profile (SIP) created by Groeneweg et al. (15). It includes 136 items grouped into 12 scales that assess sleep, rest, feeding, ambulation, work, hygiene, social interaction, the level of vigilance and emotional behavior. The study reveals an association between MHE in cirrhotic patients and deterioration of areas of social interaction, alertness, domestic organization and recreation. Some studies in which lactulose and rifaximin were administered have shown a significant association between the reversal of MHE and improvement in quality of life as measured by the SIP questionnaire (16).

In addition, it is assumed that an average of 50% of all patients with chronic liver disease and MHE do not have stable employment, and that deterioration in labor aptitude generates a large negative impact on quality of life. (2, 14) The most important impact is undoubtedly on employment in jobs that require manual dexterity due to the significant deficits found in psychomotor functions. Finally, family functionality is also compromised, and the patient becomes a burden for his or her caregivers and those who are dependent on the patient, and basal functionality is affected.

Sleep Disorders

Between 26% and 70% of all patients with cirrhosis and MHE report sleep disorders such as delayed onset of sleep and multiple nighttime awakenings. (17) Neverthless, Steindl et al. (18) have suggested that alterations of nighttime sleep are not directly linked to mechanisms of HE,

but to abnormal circadian rhythms produced by changes in the retina and suprachiasmatic nucleus and defects in processing melatonin in the liver of patients with cirrhosis. In contrast, daytime sleepiness is associated with serum ammonia levels, increased risk of hospitalization for HE, and the presence of portosystemic shunts.

Driving

Driving performance visibly deteriorates in most patients with MHE (19). People with cirrhosis should undergo cognitive rehabilitation including simulated driving. There is now scientific evidence of the benefit for psychomotor skills after treatment when MHE is reversed. (20) Theoretically, 48% of patients with MHE and 39% of patients with grade I HE should not drive. (2, 14) However, MHE does not indicate an objective limitation, so medical personnel cannot issue a legal judgment. Appropriate behavior for both the patient and the community would indicate a driving test and a recommendation that the patient discontinue driving until the responsible authorities can make an objective assessment. The criterion for driver's license suspension is a simulated driving test while lifting of suspension requires substantial improvement of performance after demonstrating treatment adherence.

The risk of falls increases secondary to deficits in attention, reaction time, visual-motor coordination and psychomotor speed. Trauma is can trigger decompensation and has high rates of morbidity and mortality. (21)

Clinical Hepatic Encephalopathy

Hartmann and colleagues (22) have studied the MHE as a predictor of risk for the development of HE within three years. They found that 56% of patients with cirrhosis and MHE had at least one clinical episode in contrast to only 8% of patients with cirrhosis without MHE. (23)

DIAGNOSIS

The initial indications for studying whether a patient is at risk of MHE are problems related to quality of life and complaints from relatives and caregivers. Ideally, patients at imminent risk including those who had previous episodes of HE, cirrhotic patients, and those who perform public risky public activities such as bus drivers should be assessed. (3, 6) Currently there is no gold standard because MHE affects multiple domains of cognitive functioning which do not necessarily deteriorate equally. The ISHEN recommends application of at least two different tests. (5) Given that availability of testing varies, a widely accepted test should be used at least to serve as a point of comparison. Strategies for detection of MHE are divided into two main types: psychometric and neuropsychological tests. Test use varies according to availability, cost and local regulations.

Psychometric Tests

Psychometric Hepatic Encephalopathy Score (PHES) Battery

There are five tests in the PHES series: digit symbol test, number connection test A, number connection test B, connect the dots test, and broken line connection test. (24) The PHES battery, a paper-pencil test that requires the presence of trained personnel, is the most widely used test. It measures complex cognitive functions including attention, accuracy, speed of work and visual orientation. On average it takes 15 minutes to complete, and completion time is a factor in calculation of the score. It is currently available in several languages and in four age adjusted versions to minimize the effects of learning phenomenon produced by repetition.

Computerized Testing

Inhibitory Control Test

In this test, the patient watches a screen upon which randomly flashing letters appear. The test requires that the patient focus only on the letters 'X' and 'Y' and that she or he press a button when one of the letters is preceded by the other. Inhibition is required in order to avoid pressing the button when the distractors 'X-X', 'Y-Y' appear. The program calculates precision of performance. Results less than 87% are considered to be abnormal. The test should be used only for high-functioning patients.

Reaction Time Test

This test is based on registration of motor reaction time every time an auditory stimulus is heard through headphones. To register stimulus detection, the patient must press a button. The result is obtained by means of CRT-Index (continuous reaction time index) which indicates reactive stability. (25) The result allows identification of whether the origin of cognitive impairment is metabolic or organic. It is not influenced by age or gender nor by learning phenomena.

The Stroop Test

The Stroop Test evaluates the speed of response to a stimulus that precipitates a motor event. It provides evidence of interference that occurs in the patient when she or he tries to indicate discord, for example when the name of a color is written in a color of ink other than the color named. There is currently a test version available for smartphones. (26,27) The Stroop test is considered to be a valid and useful method for screening for MHE.

Neurophysiological Tests

Measurement of Critical Flicker Frequency (CFF) threshold

This test evaluates the metabolic state of Müller cells which are located in the retina and which share histological features with astrocytes. For this reason, they reflect metabolic events of HE that occur in the brain. The information obtained indicates the test taker's capacity for attention and visual processing. (28) The patient wears a headset and has to press a button when she or he notices that a light has begun to flicker. The result is not influenced by age or education level and may predict the development of episodes of HE. The diagnostic accuracy of measurement of the critical flicker frequency threshold is 83.3% in relation to psychometric tests as the sole diagnostic criterion.

Electroencephalography

Electroencephalography can detect changes in the cortical activity spectrum that are characteristic of HE such as decreased frequency of electrical activity. The findings may indicate the presence of disease, however, since their specificity is low, and they are also present in other encephalopathies including uremia and carbon dioxide narcosis, they cannot make a firm diagnosis. (5)

Laboratory Tests

Serum Ammonium

The measurement of blood ammonia levels is not recommended for clarification of the diagnosis. It is indicated for assessing responses of patients undergoing treatment.

Imaging

CT Scans

CT scans do not contribute to diagnosis or classification of the disease but can be used for screening of frequent comorbidities in patients with chronic liver disease. One example is the risk of stroke for which patients with chronic liver disease have five times the normal level of risk. (3, 5)

MRI

Magnetic resonance imaging is not indicated for the study of MHE, (5) but it can be used to classify patients with metabolic disorders by spectroscopic sequencing. (29) The main difficulty for diagnosing MHE is that there is little correlation between tests due to the multidimensional effects of the disease. (30, 31) In addition, learning phenomena have been visible in some tests when applied repeatedly. The diagnosis must be made by interpretation of the results, patient history, daily functioning and the absence of signs of HE. The Clinical Practice Guidelines for HE in chronic liver disease, (5) suggests studying MHE through the use two different tests, ideally a psychometric test (PHES) and a computer or neurophysiological test, usually the Critical Flicker Frequency.

Neurocognitive domains that should be considered for testing are processing speed, working memory, visual memory, visual spatial skills, reaction time and motor functions. It is important to study limit study to patients without comorbidities, and especially to exclude people with psychiatric disorders, who use psychoactive medication or who frequently consume alcohol. In cases in which a patient tests negative for MHE, the recommendation is to repeat the test in six months.

TREATMENT

The establishment of an appropriate therapeutic regimen for the treatment of MHE should include modulation of cognitive functioning and the restoration of normal quality of life. (32) Therapeutic measures for MHE have been extensively studied and include pharmacological and nutritional measures. Currently, the anti-ammonium measures are the cornerstone of MHE treatment. (5, 20) The Clinical Practice Guidelines for HE in chronic liver disease (5) do not recommend routine treatment of MHE but does set out specific guidelines for when to implement a therapeutic regimen. It says that when a patient has clear cognitive impairment, or deterioration of quality of life, skills for driving, or ability to perform jobs that require manual labor or have high public risk, the patient should be treated.

MHE Treatments

- *Lactulose* is a widely used nonabsorbable disaccharide that increases incorporation of nitrogen products from the intestinal lumen by bacterial flora and reduces colonic transit time. This in turn reduces the absorption of ammonia. Another preparation, lactitol, uses the same mechanism of action. The usual dose of lactulose ranges from 60 to 120 ml/day and is given fractionally in order to cause at least two soft stools daily. Nevertheless, some studies have shown the benefit of treatment with doses between 30 and 60 mL in 3 daily doses because this improves cognitive abilities, the quality of life of patients with MHE, and is a safe alternative. (16, 33). Contrary to popular belief, overdoses of the drug are not beneficial because of complications that can trigger dehydration, hypernatremia and perianal irritation and which could precipitate an episode of HE. (5)
- *Rifaximin* is a nonabsorbable antibiotic derived from rifamycin. It has demonstrated utility in the treatment

of cognitive impairment and decreased serum levels of ammonium. It is usually given in doses of 1200 mg / day. (34) Clinical evidence demonstrates the efficacy of rifaximin therapy in patients with MHE only in treatments with conjugated lactulose. (5, 32)

- *L-ornithine L-aspartate (LOLA)* granulate is prepared to be administered intravenously. It consists of substrates involved in the metabolic conversion of ammonia to urea and glutamine. Studies have shown its effectiveness in treatment of HE, but no significant differences have been found between treatment with this substance and lactulose. It is currently indicated for treatment of MHE and Grade I HE. (34)
- *Probiotics* have recently been evaluated for treatment of HE. Studies have reported fewer episodes of clinical HE than in treatment with placebos for which reason it is seen as a promising therapeutic option for short-term treatment of MHE. (33)
- *Dietary measures* initially proposed consisted of protein restriction, but evidence of the role played by skeletal muscle in removing ammonium through glutamine synthesis has prompted a new hypothesis about the contribution of muscle mass to deferring development of HE. (35) The current recommendation is a normal protein diet (0.8-1.0 g/kg / day) in patients with liver cirrhosis.

Lactulose is the first line therapy for patients with MHE who have indications for treatment. In second place is the addition of rifaximin to the treatment regimen. The use of LOLA is indicated for patients who fail to respond to conventional therapy. (5, 32)

PREVENTION

Currently there is controversy between the AASLD, which does not recommend primary prophylaxis but rather proposes specific indications for the establishment of a therapeutic regimen and some schools that find primary prophylaxis useful due to the gentleness of medicines compared to regular screening tests. (5, 36)

CONCLUSION

MHE is a syndrome that affects multiple cognitive domains. Consequently, diagnosis and determination of treatment require appropriate medical knowledge. The detection of cognitive deficits is not usually difficult due to the sensitivity of diagnostic tests. However, attributing the deficit to MHE requires careful study of other causes of neuropsychological dysfunction. Implementation of anti-ammonium measures, when they are needed, reduces the incidence of chronic HE in high-risk patients. Finally, a better understanding of the impact of MHE should promote a multidisciplinary approach that focuses resources on education, finance and health education for patients and their caregivers. (14, 37)

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