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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

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Abbreviations: PHES, psychometric hepatic encephalopathy score; MHE, minimal hepatic encephalopathy; DST, digit symbol test; SDOT, serial-dotting test; eNCT, electronic Number Connection Test; LTT, line tracing time; EEG, electroencephalography; OP, ornithine phenylacetate; GP, glycerol phenylbutyrate

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.[1,2] In 1970, Zeegen et al.,[3] 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.[4]

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.[5]

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.[6] Schomerus et al.,[7] were the first to describe the impact of MHE on driving skills. Similarly Watanabe et al.,[8] & Wein et al.,[9] 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.[10]

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).

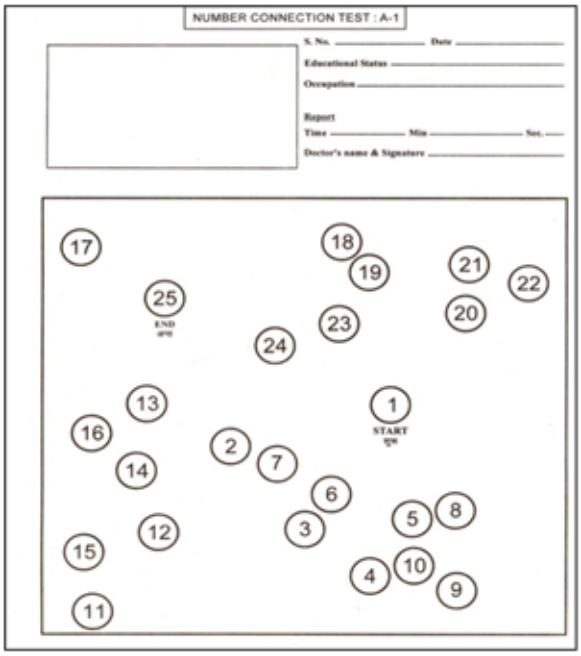

Figure 1 Paper sheet for Number connection test A.

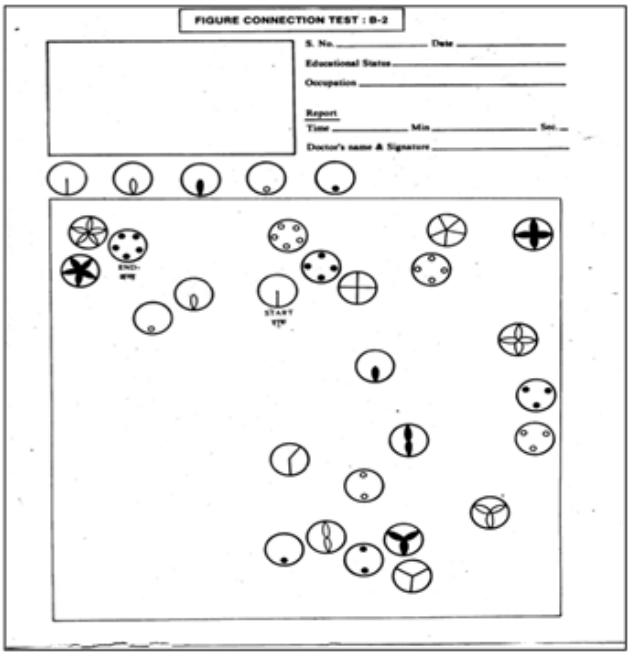

Figure 2 Paper sheet for Figure connection test.

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 to14 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 90seconds. 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 5tests: 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.

Figure 3 Paper sheet for Digital symbols Test.

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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.[11] Anterior attention system is responsible for modulate response inhibition and execute 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).[11] 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 190seconds 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

1. Evoked potentials

a. Exogenous (auditory (BAEP), visual (VEP), Somatosensory (SSEP)

b. Event related (P 300)

2. Critical flicker frequency (CFF)

EEG for the diagnosis of MHE has limited sensitivity and only remains useful in follow-up examinations. Major EEG changes are increase in wave amplitude with generalized decrease in frequency. Degree of EEG abnormalities doesn't correlate with grade of hepatic encephalopathy[12] Most sensitive test of EEG is mean dominant EEG frequency with good prognostic value.[13] Brainstem auditory evoked potentials (BAEP) is most sensitive exogenous potentials test for the diagnosis of MHE[14] but overall P300 peak obtained in an auditory oddball paradigm is the most sensitive test.[15]

CFF is the highest frequency at which fusion light (start from 60Hz downward) breaks into flickering light. It is an simple, reliable and independent of age, education or training and day timing method for the diagnosis of MHE based on principle that glial cells of retina get effected similarly to astrocyte.[16,17] The appropriate cutoff to identify abnormal CFF varies in different studies. Kircheis et al.,[18] identify that cut off of CFF threshold to be 39Hz for diagnosis of MHE. However Gomez et al.,[19] found threshold of 38Hz had better sensitivity and specificity for the same. Although earlier it was thought to be independent of age, a recent study by Dhiman et al.,[20] showed that CFF threshold decreases in elderly individuals.

Pathogenesis

Ammonia

Gut-derived neurotoxin ammonia cause gliopathy due to synthesis of glutamine by Alzheimer type II astrocytes, which is hypothesized cause brain swelling.[21,22] Astrocytes also regulate cerebral blood flow by maintaining integrity of the blood–brain barrier.[23] Ammonia induces formation of neurosteroid leading to a positive modulatory effect on the GABA-A receptor.[24] Ammonia affects cerebral blood flow and glucose utilization of various cortical regions and causing altered glioneuronal communication as a result of astrocyte swelling that correlates with the patients cognitive functions in HE. This has been noticed in MHE as well, thus forms basis of new diagnostic tests like CFF.[25] Lockwood et al.,[26] showed that higher levels of ammonia in brain can induce encephalopathy even in presence of normal arterial ammonia levels correlating with excess diffusion of ammonia across blood brain barrier in MHE.

Systemic inflammatory response

Presence of infection and inflammation adversely affects cognitive functions in liver cirrhosis. This was demonstrated by Jalan et al. and they have shown that severity of MHE correlates with higher level of infection[27] and detect much more abnormal psychometric tests in cirrhotic patients who had an ongoing infection compared with those in whom the infection had gone.[28]

Manganese

In presence of liver cirrhosis and portosystemic shunts manganese accumulates in the brains[29,30] and on MRI brain scan its levels correlate with pallidal hyper intensity and clinically with extrapyramidal signs.

Natural history

Development of OHE

The frequency of MHE increases as the liver disease worsens.[31] Over period of time MHE may improve or progress to OHE, sometime

even remain stable in long-term follow-up[31,32] and presence of MHE associated with increased mortality compared to those without MHE[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.[34] Actual probability of OHE at 3years was 56% in patients of liver cirrhosis in presence of MHE and 8% for those without MHE.[32] Presence of MHE in Cirrhosis associated with shorter survival time, especially among who had high concentrations of venous ammonia after oral glutamine load.[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.,[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.[38] Prasad et al.,[39] found the prevalence of MHE to be 67.7% based on combination of quantitative neuropsychological tests (Table 1).

When and in whom to test for MHE

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[37] 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.[33,37] Pre-existing neurological disorders and current alcohol use affect the results of psychometric tests.[40] 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 6months letter if it present at time index visit (Table 2).[37,39,41–50]

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).

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

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

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

Study	Tests	Daily doses	Duration	Results
Horsmans et al.[41]	Psychometric tests	60gm lactulose	15days	Lactulose>placebo
Watanbe et al. [42]	Psychometric tests	45ml lactulose	8weeks	Lactulose>No intervention
Dhiman et al.[43]	Psychometric tests	30-60ml lactulose	3months	Lactulose>No intervention
Prasad et al.[39]	Psychometric tests	30-60ml lactulose	3months	Lactulose>No intervention
Bajaj et al.[44]	Psychometric tests	1yogurt	2months	Probiotics>No intervention

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Table Continued.....

Study	Tests	Daily doses	Duration	Results
Sharma et al.[45]	Psychometric tests	30-60ml lactulose/3cap of probiotic	1month	Lactulose+probiotics>Lactulose>Probiotics
Mittal et al.[46]	Psychometric tests	LOLA 18gm, Lactulose 30-60ml, Probiotic 220 billion CFU	3months	LOLA=Lactulose=probiotics >No intervention
Shidhu et al.[47]	2 psychometric tests, SIP	Rifaximin 1200mg	8weeks	Rifaximin>placebo
Lunia et al.[48]	Psychometric tests, CFF	3unit probiotic	3months	Probiotics >placebo
Alvares De Silva et al.[49]	Psychometric tests and CFF	LOLA 15gm	5months	LOLA>Placebo
Sharma et al.[37]	Psychometric tests and CFF	LOLA 18gm, Rifaximin 1200mg, 2cap of velgut	3months	LOLA=Rifaximin=Probiotics>Placebo
Pratap et al.[50]	Psychometric tests	VSL# 3 450 billion CFU , 30-60ml lactulose	2months	VSL#3=Lactulose

Lactulose or lactitol are synthetic non-absorbable disaccharide 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 (NH_3) into ammonium (NH_4+). Lactulose also has a cathartic effect increasing nitrogen excretion. Few studies enumerated in[41–44,46] 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.[39] A recent study showed that greater improvement in blood ammonia levels, psychometry scores, and HRQOL after lactulose, a probiotic, and LOLA therapy.[20]

In a study,[37] 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. Orally administered LOLA decrease blood ammonia levels and improve psychometric performance. However it was observed that increase in ammonia once LOLA is discontinued.[41] This has been attributed to a paradoxical rise in glutamine levels, which generate ammonia by the kidney and gut through the effects of glutamines. LOLA were found to better than placebo or no intervention in reversal of MHE but effect was similar to lactulose and probiotics.[46,49] In a meta-analysis,[51] 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.[52]

Prebiotics, probiotics and symbiotic (probiotics and fermentable fiber) are effective in long term treatment of MHE in cirrhotic.[46] Liu et al.,[38] 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.

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