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SPECIAL ARTICLE

Minimal hepatic encephalopathy: Consensus statement of a working party of the Indian National Association for Study of the Liver

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Key words
critical clicker frequency, health-related quality of life, hepatic encephalopathy, lactulose, minimal hepatic encephalopathy, psychometric hepatic encephalopathy score, psychometry.

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Abstract

Hepatic encephalopathy (HE) is a major complication that develops in some form and at some stage in a majority of patients with liver cirrhosis. Overt HE occurs in approximately 30–45% of cirrhotic patients. Minimal HE (MHE), the mildest form of HE, is characterized by subtle motor and cognitive deficits and impairs health-related quality of life. The Indian National Association for Study of the Liver (INASL) set up a Working Party on MHE in 2008 with a mandate to develop consensus guidelines on various aspects of MHE relevant to clinical practice. Questions related to the definition of MHE, its prevalence, diagnosis, clinical characteristics, pathogenesis, natural history and treatment were addressed by the members of the Working Party.

1. Introduction

Hepatic encephalopathy (HE) is a major complication that develops in some form and at some stage in a majority of patients with liver cirrhosis. Overt HE occurs in approximately 30–45% of cirrhotic patients[2,3] and in 10–50% of patients with transjugular intrahepatic portosystemic shunt (TIPS).[1] Minimal HE (MHE), the mildest form of HE, is characterized by subtle motor and cognitive deficits, and impairs health-related quality of life (HRQOL).[2–4] The Indian National Association for Study of the Liver (INASL) set up a Working Party on MHE in 2008 with a mandate to develop consensus guidelines on various aspects of MHE relevant to clinical practice; its final report was presented at the annual meeting of the INASL on 28 March 2009. This is the first-ever Consensus Statement developed on this subject.

The following questions were addressed by the Working Party.

Definition: What is the most appropriate definition of MHE? Is there a need to broaden the definition to include liver diseases and causes of portal hypertension other than cirrhosis? (Discussion led by Dr Deepak Amarapurkar.)

Prevalence: What is the overall prevalence of MHE? What are the risk factors that influence its prevalence? Does it interfere with patients' HRQOL? What is the associated economic burden of MHE? (Discussion led by Dr Avnish K. Seth and Dr Ramesh R. Rai.)

Diagnosis: How can we differentiate grade 0 from grade 1 HE? What are the roles for neuropsychological and neurophysiological testing and current neuroimaging techniques in the diagnosis of MHE? (Discussion led by Dr Vivek A. Saraswat, Dr Barjesh K. Sharma and Dr Rakesh K. Gupta.)

Clinical characteristics: Is MHE a 'symptomatic' condition? If so, what are the cognitive symptoms? Should all cirrhotic patients be subjected to testing for the diagnosis of MHE or should it be restricted to patients with cognitive symptoms? (Discussion led by Dr Vivek A. Saraswat and Dr Samir Shah.)

Pathogenesis: What is the role of ammonia, intestinal flora and inflammation in the pathogenesis of MHE? (Discussion led by Dr Yogesh K. Chawla, Dr Praveen Sharma and Dr Kaushal Madan.)

Natural history: Does MHE predict overt HE and poor outcome? (Discussion led by Dr Rakesh Aggarwal.)

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Treatment: What is the role of non-absorbable disaccharides, pre and/or probiotic, L-ornithine–L-aspartate (LOLA), or antibiotics in the treatment of MHE? Does treatment improve HRQOL? (Discussion led by Dr Radha K. Dhiman, Dr Ajay Duseja and Dr Shiv K. Sarin.)

Dr Roger Butterworth, Dr Subrat K. Acharya, Dr Abraham Koshy, Dr Sri Prakash Mishra and Dr Jang B. Dilawari were special invitees and actively participated in the entire discussion.

1.1 Quality of evidence on which a recommendation is based

The Working Party adopted the use of the Oxford system for developing an evidence-based approach. The group assessed the level of existing evidence and accordingly ranked the recommendations, i.e. level of evidence from 1 (highest) to 5 (lowest); grade of recommendation from A (strongest) to D (weakest).[5]

2. Definition

The Working Party on Hepatic Encephalopathy convened by the Organisation Mondiale de Gastroenterologie presented its deliberations at the 11th World Congress of Gastroenterology, Vienna (1998). It defined HE as a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction, after exclusion of other known brain diseases, and proposed new nomenclature with respect to: (i) the nature of the hepatic abnormality; and (ii) the duration and characteristics of the neurological manifestations, broadly categorizing HE into three types (Table 1).[2,6] MHE was included as the third and final category of type B and C HE. Although implicit in the Vienna definition, the increasing recognition of MHE in non-cirrhotic liver diseases such as non-cirrhotic portal fibrosis,[7] extrahepatic portal venous obstruction (EHPVO)[8–10] and acute viral hepatitis[11] warrants their explicit inclusion in the definition of MHE. The INASL Working Party recommended broadening the definition of MHE to include liver diseases and causes of portal hypertension other than cirrhosis and also to include mention of neuropsychometric or neurophysiological tests, which can be performed in the outpatient setting, for diagnosis of MHE.

Consensus statement

1 MHE may be defined as the presence of measurable cognitive defects in patients with liver disease and/ or portal-systemic shunting, that are not identified by detailed clinical history and complete neurological examination, including interview of close family members, but are detected by abnormalities in neuropsychometric or neurophysiological tests that can be performed at the bedside and in the outpatient setting, in the absence of other known causes of abnormal cognitive tests. (5, D)

3. Prevalence

3.1. Prevalence of MHE among cirrhotic and noncirrhotic patients

The true prevalence of MHE in patients with portal hypertension is unknown. Though MHE has traditionally been diagnosed in patients with cirrhosis of the liver, impairment of cognitive function has also been demonstrated in patients with noncirrhotic portal hypertension.[7–10] Prevalence of MHE has been reported to vary between 22% and 74% in patients with cirrhosis of the liver,[3,4,12–22] depending on both the examinable dimensions of the disease and fixed diagnostic cut-offs. The range of diagnostic criteria used in these studies included: neuropsychological tests in different combinations with different cut-offs (abnormal scores >2 standard deviation [SD] or >1 SD below mean),[3,4,12–19,21] short neuropsychological batteries (Psychometric Hepatic Encephalopathy Score [PHES]),[20,22] various computerized tests including critical clicker frequency (CFF)[19,20,22] and inhibitory control test (ICT),[21] neurophysiological tests with different cut-off (electroencephalography [EEG], P300 evoked responses),[12–14,16,17] or their combinations.

Table 1 Nomenclature of hepatic encephalopathy (HE)

Type	Description	Category (by duration and characteristics)	Subcategory (by duration and characteristics)
A (Acute liver failure)	HE associated with acute liver failure	Not applicable	Not applicable
B (Bypass)	HE associated with portosystemic bypass and no intrinsic hepatocellular disease		
C (Cirrhosis)	HE associated with cirrhosis and portal hypertension or portosystemic shunts	Episodic	Precipitated Spontaneous Recurrent
		Persistent	Mild Severe Treatment-dependent
		Minimal	Not applicable

Adapted from Mullen KD[6]

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The reasons for large variations in the prevalence of MHE among different studies are also related to prior episodes of overt HE,[14] severity of liver disease,[4,13–16,18,22] age,[13,16,22] presence of esophageal varices,[14] and surgical porto-systemic shunts.[5] Cause of liver disease does not affect the prevalence rate of MHE.[12,13,16,18] There are no data on prevalence of MHE in patients who have undergone TIPS.

Consensus statement

2 Prevalence of MHE among patients with cirrhosis without overt HE is high. (1b)
3 Variability in diagnostic criteria used for MHE affects its prevalence rate. (1b)
4 Use of age- and education-adjusted cut-offs for neuropsychological tests may reduce variability in prevalence rates. (3a)
5 Prevalence of MHE increases with increasing severity of liver disease. (3b)
6 Prevalence of MHE is not affected by etiology once patients with recent alcohol intake are excluded. (3b)
7 MHE is present in a significant proportion of patients with portal hypertension without intrinsic liver disease. Further studies are required on this subject. (3b, B)
8 Prevalence of MHE has not been studied systematically in patients who have undergone TIPS. Further studies are required on this subject. (5, D)

3.2. Health-related quality of life

3.2.1. Effect of MHE on daily functioning

MHE is associated with cognitive impairment that may have a detrimental effect on HRQOL.[3,23,24] It mainly affects complex activities involving attention, information processing and psychomotor skills such as driving a car, planning a trip, etc. whereas basic activities of daily life, such as shopping, dressing, personal hygiene, etc. are preserved. Two studies demonstrated that patients with MHE had a significant impairment of daily functioning, such as social interaction, alertness, emotional behavior, sleep, work, home management, recreation and pastimes compared with cirrhotic patients who did not have MHE.[3,23] Treatment with lactulose improved both cognitive functions and HRQOL; improvement in the latter was linked to improvement in cognitive function.[3]

3.2.2. Effect of MHE on driving

Schomerus *et al*.[25] were the first to demonstrate a negative effect of psychomotor deficits in patients with MHE on driving fitness in 40 patients with liver cirrhosis, 60% of whom were considered unfit to drive on the basis of performance on psychometric testing. However, these authors did not elaborate on the methods applied for assessing driving fitness. Although similar results were reported by Watanabe *et al*.,[26] a pilot study that evaluated driving in a real road test in nine patients with cirrhosis and MHE did not find impaired driving performance.[27] In a recent landmark study, Wein and colleagues[28] used a standardized 90-minute on-road driving test and found that the fitness to drive a car was impaired in cirrhotic patients with MHE. Increased risk of automobile accidents was related to a decline in cognitive function.[29] Impairment in attention and speed of mental processing adversely affects an individual's ability to react to unexpected traffic conditions, such as an illegal incursion by another vehicle at an intersection. Bajaj *et al*.[30] found a higher self-reported rate of traffic violations and accidents in cirrhotic patients with MHE compared to controls. They also demonstrated a significantly higher rate of motor vehicle crashes over the preceding year in patients with MHE compared to patients without MHE,[31] which was defined by the ICT, a test of response inhibition and executive control. A recent report determined that cirrhotics with MHE had a significantly higher crash rate over the preceding year as well as on prospective follow up, compared to patients without MHE, using self-reports and Department of Transportation reports.[32] Patients with MHE also had impaired navigation skills.[33] Navigation, required for safe driving, is a complex process that depends on functioning working memory, attention, and speed of mental processing; impairment in navigation skills correlated with impairment in response inhibition and attention.

3.3. Economic burden of MHE

Although some data are available for HE, the economic burden associated with MHE has not been assessed.[1] In the USA in 2003, estimated total charges for hospitalizations related to HE were over $US930m. Total charges for unspecified encephalopathy, portal hypertension, and alcoholic and non-alcoholic cirrhosis were approximately $US268m, $US90m and $US3.3bn, respectively.[1] The impact of MHE on daily life is enormous; half of the patients with MHE do not have regular employment, compared to 15% of patients without MHE.[14] Blue-collar workers with liver cirrhosis and MHE are less likely to earn their wages than white-collar workers with MHE; 60% of 'blue collar' workers were unfit to work compared with 20% of 'white collar' workers.[24] Diminished work performance and lost wages also entail substantial costs. Socioeconomic implications of the profound negative effects of MHE on functioning in the workplace are significant.

Consensus statement

9 MHE adversely affects HRQOL. (1b)
10 MHE adversely affects driving skills. (1b)
11 Patients with MHE have higher rates of traffic violations and motor vehicle accidents. (1b)
12 Studies are needed to fully evaluate the direct and indirect costs related to MHE. (5D)

4. Diagnosis

4.1. Differentiation of grade 0 from grade 1 HE

The diagnosis of MHE rests on: (i) the presence of a disease that can cause MHE, such as, cirrhosis and/or the presence of a portal-systemic shunt (Table 1); (ii) normal mental status on clinical examination; (iii) demonstration of abnormalities of cognition

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and/or neurophysiological variables; and (iv) exclusion of concomitant neurological disorders. HE is traditionally classified into four grades according to the West Haven criteria (Table 2).[1,2] However, assignment of patients with cirrhosis to HE stages 0–2 relies strongly on the subjective impression of a physician, which does not invalidate the scale in individual cases, but may cause discrepancies between different observers and affect the results of multicenter trials. Reliability of the West Haven scale can be improved by combining it with the Mini-Mental State Examination (MMSE).[34]

The MMSE assesses mental status systematically and thoroughly in only 5–10 min. It is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall and language.[34] The maximum score on MMSE is 30; a score of 23 or lower is indicative of cognitive impairment and clinically overt HE. All high-quality studies on MHE included MMSE as a screening test before administering diagnostic tests for MHE.[3,21,22,31–33]

Table 2 West Haven criteria for semiquantitative grading of mental state

Grade 0	Lack of detectable changes in personality or behavior No asterixis
Grade 1	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impaired performance of addition Asterixis may be present
Grade 2	Lethargy or apathy Minimal disorientation for time or place Subtle personality change Inappropriate behavior, slurred speech Impaired performance of subtraction Asterixis is present
Grade 3	Somnolence to semi-stupor, but responsive to verbal stimuli Confusion Gross disorientation Asterixis is usually absent
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Adapted from Mullen KD[6]

Consensus statement

13 HE should be graded according to West Haven criteria. (1b, A)
14 The reliability of the West Haven scale can be improved by combining its use with the MMSE. (1b, A)
15 The MMSE should be performed to exclude overt cognitive impairment in all patients before formal test(s) for the diagnosis of MHE is/are administered. (1b, A)

4.2. Diagnostic methods

Various tools have been evaluated for the diagnosis of MHE and include neuropsychological tests, computerized tests, short neuropsychological and computerized test batteries and neurophysiological tests (Table 3).[35]

4.2.1. Standard neuropsychological assessment

Neuropsychological tests are established, time-tested and domains of cognitive functioning tested by particular tests are well-characterized. However, these are time-consuming, and their results are influenced by age and educational status. Determining impairment in performance using age- and education-adjusted values of at least two of the following tests is recommended: number connection test-A (NCT-A) or figure connection test-A (FCT-A), number connection test-B (NCT-B), block design test and digit symbol test.[2] FCT-A and figure connection test-B (FCT-B) can replace NCT-A and NCT-B, respectively, if there are linguistic or illiteracy concerns.[9–11,19,22,38] FCT-A and -B are universally applicable tests to assess the mental state that transcend the barriers of linguistic differences and illiteracy. Clinical significance of these tests has been evaluated in a large number of healthy volunteers and patients with MHE.[38]

4.2.2. Psychometric Hepatic Encephalopathy Score

The PHES, a standardized test battery including NCT-A and B, the line-tracing test for time (*t*) and error (*e*), the serial-dotting test,

Table 3 Diagnostic methods for the detection of minimal hepatic encephalopathy

Methods	Advantages	Disadvantages	Feasibility to administer in office setting
Expert neuropsychological assessment with series of tests	Time-tested with well-recognized clinical significance, established	Time-consuming if large number of tests are selected	Yes
Short neuropsychological battery (PHES)	High sensitivity with well-recognized clinical significance, rapid results	Limited access, limited data of normative values	Yes
Neurophysiological tests (EEG, spectral EEG, P300 evoked potentials)	Objective tests, allow for objective repeat testing	Require sophisticated equipment, limited data	No
Computerized test (CFF, ICT, reaction times, etc.)	Rapid tests, easy to apply	Requires highly functional patients and familiarity with computers. Needs standardization in different populations	Yes

CFF, critical flicker frequency; EEG, electroencephalogram; ICT, inhibitory control test; PHES, Psychometric Hepatic Encephalopathy Score.

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and the digit symbol test, has been extensively validated in the Spanish, German and Indian populations and can be performed in 15–20 min.[20,22,36,37] This battery examines many of the abnormalities seen in patients with MHE, including motor speed and accuracy, visuo-spatial orientation, visual perception, visual construction, attention, concentration, and, to a lesser extent, memory. PHES has a prognostic value for the occurrence of bouts of overt HE and mortality in cirrhotic patients.[20,22] In an Indian version, NCT-B has been replaced by the FCT-A because of concerns that some patients may be unfamiliar with English alphabets and hence unable to complete NCT-B.[38]

Consensus statement

16 Standard neuropsychological assessment is a time-tested and established methodology for measuring cognitive impairment in patients with MHE. (1b)
17 Use of age- and education-adjusted values of at least two of the following tests are recommended for the diagnosis of MHE: NCT-A or FCT-A, NCT-B or FCT-B, block design test and digit symbol test. (1b, A)
18 The PHES, which measures multiple domains of cognitive function, is a reliable test battery for the assessment of cognitive impairment in patients with MHE. (1b)
19 The PHES has a prognostic value in predicting survival. (3b)
20 Use of age- and education-adjusted PHES is recommended for diagnosing and monitoring MHE. (1b, A)

4.2.3. Neurophysiological tests

Changes in EEG/evoked responses are non-specific. Among EEG variations, the most sensitive test is computer-assisted analysis, including the mean dominant EEG frequency and the power of a particular rhythm.[39–41] Quantified-EEG has a prognostic value for occurrence of bouts of overt HE and mortality in cirrhotic patients.[41] Among evoked responses, the P300 peak obtained in an auditory oddball paradigm is the most sensitive test.[17,42–45] These tests can supplement neurological or neuropsychiatric examination. Saxena *et al*.[17] demonstrated that there was a greater likelihood of development of overt HE in cirrhotic patients with abnormal P300 event-related potential latencies and NCT than in patients with no such abnormality. Neurophysiological tests can be used during follow up to demonstrate change in a patient's condition. Their major limitations are: (i) need for specialized equipment and technical expertise for evaluation and interpretation; and (ii) inability to perform these tests in an outpatient clinic.

4.2.4. Critical flicker frequency

The CFF threshold measures visual discrimination and general arousal.[46] Two recent studies evaluated its usefulness in the diagnosis of MHE.[19,20] Both studies have demonstrated that it is a simple, reliable, and accurate method for the diagnosis of MHE. The technique shows little dependence on age, education or training. However, one study showed that CFF decreases as age advances, and therefore age-adjusted values may be required.[22]

4.2.5. Inhibitory control test

The ICT is a computerized test of response inhibition, attention and working memory, consisting of presentation of several letters at 500-ms intervals. This test has been used to characterize attention deficit disorder, schizophrenia and traumatic brain injury. It has been validated for the diagnosis and follow up of MHE in the USA, and has been found to be sensitive and reliable for this purpose.[21,47] However, it requires that the subject be familiar with the use of computers and needs to be validated in other populations. ICT, but not standard neuropsychological tests performance, is significantly associated with prior and future vehicle crashes and traffic violations.[32]

Consensus statement

21 EEG can diagnose MHE and predicts development of overt HE and mortality. (1b)
22 EEG requires technical expertise for evaluation and interpretation. (1b)
23 P300 event-related potential can diagnose MHE, but requires a trained person and specialized equipment. (1b)
24 EEG and P300 are difficult to use for diagnosis of MHE in an outpatient setting. (1b, A)
25 The CFF is a simple tool for diagnosing MHE in an outpatient setting. (1b, A)
26 The CFF predicts the development of overt HE. (1b)
27 More data are required on effect of age and education on CFF and need for adjusted CFF cut-offs. (5, D)
28 The ICT is reliable and sensitive for the detection as well as follow up of MHE patients. (1b, A)
29 The ICT requires highly functional patients and familiarity with computers. (1b, A)
30 The ICT may need validation and standardization in each population before it can be used effectively (5, D)

4.2.6. Magnetic resonance imaging and spectroscopy

Magnetic resonance imaging (MRI) has revealed alterations in basal ganglia of patients with cirrhosis. High-signal abnormalities on T1-weighted images in the globus pallidum have been observed in these patients, even without clinical evidence of HE.[48,49] Although various causes have been proposed[50] for this hyperintensity, deposition of manganese is regarded as the most likely explanation.[51] There is no direct correlation between pallidal hyperintensity and grade of encephalopathy.[52] Basal ganglion T1-weighted signal intensity and manganese accumulation appear to be related to the underlying degree of portal-systemic shunting rather than directly to neuropsychiatric impairment.[53] Hyperintense globus pallidus on MRI is common in patients with liver cirrhosis and also occurs in patients with noncirrhotic portal hypertension.[54]

Magnetic resonance spectroscopy (MRS) shows a decrease in myo-inositol/creatine and choline/creatine ratios in the white matter with an increase in the Glx (glutamine and glutamate) concentration in the basal ganglia in patients with MHE.[55,56] Liver transplantation as well as lactulose therapy have been shown to reverse these changes at 4 weeks and later after transplantation.[55] However, the ability of MRS to differentiate between cirrhotic patients without HE and those with MHE has not been conclusively shown.

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Diffusion-weighted imaging allows assessment of intracellular and extracellular water content in the brain, which helps in differentiating cytotoxic from vasogenic edema.[57,58] Diffusion tensor imaging has revealed that mean diffusivity, a measure of water movement across cell membranes, is significantly higher in patients with MHE in the regions of the corpus callosum, right internal capsule, left internal capsule, caudate nuclei and occipital white matter. Increase in mean diffusivity indicates the presence of interstitial brain edema. Mean diffusivity values increase as the grade of HE increases, suggesting that brain edema present in patients with HE may contribute to its pathogenesis.[59] Mean diffusivity values decreased significantly and there was a corresponding improvement in neuropsychological test scores in patients with MHE after three weeks of lactulose therapy.[59] MR imaging techniques therefore complement neuropsychological evaluation of MHE.

Consensus statement

31 MRS, diffusion-weighted imaging, magnetization transfer imaging and diffusion tensor imaging show abnormalities in cirrhotic patients with or without HE. (1b)
32 These techniques may be well suited for evaluating the efficacy of therapeutic interventions. (1b, A)
33 These imaging techniques are currently not considered as diagnostic modalities for MHE. (5,D)

5. Clinical characteristics

5.1. Is MHE a 'symptomatic' condition?

By definition, patients with MHE have a normal neurological examination; however they may still be symptomatic. Symptoms relate to disturbances in sleep, memory, attention, concentration and other areas of cognition.[60,61] Sleep disturbance is a classic sign of HE. On a sleep questionnaire, disturbance is seen in 47% of cirrhotics and 38% of patients with chronic renal failure compared to 4.5% of controls.[60] Studies using HRQOL questionnaires have confirmed a higher frequency of sleep disturbance in cirrhotic patients with MHE as well.[3,14] However, sleep disturbance in cirrhosis is not associated with cognitive impairment; thus it may not truly be an MHE symptom. Unsatisfactory sleep is associated with higher scores for depression and anxiety, raising the possibility that the effects of chronic disease may underlie the pathogenesis of sleep disturbance. Disturbances in cirrhotics may also be related to abnormalities of circadian rhythm.

Defective memory has also been shown to be a feature of MHE. Weissenborn *et al*.[61] have shown that patients with MHE have impaired short- and long-term memory. This impairment was predominantly related to deficits in attention and visual perception. Memory deficit of MHE seems to comprise short-term but not long-term memory impairment. This can be described as an encoding defect, in which memory recall (or retrieval) is intact.

5.2. What are the cognitive symptoms?

Several cognitive statements (i.e. complaints), have predictive value for MHE, including impaired psychomotor performance ('I have difficulty doing handwork; I am not working at all'); impaired sleep or rest ('I spend much of the day lying down in order to rest'); decreased attention ('I am confused and start several actions at a time'); and poor memory ('I forget a lot; for example, things that happened recently, where I put things, etc.').[14]

5.3. Should all cirrhotic patients be subjected to testing for the diagnosis of MHE?

It has been shown conclusively that cognitive functions improve with therapy for MHE.[3,62–67] Such therapy may improve HRQOL of patients with MHE[3,67] and delay the development of HE.[68] Hence all patients with liver cirrhosis should be subjected to testing for MHE. Special attention should be given to those who have cognitive symptoms and high-risk groups such as active drivers, patients handling heavy machines or reporting decline in work performance.

Consensus statement

34 Symptoms related to sleep disturbance, memory, and attention may be elicited or may be a presenting complaint in cirrhotic patients with MHE. (3b)
35 Cognitive functions and HRQOL improve with therapy. Hence all patients with cirrhosis of the liver should be tested for the presence of MHE. (1b, A)
36 Special attention should be given to those who have cognitive symptoms and high-risk groups such as active drivers, patients handling heavy machines or those reporting a decline in work performance. (5,D)

6. Pathogenesis

6.1. Ammonia, intestinal flora and inflammation

Ammonia, which is primarily produced in the gut, plays a key role in the pathogenesis of HE. In the brain, ammonia is metabolized in astrocytes, the only cell in the brain containing the enzyme glutamine synthetase that metabolizes ammonia. Astrocytes also provide physical and nutritional support for neurons, maintain the integrity of the blood–brain barrier and regulate cerebral blood flow.[69] Using positron emission tomography with ^{13}N-ammonia, Lockwood *et al*. provided direct evidence showing that ammonia is taken up by the brain in patients with liver disease and hyperammonemia.[70] Ammonia also modulates glutamate neurotransmission[71] and induces neurosteroid production in neurons, leading to a positive modulatory effect on the gamma-aminobutyric acid-A receptor.[72] Although the precise molecular mechanism(s) responsible for neurological alteration in HE is/are not known, several alterations in the expression of astrocytic and neuronal genes that code for various proteins have been shown; these changes may play a critical role in central nervous system function, including maintenance of cell volume and neurotransmission.[73,74]

Animal models of MHE have been developed. These include the end-to-side portacaval-shunted rat and the rat with graded portal vein ligation.[75] These models recapitulate several characteristic features of MHE including moderate hyperammonemia, manganese accumulation in basal ganglia,[53] alterations of day–night and circadian rhythms[76] and changes in glutamate,[77] monoamine,[78]

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opioid[79] and histamine[80] neurotransmission comparable to those described in cirrhotic patients. Decreased cortical activation has also been described in both experimental and human MHE.[81] Lockwood *et al*.[81] showed that both the cerebral metabolic rate for ammonia and the permeability-surface area product for ammonia were significantly higher in patients with MHE than in controls. The increased permeability-surface area product of the blood–brain barrier permits ammonia to diffuse across the blood–brain barrier into the brain more freely than normal. This may cause ammonia-induced encephalopathy even though arterial ammonia levels are normal or near normal. Accumulation of glutamine induces osmotic stress and leads to swelling of astrocyte. Using magnetic resonance imaging, Cordoba *et al*.[82] demonstrated an increase in brain water in patients with MHE as indicated by a decrease in magnetization transfer ratio (MTR). This was shown to correlate with neuropsychological function, and the abnormality was reversed by liver transplantation.[82] More recently, hyperammonemia induced by oral administration of an amino acid solution to patients with cirrhosis was shown to result in significant deterioration in neuropsychological function, an increase in brain glutamine levels and a reduction in the MTR, suggesting an increase in brain water.[83] This study provided further support for the ammonia-glutamine brain water hypothesis of HE. The effect of hyperammonemia is likely to be determined by the ability of the astrocytes to maintain osmotic equilibrium by losing osmolytes such as myo-inositol in response to the ammonia-induced increase in glutamine.[84]

6.2. Inflammation

It has been observed that severity of MHE may not correlate with severity of liver disease or the level of ammonia, suggesting presence of other pathogenic influences. Inflammation is one such factor that may contribute to the development of MHE and its progression to overt HE.[85] A recent study found that severity of MHE was independent of severity of liver disease and levels of blood ammonia but markers of inflammation were significantly higher in those with MHE compared to those without MHE.[86] Induction of hyperammonemia led to deterioration in one or more neuropsychological tests in 73.3%, which was significantly greater in those with more marked inflammation, that is, higher neutrophil counts, C-reactive protein levels, and interleukin-6 levels. These two studies suggest that inflammation plays a synergistic role with ammonia in producing and modulating MHE.

6.3. Intestinal Flora

Another link between inflammation, ammonia and MHE is through gut flora and endotoxins. Indeed, lactulose, the most commonly used standard therapy for HE, works in part by altering gut flora to decrease ammonia production and absorption. Zhao *et al*.[87] demonstrated varying degrees of imbalance of intestinal flora among cirrhotics compared to normal healthy controls; there was increase in the counts of aerobes (such as *Enterobacter* and *Enterococcus*) and anaerobes (such as *Clostridium*) and a decrease in the count of *Bifidobacterium*. The severity of imbalance in gut flora matched the degree of liver dysfunction, with the most serious imbalance observed in patients in Child–Turcotte–Pugh (CTP) class C. Liu *et al*.[65] found that cirrhotic patients with MHE had substantial derangements in the gut microecology, with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcus* species. Treatment with synbiotics significantly increased the fecal content of non-urease-producing *Lactobacillus* species at the expense of these other bacterial species. Such modulation of gut flora was associated with a significant reduction in blood ammonia levels and reversal of MHE in 50% of patients. Synbiotic treatment was also associated with a significant reduction in endotoxemia. The CTP functional class improved in nearly 50% of the patients.

Consensus statement

37 Ammonia plays a key role in the pathogenesis of MHE. Ammonia has deleterious effects on brain metabolism and neurotransmission. (1b)

38 Inflammation plays a synergistic role with ammonia in modulating MHE. (1b)

39 Gut flora play an important role in the pathogenesis of MHE. (3b)

40 There is substantial derangement in gut microecology with significant fecal overgrowth of potentially pathogenic *Escherichia coli* and *Staphylococcus* species in patients with MHE. (3b)

41 Modulation of gut flora may lead to a significant reduction in blood ammonia and endotoxin levels in patients with MHE. (3b)

7. Natural history

The frequency of MHE increases as the severity of liver disease increases.[4,13–16,18,22] In view of a high frequency of MHE in patients with liver disease, it is important to understand its impact on future clinical outcomes, such as occurrence of overt HE, quality of life and survival, and to determine whether treatment of MHE can induce improvements in these outcomes.

Several studies that looked at the frequency of development of overt HE in cirrhotic patients found that those with MHE developed overt HE more often during follow up than those without MHE (Table 4).[4,15,17,20,48,88,89] In addition, some studies have shown an increased risk of death in patients with liver cirrhosis and MHE compared to those without MHE (Table 4).[20,22,88] However, patients with MHE had poorer liver function than those without MHE in these studies, making it difficult to ascribe the poor outcome to the presence of MHE.

Das *et al*.[4] studied the relationship of progression of MHE to overt HE in relation to the severity of liver dysfunction and found that the rate of progression to overt HE was much higher in patients with MHE and a CTP score > 6 than in those with MHE and a CTP score ≤ 6. Amodio *et al*.[88] found that the presence of MHE and that of liver dysfunction were both associated with mortality on univariate analysis; however, on multivariate analysis, liver functional status was the only independent predictor of mortality. In another study, progression of MHE to overt HE was associated with abnormal response to oral glutamine challenge, which in turn was associated with poor liver function.[90] Furthermore, MHE in patients with preserved liver function but large portal-systemic shunts (congenital shunts, non-cirrhotic portal

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Table 4 Results in studies on follow up of patients with and without minimal hepatic encephalopathy

Authors, year	Number of patients with/without MHE	Duration of follow up	Results
Amodio *et al.*,[88] 1999	–	Median 426 days	On Kaplan–Meier analysis with log–rank test, patients with abnormal psychometric tests had a significantly higher rate of death (Scan test, HR 2.4 [95% CI 1.1-5.3]; Choice-2 test, HR 2.8 [1.2-6.3]).
Hartmann *et al.*,[89] 2000	25/91	–	Overt HE: 40% vs 6.7% Actuarial frequency of overt HE at 3 years: 56% in patients with MHE vs 8% in those without. However, occurrence of HE and death depended on CTP score
Saxena *et al.*,[45] 2001	28/51	Up to 16 months	Overt HE: 42.8% vs 3.9%
Romero-Gomez *et al.*,[15] 2001	34/29	Up to 7 years	Overt HE: 47.1% vs 10.3%, ($P < 0.005$)
Das *et al.*,[4] 2001	40/32	At least 6 months	Overt HE in 22.6% vs 5.6% ($P = 0.044$)) of patients with and without MHE; rate higher in patients with poorer liver function, as assessed by CTP score
Saxena *et al.*,[17] 2002	29/35	6–24 months	Overt HE: 58.6% vs 5.7%
Romero-Gomez *et al.*,[20] 2007	35/79	Median 10.2 months	Overt HE in 43.6% vs 17.3%; survival 27.3% vs 10.2%; on multivariate analysis, CTP score was the only independent predictor (HR 1.8 [1.32-2.46]; $P = 0.0002$).
Sharma *et al.*,[10] 2009	12/20	Mean 13.5 months	None of the patients with or without MHE at baseline developed HE in patients with EHPVO
Dhiman *et al.*,[22] 2009	48/52	Up to 30 months	PHES $\leq$6 (HR 2.42 [1.01–5.77]) and CTP score $\geq$ 8 (HR 2.47; 95% CI, 1.01–6.02) had prognostic value for survival.

CI, confidence interval; CTP, Child–Turcotte–Pugh; EHPVO, extrahepatic portal venous obstruction; HE, hepatic encephalopathy; HR, hazard ratio; MHE, minimal HE; PHES, psychometric hepatic encephalopathy score.

hypertension and cirrhosis with preserved liver function) appears to have a good outcome, even though these data are based on a small number of patients.[10] Thus, it appears that the higher risk of overt HE or death in patients with MHE may not be related to MHE *per se* but to the poorer liver function in patients with MHE.

Consensus statement

42 Patients with liver cirrhosis and MHE have a higher rate of subsequent development of HE than those with cirrhosis but no MHE. (1b)

43 Higher rate of development of overt HE and lower survival amongst patients with MHE is most likely related to poorer liver function in MHE patients. (1b)

44 Data on outcome of MHE in patients without liver disease are limited and further prospective studies are needed. (5, D)

8. Treatment

Treatment of MHE is primarily directed towards reduction of ammonia and includes non-absorbable disaccharides, prebiotics/probiotics and LOLA. Treatment of MHE improves psychometric performance and quality of life (Table 5). However, several issues regarding therapy remain unsettled. The effects of treating MHE on driving, complex occupational tasks, development of overt HE, and on survival have not been studied. Duration of therapy for achieving these end-points, choice of therapeutic agents and the role of combinations of therapies have also not been adequately studied and further research is needed to clarify these issues.

8.1. Non-absorbable disaccharides

Lactulose decreases blood ammonia levels, and improves psychometric performance and HRQOL (Table 5).[3,59,62,64,67,91–95] Using cerebral diffusion tensor imaging, Kale *et al.*[59] showed that interstitial brain edema observed in patients with MHE resolves after treatment for 3 weeks with lactulose in parallel with improvements in neuropsychiatric performance.

Prasad *et al.*[3] studied the effect of treatment of MHE with lactulose on psychometric performance (measured by NCT, FCT-A, FCT-B, picture completion and block-design tests) and HRQOL (measured by Sickness Impact Profile [SIP]). Patients with MHE showed significant impairment in 11 scales of the SIP, the psychosocial and physical subscores, and in the total SIP. Patients received 30–60 mL of lactulose in two or three divided doses so that the patient passed two to three semi-soft stools per day.

Following lactulose therapy for 3 months, both psychometric performance and HRQOL improved; MHE reversed in 64.5% of treated patients compared with 6.7% in the no-treatment group ($P < 0.0001$). Significant improvement was found in five (emotional behavior, ambulation, mobility, sleep/rest and recreation and pastimes) of the 12 scales of the SIP and in the total psychosocial and physical sub-scores in the treated patients compared with the untreated patients. Improvement in HRQOL was linked to improvement in cognitive function. A recent study that compared lactulose, a probiotic and LOLA with no treatment, confirmed

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Table 5 Effect of treatment on various parameters in patients with minimal hepatic encephalopathy

Authors, year	*n*	Design of the study	Therapy	Duration of therapy	Assessment tool(s)	Results
McClain *et al.*,[91] 1981	32	RCT	Lactulose vs sucrose (placebo)	–	Psychometry	Three of five psychometric tests showed improvement in lactulose-treated patients than in those receiving placebo.
Morgan *et al.*,[92] 1989	14	RCT	Lactulose vs lactitol	2 months	NCT, DS, DC and EEG	Improvement in psychometric performance; no change in EEG mean cycle frequency
Watanabe *et al.*,[93]1997	36	RCT	Lactulose ($n = 22$) vs no Rx ($n = 14$)	8 weeks	NCT, DS, BD	Improvement in psychometry, reversal of MHE in 50% of patients in treated group compared to 15% in untreated group
Horsmans *et al.*,[94] 1997	14	RCT	Lactulose ($n = 7$) vs lactose ($n = 7$)	15-day	NCT, race track test and computer-based psychometry	Improvement in psychometric tests; decline in blood ammonia levels
Dhiman *et al.*,[62] 2000	26	RCT	Lactulose ($n = 14$) vs no Rx ($n = 12$)	3 months	NCT, FCT, PC, BD	Improvement in psychometry; reversal of MHE in 57% of treated patients vs none of untreated
Nie *et al.*,[95] 2003	66	RCT	Lactulose ($n = 45$) vs no Rx ($n = 21$)	8 to 24 weeks	NCT, DS, SEP and blood ammonia	Improvement in blood ammonia and psychometric tests; prevented worsening of SEP and development of overt HE
Kale *et al.*,[59] 2006	10	Case series	Lactulose	3 weeks	Diffusion tensor imaging, psychometry (NCT, FCT, PC, DS, PA, OA, BD)	Reversal of interstitial brain edema, which correlated with improvement in neuropsychiatric performance.
Dhiman *et al.*,[3] 2007	61	RCT	Lactulose ($n = 31$) vs no treatment ($n = 30$)	3 months	NCT, FCT, PC, BD, SIP	Lactulose led to significantly greater improvement in psychometry and HRQOL after 3 months (mean total SIP score decreased from 10.39 [95% CI 9.36-11.43] to 3.77 [2.52-5.02] in treated group vs from 10.36 [95% CI 8.98-11.73] to 10.39 [95% CI 8.36-12.42] in control group)
Mittal *et al.*,[67] 2009	90	RCT	Lactulose ($n = 23$) Probiotics ($n = 23$) LOLA ($n = 22$) Placebo ($n = 22$)	3 months	NCT, FCT, PC, BD, SIP	Compared to no treatment, lactulose, probiotics and LOLA led to significantly greater improvement in blood ammonia levels, psychometry scores and HRQOL.
Liu *et al.*,[65] 2004	55	RCT	Fermentable fiber ($n = 20$), probiotic ($n = 20$), or placebo ($n = 15$)	30 days	NCT, BAEP	Synbiotic treatment led to increased fecal content of non-urease-producing *Lactobacillus* species, reduction in endotoxemia and blood ammonia levels; reversal of MHE and improvement in CTP class in 50% of patients.
Malaguarnera *et al.*,[66] 2007	60	RCT	Synbiotic ($n = 30$) Placebo ($n = 30$)	90 days	Psychometry, automated EEG analysis	Improvement in blood ammonia levels and psychometry scores in symbiotic treated group.
Bajaj *et al.*,[63] 2008	35	RCT	Probiotic yogurt ($n = 17$) vs no intervention ($n = 8$)	60 days	NCT A, BD, DS; SF 36	MHE reversed in 71% patients of yogurt patients compared with no patients without intervention. None of the former vs 25% of the latter developed overt HE. No change in SF 36 score.

BAEP, brainstem auditory evoked potential; CTP, Child–Turcotte–Pugh; BD, block design; DC, digit copying; DS, digit symbol test; EEG, electroencephalogram; FCT, figure connection test; HRQOL, health related quality of life; LOLA, L-ornithine–L-aspartate; NCT, number connection test; OA, object assembly; PA, picture arrangement; PC, picture assembly; RCT, randomized controlled trial; Rx, treatment; SEP, sensory evoked potential; SF 36, short form 36; SIP, sickness impact profile.

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these findings.[67] Lactulose or lactitol, both non-absorbable, synthetic disaccharides with multiple effects on gut flora, are regarded as intestinal prebiotics.[96] Dietary addition of lactulose can exert a bifidogenic effect accompanied by a favorable effect on colonic NH_3 metabolism.[97]

A meta-analysis of randomized trials of lactulose versus placebo or no intervention in treatment of patients with MHE showed that the treatment with lactulose was associated with improvement in psychometric (cognitive) performance.[35]

8.2. Prebiotics, probiotics or synbiotics

Prebiotics, probiotics or synbiotics (probiotics and fermentable fiber) are effective in treating patients with MHE,[63–67] and can also be used as long-term therapy. Liu *et al*.[65] showed that modulation of gut microecology and acidification of gut lumen in patients with liver cirrhosis and MHE by treatment with synbiotics resulted in increased fecal content of non-urease-producing *Lactobacillus* species, whereas the number of urease-producing pathogenic *Escherichia coli* and *Staphylococcal* species decreased. This effect persisted for 14 days after cessation of supplementation. It was associated with a significant reduction in blood ammonia and endotoxin levels and reversal of MHE in nearly 50% of the patients. The severity of liver disease, as assessed according to CTP class, also improved in nearly 50% of the patients. In a recent randomized control trial, supplementation with probiotic yogurt resulted in a significant reversal of MHE in the group receiving yogurt compared to no treatment.[63] Treatment with a probiotic preparation also improves HROQL.[67] Prebiotics, probiotics or synbiotics are efficacious in the treatment of HE by decreasing bacterial urease activity, pH in the gut lumen, ammonia absorption and total ammonia in the portal blood, and by improving nutritional status of gut epithelium resulting in decreasing intestinal permeability. In addition, they help ameliorate the inflammation and oxidative stress in the hepatocytes, leading to increased hepatic clearance of ammonia.[98] These mechanisms may be additive or synergistic in treating MHE. Probiotics may represent a safe, effective, long-term therapy for MHE and may be an alternative to lactulose.

8.3. L-ornithine–L-aspartate

Clinical studies evaluating the role of LOLA in the treatment of MHE did not show its effectiveness; however, these studies were small and underpowered. A recent study that compared lactulose, a probiotic and LOLA with no treatment, however, showed that LOLA is as effective as lactulose or a probiotic preparation in improving psychometric performance and HRQOL.[67] Larger prospective studies are warranted to evaluate the role of LOLA before it can be recommended for the treatment of MHE.

8.4. Antibiotics

The role of antibiotics in MHE has not been evaluated. Prospective studies with poorly absorbed antibiotics are required to evaluate their efficacy in improving MHE.

Consensus statement

45 Lactulose is effective in reducing blood ammonia levels and improving psychometric performance in cirrhotic patients with MHE. (1b)

46 Lactulose improves HRQOL in cirrhotic patients with MHE. (1b)

47 Treatment may be initiated with lactulose; patients with MHE should receive 30–60 mL of lactulose in two or three divided doses to achieve two to three semi-soft stools per day. Treatment should be continued for 3–6 months. (1b, A)

48 Probiotics are effective in improving ammonia levels and psychometric performance in patients with liver cirrhosis and MHE. (1b)

49 Probiotics improves endotoxemia and Child–Turcotte–Pugh functional class in patients with liver cirrhosis and MHE. (1b)

50 Probiotics also improve HRQOL in patients with liver cirrhosis and MHE. (1b)

51 Optimum doses of probiotic preparations have not been established. Prospective randomized controlled trials are required to determine the effectiveness of various doses. (5, D)

52 A single study has shown that LOLA is as effective as lactulose or a probiotic preparation in improving psychometric performance and HRQOL. Further adequately powered, prospective, randomized controlled trials are needed to assess the effectiveness of LOLA in the treatment of MHE. (1b,A)

53 The role of antibiotics in the treatment of MHE has not been evaluated till now. Prospective randomized controlled trials to determine the effectiveness of poorly absorbed antibiotics for treatment of MHE are required. (5, D)

54 The effect of treatment of MHE on the prevention of development of overt HE, on driving, complex occupational

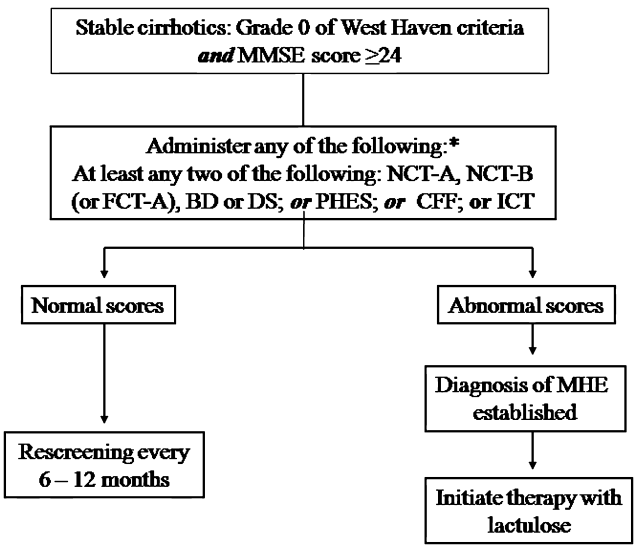

Figure 1 Algorithm for diagnosis and treatment of cirrhotic patients with minimal hepatic encephalopathy. *Any of the test(s) can be used depending upon the availability of control values. BD, block design; CFF, critical flicker frequency; DS, digit symbol; FCT, figure connection test; ICT, inhibitory control test; MHE, minimal hepatic encephalopathy; MMSE, Mini-Mental State Examination; NCT, number connection test; PHES, Psychometric Hepatic Encephalopathy Score.

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tasks and on survival has not been studied. Prospective randomized controlled studies are needed. (5, D)

9. Algorithm for diagnosis and treatment

The INASL Working Party recommends that all patients with cirrhosis be screened for the presence of MHE using a standard battery of psychometric tests, PHES, CFF or ICT, depending upon the availability of tests and their validation for local populations from different parts of the world (Fig. 1). Patients whose index psychometric or computerized test results do not indicate pathology should be screened every 6–12 months. Treatment for MHE may be initiated with lactulose; patients should receive 30–60 mL of lactulose in two or three divided doses so that they pass two to three semi-soft stools per day. Although the appropriate duration of therapy for MHE is unsettled, at least three studies suggest that treatment may be advised for 3–6 months.[3,67,95]

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