

## Minimal hepatic encephalopathy

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**Abstract** Minimal hepatic encephalopathy (MHE) is the mildest form of spectrum of hepatic encephalopathy (HE). Patients with MHE have no recognizable clinical symptoms of HE but have mild cognitive and psychomotor deficits. The prevalence of MHE is high in patients with cirrhosis of liver and varies between 30% and 84%; it is higher in patients with poor liver function. The diagnostic criteria for MHE have not been standardized but rest on careful patient history and physical examination, normal mental status examination, demonstration of abnormalities in cognition and/or neurophysiological function, and exclusion of concomitant neurological disorders. MHE is associated with impaired health-related quality of life, predicts the development of overt HE and is associated with poor survival. Hence, screening all patients with cirrhosis for MHE using psychometric tests, 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 overt HE. Thus, ammonia-lowering agents such as lactulose and probiotics have been tried. These agents have been shown to improve cognitive and psychometric deficits, and have good safety profile. Future studies will better define the role of other drugs, such as rifaximin, acetyl L-carnitine and L-ornithine L-aspartate.

**Keywords** Minimal hepatic encephalopathy · Hepatic encephalopathy · Minimal HE

Hepatic encephalopathy (HE) encompasses several neuropsychiatric abnormalities that occur in patients with liver dysfunction in the absence of other known brain disease. The heterogeneity of manifestations of HE between patients as also in an individual patient over time make the diagnosis, assessment and classification of this condition difficult. A Working Party at the 11th World Congress of Gastroenterology, Vienna under the Organisation Mondiale de Gastroentologie developed consensus recommendations regarding key issues relevant to the diagnosis and grading of HE in clinical research and practice. It proposed a nomenclature that defines HE with respect to (i) the nature of hepatic abnormality; and (ii) the duration and characteristics of neurologic manifestations (Table 1).<sup>1,2</sup> HE has been considered a continuous dimension that could be measured with one index to summarize several neurological domains, such as cognition, emotion, behavior or biologic rhythms. Minimal HE (MHE) represents a portion of this dimension, and is viewed as a mild neurocognitive disorder present in patients who have cirrhosis of the liver and/or portosystemic shunts. These subtle neurocognitive abnormalities primarily affect attention, speed of information processing, and motor abilities and coordination that are not recognizable on standard neurological examination. These neurocognitive abnormalities are independent of sleep dysfunction or problems with overall intelligence.<sup>1-4</sup>

MHE has been described previously using several different names, such as, early, low-grade, latent or subclinical HE to identify patients with subtle cognitive function abnormalities.<sup>5,6</sup> In 1970, Zeegen *et al.*<sup>7</sup> were the first to describe this condition, when they discovered that 38% of patients who had undergone portal decompression surgery scored abnormal in the Reitan trailmaking test (number connection test). Eight years later, the term subclinical HE was introduced to describe patients with abnormal psychometric tests and an abnormal EEG.<sup>8</sup> In recent years, the term MHE has been preferred to latent, preclinical or subclinical HE, which may mislead by indicating that the condition is below the threshold of significance.<sup>1,2</sup>

This article focuses on epidemiology, pathogenesis, clinical characteristics, assessment and diagnosis of MHE, its

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**Table 1** Nomenclature of hepatic encephalopathy

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	Episodic	Precipitated Spontaneous Recurrent
C (Cirrhosis)	HE associated with cirrhosis and portal hypertension or portosystemic shunts	Persistent	Mild Severe Treatment-dependent
		Minimal	Not applicable

HE: hepatic encephalopathy

effect on health-related quality of life (HRQOL) and survival, and developments in its management.

### Epidemiology

There are no accurate data on the incidence of HE. However, several studies suggest that the majority of patients with cirrhosis will develop some degree of HE at some point during the course of disease. Overt HE occurs in approximately 30% to 50% of cirrhotic patients<sup>9</sup> and 10–50% of patients with transjugular intrahepatic portosystemic shunt (TIPS).<sup>10, 11</sup> The prevalence of MHE has been reported to vary between 30% and 84% in patients with cirrhosis of liver.<sup>12–17</sup>

Reasons for a large variation in the prevalence of MHE in different studies include presence of prior episodes of overt HE,<sup>18</sup> severity of liver disease, age,<sup>19, 20</sup> presence of esophageal varices,<sup>18</sup> alcoholic etiology,<sup>18</sup> TIPS and surgical porto-systemic shunts.<sup>5</sup> Patients who develop MHE are older, more often have alcohol as etiology of cirrhosis, have history of overt HE in the past, have more severe liver disease, and more often have esophagogastric varices.<sup>18–20</sup>

The diagnosis of HE has traditionally been linked to patients with cirrhosis of liver. However, impairment of cognitive function has been shown in patients with noncirrhotic portal fibrosis<sup>21</sup> and extrahepatic portal venous obstruction,<sup>22, 23</sup> and has been related to portosystemic shunting. Neuropsychological impairment (diagnosed as MHE) has recently been shown to occur in 25% of patients with severe acute viral hepatitis;<sup>24</sup> this however resolves on follow-up with recovery of viral hepatitis. Elevated arterial blood ammonia levels during the icteric phase were associated with development of neuropsychological impairment. In this study, none of the patients with acute severe hepatitis developed HE, either among those who had MHE or those who did not had MHE at baseline.<sup>24</sup>

Cognitive impairment in chronic hepatitis, which is correlated with degree of fibrosis, is not currently considered as equivalent to MHE.<sup>25</sup> Patients with chronic hepatitis C (both with and without cirrhosis) show cognitive deficits

compared to healthy controls or patients with chronic hepatitis B.<sup>26–28</sup> The deficits are more marked in patients with moderate rather than mild fatigue.<sup>27</sup> Interferon therapy did not lead to either improvement or deterioration in cognitive deficits in patients with chronic hepatitis C demonstrating bridging fibrosis or cirrhosis.<sup>29, 30</sup>

### Pathogenesis

#### *Ammonia*

Ammonia was the first gut-derived neurotoxin implicated in the pathogenesis of HE in patients with cirrhosis. Other intestinal neurotoxins such as manganese and the benzodiazepine-GABA system are also involved. Changes in neurotransmission induced by these compounds play a major role in the development of neuropsychological disturbances observed in these patients.

HE is a form of gliopathy caused due to Alzheimer type II astrocytes, the only cell in the brain containing glutamine synthetase that metabolizes ammonia. Glutamine synthesis occurs within astrocytes and is hypothesized to cause brain swelling.<sup>31, 32</sup> In addition to glutamine synthesis, astrocytes also maintain the integrity of the blood–brain barrier and regulate cerebral blood flow.<sup>33</sup> Ammonia also affects neurons by inducing neurosteroid production leading to a positive modulatory effect on the GABA-A receptor.<sup>34</sup> Although the precise molecular mechanism(s) responsible for neurological alteration in HE are not known, HE is associated with alterations in the expression of astrocytic and neuronal genes that code for various proteins that play a critical role in central nervous system function including maintenance of cell volume and neurotransmission.

Several lines of evidence suggest that the pathogenesis of MHE is similar to that of overt HE.<sup>23, 35–38</sup> Oral administration of a specifically prepared amino acid solution identical to the amino acid profile of hemoglobin to patients with cirrhosis results in an increase in brain glutamine and brain water.<sup>35</sup> This pathophysiological change is associated with deterioration in neuropsychological performance. Ammonia

-induced alterations in cerebral blood flow and glucose metabolism are associated with a significant decrease of glucose utilization by various cortical regions that are involved in cognitive functions.<sup>37</sup> Ammonia has also been linked to cognitive deficits observed in patients with noncirrhotic portal hypertension, such as, extrahepatic portal venous obstruction.<sup>8, 23</sup> These patients exhibited abnormalities in the results of neuropsychological tests, oral glutamine challenge test, and magnetic resonance (MR) imaging and spectroscopy (an increase in glutamine, a decrease in myoinositol and a decrease in magnetization transfer ratio indicating cerebral edema) similar to those described in HE associated with cirrhosis.<sup>38</sup>

#### *Systemic inflammatory response*

Recent observations in patients with liver disease suggest that inflammatory response may be important in the pathogenesis of HE. Jalan and co-workers have highlighted the importance of infection and inflammation even in minimal alterations of cognitive function in liver disease. They showed that induced hyperammonemia resulted in significantly greater deterioration in psychometric tests in cirrhotic patients who had an ongoing infection compared with those in whom the infection had resolved.<sup>39</sup> They further showed that the presence and severity of MHE were independent of severity of liver disease and ammonia concentration, but were associated with higher levels of markers of inflammation.<sup>40</sup>

#### *Manganese*

Manganese is a neurotoxin that accumulates in the brains of patients with cirrhosis and portosystemic shunts.<sup>41, 42</sup> Its levels correlate with pallidal hyperintensity seen on MR brain scans of patients with cirrhosis, who may also demonstrate extrapyramidal signs, suggesting that altered homeostasis of manganese and other minerals could be responsible for the cognitive deficits associated with liver cirrhosis.

#### **Assessment of MHE**

##### *Diagnosis of MHE*

The diagnosis of MHE rests on the confirmation of a disease that can cause MHE, such as, cirrhosis or presence of portosystemic shunt (Table 1), exclusion of normal mental status on clinical examination,<sup>43, 44</sup> demonstration of abnormalities of cognition and/or neurophysiological variables and exclusion of concomitant neurological disorders. HE is traditionally classified, using the West Haven criteria, into four grades (Table 2).<sup>1, 2</sup> However, assignment of patients with cirrhosis to HE stages 0–2 strongly relies on the subjective impression of the physician; this inter-observer variability may affect the results of multicenter trials. The reliability of the West Haven scale can be improved by using it with the clinical hepatic encephalopathy staging scale (CHES).<sup>43</sup>

**Table 2** West Haven criteria for semiquantitative grading of mental state

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

The CHES, a linear scale that scores HE from 0 (normal mental state) to 9 (deep coma) according to presence or absence of nine items, allows easy distinction between grade 0 and grade 1 change (Table 3).<sup>43</sup>

The total score is the sum of the answers to the nine items. Minimal score=0; maximal score=9.

#### **Diagnostic methods**

Various tools have been evaluated for the diagnosis of MHE and include the neuropsychological tests, computerized tests, short neuropsychological and computerized test batteries and neurophysiological tests (Table 4). Regional cerebral blood flow changes,<sup>46</sup> and magnetic resonance imaging and spectroscopy,<sup>47</sup> though useful for understanding pathogenic mechanisms, are currently not considered of diagnostic value.

There is no ideal test for the diagnosis of MHE. However, the Working Party recommends that the diagnosis of MHE requires a normal mental status examination and impairment in the performance of at least two of the following tests: number connection test-A (NCT-A), number connection test-B (NCT-B), block design test (BDT) and digit symbol test (DST).<sup>1</sup> It also recommends the use of [PSE-Syndrome-Test or psychometric hepatic encephalopathy score (PHES)], a standardized test battery including (NCT-A) and B, the line-tracing test (LTT), the serial-dotting test (SDT), and DST.<sup>1, 48</sup> When possible, quantitative neurophysiologic tools (like EEG with mean dominant frequency, P300 auditory evoked potentials) should be used. There is no consensus regarding the frequency of testing, but experience has shown relative similarity in psychometric scores at 6

**Table 3** Clinical Hepatic Encephalopathy Staging Scale (CHESS)

Item	Score	
	0	1
1. Does the patient know which month he/she is in (i.e., January, February)?	Yes	No, or he/she does not talk
2. Does the patient know which day of the week he/she is in (i.e., Thursday, Friday, Sunday, etc.)?	Yes	No, or he/she does not talk
3. Can he/she count backward from 10 to 1 without making mistakes or stopping?	Yes	No, or he/she does not talk
4. If asked to do so, does he/she raise his/her arms?	Yes	No
5. Does he/she understand what you are saying to him/her? (based on the answers to questions 1 to 4)	Yes	No, or he/she does not talk
6. Is the patient awake and alert?	Yes	No, he/she is sleepy or fast asleep
7. Is the patient fast asleep, and is it difficult to wake him/her up?	No	Yes
8. Can he/she talk?	Yes	He/she does not talk
9. Can he/she talk correctly? In other words, can you understand everything he/she says, and he/she doesn't stammer?	Yes	No, he/she does not talk or does not talk correctly
Total CHESS score:		

The total score is the sum of the answers to the nine items. Minimal score=0; maximal score=9.

**Table 4** Diagnostic methods for the detection of MHE

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	No
Computerized tests (CFF, ICT, reaction times, etc.)	Rapid tests, easy to apply	Limited data on diagnostic significance, can be used as screening test, needs standardization	Yes
Neurophysiological tests (EEG, spectral EEG, P300 evoked potentials)	Objective, allow for repeat testing	Need sophisticated equipment, limited data	No
<i>Short batteries</i>			
Short neuropsychological battery (PHES)	High sensitivity with well recognized clinical significance, rapid results	Limited access, limited data on normative values	Yes
CDR computerized assessment battery	Sensitive, rapid results	Limited access, expensive, prior training session required for familiarization	Yes

PHES, psychometric hepatic encephalopathy score; CDR, cognitive drug research; CFF, critical flicker frequency; ICT, inhibitory control test; EEG, electroencephalogram

months intervals in the absence of acute clinical and neurological events such as development of overt HE.<sup>14</sup>

### Short Batteries

#### *Psychometric hepatic encephalopathy score (PHES)*

This battery of tests has been extensively validated in Spanish and German populations, and can be performed in 15 to 20 minutes.<sup>48, 49</sup> We have modified this battery by replacing NCT-B with figure connection test-A (FCT-A)<sup>50</sup> and have recently validated this modified battery in the Indian popula-

tion.<sup>20, 51</sup> This battery examines many of the abnormalities seen in patients with MHE; these include motor speed and accuracy, visuo-spatial orientation, visual perception, visual construction, attention concentration, and, to a lesser extent, memory.

#### *Cognitive drug research (CDR) computerized assessment battery*

A battery of tests has been developed by Cognitive Drug Research (CDR) Ltd (Goring-on-Thames, UK).<sup>52</sup> With over 50 parallel forms of each task, the CDR system (CDRS)

is widely used for the assessment of cognitive function in clinical trials<sup>53</sup> and the assessment of patient populations including those with hepatitis C.<sup>54</sup> CDRS subtests reflect 5 cognitive domains, namely, power of attention, continuity of attention, quality of episodic memory, quality of working memory and speed of memory. A recent study compared the CDRS to the PHES and showed improvement after liver transplantation and worsening after a nitrogen challenge. In this study, MHE patients were impaired in all subsets and there was worsening of the quality of working and episodic memory after a nitrogen challenge.

Recent studies indicate that PHES and the CDRS batteries may serve as a 'gold standard' for the assessment of MHE. Both these test batteries are reliable, can be performed in an office setting and evaluate cognitive deficits that are seen in MHE. However, limited access and lack of standardization in various populations remain the main obstacles for their wider use.

### Critical flicker frequency

Critical flicker frequency (CFF) and inhibitory control test (ICT) are recent additions to the tests for the diagnosis of MHE. CFF tests the ability of a patient to perceive flickering and its fusion threshold. Two recent studies that evaluated its utility in the diagnosis of MHE found it to be a simple, reliable and accurate method for the diagnosis of MHE, and to be independent of age, education or training.<sup>49, 55</sup> However, our results showed that CFF decreases as the age advances; hence, an age-adjustment of observed values may be required.<sup>20</sup>

### Inhibitory control test

Inhibitory control test (ICT) is a computerized test of attention and response inhibition that has been used to characterize attention deficit disorder, schizophrenia and traumatic brain injury.<sup>56</sup> ICT consists of presentation of several letters at 500 millisecond intervals.<sup>56</sup> Interspersed within these letters are the letters X and Y. The subject is instructed only to respond when X and Y are alternating (called targets) and to not respond when X and Y are not alternating (called lures). After the training run, 6 test runs which last about 2 minutes each are administered with a total of 40 lures, 212 targets and 1728 random letters in between. Lower lure response, higher target response and shorter lure and target reaction times indicate good psychometric performance. ICT has been validated for the diagnosis of MHE in USA and found to be reliable and sensitive for detection as well as follow-up of patients with MHE. However, it needs to be validated in other population. It is also not clear whether abnormal ICT reflects disturbances of quality of life.

### Other tests

Parameters reflecting inflammation such as interleukin (IL)-6 and IL-18 could be useful indicators of the presence of MHE. In a recent study, all patients with MHE had IL-6

levels above 11 ng/mL, whereas all patients without MHE had levels below this threshold.<sup>57</sup>

All patients with cirrhosis be screened for the presence of MHE using a standard battery of psychometric tests. PHES and CDRS batteries may serve as a 'gold standard' for the assessment of MHE. ICT or CFF analysis may be useful as screening tests.

### Clinical significance

#### *Effect of MHE on health-related quality of life (HRQoL)*

Many patients have no clinically overt signs of impaired cognition; however, others may show a decline in it. The patient himself, a family member, a colleague or an employer may notice a cognitive decline, which may not be perceived by a physician. Several cognitive statements, i.e., complaints have predictive value for MHE that include impaired psychomotor performance ('I have difficulty doing handwork; I am not working at all.')., 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.').

MHE is an important disorder that impairs patients daily functioning and HRQoL.<sup>58-62</sup> Complex activities involving attention, information processing and psychomotor skills such as driving a car, planning a trip, etc are mainly affected. However the basic activities of daily life, such as shopping, dressing, personal hygiene, etc are preserved. We have shown that patients with MHE had a significant impairment in daily functioning, such as, social interaction, alertness, emotional behavior, sleep, work, home management, and recreation and pastimes, as compared with cirrhotic patients who did not have MHE.<sup>59</sup> Blue-collar workers with cirrhosis of liver and MHE are less likely to earn their wages than the white-collar workers with similar disease state;<sup>60</sup> 60% of 'blue-collar' workers and 20% of 'white-collar' workers were unfit to work.<sup>60</sup> The impact of MHE on daily life is enormous; half of the patients with MHE do not have regular employment, compared to 15% of those without MHE.<sup>18</sup> Socioeconomic implications are significant due to adverse effects on functioning in the workplace.

Sleep disturbances are common in patients with HE. Studies using HRQoL questionnaire have confirmed higher frequency of sleep disturbance in cirrhotic patients with MHE.<sup>18, 59</sup> Cordoba *et al.*<sup>63</sup> demonstrated abnormalities in quality of sleep in nearly half the cirrhotic patients without overt HE. Unsatisfactory sleep was associated with increased sleep latency, reduced sleeping time, increased awakening episodes during night and increased daytime sleepiness and naps. Sleep disturbances were related to abnormalities in circadian rhythm, but not with the results of neuropsychological tests. This implies that sleep

disturbances co-exist with but are not the cause for psychometric impairment.

Defective memory is also a feature of MHE. Weissenborn *et al.*<sup>64</sup> found that patients with MHE had impaired performance in tests of short- and long-term memory, that require free recall or recognition. The impairment was predominantly related to deficits in attention and visual perception. The 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 (also known as retrieval) is intact.

### Effect of MHE on driving

Schomerus *et al.*<sup>65</sup> studied 40 patients with cirrhosis of liver, and considered 60% of them to be unfit to drive based on their psychometric tests performance. However, the methods used for assessing driving fitness were not specified, making their conclusion less convincing. Similar results were reported by Watanabe *et al.*<sup>66</sup> However, a pilot study that evaluated driving using a real road test in 9 patients with cirrhosis of liver with MHE, found no impairment of driving performance.<sup>67</sup>

In a recent landmark study, Wein and colleagues<sup>68</sup> used a standardized 90-minute on-the-road driving test and found that fitness to drive a car was impaired in cirrhotic patients with MHE. Patients without MHE scored similar to controls. The instructor intervened more frequently during the test to avoid accidents in patients with MHE (36%) than in patients without MHE (6%) and healthy controls (8%).<sup>68</sup> Increased risk of automobile accidents is related to a decline in cognitive function.<sup>69</sup> Bajaj *et al.*<sup>70</sup> have reported a higher self-reported occurrence of violations and accidents in patients with cirrhosis and MHE compared to healthy volunteers. Impairment of 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.

Navigation is a complex activity required for safe driving and is dependent on functioning working memory, attention and speed of mental processing. Impaired navigation skills correlate with impairment in response inhibition and attention. Patients with cirrhosis and MHE also pose navigation difficulty.<sup>72</sup> The illegal turns and accidents on the driving simulator correlated mostly with abnormal performance on the inhibitory control test (ICT), which tests response inhibition and is a measure of executive control.

### Natural history

#### *Development of overt hepatic encephalopathy*

Patients with MHE may improve, remain unchanged or deteriorate and develop overt HE over a long-term follow-up. Several studies have looked at the frequency of develop-

ment of overt HE in patients with MHE.<sup>14, 49, 72-76</sup> In these studies, patients with liver cirrhosis and MHE had a higher frequency of development of overt HE during follow-up (22.6-58.6%) compared to those without MHE (3.9-17.3%).<sup>14, 15, 49, 72-75</sup> Hartman *et al.*<sup>15</sup> have shown that episodes of overt HE were significantly more frequent in patients with MHE than in those without; however, Child-Pugh score was superior to MHE in predicting episodes of clinical HE.<sup>15</sup>

In one study, three of nine patients with cirrhosis with MHE developed overt HE during a one-year follow up.<sup>5</sup> We found that, over a mean follow-up period of 5.4 months, MHE tended to persist or worsen in patients with poorer liver function.<sup>14</sup> Although other clinical complications such as ascites, spontaneous bacterial peritonitis and gastrointestinal bleed developed with equal frequency in patients with or without MHE, overt HE developed more commonly in those who had MHE.<sup>14</sup> Yen *et al.*<sup>76</sup> found that significantly more patients with abnormal NCT-A or somatosensory evoked potentials developed overt HE than patients with normal tests, over a 6-month period. Romero-Gomez and co-workers<sup>49</sup> demonstrated that CFF <38 Hz was predictive of further bouts of overt HE.

### Survival

Presence of MHE adversely affects survival of patients with liver cirrhosis. Amodio *et al.*<sup>74</sup> found a negative effect of MHE on survival. Hartman *et al.*<sup>15</sup> found that survival was no different in cirrhotic patients with or without MHE; the survival was instead determined mainly by Child-Pugh score. A pathological oral glutamine challenge in patients with MHE also appears to be associated with the development of overt HE and poor survival.<sup>77, 78</sup> We found poor survival among patients with higher CTP score and abnormal PHES. Eighteen of 46 (39.1%) patients died among those who had MHE compared to 11 of 48 (22.9%) patients who did not have MHE. Among the several variables analyzed in this study, univariate analyses showed age, serum bilirubin level, Child-Turcotte-Pugh score and PHES were associated with a poor prognosis. The multivariate analysis identified 2 variables as significant independent prognostic factors; PHES  $\leq$  -6 and Child-Turcotte-Pugh score  $\geq$  8 predicted poor survival (Unpublished data).

Current data suggest that patients with MHE tend to have more frequent episodes of overt HE and poorer survival than in those without MHE, and indicate that patients with MHE have a more advanced liver disease.

### Treatment

Ammonia plays a key role in the pathogenesis of MHE.<sup>31-38, 79</sup> Various treatment modalities have been tried for MHE, including dietary protein manipulation,<sup>5, 80</sup> branched-chain amino acids,<sup>81, 82</sup> lactulose,<sup>59, 83-91</sup> flumazenil,<sup>92</sup> L-ornithine

L-aspartate,<sup>93</sup> acetyl L-carnitine,<sup>94</sup> and probiotics/synbiotics<sup>95-98</sup> (Table 5). A majority of these attempts were aimed at reducing blood ammonia level, and most studies have shown improvement in psychometric measurements, ammonia levels, cerebral edema and HRQoL (Table 5).

#### *Non-absorbable disaccharides*

Lactulose has been used in the treatment of MHE with success; it improves both cognitive functions and HRQOL.<sup>59, 83-91</sup> We recently investigated the effect of treatment-related improvement in cognitive functions on HRQOL.<sup>59</sup> Psychometric performance was measured by NCT- and FCT- A and B, picture completion and block design tests, and HRQOL by Sickness Impact Profile (SIP) in 90 patients with cirrhosis at inclusion into the study and 3 months thereafter. Sixty-one (67.7%) patients had MHE. They were randomly assigned to receive either lactulose for 3 months (n=31) or no treatment (n=30) in a non-blinded design. Mean number of abnormal neuropsychiatric tests decreased significantly in the treated patients than in the untreated patients in untreated group (MANOVA for time and treatment,  $p=0.001$ ). An intention-to-treat analysis showed significant improvement in MHE following lactulose therapy. Mean total SIP score improved among treated patients than in untreated patients (MANOVA for time and treatment,  $p=0.002$ ). Improvement in HRQOL was related to improvement in cognitive functions. It is believed that lactulose alters gut flora, resulting in reduced production and intestinal adsorption of ammonia, leading to a lower blood ammonia level.

A meta-analysis of randomized trials of lactulose versus either placebo or no intervention in treatment of patients with MHE showed that the treatment with lactulose was associated with improvement in psychometric (cognitive) performance (Fig. 1; unpublished data).

#### *Prebiotics and synbiotics*

Probiotics are particularly attractive since these can be used as long-term therapy. Synbiotics (probiotics and fermentable fiber) are efficacious in the treatment of HE by decreasing total ammonia in the portal blood by decreasing bacterial urease activity in the intestinal lumen, by decreasing ammonia absorption by decreasing intestinal pH, and by improving nutritional status of gut epithelium resulting in decreasing intestinal permeability, and decreasing inflammation and oxidative stress in the hepatocyte leading to increased hepatic clearance of ammonia. Probiotics also decrease uptake or formation of other toxins, such as endoepines and oxiphenols.

Liu *et al.*<sup>95</sup> used this novel approach of modulating the gut microecology and acidifying the gut lumen by treating cirrhotic patients with MHE with synbiotics. They randomized 55 cirrhotic patients to receive a synbiotic preparation (n=20), fermentable fibre (n=20) or a placebo (n=15) for 30 days. Synbiotic treatment resulted in increased fecal content of non-urease-producing *Lactobacillus* species, and a decline in urease-producing pathogenic *Escherichia coli* and *Staphylococcal* species. This effect persisted 14 days after stopping the supplementation. The modulation of gut flora was associated with a significant reduction in blood ammonia levels, reduction in endotoxemia and reversal of MHE in 50% of patients. The severity of liver disease, as assessed by Child-Pugh class, improved in nearly half of patients. This study suggests that treatment with synbiotics or fermentable fiber may be an alternative to lactulose for management of MHE.

Bajaj and colleagues<sup>96</sup> investigated the use of probiotic yogurt for the treatment of MHE in patients with non-alcoholic cirrhosis. Yogurt was chosen because it is a palatable food item, is widely available and does not require prescription, all of which favor long-term adherence. This unblinded, prospective study included 25 patients who were randomly allocated (2:1) to 12 oz of probiotic yogurt daily

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

Treatment modality	Improvement in ammonia levels	Improvement in psychometry	Improvement in quality of life	Other
Branch chain amino acids <sup>81,82</sup>	Yes	Yes	Improvement in simulated driving	Positive nitrogen balance
Non-absorbable disaccharides <sup>59, 83-191</sup>	Yes	Yes	Yes	Improvement in cerebral edema <sup>91</sup>
Probitics/synbiotics <sup>95-98</sup>	Yes	Yes	Not done	Improvement in Child-Turcotte-Pugh functional class <sup>95</sup>
L-ornithine L-aspartate <sup>93</sup>	Yes	Yes	Not done	-
Acetyl L-carnitine <sup>94</sup>	Yes	Yes	Not done	Improvement in prothrombin time, albumin, bilirubin and aspartate aminotransferase
Flumazenil <sup>92</sup>	-	No	Not done	-

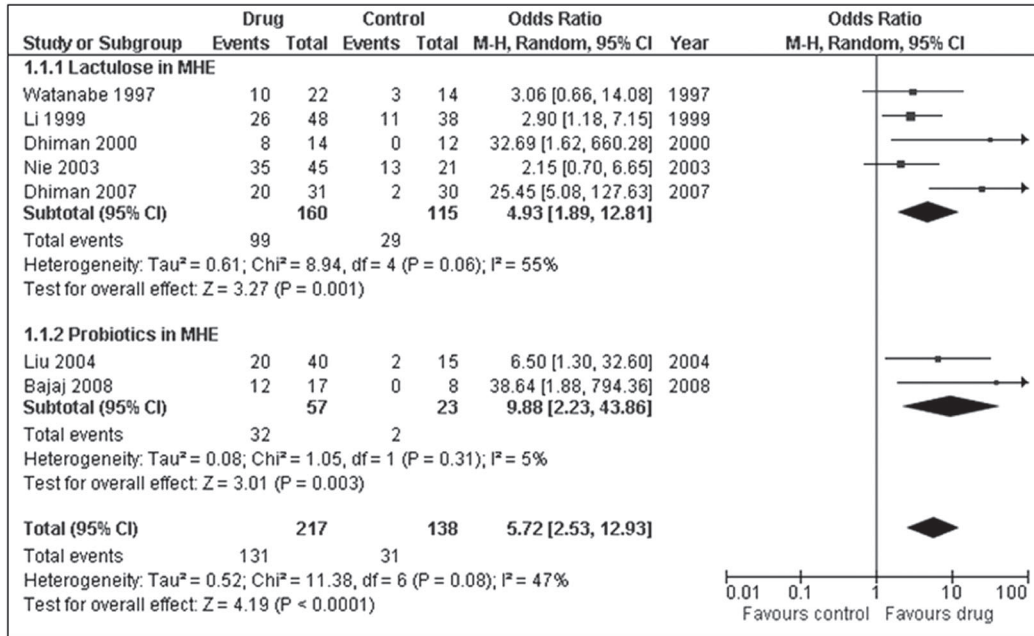


Fig. 1 Randomized trials (lactulose or probiotics versus placebo or no intervention) in treatment of patients with MHE

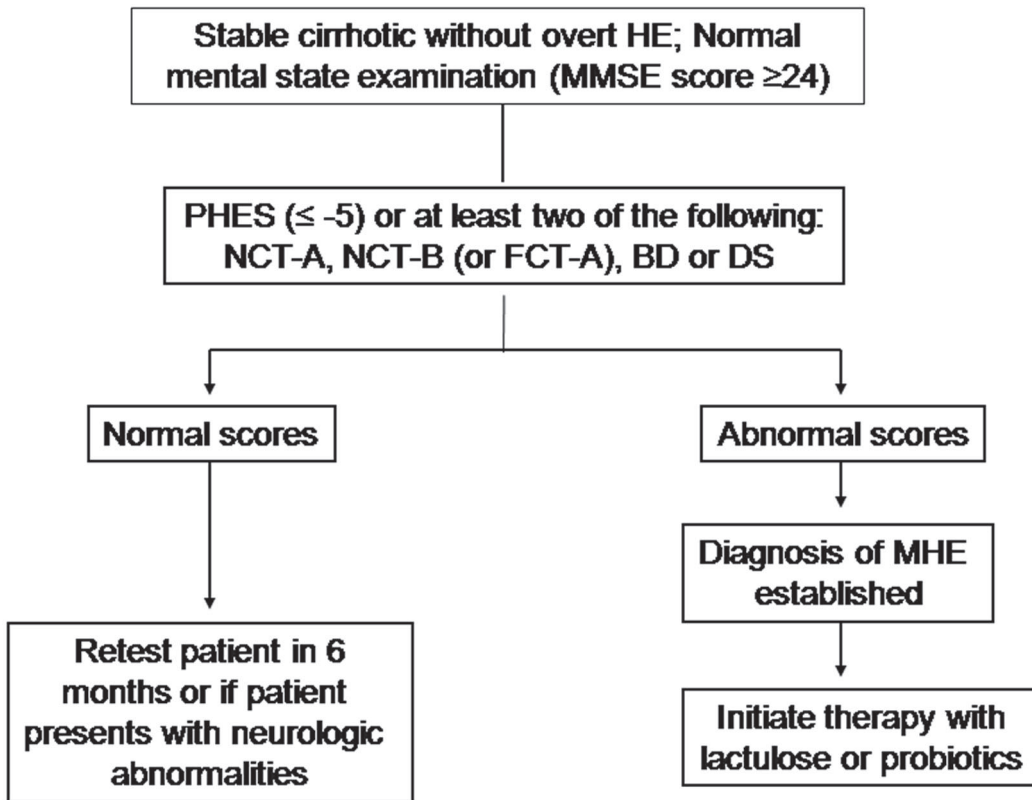


Fig. 2 Treatment algorithm for patients with minimal HE. NCT: number connection test, FCT: figure connection test, BD: block design test, DS: digit symbol test, PHES, psychometric hepatic encephalopathy score. Patients should receive 30 to 60 mL per day of lactulose in 2 to 3 divided doses so that they pass 2 to 3 semisoft stools daily or should receive a probiotics preparation (Modified from Dhiman RK, Chawla YK. Minimal hepatic encephalopathy: Time to recognize and treat. *Trop Gastroenterol* 2008;29:6–12.)

(17 patients) or no treatment (8 patients) for 60 days. Complete reversal of MHE was achieved in only those patients who consumed yoghurt (71%,  $p=0.003$ ) and was associated with improvement in psychometric test results. Probiotic yogurt may represent a safe, effective, long-term therapy for MHE; however, larger studies with longer follow-up duration are required.

### Other potential therapies

Acetyl-L-carnitine has been shown to be useful in improving blood ammonia and cognitive functions in cirrhotic patients with MHE but requires further studies with larger sample sizes.<sup>94</sup> Rifaximin, L-ornithine-L-aspartate,<sup>93</sup> or sodium benzoate are viable alternative to lactulose in patients with overt HE who are nonresponsive or resistant to lactulose treatment or who are nonadherent with therapy; however, these warrant future studies in cirrhotic patients with MHE. Flumazenil is not helpful in cirrhotic patients with MHE.<sup>92</sup>

### Conclusion

MHE is associated with significant disability and poor HRQOL. These patients have higher chance to develop overt HE and have poorer survival than those who do not have MHE. Hence, its management is crucial. Treatment not only results in improvement in cognitive and psychomotor deficits but also in HRQOL (Table 5). An early identification of MHE may improve the HRQOL and the prognosis of these patients. Lactulose and probiotics are safe and effective, and may be used for treating such patients; however, this needs further studies. This is the prime time to recognize and treat MHE.<sup>99</sup> We have proposed a modified treatment algorithm for cirrhotic patients with MHE (Fig. 2),<sup>100</sup> which is based primarily on the recommendations of a panel of experts from the United States and Europe.<sup>101</sup>

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