

The burden of minimal hepatic encephalopathy: from diagnosis to therapeutic strategies

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Abstract

Minimal hepatic encephalopathy (MHE) is the mildest form of hepatic encephalopathy (HE). It affects the performance of psychometric tests focused on attention, working memory, psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures. MHE is a frequent complication of liver disease, affecting up to 80% of tested patients. By being related to falls, an impairment in fitness to drive and the development of overt HE, MHE severely affects the lives of patients and caregivers by altering their quality of life and their socioeconomic status. MHE is detected in clinically asymptomatic patients using appropriate psychometric tests and neurophysiological methods that highlight neuropsychological alterations, such as video-spatial orientation deficits, attention disorders, memory, reaction times, electroencephalogram slowing, prolongation of latency-evoked cognitive potentials, and reduction in the critical flicker frequency. Several treatments have been proposed for MHE treatment, including non-absorbable disaccharides, poorly absorbable antibiotics such as rifaximin, probiotics and branched-chain amino acids. However, because of the multiple diagnosis methods, the various endpoints of treatment trials and the variety of agents used in trials, the treatment of MHE is not currently recommended as routine, but only on a case-by-case basis.

Keywords Cirrhosis, minimal hepatic encephalopathy, covert hepatic encephalopathy, cognitive impairment

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Introduction

Definition and epidemiology

Hepatic encephalopathy (HE) is a complex neurological syndrome, typical of liver cirrhosis, which produces a wide and complex spectrum of nonspecific neurological and psychiatric manifestations [1]. In its mild expression, i.e., minimal HE (MHE) [2,3], this condition alters the performance of psychometric tests, working memory, psychomotor speed, and visuospatial ability, as well as electrophysiological and other functional brain measures, without, however, any evidence of clinical manifestations [4,5]. MHE is a frequent complication of liver disease and is considered as one of its most debilitating

manifestations, severely affecting the life of patients and caregivers. Furthermore, cognitive impairment associated with cirrhosis results in the use of more healthcare resources in adults in comparison with other manifestations of liver disease [6-11].

Depending on the population studied and the diagnostic tool used, MHE occurs in 20-80% of patients with cirrhosis [12-17], MHE is considered as a preclinical stage of HE and is part of a wide spectrum of typical neurocognitive alterations in liver cirrhosis, particularly involving the areas of attention, alertness, response inhibition, and executive functions [18-21]. Although these typical characteristics of MHE reduce the safety and quality of life (QoL) of patients with cirrhosis, together with their caregivers, they are difficult to detect from the clinical point of view. Moreover, cirrhotic patients with sleep disorders [22-25] also show deficits in executive functions and in specific activities such as driving, which are dangerous for themselves and for others. As low-grade HE is difficult to diagnose (grade I), a recent classification, introducing the term “covert”, has been established that combines MHE and Grade I HE. The aim is to simplify the clinical pattern thereby easily and uniformly diagnosing the presence of clinically overt HE (OHE), as reported in Fig. 1 [26]. The term “covert” has been debated since the condition is not really unapparent (latent, subclinical, minimal), but is simply not overt, obvious and severe or clinically unquestionable. The operative characteristics of MHE and covert HE (CHE) are reported in Table 1.

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Table 1 Operative characteristics of minimal and covert hepatic encephalopathy

Minimal hepatic encephalopathy	Covert	<ul style="list-style-type: none"> • Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change
Grade I		<ul style="list-style-type: none"> • Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm

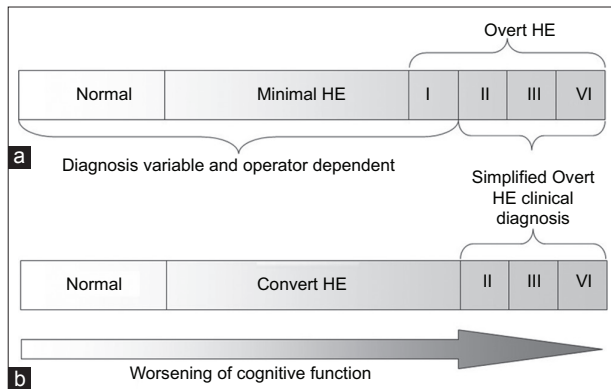


Figure 1 Box A: Classic classification of minimal and overt hepatic encephalopathy (HE). Box B: New classification combining minimal HE and Grade I HE, in order to simplify the clinical pattern and easily and uniformly diagnose the presence of clinical overt HE

MHE and CHE are risk factors for the development of OHE. In fact, the risk for the first bout of OHE is 5-25% within 5 years after cirrhosis diagnosis, depending on risk factors, such as other complications related to cirrhosis (MHE or CHE, infections, variceal bleeding, or ascites) and possibly diabetes and hepatitis C [27-31].

The burden of MHE

Up to 80% [1,4,16,32] of patients with liver cirrhosis show neuropsychological and neurophysiological abnormalities that are not detectable by the clinical evaluation usually used to identify the presence of HE; these include cognitive and attention deficits, loss of inhibitory response, loss of working memory, and lack of visuomotor coordination. MHE is detected in clinically asymptomatic patients using appropriate psychometric tests and neurophysiological methods (Table 2) that highlight neuropsychological alterations, such as video-spatial orientation deficits, attention disorders, memory, reaction time, electroencephalogram (EEG) slowing, prolongation of latency-evoked cognitive potentials and reduction in the critical flicker frequency (CFF).

The optimal diagnostic criteria for MHE remain controversial, also because an essential condition for MHE diagnosis is the correct standardization of the tests used by age, education and also employment of the patient. To overcome the difficulties in the execution of complex psychometric batteries, which may require specialist staff for their administration,

are time and money consuming, other techniques have been proposed, such as the CFF, the smooth pursuit eye movement, and the use of cognitive evoked potentials. Computerized psychometric tests, including the scan test [32] and the inhibitory control test (ICT) [33], which may be more specific and repeatable, have also been proposed. An EEG [34] is also useful for detecting MHE conditions, especially if a spectral analysis is carried out [7]. A comprehensive discussion of these diagnostic techniques is given below.

A survey of the American Association for the Study of Liver Diseases, conducted in 2007 [35], showed that most clinicians believe MHE to be a significant problem. However, only 50% of clinicians had investigated whether their patients might have MHE, and 38% had never studied their patients with liver cirrhosis using psychometric assessment. MHE reduces patients' QoL, increases the incidence of disability, and has a negative effect on their daily activities. The impact of the perception of the disease, in the form of a "Sickness Impact Profile", has been studied in a group of patients with cirrhosis to assess the indicators of QoL, such as sleep, rest, eating, work, home management, recreation, walking, daily care, movement and emotional behavior. Each profile was significantly reduced in patients with MHE compared to individuals without MHE [36]. In addition, in the presence of MHE, QoL indicators, such as the ability to drive a car, and the incidence of sleep disorders were also negatively affected [37].

MHE and QoL

Although cirrhosis has a poor prognosis, recent advances in the treatment strategies and general management of this disease have significantly improved survival rates. The majority of patients eligible for liver transplantation now survive until the transplant for between 1 and 4 years. In addition to the stabilization of the disease, it is thus essential for the economic impact, as well as the human and emotional burden of liver cirrhosis, to be taken into account in the management of these patients.

Several studies have shown that liver diseases severely worsen the health-related QoL (HRQoL) [38-40], especially in relation to hospitalizations, severity of the disease, and its complications such as recurrent HE or OHE. Recent evidence suggests that OHE leads to persistent cognitive impairment even after its resolution. In fact, those patients with a prior episode of OHE, although clinically free, may show an increase in the prevalence of cognitive impairment, which can

be identified by testing for the presence of MHE or learning ability [41,42].

In accordance with the growing interest in the central role of perception in a patient's state of health, the evaluation of HRQoL is acquiring great importance in clinical practice as well as in planning therapeutic strategies. It has in fact already

been shown that "quality" and "disability" have a stronger impact than "longevity" on patients' expectation of life [43]. Although HRQoL may appear to be influenced by the presence of MHE [10,36,37,44,45], this evidence is controversial and little is known about the effects of a previous history of HE on HRQoL. Moreover, in patients with a history of

Table 2* Testing strategies for minimal hepatic encephalopathy

Test	Tested domain	Copyright	Dedicated (Europe-Asia/USA)	Time required for administration and interpretation (min)	Comments
<i>NCT-A</i>	Psychomotor speed	Yes	No/No	1-2	Poor specificity
<i>NCT-B</i>	Psychomotor speed, set shifting, divided attention	Yes	No/No	1-3	Poor specificity
<i>BDT</i>	Visuospatial reasoning, praxis, psychomotor speed	Yes	No/Yes	10-20	It can be used for dementia testing as well
<i>DST</i>	Psychomotor speed, attention	Yes	No/Yes	4	Tends to be very sensitive and is an early indicator
<i>LTT</i>	Psychomotor speed, visuomotor ability	Yes	No/Yes	2-4	Outcomes are errors and time; tests a balance between speed and accuracy
<i>SDT</i>	Psychomotor speed	Yes	No/Yes	1-2	Only tests psychomotor speed but has a higher sensitivity than DST
<i>PHES</i>	Psychomotor speed, set shifting, attention, visual perception and visuospatial orientation, visuomotor ability	Yes	No/Not for all tests	15	
<i>R-BANS</i>	Verbal/visual/working memory, visuospatial, language, and psychomotor speed	Yes	No/Yes	35	Has been primarily studied in dementia and brain injury. Limited HE experience
<i>Animal-naming test</i>	Semantic fluency test, verbal retrieval and recall	No	No	1	Easy tool for caregivers for identify mental status alterations, for illiterate patients,
<i>ICT</i>	Response inhibition, working memory, vigilance, attention	Yes	No/No	15-20	Need highly functional patients, familiarity with computers may be needed
<i>SCAN test</i>	Working memory, vigilance, attention	Yes	No/No	15-20	
<i>EEG</i>	Generalized brain activity	No	Yes/Yes	10-15	Can be performed in comatose patients
<i>Visual evoked potentials</i>	Interval between visual stimulus and activity	No	Yes/Yes	May vary	Highly variable and poor overall results
<i>Brainstem auditory evoked potentials</i>	Response in the cortex after auditory click stimuli	No	Yes/Yes	May vary	Inconsistent response with HE testing/prognostication
<i>P300 cognitive evoked potentials</i>	An infrequent stimulus embedded in irrelevant stimuli is studied	No	Yes/Yes	Different ranges	
<i>CFE</i>	Visual discrimination and general arousal	No	Yes/Yes	10	Need highly functional patients

*modified from: Kappus MR, Bajaj JS. Covert hepatic encephalopathy: not as minimal as you might think. *Clin Gastroenterol Hepatol* 2012;10:1208-1219

NCT-A, number connection test-A; *NCT-B*, number connection test-B; *BDT*, block design test; *SDT*, serial dotting test; *DST*, digit symbol test; *LTT*, line tracing test; *PHES*, psychometric hepatic encephalopathy score; *ICT*, inhibitory control test; *CFE*, critical flicker frequency; *EEG*, electroencephalogram

previous OHE, a higher prevalence of MHE has already been demonstrated [41]. These findings have attracted increasing interest from the scientific community to verify whether the specific treatment of one or more of these conditions could lead to a consequent improvement in HRQoL.

HRQoL scores were impaired in almost all “Sickness Impact Profile” scales in patients with MHE compared to patients without. Significant impairment is seen in social interaction, alertness, emotional behavior, sleep, work, home management, and recreation and pastimes.

In a study using SF-3, Marchesini *et al* [46] showed that the etiology and duration of cirrhosis had no effect on HRQoL, whereas minor symptoms, such as pruritus and muscle cramps, had a significant negative impact. In decompensated cirrhosis, MHE impairs the domains of activity, emotional function and global scoring on the chronic liver disease questionnaire. MHE also reduces appetite in cirrhosis and as the liver dysfunction worsens malnutrition occurs, which adversely impacts HRQoL [47].

Prasad *et al* [10] showed that treating MHE patients with lactulose significantly improved not only their psychometric performance, but also their HRQoL. Such observations have since been confirmed in 115 patients with MHE. In 75% of patients with MHE resolution, a significant improvement in the “Sickness Impact Profile” and a correlation between improvement in psychometric performance and QoL were observed [45]. Sanyal *et al* demonstrated that the chronic administration of rifaximin in patients without OHE at enrollment, but with a history of recurring HE, significantly improved HRQoL [48].

MHE and falls

Patients with liver cirrhosis are at risk of fractures due to osteoporosis secondary to malnutrition, hypogonadism and liver failure [49-51]. The injuries, especially fractures and subsequent surgical sequelae, as well as related hospitalizations, are an important cause of morbidity and mortality in heart failure patients with cirrhosis [52]. The falls and subsequent fractures also have a serious impact on the patient's family and community, and have a high economic impact on the whole of society [53,54]. Roman *et al* [55] have shown that, because of falls, the need for healthcare (8.8% vs. 0%, $P=0.004$) and hospitalization (6.6 vs. 2.3%, $P=NS$) was greater in patients with MHE than in cirrhotic patients without MHE. The authors also demonstrated that the intake of psychoactive drugs was related to the presence of MHE and falls (75% vs. 15%). Multivariate analysis identified MHE (odds ratio [OR] 2.91, 95% confidence interval [CI] 1.13-7.48, $P=0.02$), in addition to a previous history of OHE (OR 2.87, 95%CI 1.10-7.50, $P=0.03$) and taking psychoactive drugs (OR 3.91, 95%CI 0.96-15.9, $P=0.05$), as independent factors associated with falls. These findings were subsequently confirmed by Soriano *et al* in a larger patient cohort [56]. The authors were able to conclude, using multivariate analysis, that the presence of cognitive impairment, or the presence of MHE diagnosed by

an abnormal Psychometric Hepatic Encephalopathy Score (PHES) were the only independent factors predictive of a fall (OR 10.2 95%CI 3.4-30.4, $P<0.001$). Moreover, the probability of a fall in one year was found to be significantly higher in patients with MHE (52% vs. 6.5%, $P<0.0001$) compared to those without MHE. Urios *et al* demonstrated that MHE patients show impaired balance, mainly on an unstable surface with eyes open, with longer reaction and confinement times and lower success in stability test limits compared to patients without MHE. In addition, the performance in attention and motor coordination tests correlated with most post-urography parameter alterations. Logistic regression analysis shows that post-urography parameters and the bimanual coordination test seem to be good predictors of falls [57].

Multidimensional impact of cirrhosis and HE on patients, family members, and caregivers

Liver cirrhosis is a major cause of morbidity and mortality in the United States [58, 59]. However, in addition to the burden of cirrhosis on the national health system, the impact of cirrhosis and complications such as HE on the family group (represented by both the patient and caregivers, taking account of health, economic and emotional status) is currently being assessed. In fact, eligibility for liver transplantation depends on the family's ability to take on the daily challenges presented by this medical condition, especially in view of the increasing financial impact associated with cirrhosis. Bajaj *et al* [11] have shown that cirrhosis has a severe impact on the family group in terms of employment (only 56% of members are in employment) and finances. Patients with previous HE had worse unemployment (87.5 vs. 19%, $P=0.0001$) and financial status (85 vs. 61%, $P=0.019$) compared with others.

Agrawal *et al* confirmed that, because of slowing of psychomotor function and reduced work performance, almost half of MHE patients do not have regular employment, compared to only 15% of patients without MHE. About 60% of blue-collar workers are unfit to work, compared to only 20% of white collar workers, as manual labor is affected more by MHE, whereas verbal intelligence remains preserved. Patients with MHE involved in complex occupational tasks are especially affected, as they endanger themselves as well as others. The impact of MHE on daily life is severe. Diminished work performance and lost wages also involve substantial costs. The socioeconomic implications of the profound negative effects of MHE on functioning in the workplace are significant [60].

Finally, in the liver transplantation setting, Aberg suggests that the prevention of pre-transplant disability by effective treatment of (minimal) HE, maintaining mobility, and planning work adjustments early during chronic liver disease, as well as timely post-transplant physical rehabilitation, continuous encouragement, self-efficacy improvements, and depression management, are key elements in successful employment-promoting strategies [61].

MHE and driving skills

Driving is a complex and potentially dangerous function, since it involves the integration of visuomotor coordination and selective attention. Visuomotor coordination is governed by all the information and stimuli produced by traffic, road signs and traffic lights, while orientation is an executive function that involves planning, making decisions, calculation of the potential errors, and the inhibitory response. In the US in 2009 there were about 34,000 fatal car crashes with an economic impact of millions of dollars. Thus, it is easy to understand how patients with cirrhosis, especially in cases of cognitive impairment, could be considered as being at extreme risk of road accidents.

Many papers have been published that analyze the relationship between MHE and driving capacity [62-64]. Bajaj *et al* have shown that patients with MHE diagnosed by ICTs have a 22% increase in the probability of committing violations of the highway code, compared with 7% of subjects without MHE [65]. Kircheis *et al* [66] showed that 52% of patients with HE did not possess the minimum eligibility requirements to drive. In the US there are approximately 4 million people suffering from liver cirrhosis and, depending on the case studies, the incidence of MHE amounts to about 60%. Patients with liver cirrhosis and HE also have a generally optimistic view of their driving skills [67].

Kircheis *et al* showed that all patients with mild to moderate OHE and 96% of patients with MHE believed that they were excellent drivers, compared to 92% of control subjects [66]. However, the driving abilities of individuals with MHE are limited, particularly if analyzed according to criteria based on: 1) a neuropsychological assessment of the cognitive domains involved in the ability to drive [68]; 2) on virtual simulators; or 3) on real driving road tests [64,66]. Bajaj *et al* [69] also showed how treatment with rifaximin, a slightly absorbable gut antibiotic proposed for the prophylaxis of recurrent OHE [70], also improved psychometric performance (91% vs. 61% placebo, $P=0.01$). They revealed how, in their 8-week study, the treatment significantly reduced the errors in simulated driving (31% vs. 76%, $P=0.013$), speeding (33% vs. 81%, $P=0.005$), and illegal activities (19% vs. 62%, $P=0.01$).

MHE and prognosis (survival and development OHE)

Although MHE represents an early stage in the spectrum of cognitive disorders associated with liver cirrhosis, its presence may correlate with an increase in mortality. Amodio *et al* [32] were among the first to examine the role of psychometric tests in the prognosis of patients with liver cirrhosis. The results of their "Choice 2" test were, in fact, associated with survival times. Although the model for end-stage liver disease and Child-Pugh scores are currently used in the prognosis, cognitive function also has a significant prognostic value, and thus may be used in combination with these staging systems of the patient's level of severity in terms of liver disease. Dhiman *et al* [71] studied the

correlation of age, level of serum bilirubin, Child-Pugh score, and PHES with prognosis. Patients with MHE showed a higher mortality rate than those without (39.1% vs. 22.9%). Moreover, the multivariate analysis identified two variables as significant independent prognostic factors; psychometric hepatic encephalopathy score $< \text{or} = -6$ [hazard ratio 2.419 (95%CI, 1.014-5.769)] and Child-Turcotte-Pugh score $> \text{or} = 8$ [hazard ratio 2.466 (95%CI, 1.010-6.023)] predicted poor survival. In another series, patients suffering from MHE were found to be at risk of developing OHE [59].

Diagnosis of MHE

There is no single optimal measure for assessing the presence of MHE. In fact, none of the methods proposed cover all aspects of HE: appropriate norms are needed for good sensitivity and specificity in identifying patients at risk of OHE; the rate of pathological results in patient groups without OHE differs markedly; and finally, the results of the various methods are not consistent. However, despite its significant negative impact on the daily lives of patients and caregivers, MHE is still likely to be ignored by most clinicians if standards of neuropsychological testing are not followed while testing a patient for MHE.

PHES test

This is a battery of tests consisting in five paper-pencil tests that evaluate cognitive and psychomotor processing speed and visuomotor coordination. The tests are relatively easy to administer and have good external validity [21]. PHES is the sum of the scores from all subtests of the battery, normalized for age and level of education. A simplified form of PHES, developed using only three of the original five tests, can be as good as the PHES in diagnosing MHE and in predicting the occurrence of OHE [72]. Table 2 summarizes the most used diagnostic tests.

CFF test

CFF test is a psychophysiological tool that studies the frequency at which a fused light (presented from 60 Hz downward) appears to be flickering to the observer. Previous studies have shown a reduction in its performance with worsening cognition and improvement after therapy. The CFF test requires several trials, intact binocular vision, absence of red-green blindness, and specialized equipment [17,73].

Continuous reaction time (CRT) test

CRT test evaluates the motor reaction time by having the patient press a button in response to auditory stimuli (through headphones). The results give the CRT index, which measures the stability of the reaction times. The test result can

differentiate between organic and metabolic brain impairment and is not influenced by the patient's age or gender; there is no learning or tiring effect. Simple software and hardware are required [74].

ICT

ICT is a computerized test that studies the response to inhibitory stimuli and working memory [33,75]. The ICT test has been judged to have good validity, but requires highly functional patients.

Stroop test

Stroop test, also available as an app for a smart phone or tablet, is used to evaluate psychomotor speed and cognitive flexibility by identifying the interference between recognition reaction time to a colored field and a written color name [76].

SCAN test

SCAN test is a computerized test that measures speed and accuracy in performing a digit recognition memory task of increasing complexity; the test has also been shown to be of prognostic value [32, 77].

Animal-naming test

The animal-naming test, which counts the maximum number of animals listed in 1 min, is also an efficient tool for illiterate patients; it provides an easily obtainable useful measure for the assessment of CHE/MHE [78].

EEG

EEG is used to detect changes in cortical cerebral activity across the wide spectrum of HE without patient cooperation or risk of a learning effect. The reliability of EEG analysis can increase with quantitative analysis (including the background frequency with mean dominant frequency or spectral band analysis) [79]. However, it is nonspecific and may be influenced by accompanying metabolic disturbances, such as hyponatremia as well as drugs. In most situations, the EEG requires an institutional setup and neurological expertise in evaluation, and the cost varies among hospitals.

Imaging

Abnormalities in brain white matter (WM), such as low-grade edema and structural impairments, have been well-

revealed in MHE by magnetic resonance imaging. These WM abnormalities are believed to be responsible for poor neurological performance and brain dysfunctions in MHE and to be associated with HE development. This thus suggests that WM imaging may be useful in characterizing potential MHE biomarkers. Chen *et al* used a Bayesian machine-learning technique, called a Graphical-Model-based Multivariate Analysis, to determine WM regions that characterize group differences. They concluded that WM DTI provides useful biomarkers capable of differentiating between MHE and no HE, which would be helpful for the detection of MHE [80]. In a paper by Hassan, MHE that preceded the development of neuropsychological changes was identified by brain (hydrogen-1) magnetic resonance spectroscopy (¹H-MRS). The authors suggest that ¹H-MRS may therefore be considered as a potential tool for the diagnosis of cirrhosis-associated cerebral dysfunction and a promising method for prioritization of subjects awaiting liver transplantation [81].

However, there is unfortunately still no optimal diagnostic protocol for the diagnosis of MHE. The "ideal" diagnostic tool should be based on a comparison between the different methods, on the evidence of the association of each of them with significant clinical outcomes—such as the ability to perform tasks that are potentially dangerous in real life, such as driving—and on patients' QoL, development of episodes of OHE and survival.

The diagnostic tools mentioned above are also used to test for MHE and CHE; however, they do not correlate well with each other because HE is a multidimensional dysfunction [82]. Moreover, there is often a learning effect with psychometric tests and it is unclear whether current HE therapy plays a role in the test performance. Therefore, the interpretation of these tests and the use of the results for further management require a complete evaluation of the patient's history, the current therapy, as well as the effect on the patient's daily activities. Due to the high incidence of MHE and CHE in patients with liver cirrhosis, each patient considered at risk should "ideally" be tested. However, this strategy may be costly [63]. In addition, the consequences of this screening strategy are still not always clear and a specific treatment—i.e., rifaximin, non-absorbable disaccharides, probiotics—is not always recommended unless on a case-by-case basis.

A cost-effective diagnostic approach may be to test patients who have an impairment in their QoL or fitness to drive [83]. It is also important to test only those patients who do not have confounding factors, such as neuropsychiatric disorders, those on psychoactive medication, or those who report current alcohol use or pharmacological treatment for HE; moreover, testing should be done only by a trained examiner [84]. If the test result is normal (i.e., negative for MHE or CHE), guidelines suggest repeating the test after six months [85]. For multicenter studies, AASLD/EASL guidelines for the management of HE [86] suggest that the diagnosis of MHE or CHE by consensus should use at least two of the current validated testing strategies: paper-pencil (PHES) and one of the following: computerized (CRT, ICT, SCAN, or Stroop) or neurophysiological (CFF or EEG).

Treatment

Despite its subtle nature, MHE and CHE can have a significant effect on a patient's daily life, and in special circumstances (e.g., impairment of driving skills or work performance, poor QoL, or cognitive complaints) the indication to treat the patient may prevail. However, because of the multiple methods used to define MHE and CHE (even based on normative data for a studied population), the varying and multiple endpoints, short-term treatment trials, and differing agents used in trials to date, recently published guidelines state that treatment of MHE and CHE is not routinely recommended apart from on a case-by-case basis [85]. Table 3 provides a complete overview of the studies of MHE treatment.

Rifaximin

Rifaximin is an oral non-systemic broad-spectrum antibiotic, structurally similar to rifampin. By binding to bacterial DNA-dependent RNA polymerase, rifaximin inhibits bacterial RNA/protein synthesis. Structurally, the benzimidazole ring limits systemic absorption by 0.4%, with the primary mode of excretion via feces and low levels of drug excreted in the urine or bile. Concentrated in the gut, rifaximin is presumed to modulate intestinal bacteria, thereby reducing intestinal ammonia and toxin formation. Bajaj *et al* demonstrated that patients with MHE treated with rifaximin for an 8-week period showed significantly greater improvements in driving and cognitive performance and in the psychosocial dimension of the Sickness Impact Profile than those given a placebo [69]. These results were confirmed in another randomized controlled trial (RCT), in which the authors demonstrated that rifaximin significantly improves both cognitive functions and HRQoL in patients with MHE [45]. Recently, an RCT comparing rifaximin with lactulose for MHE reversal and HrQoL amelioration failed to demonstrate significant differences between groups [86].

Non-absorbable disaccharides

Lactulose or lactitol are synthetic non-absorbable disaccharides extensively used in the management of OHE. Lactulose is fermented in the colon into acetic and lactic acid, resulting in the acidification of intestinal contents and conversion of ammonia (NH_3) to ammonium (NH_4^+). Unlike ammonia, ammonium is not systemically absorbed and is excreted in stool. Lactulose also has a cathartic effect, increasing nitrogen excretion fourfold.

Although Prasad *et al* [10] concluded that treatment with lactulose improves both cognitive function and HRQoL in patients with cirrhosis who have MHE, most subsequent studies have not provided strong evidence on the efficacy of non-absorbable disaccharides in MHE treatment [45,87-90]. A meta-analysis evaluating the role of pharmacological

treatment with non-absorbable disaccharides in patients with MHE failed to show clear evidence that any treatment played a convincing role in improving cognitive function and HRQoL [91].

Probiotics

Probiotics are live microorganisms that alter the balance of intestinal microflora, and synbiotics are probiotics with the addition of fermentable fiber. It is presumed that reducing intestinal bacterial urease activity decreases the absorption of ammonia and other gut-derived toxins that result in oxidative stress/inflammation.

Seven recently published RCTs have tried to evaluate the role of probiotic treatment/supplementation in treating MHE. Unfortunately, the results do not support the evidence on the efficacy in MHE reversal of a treatment with probiotics alone or in addition to other drugs [88-90,92-95]. In fact, no significant difference in the improvement of MHE, hospitalization rates, or progression to OHE has been reported when probiotics were compared with lactulose [96].

Branched-chain amino acids

A meta-analysis that evaluated the role of pharmacological treatment with branched-chain amino acids in patients with MHE reported no significant difference in the improvement of MHE [97].

LOLA (L-ornithine-L-aspartate)

LOLA has been shown to reduce ammonia levels [98,99] by upregulating glutamine synthetase and urea cycle activity [100]. L-ornithine and L-aspartate are separately metabolized to form glutamate, which, combined with ammonia, results in the formation of glutamine. Therefore, LOLA lowers plasma ammonia concentrations by enhancing the metabolism of ammonia to glutamine. Bai *et al* evaluated eight RCTs (646 total patients, 46% diagnosed with MHE), assessing the efficacy of LOLA compared to placebo in patients with cirrhosis. Treatment with LOLA diminished serum ammonia levels with no increase in adverse reactions [100].

Grey areas and future needs

MHE and CHE correspond to a broad spectrum of neuropsychological manifestations of liver disease that require quantification and in which differential diagnoses should be carefully considered. The detection of risk thresholds for the occurrence of OHE, impairment in daily life activities and in QoL has unfortunately not yet been well defined. Therefore, future clinical research should try to detect such thresholds.

Table 3 Published studies on treatment of minimal hepatic encephalopathy

First Author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Plauth [115]	1993	Original (only abstract)	Psychometry	BCAA	17	8	Psychometry and driving ability	BCAA superior to placebo on both outcomes
Watanabe [101]	1997	Original, randomized	NCT A, symbol digit test, BDT	Lactulose	22 out of 36	8	Psychometry	MHE had disappeared in 10 (50%) of the 20 treated patients at week 8, but it persisted in 11 (85%) of the untreated 13 patients
Horsmans [102]	1997	Original, randomized	NCT, RTT, sinusoid test, psychomotor performance tests	Lactulose	7 out of 14	2	Psychometry, ammonia	NCT improved respectively in 5/7 vs. 1/7; RRT in 6/7 vs. 4/7 and ammonia levels in 5/7 vs. 1/7
Dhiman [103]	2000	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose	10 out of 18	12	Psychometry	Psychometry improvement in 8/10 vs. 0/8
Prasad [10]	2007	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose	45 (25)	12	Psychometry, QoL	Significant improvement in psychometry: $P < 0.001$; and QoL: $P < 0.002$. Improvement in HRQoL was related to the improvement in psychometry.
Sharma [90]	2008	Original, randomized controlled trial	NCT A, NCT B or FCT A and FCT B, CEP	Lactulose or Probiotic or Lactulose+Probiotic	92 (31/31)	4	Psychometry, CEP, ammonia	Normalization of all parameters in half of treated patients (17/31, 16/31 and 17/30 respectively)
Mittal [89]	2011	Original, randomized	NCT A, NCT B, FCT A, FCT B, PC, BDT	Lactulose or Probiotics or LOLA	160 (40/40/40)	12	Psychometry, ammonia, QoL	MHE reversal in 19/40 vs. 14/40 vs. 14/40 vs. 4/40. Improvement in QoL.
Sharma [104]	2012	Original, randomized	NCT A, NCT B, FCT A, FCT B, Digit symbol test, serial dotting test, LTT, CFF	Lactulose	105 (55)	12	Psychometry; OHE development	Improvement of MHE in 21/32 (66%) vs. 9/36 (25%)
Bajaj [11]	2012	Cost effectiveness Markov analysis	Psychometry, ICT	Lactulose vs. Rifaximin	1000	260	Prevention of road traffic accidents	Suggestions: MHE diagnosis with ICT and treatment with lactulose
Ziada [105]	2013	Original, open label randomized controlled trial	NCT A, Digit symbol test, serial dotting test	Lactulose or Probiotic	75 (24/26)	4	MHE measures, ammonia, progression to OHE	Normalization of psychometry in half of patients treated (13/24 vs. 14/26 vs. 3/25). Reduction of OHE risk development

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Table 3 (Continued)

First Author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Sidhu [86]	2016	Original, randomized	NCT A, FCT A, digit symbol test, BDT, PC	Lactulose vs. Rifaximin	112 (55/57)	12	MHE reversal, QoL	MHE reversal in 38/55 and in 42/57; HRQoL was significantly improved in both groups
Rai [106]	2015	Original	PHES battery	Lactulose and Rifaximin	7 (7)	8	Reversal of cerebral edema, ammonia, cytokine levels, Psychometry	Psychometric improvement (P=0.044); reversal of low-grade cerebral edema
Pratap [107]	2015	Original, randomized	NCT A, FCT B (or FCT A, FCT B), CEP	Lactulose or Probiotic	73 (40/33)	8	MHE measures, ammonia	Psychometric improvement in 23/33 and in 25/40. Improvement in MHE correlated with reduction of ammonia levels.
Sidhu [45]	2011	Original, randomized	NCT A, FCT A, Digit symbol Test, BDT, PC	Rifaximin	94 (49)	8	MHE reversal, QoL	MHE reversal in 37/49 vs. 9/45. Improvement in QoL. Improvement in HRQoL correlated with improvement in psychometry
Bajaj [67]	2011	Original, randomized	NCT A, NCT B, digit symbol test, BDT, ICT	Rifaximin	42 (21)	8s	Psychometry, QoL, driving ability, anti-inflammatory interleukins	Improvement in psychometry, driving performance and QoL
Bajaj [108]	2013	Original	PHES battery, BDT	Rifaximin	20 (20)	8	MHE measures, ammonia	Significant improvement in cognitive performance (6/7 psychometric tests)
Zhang [109]	2015	Original	NCT A, NCT B, digit symbol test	Rifaximin	26 (26)	1	Psychometry, ammonia, SIBO	MHE reversal in 15/26; reduction in SIBO and ammonia levels
Liu [110]	2004	Original, randomized	NCT, Brainstem Evoked Potentials	Synbiotics or fiber	55 (20/20)	4	Psychometry, Ammonia Psychometry:	Modulation of the 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 Child-Turcotte-Pugh functional class improved in nearly 50% of cases
Malaguarnera [92]	2007	Original, randomized	TMT A, TMT B, Symbol Digit Test, BD, MMSE, EEG	Probiotic+prebiotic	60 (30)	12	Psychometry, Ammonia, EEG	Improvement in psychometry and ammonia; no EEG modifications

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Table 3 (Continued)

First Author	Year	Study type	MHE/CHE diagnosis	Active treatment (s)	Patients treated	Weeks of treatment	Objectives	Main results
Bajaj [95]	2008	Original, randomized	NCT A, Digit symbol test, BDT	Probiotic yogurt	25 (17)	8	MHE reversal, OHE development, QoL, ammonia, cytokines	MHE reversal in 71% vs. 0%; OHE development in 0% vs. 25%; no differences in QoL and cytokine Levels. Excellent adherence in cirrhotics after probiotic yogurt supplementation with potential for long-term adherence
Bajaj [111]	2014	Original, randomized	NCT A NCT B, Digit symbol test, BDT	Probiotics	30 (14)	8	Psychometry, ammonia, inflammatory markers, QoL	Reduction in endotoxin and TNF- α but not in cytokines. No effects on psychometric performance
Burkard [112]	2013	Original, randomized	PHES battery	Potassium-iron-phosphate-citrate	51 (25)	4	Psychometry	Normalization of psychometry in 72% vs. 26.9%. QoL improvement.
Shukla [113]	2011	Meta-analysis	Different diagnostic tools	Lactulose, probiotics, prebiotics, synbiotics	349	Variable	Psychometry, ammonia	All treatment were effective in improving MHE (RR 0.40, 95% CI 0.32-0.50; P<0.001) and in reducing blood ammonia levels
Luo [114]	2011	Meta-analysis	Different diagnostic tools	Lactulose	434	Variable	Psychometry, ammonia levels, QoL, progression to OHE	Lactulose superior to placebo on all outcomes (psychometry: RR 0.52, 95%CI 0.44-0.62, P<0.00001)

MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; HRQoL, health-related quality of life; NCT-A, number connection test-A; NCT-B, number connection test-B; BDT, block design test; SDT, serial dotting test; DST, digit symbol test; LTT, line tracing test; PHES, psychometric hepatic encephalopathy score; ICT, inhibitory control test; CFF, critical flicker frequency; EEG, electroencephalogram; ICT, inhibitory control test; BCAA, branched chain amino acids; SIBO, small intestinal bacterial overgrowth; CEP, cognitive evoked potentials

The diagnostic methods needed to form the basis for clinical trials also need to be investigated. The diagnosis of MHE and CHE has received considerable interest; however, it is still not possible to compare results among studies and the precision needs improving.

One important area of uncertainty is whether the term CHE, introduced to expand MHE to grade I oriented patients, is actually informative and clinically valuable. A closer scientific collaboration between clinical hepatologists and brain researchers, including functional brain imaging experts, is needed, and neuropsychologists and psychiatrists may also be needed to clarify the broad spectrum of neuropsychiatric symptoms observed in patients with liver disease.

The proposed treatment for MHE and CHE is actually the same as the one used for the treatment/prophylaxis of OHE; however, in most cases these strategies only manage to ameliorate the indices of brain function (psychometric or neurophysiological) or lower ammonia. In addition, other treatment strategies are reasonably based on an alternative approach that considers drug use after having tested the efficacy of dietetic counseling, modification of gut microflora, as well as the correction of confounders or precipitating factors for HE, such as hyponatremia, or possibly based on a more complete knowledge of changes in human gut microbiota and the neurobiology of the encephalopathy.

Studies specifically aimed at establishing whether the treatment of MHE is able to affect clinically relevant endpoints are therefore greatly needed. The patients' inclusion should be based on the objective definition of the presence of minimal or CHE. The modification of psychometric tests should not be chosen as the main endpoint of the study; the tests should instead be used merely as a criterion to include comparable patients. The sample size should be calculated according to one of the clinically relevant endpoints, such as the QoL or the incidence of OHE; data on these outcomes are available in the literature. The assessment of the efficacy of a given treatment to prevent OHE in patients with MHE requires the organization of large multicenter studies. A parallel design with a placebo or a no-treatment arm is mandatory. Because MHE is a chronic condition, the choice of the drug to be tested should be limited to those that can be administered for a very long period of time without significant side-effects. Among the emerging drugs, modulators of the intestinal bacterial flora should be the first candidates to be tested in this field. Future studies should fill the gaps in our knowledge.

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