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Chapter

Minimal Hepatic Encephalopathy: Silent Tragedy

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Abstract

Hepatic encephalopathy (HE) is brain dysfunction caused by both acute and chronic liver diseases that produces a spectrum of neuropsychiatric symptoms in the absence of other known brain diseases. Minimal hepatic encephalopathy (MHE) is the mildest form of this spectrum. MHE is defined as HE without symptoms on clinical or neurological examination, but with deficits in the performance of psychometric tests, working memory, psychomotor speed, and visuospatial ability. Minimal hepatic encephalopathy is associated with impaired driving skills and increased risk of motor vehicle accidents and has been associated with increased hospitalizations and death. Despite its clinical importance, a large number of clinicians had never investigated whether their cirrhotic patients might have MHE. Although, there is no single gold standard test for diagnosis of MHE, a combination of two neuropsychological tests or psychometric hepatic encephalopathy score battery test and/or neurophysiological test is standard for diagnosis of MHE. It was found that, treatment for MHE improves neuropsychiatric performance and quality of life and decreases the risk of developing overt HE (OHE). The agents used to treat OHE have been tested in patients with MHE. In particular, lactulose, rifaximin, probiotics and L-ornithine and L-aspartate (LOLA) have all been shown to be beneficial, with documented improvement in psychometric performance after treatment.

Keywords: liver cirrhosis, hepatic encephalopathy, minimal hepatic encephalopathy, ammonia, neuropsychological testing, motor vehicle accident, lactulose and rifaximin

1. Introduction

Hepatic encephalopathy (HE) is a serious clinical problem of portal hypertension and cirrhosis that is characterized by neurologic and neuropsychiatric abnormalities. It is manifested by personality changes, cognitive dysfunction, and altered level of consciousness [1, 2]. Based on the severity, HE is classified into two groups: overt HE (OHE) presents episodically or continuously with obvious and clinically detectable symptoms; in contrast, covert HE (CHE) combines the two lowest grades of HE (minimal HE (MHE) and HE grade 1) [3]. Therefore, under the new classification (**Table 1**), OHE starts with grade 2 or with evidence of asterixis and disorientation. MHE is characterized by subtle cognitive and psychomotor deficits in the absence of recognizable clinical symptoms and signs of HE and is documented by neuropsychometric (NP) tests and neurophysiological tests, but HE grade 1 is defined by the presence of mild clinical alterations like euphoria, anxiety, or a shortened attention span. Although the consequences are serious, mostly CHE

Classification	Covert HE		Overt HE		
	MHE	Grade I	Grade II	Grade III	Grade IV
Description	* Absence of recognizable clinical symptoms and signs * Impairments only measurable with psychometric tests (psychomotor speed/ executive functions or neurophysiological alterations)	* Minor lack of awareness * Euphoria or anxiety * Shortened attention span * Altered sleep rhythm	* Fatigue, apathy, or lethargy * Slight disorientation for time and place * Obvious personality change * Inappropriate behavior * Asterixis	* Somnolence to semi-stupor * Confused * Marked disorientation to time and place *Aggression	* Coma * Signs of increased intracranial pressure

Table 1.
New classification combining covert and overt HE.

is often unnoticed or even neglected in routine clinical practice due to only very mild symptoms associated with grade 1, or no diagnostics in case of MHE [4, 5].

Minimal hepatic encephalopathy may have a bad impact on quality of life, risk of road traffic accidents, and can progress to overt HE [6, 7]. Still, there are no current guidelines for the ascertained diagnosis of MHE. The Working Group on HE endorsed that, at least two of the following neuropsychologic tests should be used for diagnosing MHE: number connection test-A (NCT-A), NCT-B, block-design test (BDT), and the digit-symbol test (DST) [4]. The existing definition of MHE is built on psychometric test results that are two SDs more than normal on at least two psychometric tests [8]. Therapy for MHE is targeted toward the gut, due to the ammoniagenic role of the gut contents, which have been hypothesized to play a part in MHE pathogenesis. Guidelines for HE in chronic liver disease do not recommend routine treatment of MHE. However, they state that when a patient has clear cognitive impairment, or deterioration of quality of life (QoL), skills for driving, or ability to perform jobs that require manual labor or have high public risk, the patient should be treated [3, 9].

2. Prevalence of MHE

MHE is considered as a part of wide spectrum of typical neurocognitive alterations in liver cirrhosis, mostly involving the areas of attention, alertness, response inhibition, and executive functions [10, 11]. Depending on the population studied, patient level of education, age of the patients, and the diagnostic tool used, MHE incidence varies from 20 to 80% of cirrhotic patients [12–15].

3. Physiopathology

The pathogenesis of MHE is nearly similar to that of OHE [16]. The ammonia toxicity remains the key factor, but recently there is increased evidence that, hyperammonemia acts synergistically with systemic inflammation, oxidative stress, and gut microbiota [17, 18]. Numerous investigators suggested that, hepatic encephalopathy is a disorder of astrocyte function that plays a role in the detoxification of ammonia [19].

3.1 The role of ammonia

Ammonia is a key intermediate product in the metabolism of proteins. It is manufactured by the bacterial metabolism of amino acids and purines that are consumed in the human diet [20]. Under physiological environment, about 90% of the ammonium is primarily cleared by the synthesis of urea in the liver (by the Krebs cycle) and subsequently cleared by the kidneys and to a lesser extent by the muscles (**Figure 1**). Ammonia is also consumed in the conversion of glutamate to glutamine, a reaction that depends upon the activity of glutamine synthetase [21]. In liver cirrhosis, there are two factors that contribute to hyperammonemia: the first is a decrease in the healthy hepatocytes, resulting in deficiency of NH_3 detoxification; the second is the existence of porto-systemic shunting that results in shifting of NH_3-rich portal blood to the systemic circulation without hepatic detoxification—subsequently, the extrahepatic metabolization of ammonia by the brain and skeletal muscle cells becomes more important [17, 22, 23]. The skeletal muscle plays a significant role in ammonia metabolism as it contains glutamine synthetase. However, the muscle wasting that is clear in advanced cirrhosis may increase hyperammonemia. The kidneys express glutaminase and, somewhat, play a role in ammonia production. Similarly, the kidneys express glutamine synthetase and play a key role in ammonia metabolism and excretion [20]. Ammonia crosses the blood-brain barrier and is metabolized in the astrocytes by glutamine synthetase, which converts NH_3 and glutamate to glutamine [17]. Increasing glutamine in astrocytes produces an osmotic gradient (**Figure 2**), promotes water shift into astrocyte producing edema [23], and generation of reactive oxygen species,

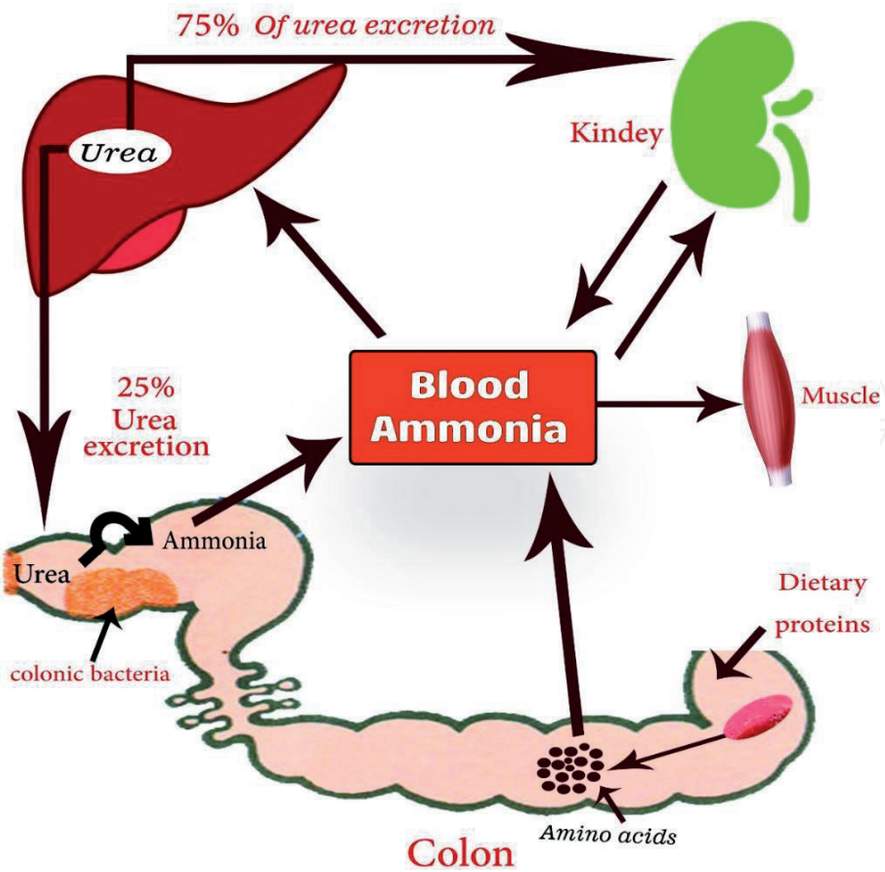


Figure 1.
Ammonia is produced primarily in colon from breakdown of amino acids and urea by bacteria. The ammonia is taken up by hepatocytes and converted, in the urea cycle, to urea, which is passed into blood. Urea is primarily excreted in the kidneys (75%) and the intestine (around 25%).

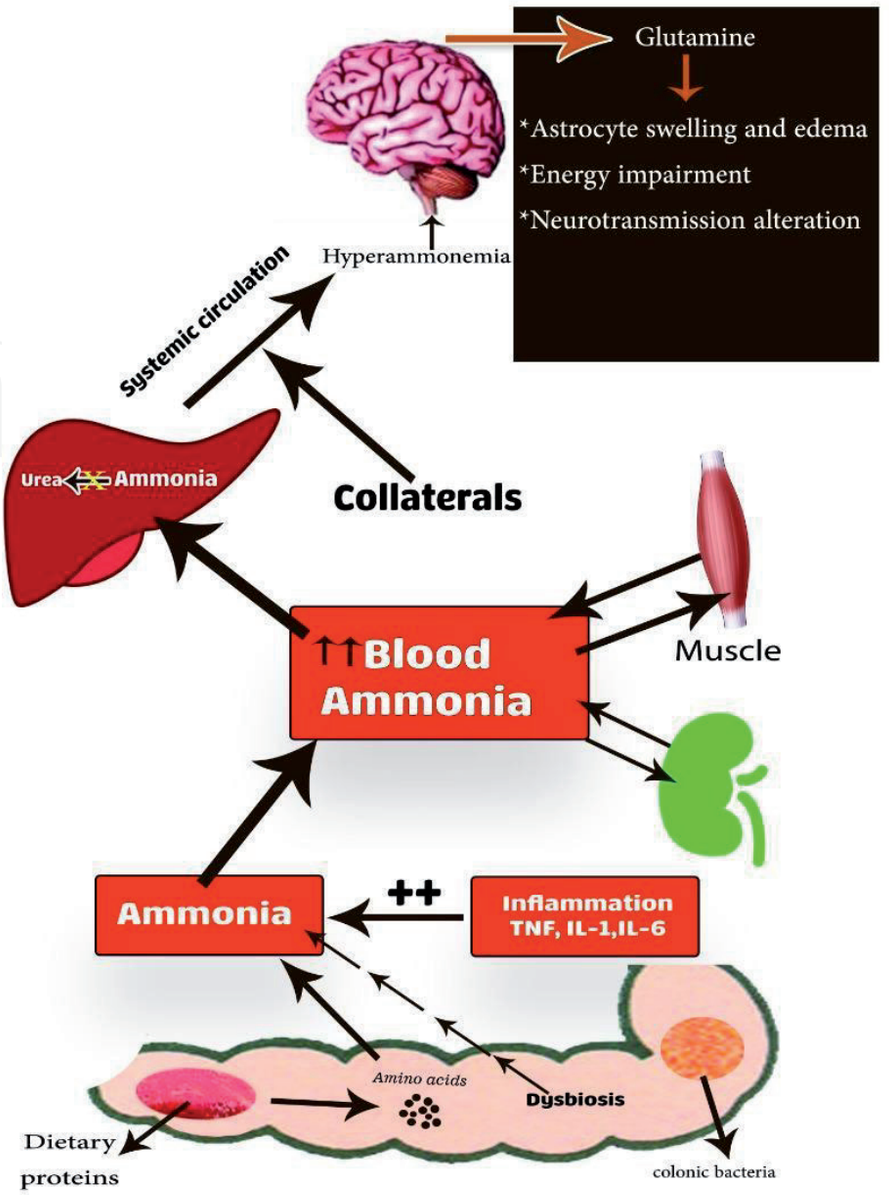


Figure 2.
Pathogenesis of hepatic encephalopathy. In normal conditions, gut release of ammonia results in high portal vein ammonia levels. Microbiota is also responsible for the formation of ammonia, endotoxins. In liver cirrhosis, the liver extracts portal venous ammonia poorly. The subsequent increase of arterial ammonia levels leads to increased disposition of ammonia in other tissues. Both the brain and muscle lack a complete urea cycle and rely on the formation of glutamine. Thus, the brain and muscle become ammonia-uptake and glutamine-releasing organs. In the brain, astrocytes metabolize ammonia through glutamine synthetase, converting glutamate and ammonia to glutamine which is osmotically active and promotes water shift into the astrocyte, thus producing intracellular swelling and edema.

thereby contributing to the cerebral dysfunction seen in HE [17]. The high-energy consumption by this process leads to oxidative stress which is accompanied by cellular dysfunction and disruption of neurotransmission predominantly of glutamate and γ-aminobutyric acid [24]. In the brain, NH_3 produces inactivation of neuronal chloride extrusion pumps; these processes result in inhibition of both axonal conduction and excitatory postsynaptic potentials, subsequently suppressing inhibitory postsynaptic potential formation and depolarizing neurons [25, 26].

3.2 Inflammation

Studies demonstrated that, severity of MHE might not correlate with severity of liver disease or the level of ammonia, proposing the existence of other pathogenic

stimuli. Inflammation is one such stimulus that may add to the advancement of MHE and its progression to overt HE [27]. The studies suggested that, inflammation plays a synergistic role with ammonia in producing and modulating MHE [27–29]. Studies in patients with cirrhosis have documented higher levels of proinflammatory cytokines like tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6. This reflects the possibility of developing a systemic inflammatory response that alters the blood-brain barrier (BBB) permeability and allows diffusion of ammonia moreover [30, 31].

3.3 Microbiota

Studies suggested that, many interactions with gut microbiota can play an active role in MHE (**Figure 2**). Microbiota changes have been linked with impaired cognition, endotoxemia, and inflammation. With the progression of cirrhosis, there is dysbiosis (unfavorable change in the composition of the microbiome) with decreased levels of autochthonous taxa (native Firmicutes) bacteria and increased levels of other taxa (Bacteroidetes, Actinobacteria). The native bacteria are important for the harmony of the gastrointestinal flora and for the well-being of the entire body. The autochthonous bacteria produce short-chain fatty acids that feed the colonic mucosal cells and reduce local colonic inflammation, and produce anti-bacterial peptides [32]. In patients with minimal HE, stool microbiota studies demonstrated an increase in *Streptococcus salivarius* [33]. Zhang et al. found worse dysbiosis in all cirrhotic patients versus healthy controls and also found over-representation of two bacterial families, Streptococcaceae and Veillonellaceae, in cirrhotic patients with and without MHE as compared with controls. Moreover, patients with MHE had an overabundance of *Streptococcus salivarius*. This dysbiosis could increase ammonia production due to its urease activity, and its count positively correlated with ammonia levels and cognitive testing in patients with MHE [34]. The cirrhosis dysbiosis ratio (CDR) is the ratio of autochthonous to non-autochthonous taxa in cirrhosis. The lower the CDR the more the endotoxemia and more decompensated the cirrhosis [35].

4. Natural history of MHE

The incidence of MHE increases with progression of liver disease. With time, MHE may improve or progress to OHE [36, 37]. The rate of progression to overt HE was much higher in patients with MHE and Child-Pugh score > 6 than in those with MHE and Child-Pugh score ≤ 6 [38]. Moreover, MHE in patients with large portal-systemic shunts had a better outcome due to preserved hepatocytes [39]. Real probability of OHE at 3 years was 56% in patients of liver cirrhosis in the presence of MHE and 8% for those without MHE [37]. In addition, existence of MHE in cirrhosis associated with shorter survival time and increased mortality rate compared to those without MHE [40–43].

5. Clinical significance

MHE has a significant impact on daily activities. It decreases patients' quality of life (QoL) [43, 44] and driving impairment due to the attention and visuomotor coordination deficits [45–47]. The Sickness Impact Profile was studied in a group of patients with cirrhosis to evaluate QoL indicators such as sleep, rest, eating, work, home management, recreation, ambulation, daily care, movement, and emotional behavior. All scales were significantly decreased in patients with MHE compared

with individuals without MHE [48]. Moreover, those patients suffer from falls [49] and have a high risk of development of episodic HE [2].

5.1 Health-related quality of life (HRQoL)

Quality of life is a multidimensional index that reports all aspects of human well-being, including physical and cognitive capabilities, functional behavior, emotional status, and psychosocial adjustment [50]. The American Association for the Study of Liver Diseases survey conducted in 2007 demonstrated that, most clinicians believe MHE to be a significant problem. However, only 50% of clinicians had examined whether their patients might have MHE, and 38% had never studied their patients with liver cirrhosis [51]. Several evidences show that, HRQoL may seem to be influenced by the coexistence of MHE [48, 52–56]. MHE increases the incidence of disability, and has a negative effect on daily activities. The impact of the perception of the disease, in the form of a "Sickness Impact Profile," has been studied in cirrhotic patients to assess the indicators of QoL. Each profile was significantly reduced in patients with MHE compared to individuals without MHE [48]. In addition, in the presence of MHE, QoL indicators, such as the capacity to drive a car, and the incidence of sleep disorders were also negatively affected [57, 58].

5.2 MHE and falls

Minimal hepatic encephalopathy is significantly associated with high risk of falls explaining the increased healthcare and hospitalization rate in patients with MHE compared to cirrhotic patients without MHE [49, 59, 60]. The presence of cognitive impairment was the only independent factor predictive of a fall. The chance of a fall in 1 year was found to be significantly higher in patients with MHE 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 [61].

5.3 Effect of MHE on driving

Traffic accidents are more common in patients with MHE compared to normal individuals, as the driving process in patients with MHE is affected by defects in many factors such as, defects in attention and information processing, slow reactions, improper estimation of traffic conditions, and lack of coordination [48, 62]. As many as 33% of MHE patients reported a traffic accident or violation within the past year [63]. Interestingly, treatment with lactulose could substantially reduce societal costs by preventing motor vehicle accidents [64].

5.4 Risk of overt HE

MHE has been found to predict the development of overt HE in cirrhotic patients [2]. A recent study demonstrated that, CHE and elevated blood NH_3 levels contributed to OHE development in cirrhotic patients [65]. The results of Wang et al. showed that, solely serum albumin level < 30 g/L is the predictor for developing OHE in CHE patients [66]. In a study of Thomsen et al., that enrolled 106 clinically stable cirrhotic patients with no previous history of OHE and followed them for 230 ± 95 d, it was found that, 13.3% of CHE patients developed OHE [67]. In a multicenter study by Patidar et al., a total of 170 cirrhotic patients were followed for

a mean of 13 months. They found that 30% of cirrhotic patients developed at least one OHE episode, and that CHE increased their risk of developing OHE, hospitalization, and death/transplant [36].

6. Diagnosis of MHE and CHE

There is no single optimal measure for diagnosis of MHE because none of the diagnostic strategies covers all aspects of deficits that are present in MHE [68, 69]. Testing approaches can be divided into two major types: psychometric and neurophysiological [70, 71]. As MHE affects many elements of cognitive functioning, which may not be impaired to identical degrees, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommends the use of at least two tests, based on the local population norms and availability, and if possible, with one of the tests being more widely accepted to serve as a comparator [72].

6.1 Diseases associated with minimal hepatic encephalopathy

The diagnosis requires the indication of tests in subjects who appear normal, but may suffer from cirrhosis, as the physician usually does not observe MHE [73]. Further group of patients who are not cirrhotic and may develop MHE are those with porto-systemic shunts of inborn origin or secondary to portal thrombosis. The available data of the neuropsychological characteristics of these patients indicate that cognitive abnormalities are indistinguishable from MHE [74].

6.2 Indications for testing

There is no consensus on patients to test for MHE. Some physicians recommend screening of all cirrhotic patients. However, testing should be completed in patients at risk (**Table 2**) for MHE such as, cirrhosis or porto-systemic shunts [5]. Special attention should be given to active drivers, patients handling heavy machines or reporting decline in work performance [75, 76].

6.3 Neuropsychological (paper-and-pencil) tests

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver recommended neurophysiological

Patients at risk of accidents
• Risks at work, e.g., machine worker
• Driving accident within the past year
• Unprovoked falls
Patients who complain of cognitive symptoms
• Psychomotor performance: “I have difficulty in carrying out fine motor tasks.”
• Decreased attention: “I am frequent feelig of confused.”
• Poor memory: “I forget a lot”.
Patients with decline in work performance observed by relatives or colleagues
Patients with previous history of episodic HE

Table 2.
Patients with cirrhosis, portal vein thrombosis, or porto-systemic shunts who should undergo tests for MHE.

Test	Tested domain	Time required (minuets)	Advantages	Disadvantages	Impact factor
NCT-A	Psychomotor speed	1–2	Gold standard for MHE diagnosis validated internationally	Learning effects	Age and culture
NCT-B	Psychomotor speed, set shifting, divided attention	1–3	Validated internationally	Learning effects	Age and culture
DST	Psychomotor speed, attention	4	Very sensitive and is an early indicator	Learning effects	Age and culture
BDT	Visuospatial reasoning, praxis, psychomotor speed	10–20	It can be used for dementia testing as well	Learning effects	Age and culture
SDT	Psychomotor speed	1–2	Only tests psychomotor speed, a higher sensitivity	Learning effects; only tests psychomotor speed	Age and culture
LTT	Psychomotor speed, visuomotor ability	2–4	Tests a balance between speed and accuracy	Learning effects, outcomes are errors and time	Age and culture
Animal-naming test	Semantic fluency test, verbal retrieval and recall	1	Easy test that has the required characteristics of simplicity, speed, for illiterate patients	Less validated test	
CFF	Visual discrimination and general arousal	10	Easy administration, application by a non-specialist, and results are independent of literacy and age, test can be administered at bedside	Not suitable for red-green blindness and visual impairment	Age
ICT	Response inhibition, working memory, vigilance, attention	15–20	Simple administration, higher sensitivity/specificity	Need highly functional patients, not suitable for non-English-speaking patients	Age and education
Stroop test	Psychomotor speed and cognitive alertness	10	Quick to explain to patients, and simple to score and evaluate	Should be familiar with iPhone/iPad	Age and education
The SCAN Test	Working memory, vigilance, attention	15–20	Simple administration	Learning effects	Age and education
CDR assessment battery	Reaction time, memory, and recognition	15	Appreciable test-retest reliability	Learning effects	Age, education, and culture
EEG	Generalized brain activity	10–15	Can be done in comatose patients, no need of patient cooperation or risk of a learning effect	Nonspecific and may be influenced by accompanying metabolic disturbances	Requires neurological expertise in evaluation

Table 3.
Psychometric tests recommended for diagnosing minimal hepatic encephalopathy.

and psychometric tests to diagnose MHE [3, 51]. Many tests are used for diagnosis of MHE (**Table 3**); however, the gold standard and the most frequently used psychometric test for MHE diagnosis is psychometric hepatic encephalopathy score (PHES) [3, 4, 42].

6.3.1 Standard neuropsychological assessment

Neuropsychological testing is a useful methodology for quantifying cognitive impairment. These tests directly measure cognitive functions that are directly related to activities of daily living. These include the number connection test A (NCT-A), number connection test B (NCT-B), figure connection test (FCT A), figure connection test B (FCT B), digit symbol test (DST), and serial-dotting test (SDOT) [77].

6.3.1.1 Number connection tests

The NCT-A accesses the visual-spatial orientation and psychomotor speed. Twenty-five circles numbered from 1 to 25 are scattered randomly on a sheet of paper. The patients must connect the numbers in order in the shortest time possible without mistakes. If a mistake is made, the subject must stop, correct the error, and then continue without stopping the clock. The test score is the time needed to perform the test, including the time needed to correct all errors. Poorer performance is shown by a longer time for completion (**Figure 3**). In the NCT-B (**Figure 4**), the numbers from 1 to 13 and the letters from A to L were included in circles. The patient is asked to connect numbers and letters in alternating manner, that means go from 1-A-2-B-3-C and so on. Test outcome is the time needed by the patient to perform the test, including error correction time. Besides visuospatial orientation and psychomotor speed, this test is suitable to study the ability to shift attention [78].

According to the guidelines of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism [79], the results of NCT-A will be considered abnormal when the test scores are more than the mean + 2 standard deviations (SDs) from the age-matched normal values. A newly developed electronic number connection test (eNCT) was developed. This test flashes the numbers 1–25 on a screen and needs the participant to click them in order while being timed [80]. These tests are time-consuming, and their results are influenced by age and educational status. However, these tests are recommended for diagnosis of MHE [42, 81].



Figure 3.
Number connection tests-A.

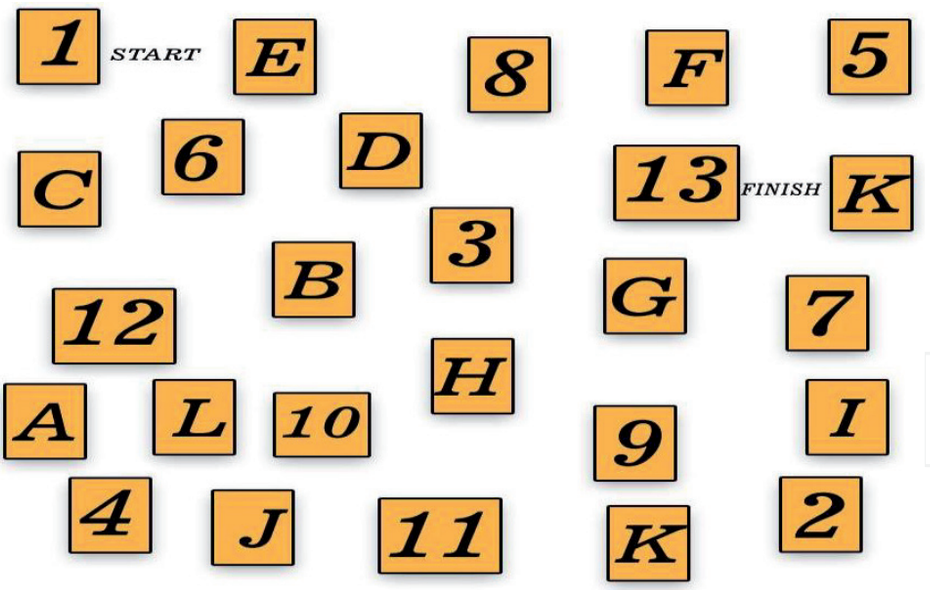


Figure 4.
Number connection tests-B.

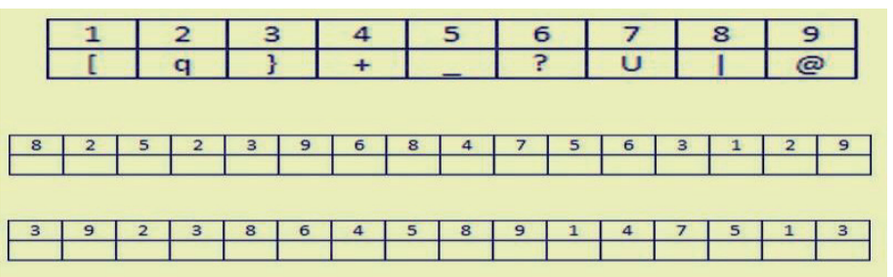


Figure 5.
Digit symbol test.

6.3.1.2 Digit symbol test DST

Nine fixed pairs of numbers and symbols are present at the top of the test sheet. The patient is given a series of double boxes with a number given in the upper part. The target is to draw a symbol related to this number into the lower part of the boxes. The test result is the number of boxes correctly filled in 90 s (**Figure 5**). Pathological test results indicate a deficit in visuoconstructive abilities. [82]. DST will be considered abnormal when the test scores are less than the mean − 2 SDs from the age-matched normal values [79].

6.3.1.3 Block design test

This test recorded speed and accuracy. The task is to take 6–9 blocks that have all white sides, all red sides, and red-and-white sides followed by arranging them according to a pattern formed by examiner or shown on a card [83].

6.3.1.4 Psychometric hepatic encephalopathy score (PHES)

It consists of five paper-pencil tests: NCT-A/B, line tracing time (LTT), digit symbol test, and serial-dotting test (SDOT). This battery measures psychomotor speed and precision, visual perception, visuospatial orientation, visual

construction, concentration, attention, and memory and can be completed in less than 20 minutes [68]. The results of PHES can be affected by age and education status of patients. A score is defined as the number of standard deviations of the difference between the two values for each test. MHE was diagnosed with the sum of all scores less than or equal to −4 points. Score < −4 suggests the presence of MHE [1, 84]. A simplified form of PHES, developed using only three of the original five tests, can be as good as the PHES in diagnosing [84]. For illiterate patients, the figure connection test has been used as a subtest instead of the number connection test [1]. PHES has a prognostic value for the occurrence of attacks of overt HE and mortality in cirrhotic patients [42, 43].

6.3.1.5 The animal naming test (ANT)

The ANT (maximum number of animals listed in 1 minute) has recently been developed to predict OHE. ANT is an easy test that has all the required characteristics of simplicity, speed, no cost, and relationship with clinical events to be used routinely for rapid investigation of HE in patients with cirrhosis at the office and at the bedside [85].

6.3.2 Computer-aided psychometric tests

Numerous current studies have showed that, computerization of psychometric tests could lead to simplification and easy administration in the clinic within a few minutes [10, 86, 87].

6.3.2.1 The critical flicker frequency (CFF)

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. Similarly, the general arousal of the patient is measured. Earlier studies have shown a reduction in its performance with worsening cognition and improvement after therapy. The CFF test needs numerous trials, intact binocular vision, absence of red-green blindness, and specialized equipment [15]. CFF predicts the first episode of OHE in cirrhotic patients who had never experienced OHE, and predicts mortality risk [88]. CFF test has many advantages, for example, easy administration, application by a non-specialist personal, and results that are independent of numeracy, literacy, and age [89].

6.3.2.2 Continuous reaction time (CRT) test

This test assesses the motor reaction time by having the patient press a button in response to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. The test result can differentiate between organic and metabolic brain impairment. The test is not affected by the patient's age, gender with no learning or tiring impact [90, 91].

6.3.2.3 The inhibitory control test (ICT)

It is a computerized test of response inhibition and working. The ICT requires highly functional patients (**Figure 6**). The ICT can be done using a laptop and is analyzed using an automatic computerized system that significantly improves the

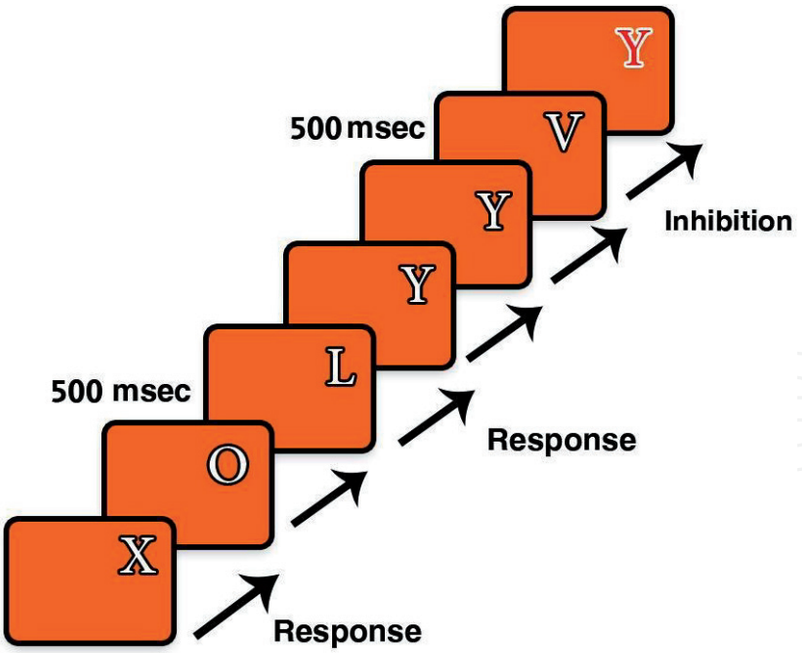


Figure 6.
Inhibitory control test. A continuous sequence of letters is displayed on the computer screen every 500 ms. The patient is educated to respond only if an X is preceded by a Y, or a Y is preceded by an X, but responses must be inhibited if an X is followed by an X, or a Y is followed by a Y.

convenience and flexibility of using this test in the clinical situation [92]. It has been validated for the diagnosis and follow-up of MHE in the USA. It was found that the ICT is simple to administer and has higher sensitivity/specificity for screening MHE than the standard psychometric test (SPT). On the other side, Taneja et al. found that the ICT is not as useful as the PHES in diagnosing MHE in patients with cirrhosis [93].

6.3.2.4 The Stroop test

In 2013, Bajaj et al. developed an application, the EncephalApp-Stroop App, for screening MHE that is operated by the iOS system on the iPhone and iPad. The core of this innovative application is the Stroop test, which assesses psychomotor speed and cognitive alertness by measuring the time required to correctly identify a series of symbols and printed words with different colors [86]. The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a colored field and a written color name. [86]. In a multicenter study that compared the EncephalApp-Stroop App to the PHES and ICT, the EncephalApp-Stroop App had good sensitivity (70–80%) for MHE screening and was predictive of the progression to OHE [94].

6.3.2.5 The SCAN test

It is a computerized test that measures the patient's speed and accuracy to perform a digit recognition memory task of increasing complexity [40, 95]. It is done by randomly displaying a series of 72 sorted pairs of numbers for 3 s on a computer screen. Patients are instructed to press the appropriate number on a keyboard if they identify a common digit in the sequence of numbers presented. The mean reaction times and the percentage of errors are recorded, and the results are evaluated using the reaction times weighted by the number of errors [96].

6.3.2.6 Cognitive drug research (CDR) assessment battery

It is a computerized battery of cognitive tests designed by the Cognitive Drug Research Ltd. (Goring-on-Thames, UK). The test contains five psychometric subsets that test attention power, attention continuity, speed of memory, and quality of episodic and working memory. It measures reaction time, memory, and recognition. The task stimuli are existing on a laptop, and patients provide the correct response using the "YES" and "NO" buttons on a two-button response box, which records both accuracy and reaction time. The sensitivity and specificity of the CDR assessment battery for screening MHE are 86.4 and 81%, respectively [10].

6.3.3 Electroencephalography examination (EEG)

EEG can discover changes in cortical cerebral activity across the spectrum of HE without patient cooperation or risk of a learning effect [97]. Newly, an-economy friendly device has been found to produce similar results compared with a standard EEG machine across the HE spectrum [97].

7. Treatment

Treatment of minimal hepatic encephalopathy with lactulose, probiotics, or L-ornithine-L-aspartate was seen to be effective in reducing abnormal tests and delay or eradicating risky motor car accident [47, 98–103]. It is therefore rational, especially if the patients or their family/caregivers report symptoms/signs compatible with MHE, to introduce treatment specially in patients who are at particular risk of the consequences of MHE, such as falls, impaired, and driving ability.

7.1 Rifaximin

Rifaximin is an orally administered, non-absorbable, semi-synthetic antibiotic with a broad spectrum of effect on both Gram-positive and Gram-negative bacteria [11, , 104]. It was found 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 [67]. Recently, a randomized controlled trial compared the efficacy of rifaximin with lactulose in reversal of MHE and improvement in HRQoL in cirrhotic patients with MHE. The study concluded that both drugs improve HRQoL equally well, in cirrhotic patients with MHE [105].

7.2 Non-absorbable disaccharides

The recommended standard of care for people with hepatic encephalopathy includes use of the non-absorbable disaccharides (lactulose and lactitol) [106, 107]. It was found that cirrhotic patients with MHE had improvement in health-related quality of life and psychometric performance after lactulose therapy [108]. Lactulose and lactitol, both, have effects on gut flora and are regarded as intestinal prebiotics. Adding lactulose to food can produce a bifidogenic effect connected to a favorable effect on colonic ammonia metabolism [109]. However, a recent meta-analysis evaluating the role of non-absorbable disaccharides in patients with MHE failed to show clear evidence in improving cognitive function and HRQoL [110].

7.3 LOLA (L-ornithine-L-aspartate)

Ammonia scavengers, including L-ornithine-L-aspartate, are agents that reduce blood ammonia concentration by enhancing the metabolism of ammonia to glutamine [111–113]. Bai et al. assessed eight RCTs (646 total patients, 46% diagnosed with MHE), evaluating the efficacy of LOLA compared to placebo in patients with cirrhosis. He found that treatment with LOLA diminished serum ammonia levels [114]. Evidence of important benefit of LOLA was also described in RCTs of patients with MHE assessed by psychometric testing or critical flicker frequency analysis. The oral formulation of LOLA was determined to be particularly effective for the treatment of OHE or MHE [115].

7.4 Probiotics

Prebiotics are non-digestible food ingredients that selectively stimulate the growth and/or activity of the bacteria in the colon. Probiotics are live microbes that alter the intestinal balance of the microflora. The combination of prebiotics and probiotics is named synbiotics. The meta-analysis of nine studies showed substantial evidence for the efficacy of prebiotics, probiotics, and synbiotics in the treatment of MHE [116]. A Cochrane Review examining the use of probiotics in the treatment of HE included seven trials and presented an advantage of probiotics to no treatment in all-cause mortality, number of adverse events, and QoL. Findings included reduced plasma concentrations of ammonia [117].

7.5 Zinc

Zinc, considered as a cofactor of urea cycle enzymes, is deficient in patients with cirrhosis, especially with malnutrition or encephalopathy [118]. Zinc is essential for the synthesis of coenzymes that mediate biogenic amine synthesis and metabolism [14]. Zinc deficiency also leads to change of neurotransmitters like γ aminobutyric acid and norepinephrine [119]. A recent RCT revealed that zinc supplementation can improve MHE in patients with liver cirrhosis associated with significant improvement in neuropsychometric tests and significantly decreased arterial ammonia level [76].

8. Conclusion

The prevalence of MHE is high in liver cirrhosis. MHE is characterized by subtle motor and cognitive deficits, and impairs health-related quality of life. Detection of MHE and subsequent treatment could substantially reduce societal costs by preventing motor vehicle accident.

Conflict of interest

The authors declare that there is no conflict of interest.

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