Review

A Narrative Review Of Minimal Hepatic Encephalopathy

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Jamir Pitton Rissardo [1],*, Ibrahim Khalil [2], Reem Sayad [3], Ahmed M. Kedwany [3], Hager Hamdy Sayed [4], Abhishek A. Chouthai [5] and Ana Letícia Fornari Caprara [1]

[1] Neurology Department, Cooper University Hospital, NJ 08103, USA

[2] Faculty of Medicine, Alexandria University, Alexandria 5372066, Egypt

[3] Faculty of Medicine, Assiut University, Assiut 71515, Egypt

[4] Department of nuclear medicine, South Egypt Cancer Institute, Assiut University, Assiut 71515, Egypt

[5] Division of Gastroenterology and Hepatology, Saint Peter's University Hospital, NJ 08901

* Correspondence: jamirrissardo@gmail.com

Abstract: Minimal hepatic encephalopathy (MHE) is primarily a cognitive disorder linked to chronic liver disease that often remains underdiagnosed due to the subtlety of its clinical manifestations. These symptoms are frequently overlooked or dismissed as inconsequential in clinical practice, leading to many undiagnosed cases. The standard neurological examination is usually normal in individuals with MHE. Regular and systematic screening for MHE is essential for early detection, which can improve cognitive outcomes and prevent progression to a more serious and debilitating condition also known as overt hepatic encephalopathy. The pathophysiology of MHE is very complex and multifactorial, involving several interplaying mechanisms. Mainly, hyperammonemia, system-wide inflammation, gut-derived neurotoxins, oxidative stress, and mitochondrial dysfunction are at its root. Any of these factors may interfere with the normal functioning of neurotransmitters, giving rise to the typical subtle cognitive impairments that are hallmarks of MHE. The Animal Naming Test and EncephalApp-Stroop tests are useful for screening for minimal encephalopathy in office or bedside settings. The role potentially played by emerging diagnostic technologies of advanced neuroimaging and biomarkers has been reviewed, underscoring its promise in improving early detection and diagnosis of MHE.

Keywords: minimal hepatic encephalopathy; hepatic encephalopathy; minimal he; chronic liver diseases; driving impairment; neurocognitive testing; neuropsychological testing; psychometric tests; electroencephalography; quality of life

1. Introduction

Chronic liver disease (CLD) and the resulting cirrhosis lead to around 1 million deaths annually. Beyond its clinical impact, CLD significantly affects health-related quality of life (HRQL) and imposes an economic burden. While there are various causes of liver disease, the four primary contributors to the burden associated with CLD are chronic hepatitis C virus (CHC), chronic hepatitis B virus (CHB), alcohol-related liver disease (ALD), and nonalcoholic fatty liver disease (NAFLD) [1]. Over 100 million people in the United States experience some form of liver disease. Approximately 4.5 million U.S. adults (1.8%) have received a liver disease diagnosis, but it is estimated that 80-100 million adults in the U.S. have fatty liver disease, with many unaware of their condition. In 2020, 51,642 adults in the U.S. died from liver disease [2]. Despite the availability of a highly effective vaccine and antiviral regimens for treatment and cure, the global burden of CLD continues to increase, most likely owing to the increasing rates of NAFLD and ALD [2].

CLD can manifest with nonspecific symptoms like fatigue, anorexia, and weight loss. However, the specific presentation depends on the complications the patient has developed. The major

complications of CLD include portal hypertension (leading to esophageal varices and ascites), hepatocellular insufficiency (resulting in jaundice and Hepatic Encephalopathy [HE]), and hepatocellular carcinoma.

HE is a significant complication associated with severe acute or chronic liver insufficiency. HE is a condition characterized by brain dysfunction resulting from liver insufficiency or portal-systemic shunting [3]. It presents a wide range of neurological or psychiatric abnormalities, spanning from subtle subclinical changes to coma. Notably, this definition of HE does not consider the underlying cause of liver disease. However, various factors associated with CLDs, including ALD, non-alcoholic fatty liver disease, viral hepatitis, and primary biliary cholangitis, can independently impact brain function beyond the effects triggered by liver failure or dysfunction [4].

HE primarily manifests as alterations in personality, consciousness, cognition, and motor function. Traditionally, three types of HE have been identified based on their underlying causes: Type A occurs as an essential component of acute liver failure; type B arises due to portosystemic shunts in the absence of liver dysfunction; and type C presents in patients with liver cirrhosis and portosystemic bypass. There is ongoing discussion about whether HE in patients with acute-on-chronic liver failure should be classified separately (as type D), given its distinct clinical, pathophysiological, and prognostic features [5].

The West Haven criteria (WHC) are commonly used to grade HE. This system distinguishes four clinically presentation: Grade I: Patients exhibit a lack of attention and subtle personality changes, often noticeable to their relatives; Grade II: The most intriguing finding is disorientation for time, combined with inappropriate behavior and lethargy; Grade III: Patients are stuporous but respond to stimuli, they are also disoriented by place and situation and may exhibit bizarre behavior; Grade IV: Patients are in a coma. Additionally, a fifth grade was added for patients without clinical signs of HE: the so-called subclinical or minimal HE (MHE) [6] (Figure 1). The International Society for HE and Nitrogen Metabolism classifies Covert HE, also known as clinically undetectable HE. According to the West Haven Criteria, this category includes minimal and grade I disease categories. Patients falling into these categories are considered to have MHE [7].
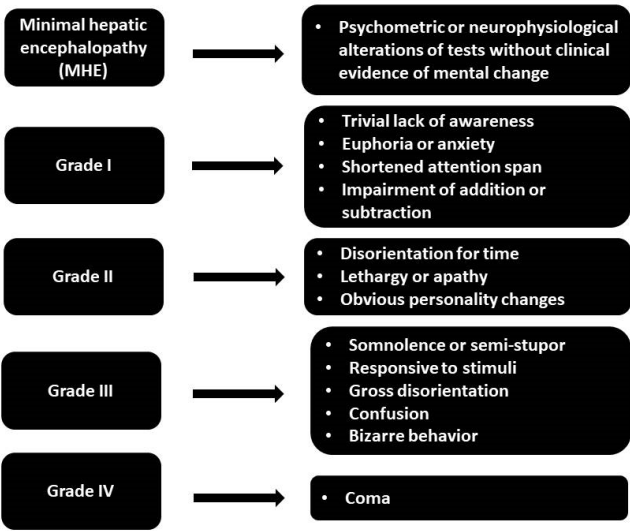
Figure 1. Grades of hepatic encephalopathy (HE). These grades started with MHE, in which there are psychometric or neuropsychological alterations of tests without evidence of any mental changes, and ended with coma.

MHE, previously known as subclinical HE, is the earliest and mildest HE form [8]. Importantly, it needs to be more recognized and often needs to be diagnosed. Patients with MHE do not display clinical evidence of cognitive changes; instead, they experience subtle alterations in psychomotor or neuropsychiatric functioning [3]. Up to 80% of patients with CLD are estimated to experience MHE [9]. While there is no definitive gold standard for diagnosing MHE, several validated testing methods

have been developed to detect this neurocognitive complication. Additionally, some of these diagnostic tools can also predict the risk of progression to Overt Hepatic Encephalopathy (OHE) [10].

While recognizing MHE can be challenging, early detection is crucial due to its association with worse clinical outcomes. Patients with MHE face an increased risk of hospitalization and motor vehicle collisions [11]. Moreover, individuals with MHE are more likely to progress to OHE, experience impaired quality of life, and have higher overall mortality rates [12]. Therefore, this narrative review aims to provide an overview of the current literature on MHE, summarize its main features, and provide current perspectives, including diagnosis and management.

2. Pathophysiology

The pathophysiology of HE is complex, as it is multifactorial, encompassing ammonia toxicity, dysregulation of central nervous system (CNS) activity, and an excess of inflammatory cytokines. Ammonia plays a crucial role in the pathophysiology of HE. Ammonia is a small nitrogenous metabolite that results from the breakdown of proteins and amino acids. While the pathophysiology of HE involves multiple factors, extensive research has centered on accumulating this nitrogenous waste product in the blood and brain. Although hyperammonemia is not the sole mechanism in HE development, it significantly impacts cellular function (Figure 2).
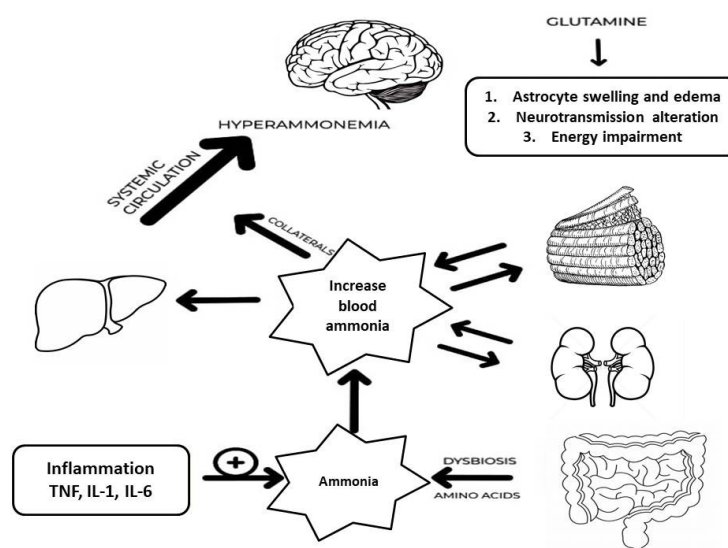
Figure 2. Role of ammonia in the pathophysiology of hepatic encephalopathy (HE). Ammonia plays a central role in the pathophysiology of HE. Its accumulation due to liver dysfunction leads to a cascade of events in the brain, ultimately resulting in the neuropsychiatric symptoms characteristic of HE.

2.1. Role of Ammonia

2.1.1. Ammonia Production

Ammonia is primarily produced in the small and large intestines (50%) and the kidneys (40%). In the intestine, there are two mechanisms: (1) urea from dietary protein is broken down into ammonia and carbon dioxide by urease-producing bacteria (such as Klebsiella and Proteus), mainly in the large intestine, and (2) glutamate is directly degraded into glutamate and free ammonia by glutaminase in enterocytes. This unionized ammonia can freely cross the intestinal epithelium and enter the portal circulation. The ionization of ammonia depends on the colonic luminal pH. A more acidic pH leads to protonation and trapping of ammonium (NH_4^+) within the lumen. Additionally, nonabsorbable disaccharides like lactulose can lower colonic pH, reducing ammonia reabsorption [13].

While gut bacteria contribute significantly to ammonia production through protein breakdown, low-protein diets should be avoided in patients with HE. Protein malnutrition can lead to sarcopenia,

which is associated with higher mortality and an increased risk of HE. Muscles play a crucial role in nitrogen metabolism for patients with cirrhosis. Additionally, increased fiber intake reduces bowel transit time and decreases ammonia absorption [14].

Renal ammoniagenesis occurs in the proximal tubular cells, in which these cells generate ammonia from glutamine, producing bicarbonate as a byproduct. Renal ammonia production is influenced by acid-base status and potassium balance. In metabolic acidosis or hypokalemia, glutamine helps with acid disposal or potassium recovery, leading to increased arterial ammonia levels [15]. Intravascular hypovolemia (e.g., due to gastrointestinal bleeding or over-diuresis) enhances renal ammonia production via angiotensin II. Volume expansion (e.g., stopping diuretics) benefits patients with worsening HE [16].

Muscles also have a minor contribution as they release ammonia through adenylic acid metabolism (part of the purine nucleotide cycle). Senescent red blood cells release glutamine, contributing to ammonia production [17].

2.1.2. Ammonia Excretion

The primary site of ammonia breakdown occurs in the liver through the urea cycle (also known as the Krebs-Henseleit cycle). In this process, two molecules of ammonia and one molecule of carbon dioxide combine to produce urea and water. Due to its small size, urea can easily cross membranes and return to the intestines and kidneys for excretion. Interestingly, the ammonia concentration in the portal vein is 5 to 10 times higher than in the systemic circulation. When liver function is compromised—either due to hepatocellular damage or shunting around the liver (such as from portal hypertension or portosystemic shunts)—ammonia accumulates in the systemic circulation [17].

The kidneys contribute to ammonia excretion by generating ammonium through parallel H1 and ammonia secretion in the collecting duct. Most urinary ammonia results from renal ammonia genesis. Factors like acid-base balance, potassium levels, protein intake, and glucocorticoid hormones influence the proportion of ammonia excreted in urine. Interestingly, renal venous ammonia exceeds arterial ammonia, indicating that the kidneys actually increase systemic ammonia [18]. In normal physiology, about 50% of ammonia is excreted in urine, while the rest returns to the systemic circulation via the renal vein. In acidosis, the kidneys excrete hydrogen ions and convert ammonia to ammonium. Conversely, alkalosis reduces renal ammonia excretion, and reduced renal perfusion (e.g., dehydration) also decreases ammonia excretion [17].

In patients with cirrhosis, skeletal muscles play a significant role in detoxifying ammonia by converting it into glutamine via glutamine synthetase (GS). Sarcopenia (muscle loss) is a risk factor for HE, so improving muscle mass is beneficial. Abnormal ratios of branched-chain amino acids (BCAAs) and aromatic amino acids in cirrhotic patients affect ammonia metabolism. BCAA supplementation has shown promise in treating HE, especially in non-responsive cases [19].

Therapeutic options such as L-Ornithine L-Aspartate (LOLA) enhance both ureagenesis and glutamine synthesis. L-ornithine plays a role in the urea cycle in periportal hepatocytes, while L-aspartate contributes to glutamate production via transamination in perivenous hepatocytes, skeletal muscle, and the brain. Intravenous LOLA has improved psychometric testing and postprandial venous ammonia levels in patients with persistent HE [20].

2.2. Ammonia Neurotoxicity

Under normal conditions, most ammonia exists in the weakly acidic NH_4^+ form. Interestingly, this ion has a similar ionic radius and diffusion coefficient to potassium (K^+). As a result, it can compete with and bind to various K^+ channels and transporters. Ammonia can cross the blood-brain barrier through passive diffusion in its uncharged form and also via active transport using ion transporters in its NH_4^+ form [21]. Some evidence suggests that specific mammalian ammonia transporters and aquaporin channels (such as aquaporin-8) are involved in this process [22].

2.2.1. Astrocyte Dysfunction Theory

Ammonia, when detoxified by astrocytes, leads to cellular changes that can alter brain function. These changes include pH shifts, membrane potential alterations, and impaired oxidative metabolism [23]. Glutamine synthetase (GS) plays a key role in detoxifying ammonia by converting it into glutamine. However, excessive ammonia can cause astrocyte swelling and dysfunction [24]. CLD results in mild swelling, while acute liver failure leads to significant swelling and increased intracranial pressure [25]. Additionally, hyponatremia can contribute to astrocyte swelling. Therefore, correcting electrolyte imbalances is crucial for preventing or treating HE [26].

In addition to astrocyte dysfunction, neuropathology studies have observed microglial cell activation [27]. This leads to a pro-inflammatory state, monocyte recruitment, and increased cytokine gene expression in the brain. PET imaging reveals heightened signal intensity in the anterior cingulate cortex, which is associated with attention control. Neuronal damage and death contribute to acquired hepatocerebral degeneration, post-shunt myelopathy, and direct cerebellar damage [28]. Liver failure can also cause neuronal death in Wernicke encephalopathy due to impaired thiamine synthesis. Mechanisms of neuronal damage include NMDA receptor-mediated excitotoxicity, lactic acidosis, oxidative stress, and proinflammatory cytokines. Despite ammonia's role in HE, other factors play a significant role, and ammonia levels do not always correlate directly with HE severity. Neurotoxins, nutritional deficiencies, inflammation, and neurotransmission changes are major contributors to HE [29].

2.3. Role of Tumor Necrosis Factor-Alpha

Systemic inflammation plays a crucial role in HE. Cirrhotic patients often have elevated levels of tumor necrosis factor (TNF)-alpha. Common triggers include infection or direct hepatocellular injury, leading to the release of proinflammatory cytokines like TNF-alpha, interleukin (IL)-1B, and IL-6 [30]. Gut flora translocation contributes to increased TNF-alpha levels. Additionally, proton pump inhibitors (PPIs) may exacerbate bacterial translocation. TNF-alpha affects neurotransmission, astrocyte function, and blood-brain barrier permeability, emphasizing its role in HE [31].

2.4. Role of Gut Microbiota: Gut-Liver-Brain Axis

Changes in gut flora contribute to HE. Reduced bile acid production in liver disease leads to pathogenic bacteria (e.g., Enterobacteriaceae) proliferation and reduced protective commensals (e.g., Lachnospiraceae) [32]. Patients with HE exhibit dysbiosis, hyperammonemia, and systemic inflammation. Specific gut microbial changes correlate with inflammation and neuronal dysfunction. Probiotics may reduce ammonia and endotoxin levels, improving HE. Fecal microbiota transplant (FMT) shows promise in treating recurrent HE [33].

2.5. Neurotransmitters and Minerals Involved in the Pathophysiology of Hepatic Encephalopathy

2.5.1. Glutamate

In HE, glutamate, the brain's main excitatory neurotransmitter, experiences reduced transmission. Elevated ammonia levels within the CNS lead to various changes in the glutamate system [34]. These include altered expression and activity of glutamate transporters in the synaptic cleft, reduced glutamate release from nerve terminals due to decreased synthesis from glutamine, prevention of action potential invasion in presynaptic terminals, and blockage of glutamate receptors [35]. These alterations contribute to the neurological symptoms observed in HE. Additionally, acute ammonia elevations lead to excessive NMDA receptor activation, resulting in significant neurotoxicity, although this effect is not seen with chronic hyperammonemia [36].

2.5.2. Monoamines: Histamine and Serotonin

The monoamine system, affected by ammonia, plays a role in HE. The activation of histaminergic systems contributes to symptoms like disturbances in the sleep cycle and altered motor functions. Studies have reported elevated histamine levels in plasma and the brain tissue, possibly due to changes in the brain's neutral amino acid transporter system [37]. Additionally, increased concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a serotonin (5-HT) metabolite, correlate with

plasma ammonia levels. In patients with cirrhosis who died in hepatic comas, cerebrospinal fluid (CSF) 5-HIAA levels were elevated, suggesting increased 5-HT turnover and metabolism [38]. Mechanisms include stimulation of precursor L-tryptophan uptake, increased expression of monoamine oxidase A, and altered 5-HT storage and release from presynaptic terminals. These changes contribute to neuropsychiatric symptoms such as depression and disrupted sleep patterns [39].

2.5.3. Gamma-Aminobutyric Acid

GABA is the primary inhibitory neurotransmitter in the brain. Increased GABAergic transmission has been linked to HE [40]. Factors contributing to this include upregulation of the 18-kDa translator protein, which produces endogenous benzodiazepines (neurosteroids) that modulate GABA type A receptors. Additionally, increased peripheral benzodiazepine receptor concentrations in astrocyte mitochondria may alter energy metabolism. Clinical studies using benzodiazepine site antagonists like flumazenil have shown improvement in HE patients. The exact pathophysiology remains incompletely understood, but it involves gene expression changes, increased brain GABA agonists, and endogenous modulators [41]. Allopregnanolone, a neurosteroid activating GABA type A receptors, is elevated in advanced HE. The agent GR 3027, a neurosteroid-site antagonist, shows promise in symptom improvement [42].

2.5.4. Manganese

Manganese (Mn) is essential for physiological functions but can become a neurotoxin in end-stage liver disease. Elevated Mn levels due to CLD lead to CNS deposition, primarily in the basal ganglia [43]. Astrocytes are particularly affected. Mn disrupts oxidative phosphorylation by sequestering in mitochondria. Impaired glutamate transport and dopamine-D2 binding result in extrapyramidal symptoms similar to Parkinson's disease. L-Dopa treatment may improve symptoms, and liver transplantation can resolve them in some patients [44].

2.6. Risk Factors Contributing to the Development of Minimal Hepatic Encephalopathy

In a multicenter, cross-sectional study, 1879 patients with confirmed cirrhosis were enrolled across 40 hospitals [45]. Researchers conducted both univariate and multivariate logistic analyses to explore risk factors for MHE in cirrhotic patients. The study focused on age, duration of education, etiology, and MELD-Na score. Age was identified as an independent risk factor ($p < 0.001$). A longer duration of education was associated with a reduced risk ($p = 0.001$). Etiology ($p = 0.039$) and MELD-Na score ($p = 0.009$) were also significant risk factors. For HBV-related cirrhosis, age ($p = 0.001$) and duration of education ($p = 0.001$) influenced MHE risk. For HCV-related cirrhosis, age ($p = 0.009$) and creatinine concentration ($p = 0.042$) were risk factors. No significant risk factors were found for ALD-related cirrhosis. In alcoholic cirrhosis, platelet count ($p = 0.045$) was associated with MHE risk.

On the other hand, risk factors for OHE in cirrhosis include MHE, prior history of OHE, sarcopenia, hyponatremia, epilepsy, type 2 diabetes mellitus, elevated creatinine levels, elevated bilirubin levels, low albumin levels, proton pump inhibitor (PPI) use, nonselective beta-blocker use, and statin use [46,47].

2.7. Mechanisms Underlying Cognitive Dysfunction in Minimal Hepatic Encephalopathy

Current understanding suggests that both hyperammonemia and inflammation play significant roles in causing cognitive impairment in MHE [48]. Consequently, it is not unexpected that certain diseases, which result in similar changes in ammonia levels and inflammatory factors akin to those seen in liver cirrhosis, may also lead to mild cognitive impairment affecting performance in similar psychometric tests [49].

Felipo et al. assessed cognitive function using the PHES battery of psychometric tests in patients with varying degrees of hyperammonemia and inflammation caused by different diseases, both with and without liver failure. It was noticed that all patient groups exhibit some level of inflammation [50]. However, the severity and nature of inflammation vary among different patient types, with distinct contributions from increased IL-6 and IL-18 levels. The findings indicate that mild cognitive impairment, as evaluated using the PHES battery, necessitates the simultaneous presence of

moderate hyperammonemia and inflammation. While it remains possible that hyperammonemia or inflammation alone may affect other cognitive functions, impairment, specifically in the cognitive domains assessed by the PHES battery, appears to require a combination of both factors [51].

In rat models of MHE, impaired cognition is induced by reduced synthesis of cyclase guanylyl monophosphate (cGMP) through various mechanisms. This cognitive impairment is evident in the reduced learning ability observed during a Y-maze task. Neuroinflammation, characterized by increased extracellular GABA and hyperammonemia, which activates N-methyl-D-aspartate receptors, ultimately leads to decreased neuronal NO synthase activity, resulting in reduced cGMP synthesis [52].

2.8. Differences in Brain Activity Between Averted Hepatic Encephalopathy and Minimal Hepatic Encephalopathy

In addition to the common alterations in brain activity observed in patients with OHE and MHE, quantitative comparison analysis revealed that OHE patients exhibit reduced brain activity in regions associated with the default mode network (DMN) compared to MHE patients [53]. The DMN plays a role in various cognitive functions, including memory, visual and auditory attention, motor activity, and language processing. Specifically, the precuneus, a key component of the DMN, is closely linked to visuospatial information integration, episodic memory retrieval, and self-processing operations.

Consistent with these findings, a resting-state functional MRI (rs-fMRI) study demonstrated decreased functional connectivity within the DMN in patients with prior OHE compared to those with current MHE. These results suggest that resting-state brain activity in the DMN could serve as a noninvasive and sensitive neuroimaging biomarker for detecting the progression from MHE to OHE. Furthermore, OHE patients exhibited increased brain activity in specific regions, including the left olfactory cortex, left cerebellum (crus I), right superior temporal gyrus (STG), and right putamen, when compared to MHE patients. Such increased activity is often interpreted as a compensatory mechanism resulting from neural reorganization. Thus, the heightened brain activity in these regions among OHE patients may play a compensatory role as the severity of HE worsens. These findings suggest that rs-fMRI could be a valuable imaging technique for assessing HE severity in clinical practice [54].

3. Definition

Modern diagnostic methods enable the detection of functional abnormalities even before symptoms manifest. Identifying impairments early can help prevent or delay disease progression. This approach is essential for recognizing and modifying risk factors, such as hypercholesterolemia or arterial hypertension [55]. Neurologists, recognizing the significance of early Alzheimer's disease diagnosis, coined the term "mild cognitive impairment" to identify patients in the initial stages of the disease—candidates who may benefit from available treatments. Similarly, early identification of HE patients can enhance their quality of life and prognosis.

The concept of "subclinical HE" was introduced to identify patients exhibiting subtle manifestations of HE that are challenging to recognize. This term underscores the importance of using complementary tests to diagnose brain dysfunction that might not be detectable through standard clinical examination [56].

Other researchers have preferred terms like "latent" or "early" to emphasize the potential progression to OHE [57,58]. However, once the impact on patients' quality of life became evident, the term "subclinical" faced criticism. To prevent medical misunderstandings, alternative terms were suggested, avoiding the implications that the condition is insignificant [59]. The current consensus is to use the term "minimal hepatic encephalopathy" (MHE), as proposed by the Working Party commissioned by the XI World Congress of Gastroenterology [60]. The American Association for the Study of Liver Diseases (AASLD) defines MHE as the presence of test-dependent or clinical signs of brain dysfunction in cirrhotic patients who are not disoriented or displaying asterixis [3].

3.1. Clinical Manifestations

The International Society for HE and Nitrogen Metabolism (ISHEN) consensus delineated the symptoms and their grading into covert (MHE and grade I) and OHE (OHE; grades II-IV) in

September 2014. Motor manifestations of stage I HE begin with impaired handwriting and incoordination. Stage II HE is characterized by asterixis. As encephalopathy progresses, flapping tremors weaken in stage III and disappear in stage IV. Later stages involve hyporeflexia, ataxia, hyperreflexia, clonus, and rigidity and may culminate in opisthotonus and coma [3].

MHE is often underrecognized, significantly impacting patients' quality of life and their families. It is highly prevalent among cirrhotic patients, affecting up to 80% of this population. Despite normal clinical examination findings, patients with MHE exhibit abnormal psychometric test results. These subtle symptoms necessitate specialized neuropsychiatric diagnostic testing [61]. MHE primarily affects executive functioning, leading to deficits in vigilance, response inhibition, working memory, and orientation [62]. Importantly, MHE can impair daily functioning, including safe automobile operation [63]. The ISHEN consensus defines the onset of OHE as the appearance of disorientation or asterixis [64]. As awareness of MHE grows, early treatment may significantly enhance the quality of life for cirrhotic patients.

3.2. Clinical Significance

3.2.1. Effect of Minimal Hepatic Encephalopathy on Quality of Life

QOL encompasses physical, cognitive, emotional, and psychosocial well-being. It is assessed using various scales, such as the Nottingham Health Profile (NHP), the Sickness Impact Profile (SIP), and disease-specific questionnaires [65,66].

MHE negatively impacts health-related quality of life (HRQOL). Complex tasks requiring attention, information processing, and psychomotor skills are affected. Basic self-care functions remain preserved [67]. Patients with MHE show impaired scores across SIP scales, affecting social interaction, alertness, emotional behavior, sleep, work, and recreation [68].

Minor symptoms (e.g., pruritus, muscle cramps) impact HRQOL. Depression, anxiety, and malnutrition worsen HRQOL [69]. Lactulose, rifaximin, and probiotics can reverse MHE and improve HRQOL. Driving performance also improves after MHE reversal with rifaximin therapy [70].

3.2.2. Sleep and Health-Related Quality of Life

Sleep disturbances are common in cirrhosis patients, affecting 26–70% of cases. Patients with MHE experience more sleep disturbances than those without MHE. Homeostatic and circadian processes regulate sleep. MHE disrupts these processes. Unsatisfactory night sleep, delayed onset, and multiple awakenings lead to reduced sleep time and daytime sleepiness [71]. Excessive daytime sleepiness correlates with ammonia levels and increases HE-related hospitalization risk. Sleep disturbances can impair health-related quality of life (HRQOL) in MHE patients [72].

3.2.3. Memory and Learning Difficulties in Minimal Hepatic Encephalopathy

MHE involves subcortical dysfunction, including slowed mental processing, attention disturbances, executive disabilities, psychomotor slowing, and memory issues. MHE primarily affects short-term memory due to attention deficits, leading to encoding defects and learning impairments [73]. FDG PET studies reveal decreased glucose metabolism in the parieto-occipital region (related to visual perception) and preserved metabolism in the temporomesial area (associated with memory) [74]. Learning impairment in MHE may result from hyperammonemia, affecting cGMP levels. Pharmacological interventions may help [75].

3.2.4. Driving and Navigational Skills in Minimal Hepatic Encephalopathy

MHE patients show impaired driving performance in real road tests and driving simulators. The categories most affected include car handling, maneuvering, adaptation, and cautiousness [76]. The increased risk of accidents is attributed to cognitive decline in MHE patients. Difficulties in following maps and higher self-reported traffic violations are observed. Fatigue worsens driving performance over time. Navigation relies on working memory, attention, response inhibition, visuomotor coordination, and executive control [77]. MHE patients have navigation difficulties, leading to illegal

turns and accidents. Rifaximin improves driving performance in MHE patients, correlating with cognitive improvement [11].

3.2.5. Falls in Minimal Hepatic Encephalopathy

MHE is linked to an elevated risk of falls, impacting patients' quality of life. While only 12% of patients without MHE experience falls, nearly 40% of those with MHE suffer falls that often require hospitalization [78]. The risk is further heightened for patients taking psychoactive drugs. Impaired attention, visuomotor coordination, and slowed reaction time increase the fall risk in MHE patients [79]. Additionally, the higher incidence of falls in these patients can lead to osteoporosis-related fractures, surgeries, and associated morbidity, ultimately affecting both patients and their families [80].

3.2.6. Employment and Socioeconomic Burden of Minimal Hepatic Encephalopathy

Patients with MHE experience reduced work performance due to psychomotor slowing [81]. Nearly half are unemployed, compared to only 15% of patients without MHE. Blue-collar workers are particularly affected, with 60% unfit for work, while verbal intelligence remains preserved [82].

3.2.7. Natural History and Survival in Minimal Hepatic Encephalopathy

Patients with MHE can experience improvement, stability, or deterioration over the long term. The frequency of MHE increases with the severity of liver dysfunction. MHE predicts the development of OHE and adversely affects survival [83]. Studies have shown that both abnormal psychometric scores for HE and the Child-Turcotte-Pugh (CTP) score independently correlate with survival. Additionally, covert HE is associated with worsened survival, increased hospitalization risk, and overted HE development [84].

4. Diagnosis and Available Tests

MHE is the mildest clinical manifestation of HE. It can impact as many as 80% of individuals with liver cirrhosis, varying depending on the specific population examined and the diagnostic method employed [85]. Thus, every patient who is at risk should undergo testing for this condition. This is because MHE is a significant health issue and, even in its mildest form, it is linked to carer burden, poor prognosis, increased risk of experiencing episodes of OHE, inability to drive, sleep disorders, falls, and ultimately, a impairment of the quality of life [86,87]. The most effective method for identifying MHE is still an ongoing issue. None of the offered strategies adequately address the intricate and diverse nature of cognitive impairment in MHE (Figure 3).
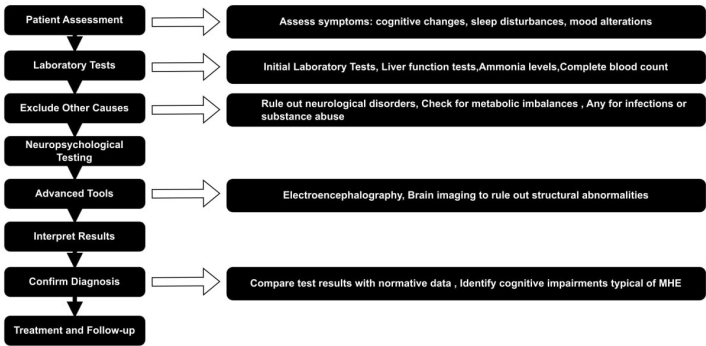
Figure 3. The Algorithm for arriving at the diagnostically appropriate diagnosis of MHE starts with the patient's history, clinical examination, and exclusion of other causes of encephalopathy. Then, neuropsychological tests and appropriate tools are performed. Finally, the diagnosis is reached through the interpretation of the data from the previous steps.

Additionally, suitable norms are frequently necessary, and MHE still needs to be recognized or underdiagnosed by most clinicians [88]. The diagnosis of MHE might frequently be missed due to various factors, including the fact that diagnosing MHE is challenging with objective neurological examination alone, hence requiring specific neuropsychological and neurophysiological studies, and cognitive impairment affects overall performance and psychomotor skills [9]. In contrast, verbal skills typically remain intact [85]. Certain tests can be costly and necessitate highly skilled personnel and specialized testing equipment [83]. The absence of diagnostic criteria and age- and education-adjusted normal distribution values is notable [85]. There is no singularly ideal approach to evaluating the existence of MHE, as none of the proposed tests comprehensively address all aspects of HE; each method investigates distinct brain functions [9].

4.1. Psychometric Testing

Psychometric testing is a cornerstone in diagnosing MHE, providing valuable insights into the often subtle cognitive impairments that accompany this condition. Sharma et al. reported that these tests assess a range of psychological functions frequently impacted by MHE, including attention, memory, and visuospatial abilities. Psychometric hepatic encephalopathy score (PHES), specifically designed and validated across numerous populations and clinical scenarios to detect and stage HE [89]. For a broader neuropsychological evaluation, the repeatable battery for the assessment of neuropsychological status (RBANS), also described in the table, can identify cognitive deficits, including those characteristic of MHE [90]. Even simpler tests like the animal naming test (ANT), measuring verbal fluency, a function often impaired in MHE, can be helpful [91]. Factors such as age, education level, and previous test experience can influence results, making it essential to interpret findings carefully and within the context of each patient's overall clinical picture.

Furthermore, the field is continuously evolving, with ongoing research refining existing tests and exploring innovative digital assessments, such as EncephalApp [92] and QuickStroop [93], for their potential advantages in accessibility and ease of administration. Ultimately, a comprehensive approach to diagnosing MHE often entails integrating findings from various psychometric tests with clinical observations and laboratory markers to gain a holistic understanding of each patient's condition [94]. A summary of diagnostic methods for the detection of MHE is presented in Table 1.

Table 1. Diagnostic methods for the detection of MHE.

Method	Advantages	Disadvantages	References
Psychometric testing			
PHES	-Validation across many populations and a wide range of therapeutic instances -Assists in diagnosing MHE and predicting the developing OHE. -High sensitivity and specificity when diagnosing MHE	-Insufficient localization -Age and education levels greatly affect scores, requiring adjustment and complicating interpretation -Repeated use may provide practice effects when patients do better owing to familiarity with the tests rather than cognitive progress	Amodio *et al*. (2008) [95] Dhiman *et al*. (2010) [89] Duarte-Rojo *et al*. (2011) [96] Seo *et al*. (2012) [97] Li *et al*. (2013) [98]
RBANS	-Time-limitation to be performed in the clinical setting (30 minutes) -Efficacy in evaluating cognitive deficiencies in a variety of conditions -Initial diagnosis and monitoring of cognitive changes over time	-Certain factor configurations may be more suitable for specific populations -Demographic characteristics can impact performance -May not evaluate some specific cognitive areas, such as executive function	Duff *et al*. (2015) [90] Schmitt *et al*. (2010) [99] Garcia *et al*. (2008) [100] McKay *et al*. (2008) [101]

ANT	-Convenient for regular screenings -Do not require equipment or considerable training -Correlation with other diagnostic instruments, such as the PHES and EEG	-Demographic characteristics can impact performance -Restrictive data on cognitive function requiring more extensive neuropsychological assessments -Dependence on verbal fluency might create bias, especially for those with speech or language difficulties, who may not adequately represent their cognitive capabilities	Campagna *et al.* (2017) [91] Labenz *et al.* (2019) [102] Agarwal *et al.* (2020) [103] Qu *et al.* (2021) [104] Gairing *et al.* (2023) [105]
CRT	-Treatment-response evaluation -Assess the consistency of reaction times -Unaffected by age and gender	-Less stable than CFF -There was no correlation between CRT and laboratory tests -Long duration, requiring around 10 minutes to be performed	Lauridsen *et al.* (2015) [10] Lauridsen *et al.* (2017) [106]
ICT	-Notable level of sensitivity (88-90%) and specificity (up to 90%) in the diagnosis of MHE -Goog prediction for the onset of OHE -Strong test-retest reliability	-Weak correlation between ICT results and the severity of liver disease (Child-Turcotte-Pugh or MELD scores) -ICT may have lower diagnosis accuracy than alternative approaches like the PHES	Taneja *et al.* (2012) [107] Goldbecker *et al.* (2013) [108] Gupta *et al.* (2015) [109]
EncephalApp (Stroop test)	-Accessible in clinical and non-clinical environments -Strong test-retest reliability -Weakly affected by demographic factors -Correlation of scores with sleep disruptions in patients with cirrhosis	-Learning effect with repeated testing -Affected by age, education level, and smartphone experience -The ideal threshold values for detecting MHE using EncephalApp exhibit significant variation among different studies	Bajaj *et al.* (2015) [92] Luo *et al.* (2020) [110] Cunha-Silva *et al.* (2022) [111] Lupescu *et al.* (2023) [112]
QuickStroop	-High accuracy and specificity to detect MHE -Can be performed within 40 seconds, potentially enhancing CHE testing and treatment	-Disadvantages are similar to the EncephalApp	Acharya *et al.* (2023) [93]
SIP-CHE	-High level of sensitivity (80%) and specificity (79%) in identifying MHE -Does not require specific equipment or substantial training -Useful for monitoring the progress of HRQOL and cognitive function	-Clinicometric features verified in specific populations, but their use in many cultural contexts is limited -Primarily a screening tool and does not thoroughly evaluate cognitive function (additional tests are usually necessary)	Nabi *et al.* (2014) [113] Maharshi *et al.* (2016) [114] Lauridsen *et al.* (2020) [115]
SCAN test	-Detects varying levels of hepatic encephalopathy by monitoring reaction times corresponding to the condition's seriousness -High sensitivity and specificity in differentiating between different HE degrees -Impartial assessments of response times, minimizing the subjectivity	-Influenced by the patient's cooperation level and cognitive condition -The absence of established standards for the administration and interpretation in various healthcare settings leads to variations and inconsistencies in the diagnosis of MHE	Montagnese *et al.* (2012) [94] Luo *et al.* (2019) [116]
Electrophysiologic tests			
EEG monitoring	-Objective data, quantifiable parameters connected with mental state -Minor alterations in brain activity can be identified that may not be evident only by clinical assessment -EEG can be performed in various clinical environments, including those with minimal resources	-Results interpretation can be subjective (high interrater variability) -The association between EEG alterations and clinical and psychometric findings regarding MHE can sometimes be variable -Standardized signal amplification, filtration, and spectral analysis techniques are necessary for precise EEG analysis	McLaughlin *et al.* (1989) [117] Amodio *et al.* (1999) [118] Amodio *et al.* (2006) [119] Pascoli *et al.* (2006) [120] Schiff *et al.* (2016) [121]

Evoked potentials	-Minimally invasive, uncomplicated, and can be readily conducted, even in intensive care units -Useful for patients with different levels of consciousness because they do not rely much on patient cooperation -Specific patterns have a strong correlation with cognitive deficits and psychometric test outcomes	-Advanced equipment and specialized knowledge needed -Standardized methods for recording and interpretation are necessary	Amodio *et al*. (2005) [122] Kullmann *et al*. (1995) [123] Zeneroli *et al*. (1984) [124]
CFF	-High level of sensitivity (96%) and specificity (77%) in diagnosing MHE -Unaffected by the patient's age or literacy level -Predict the risk of progression to OHE	-Patient's state and the severity of liver disease can impact outcomes -There is usually no significant correlation between CFF and other psychometric tests	Sharma *et al*. (2007) [125] Sharma *et al*. (2010) [126] Lauridsen *et al*. (2011) [127] Barone *et al*. (2018) [128] Romero-Gomez *et al*. (2007) [83]
Laboratory tests			
Biomarkers	-Ammonia is reliable for evaluating the occurrence of HE -Unbiased biomarker that minimizes the subjective inconsistencies in psychometric assessments and identifies the risk of OHE -There is a correlation between ammonia levels and cognitive impairment in MHE	-Ammonia levels alone have limited clinical value in identifying MHE, and a comprehensive diagnostic strategy is recommended.	Direkze *et al*. (2015) [129] Suzuki *et al*. (2016) [130] Fiati *et al*. (2019) [131]
	-3-NT is a reliable biomarker with high sensitivity (90%) and specificity (93.33%) -Superior diagnostic accuracy of 3-NT compared to other markers like plasma ammonia	-Specialized technology and experience are necessary for detecting 3-NT -It is advisable to utilize this tool alongside other diagnostic instruments to improve precision.	Montoliu *et al*. (2011) [132] Salman *et al*. (2021) [133]

Abbreviations: ANT, animal naming test; CFF, critical flicker frequency testing; CHE, covert hepatic encephalopathy; CRT, continuous response time test; EEG, electroencephalography; HRQOL, health-related quality of life; ICT, inhibitory control test; MHE, minimal hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; RBANS, repeatable battery for the assessment of neuropsychological status; SIP, Sickness Impact Profile; 3-NT, 3-nitrotyrosine.

4.1.1. Psychometric Hepatic Encephalopathy Score (PHES)

The PHES, a set of psychometric test techniques, is currently recognized as the worldwide preferred and most reliable method for diagnosing MHE [96]. PHES was specifically designed for individuals with MHE and has been confirmed reliable and valid for MHE diagnosis. The PHES consists of five tests: number connection test A, number connection test B, serial dotting test, line tracing test, and digit symbol test. The PHES evaluates various cognitive functions, including motor speed, accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction, and memory [6].

A cohort of Thailand adults with cirrhosis assessed the efficacy of PHES in diagnosing MHE [134]. The authors described that a PHES threshold of ≤−5 points suggests MHE. MHE was detected in 26.6% of cirrhotic patients who did not exhibit OHE. However, some authors reported that test findings with a score (≤-2SD) were considered abnormal [6,95]. Furthermore, validation studies have been conducted in Italy [95], Spain [83], Germany [6], Korea [97], China [98], and India [89]. Standardizing these tests using a large control group must account for variations in mathematics, literacy, and language skills that may affect test outcomes [94]. The test findings are additionally impacted by factors such as age, gender, level of education, alcohol consumption, and visual abilities of the individual being tested [135]. While adjusting the findings based on age and education is possible, managing the impact of other variables is challenging. Another issue arises from the diminishing sensitivity of these tests due to many repetitions [136].

4.1.2. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS has been confirmed by a working committee established by the International Society for HE and Nitrogen Metabolism (ISHEN) to evaluate the existing evidence on the neuropsychological evaluation of HE, and it is recommended for diagnosis [135]. ISHEN suggests conducting the RBANS test together with the PHES test. The RBANS assesses verbal and visual anterograde memory, working memory, cognitive processing speed, language, and visuospatial function [137]. It specifically evaluates cognitive skills that are not impacted by HE but are often affected [6]. The test battery was developed to evaluate dementia and identify cognitive impairment in other conditions. Thus far, the utilization of this method for identifying MHE has been limited [138]. The RBANS test has a low sensitivity of just 38% in accurately detecting OHE. Therefore, it is not recommended to utilize RBANS to diagnose MHE [108].

4.1.3. Animal Naming Test (ANT)

Campagna et al. confirmed the effectiveness of the ANT in assessing cognitive impairment in individuals diagnosed with cirrhosis [91]. This highly straightforward test requires the patient to enumerate as many species of animals as they can within 1 minute. Furthermore, a study revealed that the ANT is an effective, uncomplicated, and flexible instrument for assessing cognitive impairment. While the data does not directly establish a connection between the ANT and HE, it does indicate that the ANT identifies a group of individuals with low health status and higher rates of frailty and impairment. This suggests that further investigation is needed to understand the underlying causes of these conditions [139].

4.1.4. Continuous Response Time (CRT) Test

This test evaluates the motor response time by instructing the patient to press a button when they hear auditory stimuli through headphones. The CRT index is the most crucial test result as it quantifies the stability of reaction times. The test result can distinguish between organic and metabolic brain dysfunction. The test is unaffected by the patient's age or gender, and it does not have any impact on learning or fatigue [140].

4.1.5. Inhibitory Control Test (ICT)

ICT can be easily and quickly used to diagnose MHE in a clinical setting in just a few minutes [87]. The effectiveness of ICT in diagnosing MHE has been confirmed by multiple studies [141]. There was no disparity in ICT efficiency between patients with alcoholic cirrhosis and people with nonalcoholic cirrhosis [142]. These findings suggest that the various causes of liver cirrhosis do not influence the use of ICT for MHE diagnosis [143]. The findings of ICT are also not influenced by age in both cirrhotic patients and controls [144].

Moreover, the findings of ICT show improvement following lactulose therapy and deterioration after a transjugular intrahepatic portosystemic shunt. This suggests that ICT can be utilized to assess the psychometric changes caused by these treatments [143]. In clinical settings, the ICT, is widely recognized as a reliable diagnostic tool for MHE. Consequently, it enables clinicians to identify cirrhotic patients at a heightened risk of MHE accurately. These patients can then be recommended to undertake other neurophysiological and psychometric tests for further evaluation [109].

4.1.6. EncephalApp (Stroop App) and QuickStroop

It is available as a mobile application. The application has been accessible since 2013 [145]. Presently available for both iOS and Android devices. The program utilizes the Stroop effect to evaluate psychomotor speed and cognitive awareness. The objective for the patient is to determine the colors of the stimulus displayed on the screen. The comprehensive assessment comprises three steps. Initially, the patient selects the color in which a randomly chosen word is presented on the screen. In the second task, the patient must identify the color of the word that corresponds to its color definition, as indicated by its name. During the third phase, there is a discrepancy between the name of the color and the actual color of the word. The test result is promptly accessible upon completion [145]. A multicenter study comparing it to the PHES and ICT showed a high level of accuracy in

detecting the condition and is effective in evaluating the likelihood of developing OHE with a favorable sensitivity (70-80%) for screening minimal MHE [146].

The Quick Stroop test is a version of the EncephalApp Stroop test and is a reliable substitute for the full EncephalApp Stroop and PHES. It can accurately and specifically detect cognitive impairment associated with rapid cognitive health evaluation in real-world scenarios [93]. Furthermore, a study by Kanagalingam et al. suggested that the QuickStroop test, which can be completed in about a minute and utilizes the early runs of the EncephalApp Stroop's "Off" stage, is a dependable method for diagnosing covert or MHE. CHE was linked to elevated odds of developing OHE and necessitating hospitalizations [147].

4.1.7. SCAN Test

The test is a computerized assessment that evaluates the patient's ability to accurately and quickly complete a task involving the recognition of digits. The task's difficulty increases as the test progresses [94,148]. The process involves randomly presenting a sequence of 72 ordered pairs of numbers on a computer screen for 3 seconds. Patients are directed to press the corresponding number on a keyboard if they recognize a familiar digit in the series of digits displayed. The study records the average reaction times and the proportion of errors and then evaluates the results by considering the reaction times in relation to the number of errors [149].

4.2. Electrophysiologic Tests

4.2.1. Electroencephalogram Monitoring

The EEG can serve as a valuable tool in the differential diagnosis of disoriented or comatose persons with liver insufficiency/shunt, particularly when the diagnosis of HE is uncertain. It can help guide the diagnosis toward alternative illnesses [150]. HE is defined by changes in the oscillatory characteristics of neural networks in the brain [151]. The EEG readily detects a broad range of irregularities, which have been conclusively linked to behavioral changes in HE. The EEG consists of two primary components: repetitive background activity and transients. Patients' HE sees a gradual decrease in the fundamental rhythmic activity of their EEG.

Furthermore, the waking EEG's responsiveness to opening the eyes diminishes and ultimately ceases. Transient phenomena, specifically called 'triphasic waves,' can be detected in the EEG of patients with moderate/severe HE. However, it is worth noting that these waves are not exclusive to this particular metabolic disorder [152]. It detects alterations in brain activity, even in uncooperative patients [9].

In individuals with MHE, quantitative electroencephalography (q-EEG) examination reveals an elevated proportion of theta wave activity and a reduced mean dominant frequency (MDF) in the posterior derivations. These alterations are associated with indicators of liver dysfunction and can predict the development of HE and death related to liver disease [153]. An EEG study conducted during sleep can benefit cirrhotic patients by detecting variations in mean dominant frequency (MDF) that early indicate brain dysfunction in individuals with MHE [118]. During this scenario, q-EEG reveals changes in the slow oscillatory activity, characterized by an elevated frequency of the prominent delta rhythm [85]. At first, the EEG does not show overall slowing but simply periods of theta activity. Quantitative EEG demonstrates no decrease in the average dominant frequency (MDF) of the EEG [154]. However, it does show an increase in theta activity, specifically in the posterior regions of the scalp [155]. A study discussed an early marker of EEG (alpha rhythm). The paper presents a new biophysical model called MHE-AWD-NCM, which includes communication dynamics between the cortical neuron population (CNP) and astrocyte population (AP). This model aims to comprehend the role of disrupted communication between astrocytes and neurons in developing alpha wave disturbances (AWD) in MHE [156].

4.2.2. Evoked Potentials

Electrical signals can be created by adequately stimulating excitable tissues using light (visual evoked potentials, [VEPs]), acoustic signals (brainstem auditory evoked potentials [AEPs]), or electrical stimulation of somatosensory nerves [123]. The latency of VEPs is determined by the passage of signals from the retina to the visual brain through several connections [157]. VEPs can be

affected by several factors, such as optic nerve illnesses, demyelinating processes, disorders of subcortical or cortical neurons in the cerebral hemispheres, metabolic abnormalities, and the use of psychoactive medicines [158]. The latency of the P100 wave of pattern visual evoked potentials (pVEPs) has been utilized to monitor MHE [159]. VEPs measure the time delay between visual input and the corresponding brain activity; however, the outcomes can vary. The variability in the assessment of subclinical HE may be attributed to the utilization of an N3 instead of the commonly used P100 component in routine neurological examinations. Furthermore, the definition of subclinical HE varies across different studies, making it challenging to compare the results. Consequently, using VEPs in patients with MHE seems to have limited diagnostic significance [160].

The significant incidence (about 40%) of flash visual evoked potential abnormalities in cirrhotic patients with normal EEG and psychometric performance indicates that this approach is highly sensitive in diagnosing HE [124,161]. Brainstem AEPs (BAEPs) are generated by delivering rapid sequences of monaural auditory stimuli, typically consisting of 1000 to 2000 clicks. The stimulation of several regions inside the brainstem subsequently accompanies the activation of the auditory nerve. Healthy individuals can have a total of seven detectable positive and negative waves. Patients in HE stages 0-I do not exhibit any notable elongation of BAEP-peaks I-V or the interpeak delay I-V. BAEPs have an erratic reaction when subjected to HE testing [123].

4.2.3. Critical Flicker Frequency Testing

CFF is a widely recognized neurophysiological method that assesses the CNS's capacity to perceive rapid changes in light intensity. This measurement is directly impacted by cortical activity [162]. It involves presenting light pulses at progressively lower frequencies (starting at 60 Hz) and requiring the patient to touch a button as soon as the perception of steady light transitions to flickering light. Following a training period, the test is conducted on eight occasions, and the average value of these trials is computed as CFF, which serves as a metric for visual temporal resolution. The threshold value is between 38 and 39 Hz, and the duration is approximately 10 minutes [125]. CFF can identify a wide range of neuropsychological disorders, including issues with visual signal processing (retinal gliopathy) as well as cognitive functioning.

Furthermore, PHES investigates the interplay between visual perception, construction, visual/spatial orientation, motor speed, accuracy, focus, and attention. Therefore, the two ways could be mutually beneficial [163]. There has been a reported discrepancy between neurophysiological research, which primarily focuses on externally stimulated brain responses, and psychometric testing [164].

4.3. Biomarkers

Ammonia is a serum biomarker that 60-95% of clinicians in their medical practice use to diagnose HE [165]. However, if the blood ammonia level is within the normal range in a patient with OHE, it should arouse suspicion of a different diagnosis [136].

Hyperammonemia can cause cell death by activating N-methyl-D-aspartic acid (NMDA) receptors excessively through glutamate, as well as increasing the activity of GABAergic receptors, which can be temporarily reversed with flumazenil [166]. A research team in Valencia studied the harmful oxidant 3-nitro-tyrosine as a biomarker. The reason for this choice was the well-established fact that hyperammonemia can cause oxidative stress. Indeed, 3-nitro-tyrosine has been identified as a toxic substance that has a role in the development of HE. Their preliminary study demonstrated encouraging findings, indicating that 3-nitro-tyrosine levels above 14 nM exhibited about 90% sensitivity, specificity, positive predictive value, and negative predictive value for MHE [132]. Another study conducted in Egypt between 2016-2018 The quantification of 3-nitro-tyrosine in serum is an easy and efficient process that does not require a significant amount of time, and this would enable the expansion of the diagnostic of MHE to a wide range of clinical environments, facilitating the identification of patients with MHE. 3-nitro-tyrosine serum levels serve as a reliable indicator for the existence of MHE in individuals with liver cirrhosis. These levels exhibit a high sensitivity of 90% and a specificity of 93.33%. Additionally, the positive and negative predictive values at a cutoff of 14 ng are 93.1% and 90.3%, respectively [167].

Inflammation is another factor contributing to the development of HE. Indeed, chemokines, cytokines, and ammonia can stimulate microglia, leading to neuroinflammation and worsening

cognitive performance. Preliminary investigations assessing the levels of IL-18, namely IL-6, demonstrated strong associations with the occurrence and intensity of HE [168]. A level of IL-6 higher than 11 pg/mL is a potentially effective threshold for identifying MHE [49]. Other studies have also examined the role of S100β as a biomarker in HE, specifically in the context of acute liver failure (ALF) [169]. During ALF, the concentration of S100β protein in the blood increased by up to three times upon admission and remained elevated for 72 hours [170]. However, there was no association between S100β levels and the severity of HE, the occurrence of brain herniation, or the final result [171]. Two smaller studies conducted in patients with CLD discovered that individuals without HE had normal levels of S100β. However, patients with HE had a two-fold rise in S100β levels. S100β levels higher than 0.13 µg/L can achieve 83% sensitivity and 64% specificity in detecting HE. The correlation between S100β and HE severity was not seen, indicating its inability to differentiate between OHE and MHE [172,173].

4.4. Evaluation for Precipitating Causes

Numerous studies have documented multiple risk factors, which can be categorized into two main groups: precipitating events and predisposing factors (Table 2).

Table 2. Precipitating factors diagnosis and management.

Precipitant factor	Diagnosis	Management
Alcohol and drugs	Anamnesis	Alcohol consumption counseling and discontinuation of hepatotoxic drugs
Constipation	More than 24 hours without passing stool or demonstration of significant fecal retention in the colon	Oral laxatives and/or cathartics, bowel enemas
Dehydration	Any sign of dehydration (skin and mucosal dryness, confused state) in a suitable context (patient with vomiting, diarrhea, diuretics abuse), as well as sodium, creatinine, and hematocrit increase	Correct dehydration (fluid therapy, stop diuretics)
Portosystemic shunt (spontaneous and TIPS)	Evidence of SPSS at radiologic imaging. Anamnesis and/or evidence of TIPS at radiologic imaging	Radiological shunt obliteration (BRTO, CARTO, PARTO) in case of recurrent/persistent HE
Electrolyte disorder	Hyponatremia (sodium < 130 mEq/L)	Hypovolemic hyponatremia: administration of normal saline. Hypervolemic hyponatremia: fluid restriction (<1000 mL/day); consider hypertonic saline or albumin administration.
	Hypokalemia (potassium < 3 mEq/L)	Administer oral or IV potassium supplementation
Malnutrition	Non-instrumental tools: BMI, food diary, objective examination, biochemical parameters, anthropometric measurements, creatinine-to-weight ratio, subjective global assessment questionnaire. Instrumental tools: bioimpedance test, handgrip strength test, DEXA, computed tomography scan	Dietary consult and advice for a correct supply of nutrients. Physical exercise to improve muscle tropism based on the patient's potential
Gastrointestinal bleeding	-Any evidence of upper GI tract bleeding (hematemesis or melena)	Variceal bleeding: stabilize the patient if unstable, start vasoactive drugs and

antibiotic prophylaxis, and perform an upper endoscopy. Consider TIPS placement in selected cases. Non-Variceal Bleeding: stabilize the patient if unstable, start PPI IV at high dosage, perform upper endoscopy within 24 h (<12 h if high-risk patient), and endoscopic hemostasis if indicated.

Abbreviations: BRTO, Balloon-Occluded Transvenous Retrograde Obliteration; CARTO, Coil-Assisted Retrograde Transvenous Obliteration; PARTO, Plug-assisted BRTO.

Age, liver function, the existence of portal hypertension, medication, renal function, genetic predispositions, underlying medical conditions, and the pathophysiology of liver cirrhosis (alcoholic or nonalcoholic) are risk factors [12]. Common risk factors that might trigger or worsen the condition include problems associated with decompensated liver cirrhosis, such as acute-on-chronic liver failure, hepatorenal syndrome, and gastrointestinal hemorrhage [174]. Additional risk factors involve infection, hypokalemia, hyponatremia, constipation, disruption of the gut-liver axis, type 2 diabetes mellitus, malnutrition, and sarcopenia [88,175]. Certain pharmacological substances can worsen HE, such as opioids, proton pump inhibitors, benzodiazepines, and other sedative medications. Infection is the primary precipitating factor, while electrolyte imbalance is the secondary precipitating factor [176]. All patients diagnosed with HE who were admitted to the intensive care unit (ICU) had a minimum PF, and the majority had multiple PFs. Increased mortality was independently associated with PF or an infection [177].

Moreover, there is a direct relationship between the severity of portosystemic shunt and an increased likelihood of HE. A study discovered that individuals with cirrhosis with a total cross-sectional spontaneous portosystemic shunting area greater than 83 mm2 had a higher risk of experiencing HE [178]. In individuals with cirrhosis, some genetic risk factors, including single nucleotide polymorphisms of fucosyltransferase 2, toll-like receptor 9, solute carrier family one member 3, solute carrier family one member 5, and have been linked to an increased likelihood of developing HE. Moreover, these genetic risk variables have demonstrated the ability to estimate the intensity of HE [179]. Furthermore, patients carrying genetic variations in the promoter region of GLS1, which encodes kidney-type glutaminase, had a higher occurrence of HE [180]. This finding establishes a connection between specific genes and an elevated HE risk in patients who have experienced previous episodes [12].

4.5. Challenges in Diagnosing Minimal Hepatic Encephalopathy

In fact, there needs to be more comprehensive knowledge on how to combine different test methodologies and interpret the results effectively. Additionally, studies have often needed better agreement between different tests. Diagnosing HE poses challenges. Clinical scales have faced criticism because of their poor specificity and significant variability amongst operators, particularly regarding mild HE [181]. MHE remains a condition that is not diagnosed frequently enough. This might be attributed to the limited quantity of multicentre randomized studies, the need for definitive guidelines for suggested diagnostic methods, and a shortage of experienced professionals [182]. A wide range of variation is due to the absence of standardized research methodologies and the unique characteristics of the examined populations. Although patients with MHE may not exhibit clear clinical symptoms, it still significantly impacts their everyday functioning. At the same time, Individuals diagnosed with MHE experience a notable decline in their overall well-being and quality of life as it relates to their health [69]. The diagnosis of MHE can be ignored due to the predominant impairments in global cognitive functioning and motor skills, while linguistic abilities typically remain intact. A survey conducted among members of the American Association for the Study of the Liver revealed that while 84% of participants recognized the clinical significance of MHE, nearly 40% of respondents had never undergone testing for MHE [183].

5. Management

5.1. Pharmacological Management

The recommendation is that only OHE should be routinely treated [17]. The target of treating the first attack of OHE should be limiting the result, reducing the duration, and treating the cause (Table 3). After that, we should focus on limiting hospital stays, preventing recurrence, and improving quality of life [184,185]. Treatment targets decreasing ammonia production and stimulating its elimination [186]. However, preventing recurrence by focusing on the related factors should also be assessed.

Table 3. Published studies on the management of minimal hepatic encephalopathy.

Reference	Population	Intervention	Comparison	Outcomes
Lactulose therapy				
Morgan *et al.* (1989) [187]	14/ 14	Lactulose	Lactitol	No differences between treatments in a median change in psychometric time or scores
Horsmans *et al.* (1997) [188]	7/ 7	Lactulose	Lactose as placebo	Improvement in time on Psychometric test on lactulose group with respect to basal values. Rate of improvement NCT: 5/7 (71.42%) vs 1/7 (14.28%); NNT:2
Watanabe *et al.* (1997) [189]	22/36	Lactulose	No treatment	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
Dhiman *et al.* (2000) [190]	14/ 12	Lactulose	No lactulose	Improvement in 8/10 (80.0%) vs 0/8 (0.0%), P < 0.001)
Prasad *et al.* (2007) [191]	31/ 30	Lactulose	No treatment	ITT analysis: Improvement in 20/31 (64.5%) vs 2/30 (6.7%); NNT:2
Bajaj *et al.* (2012) [192]	1000	Lactulose	Rifaximin	Suggestions: MHE diagnosis with ICT and treatment with lactulose
Sharma *et al.* (2012) [193]	105/ 55	Lactulose	No lactulose	Improvement of MHE in 21/32 (66%) vs. 9/36 (25%)
Ziada *et al.* (2013) [194]	24/ 26	Lactulose or Probiotic	No treatment	Normalization of psychometry in half of treated patients (13/24 vs. 14/26 vs. 3/25). Reduction of OHE risk development
Pratap *et al.* (2015) [195]	40/ 33	Lactulose or probiotic	No treatment	Psychometric improvement in 23/33 and in 25/40. Improvement in MHE correlated with a reduction of ammonia levels.
Sidhu *et al.* (2016) [196]	55/ 57	Lactulose	Rifaximin	MHE reversal in 38/55 and in 42/57; HRQoL was significantly improved in both groups
Wang *et al.* (2019) [197]	67/ 31	Lactulose	No lactulose	ITT analysis: 43/67 (64.2%) *vs* 7/31 (22.6%); NNT: 3PPS: 41/59 (69.5%) *vs* 6/28 (21.4%); NNT: 2
Wang *et al.* (2023) [198]	52 (Pro, n = 34) , (Rif, n = 11) , (Lac, n = 7)	Probiotics, Rifaximin , Lactulose	Baseline before Probiotics, Rifaximin , Lactulose	MHE Recovery Rates: Probiotics: 58.8% (20/34) Rifaximin: 45.5% (5/11) Lactulose: 57.1% (4/7) No significant difference in efficacy between the three groups (p = 0.843).

Rifaximin therapy				
Sidhu *et al*. (2011) [199]	49/ 45	Rifaximin	Placebo	Reversal at 2 wk: 57% vs 18% (NNT: 3)At 8 wk: Reversal of 75.5% vs 20% (NNT: 2)
Ballester *et al*. (2022) [200]	32	Rifaximin	Patients without metabolic syndrome manifestations	Mean PHES in responders (21 patients 66 %) was -7.3 ± 0.7, -3.2 ± 0.3, and -3.3 ± 0.6 at study initiation and at 3 and 6 months of rifaximin, respectively
Bajaj *et al*. (2013) [201]	20	Rifaximin	Baseline (before Rifaximin)	Significant improvement in cognitive performance (6/7 psychometric tests)
Ahluwalia *et al*. (2014) [202]	20	Rifaximin	Baseline (before Rifaximin)	Changes in ICT, improvement of 12% respect to baseline, indicating a better cognition
Zhang *et al*. (2015) [203]	26	Rifaximin	Baseline (before Rifaximin)	MHE reversal in 15/26; reduction in SIBO and ammonia levels
Goyal *et al*. (2017) [204]	42/ 38	Rifaximin	Lactulose	Still free of MHE: Rifaximin 42.8% *vs* lactulose 50.0% (NNT: 14)
Bakulin *et al*. (2023) [205]	258	Rifaximin	Cyclic therapy	Continuous rifaximin-alfa therapy significantly improves cognitive function and quality of life in patients with liver cirrhosis and MHE compared to cyclic therapy
Fiorillo *et al*. (2023) [206]	31	Rifaximin	Patients without MHE, controls, baseline (before Rifaximin)	NFL levels in MHE patients who responded to the treatment significantly decreased 16.1 ± 2.7 to 11.9 ± 1.8
Casanova-Ferrer *et al*. (2024) [207]	18/ 57	Rifaximin	No treatment	Rifaximin treatment improved cognitive functions, as evidenced by better scores on the PPHES, OSDMT, and Stroop tests.
l-Ornithine l-Aspartate (LOLA)				
Kircheis *et al*. (1997) [20]	26/ 27	LOLA infusion	Placebo	Improvement in the mean time to respond NCT-A from baseline (29% vs. 9.73%)
Branched-chain amino acid (BCAA) therapy				
Egberts *et al*. (1985) [208]	11/ 11	BCAA	Placebo	Improvement in the psychometric test from 0 to 13.63% with respect to basal values in DST
Plauth *et al*. (1993) [209]	17	BCAA	Placebo	BCAA is superior to placebo in Psychometry and driving ability
Marchesini *et al*. (2003) [210]	174 patients with advanced cirrhosis	12-month BCAA supplementation	Lactoalbumin or maltodextrins	BCAA significantly reduced the combined event rate (death or deterioration) compared to lactoalbumin. BCAA group had fewer hospital admissions and improved nutritional parameters, liver function, anorexia, and quality of life.
Les *et al*. (2011) [211]	116 patients with cirrhosis and	56-week supplementation with 30g BCAA	Maltodextrin	There was no significant difference in HE-free survival. The BCAA group showed better performance on two

	prior HE episode			neuropsychological tests and increased mid-arm muscle circumference.
Probiotic therapy				
Liu *et al*. (2004) [32]	40 patients with cirrhosis and MHE. 15 healthy volunteers (controls).	Probiotic, Prebiotic	Baseline (before synbiotic administration) Healthy controls	MHE Reversal: Synbiotic group: 50% (20/40) showed significant improvement in psychometric test scores. No significant changes in the placebo group. Blood Ammonia: Significant reduction in arterial and venous ammonia levels in the synbiotic group ($p < 0.01$). No significant change in the placebo group. Endotoxemia: Significant reduction in plasma endotoxin levels in the synbiotic group ($p < 0.01$). No significant change in the placebo group.
Malaguarnera *et al*. (2007) [212]	30/ 30	Bifidobacterium longum + FOS	Placebo	No statistical or clinical change was found with respect to basal values at 30, 60, 90, and 120 d
Bajaj *et al*. (2008) [213]	17/ 8	Probiotic yogurt	No treatment	ITT analysis: Reversal in 12/17 (70.58%) vs 0/7 (0%)
Sharma *et al*. (2008) [214]	31/ 31	Lactulose or probiotic or lactulose + probiotic	No treatment	Normalization of all parameters in half of the treated patients (17/31, 16/31, and 17/30, respectively)
Mittal *et al*. (2011) [215]	40/ 40/ 40/ 40	Lactulose/ VSL#3, LOLA	No treatment	ITT analysis: Reversal of 4 (10%) in no treatment group, 19 (47.5%), 14 (35%) and 14 (35%)
Bajaj *et al*. (2014) [216]	14	Probiotics	Placebo	Reduction in endotoxin and TNF-α but not in cytokines. No effects on psychometric performance
Lunia *et al*. (2014) [217]	86/74	Probiotic	No treatment	Probiotics prevented HE. Reduced arterial ammonia, SIBO, OCTT; increased PHES and CFF thresholds compared to control.
Sharma *et al*. (2014) [218]	32/ 31/ 31/ 30	Probiotics	LOLA, rifaximin, placebo	All three treatments were better than placebo in improving CFF and abnormal neuropsychiatric test results. Rifaximin and LOLA significantly improved CFF compared to placebo.
Pratap Mouli *et al*. (2015) [195]	33/ 40	Probiotic	Lactulose	Probiotics non-inferior to lactulose in improving MHE. Improvement in both groups correlated with a reduction in ammonia levels.
Xia *et al*. (2018) [219]	30/ 37	Probiotic	No treatment	Improved cognition, enriched Clostridium cluster I and Bifidobacterium, decreased Enterococcus and Enterobacteriaceae. Reduced venous ammonia and improved intestinal mucosal barrier parameters.
Combined therapy				

Liu *et al*. (2004) [32]	20/ 20/ 15	Symbiotics + fermentable fibers	Fermentable fibers/ placebo	Reversal of 50% in the symbiotic group, 50% in the fermentable fibers group, and 13% in the placebo. Not statistically significant until compression of treatment groups vs placebo (P = 0.03)
Ndraha *et al*. (2011) [220]	17/ 17	BCAAs + LOLA	BCAAs	Improvement in CFF 7.0% and 1.96% values (Hz), with respect to baseline
Kato *et al*. (2013) [221]	19	30-35 Kcal + 1.0-1.5 g/kg of protein/d	baseline (before treatment)	11/19 (57.8%) recovered at 4 wk, and 13/19 (68.4%) at 8 wk
Rai *et al*. (2015) [222]	7	Lactulose and Rifaximin	Controls, NMHE group, baseline (before treatment)	Psychometric improvement (P=0.044); reversal of low-grade cerebral edema
Shi *et al*. (2023) [223]	44/ 44	Combination of probiotics and lactulose.	Lactulose alone.	A combination of probiotics and lactulose is more effective than lactulose alone in improving cognitive function and quality of life in patients with MHE
Others				
Malaguarnera *et al*. (2008) [224]	60/ 55	Acetyl-L-carnitine	Placebo	Changes of mean values in at least 20.71% to 32.79% with respect to basal values
Agrawal *et al*. (2011) [225]	35	For patients with MHE and H. pylori infection, Clarithromycin, lansoprazole, tinidazole	Relationship between H. pylori and MHE, rather than directly contrasting different treatment approaches.	Improvement in 12.7%, 13.3%, and 18.7% with respect to basal mean time in NCT, FCT, and LTT
Bajaj *et al*. (2014) [216]	18/ 19	Lactobacillus GG	Placebo	Improvement from 1.02% to 15.89% from baseline values
Burkard *et al*. (2013) [226]	25	Potassium–iron–phosphate–citrate	baseline (before treatment)	Normalization of psychometry in 72% vs. 26.9%. QoL improvement.
Maharshi *et al*. (2016) [114]	60/ 60	Nutritional education	No nutritional therapy	27/38 (71.1%) *vs* 8/35 (22.8%); 27/60 (45%) *vs* 8/60 (13.3%) when considering PPS and ITT analysis.
Janyajirawong *et al*. (2021) [227]	34/ 32	Zinc supplementation	Placebo	A 12-week course of zinc supplementation significantly improved psychomotor performance in cirrhotic patients with MHE. Patients receiving zinc performed better in neuropsychiatric tests (NCT-A, NCT-B, SDT, DST) than placebo patients.
Sharma *et al*. (2023) [228]	75/ 75	Nutritional therapy	No nutritional therapy	Nutritional therapy is effective in treating MHE and is associated with improving nutritional status, HRQOL, ammonia, endotoxins, inflammatory markers, and myostatin levels.

Abbreviations: BCAA, branched-chain amino acids; BDT, block design test; CFF, critical flicker frequency; CEP, cognitive evoked potentials; DST, digit symbol test; EEG, electroencephalogram; FOS, fructooligosaccharide; HRQoL, health-related quality of life; ICT, inhibitory control test; LTT, line tracing test; MHE, minimal hepatic encephalopathy; NCT-A, number connection test-A; NCT-B, number connection test-B; NfL, Neurofilament

light; OHE, overt hepatic encephalopathy; PHES, psychometric hepatic encephalopathy score; SDT, serial dotting test; SIBO, small intestinal bacterial overgrowth.

Nondigestible lactitol, lactulose, and disaccharides are the first line of treatment. These substances are broken down into organic acids (of short chain) in the colon [5]. The acidity reduces the bacteria that produce ammonia, reducing the production of ammonia and converting ammonia into ammonium (nonabsorbable), thus decreasing the absorption of ammonia. Also, they increase osmolarity and thus lead to rapid intestinal transit and remove excess nitrogen from feces by the laxative role [184–186]. Lactose additionally increases zinc absorption [229]. Lactulose enema improves the electroencephalograms and asterixis by the same degree as neomycin tablets, but lactose enema additionally acidifies the pH of the stool, thus improving the number connection test [230]. It was proven that there was nearly no difference between lactulose and lactitol regarding efficacy and safety [231]. Gluud et al. found that nonabsorbable disaccharides play a role in HE treatment and mortality [232]. PEG or Polyethylene glycol 3350-electrolyte solution is an osmotic laxative that can be used instead of lactulose in the treatment of hospitalized HE patients [233,234].

Antibiotics targeting the reduction of the number of intestinal bacteria that produce ammonia can be used in therapy [186]. The first antibiotic to be used was neomycin, which reduced the concentration of colonic ammonia [235]. Rifaximin (non-absorbable antibiotic) inhibits RNA synthesis in gram-negative, gram-positive, anaerobic, and aerobic intestinal bacteria [184]. Rifaximin was proven to be as effective as neomycin and also as effective and safe as lactulose [236,237]. Also, studies proved that the use of rifaximin plus lactulose has a better response than lactulose alone in the treatment of HE and mortality reduction [238]. Rifaximin was found to have the same effect as nonabsorbable disaccharides or other antibiotics but with more safety in asterixis reduction and improving the mental state [239].

5.2. Nutritional Therapies and Dietary Modifications

Metabolic ammonia scavengers are substances that increase the excretion of ammonia in urine through an alternative pathway. One of the firstly used scavengers was sodium benzoate, which is conjugated in the liver with glycerin and then passed in urine as Hippurate [240]. It has proved to be as effective as nonabsorbable disaccharides in treating HE [241]. Glycerol phenylbutyrate also eliminates ammonia through excretion in the urinary tract, such as phenylacetylglutamine. Ammonia level with Glycerol phenylbutyrate was found to be lower than that with rifaximin and lactulose use [238]. Ornithine phenylacetate activates glutamine synthetase, inducing muscle trap of ammonia (as glutamine) followed by its conjugation with phenylacetic acid, forming phenylacetylglutamine and then excreted in urine [242]. Ornithine phenylacetate administration after GIT bleeding (upper tract) reduces ammonia levels in the plasma and appears to be safe [243].

L-ornithine-L-aspartate converts ammonia into glutamine and urea, thus reducing the level of blood ammonia [185,186]. Oral L-ornithine-L-aspartate appears to have the same effect as lactulose in improving asterixis, mental state and reducing ammonia levels [244]. A Cochrane review proved that L-ornithine-L-aspartate has a beneficial effect on mortality and improves HE, but there still needs to be a clear recommendation for its use [245].

The liver synthesizes albumin protein, which modulates the antiinflammatory response and detoxification [5,184]. Studies have proven that using albumin with lactulose is more effective in treating HE and reducing mortality than using lactulose alone [246].

Probiotics are living microorganisms that, at a certain level, have a beneficial role in the host through modulating GIT immunity [247]. Some probiotics can reduce inflammation, restore microbiota, and prevent the translocation of bacteria by maintaining the integrity of the intestinal barrier [248]. VSL#3 was the most commonly used probiotic [249]. The use of fibers with probiotics appeared to reverse the minimal HE [250]. Studies have shown that using lactulose with probiotics can decrease the risk of unimprovement among HE patients [251].

The nutritional state, portosystemic shunt, and level of decompensation are very important and affect the response of the patient to diet. Studies found no difference between the effect of vegetable protein and psyllium Plantago in comparison with animal protein in patients with type 2 DM and HE [252]. The current recommendations suggest an intake of 35–40 kcal/kg of body weight and 1.2–1.5 g/kg of protein per day in case of the presence or absence of HE, and it is better to be vegetable and animal protein [253].

5.3. Role of Liver Transplant

Persistent HE, especially when liver function is not severely affected, suggests portocaval shunts (spontaneous). These patients can benefit from embolization in the form of a decrease in the number of HE attacks [254]. Also, shunt embolization was associated with better survival in these patients if MELD < 15 and did not have hepatocellular carcinoma [255]. Liver transplantation may be a treatment option in some HE patients [184].

Microbiota plays an important role in the pathogenesis of HE. A trial showed that patients using standard lines of therapy had a poorer response than those using transplanted fecal microbiota. Also, cognition was improved compared to the standard [256]. The neurological state also improved, and the hospitalization period decreased with it [33]. However, there is still no recommendation for its use [257].

Low zinc levels can increase the ammonia level in the blood by impairing enzyme sharing in the urea cycle and glutamine synthetase. Zinc supplements were associated with improvement in the number connection test but did not affect HE recurrence [258].

Lactulose plus rifaximin is considered the best prophylaxis against HE recurrence [259]. Studies have also proved that lactulose is a very strong prophylactic agent for preventing HE after variceal bleeding (acute attack)[260]. Also, using rifampicin can decrease the hospitalization rate in the long run [261]. Long-term use of albumin can also prevent HE recurrence and reduce the incidence of grades 3 and 4 of HE [262].

Patients with end-stage liver failure may suffer from HE and confusion. This is due to manganese accumulation in the pituitary gland, mesencephalon, and lentiform nucleus, which can be seen using MRI. After liver transplantation, these changes disappear due to the functioning of a new liver [263]. Some studies showed that the degree of HE before liver transplantation affects the degree of awareness after transplantation [264–266]. After transplantation, cases with fourth-stage HE need nearly five days for recovery [266,267]. Intraoperative brain ischemia, permanent Ischemia to the brain with or without persistent shunt before transplantation, can make HE irreversible after transplantation [268–270]. Studies proved that after liver transplantation, HE will show incomplete regression. So, it is necessary to develop different treatment plans after transplantation for complete HE recovery [271].

6. Interesting Points of Discussion

6.1. Prevalence and Incidence of Minimal Hepatic Encephalopathy

MHE, which is the mildest subtype of HE, is associated with psychomotor and cognitive affection with no clinical symptoms of HE [272]. Zeegen et al. first described MHE, in which it was found that many patients who underwent surgery for portal decompression had abnormal scores (in trail-making tests) [273]. After nearly eight years, the definition of subclinical HE appeared in the literature. The definition of OHE appeared to combine the first grade of HE with MHE [274].

The incidence of MHE ranges between 20 to 80 % among cirrhotic patients early or during the disease course. This wide range is due to different tests and different diagnostic symptoms [191,275]. HE prevalence is about 10 to 14 % at the time of cirrhosis diagnosis and about 16 to 21% in patients with decompensated cirrhosis. It reaches about 50% after intrahepatic portosystemic shunt. The risk for the first attack of HE within five years of cirrhosis diagnosis can reach about 25% [184].

6.2. Impact of Minimal Hepatic Encephalopathy on Quality of Life

Liver disease affects the patient's health and quality of life. The most affected activities are psychomotor skills, information processing, and those requiring attention. However, usual activities such as dressing, shopping, and maintaining personal hygiene are maintained [191]. Several mechanisms may impair the quality of life among cirrhotic patients. Impairment of physical performance forces these patients to limit their activities, especially in the late stages of the disease. Also, cirrhosis complications such as bleeding and ascites can impair quality of life. Marchesini et al. showed that cirrhosis symptoms such as muscle cramps and itching can strongly affect quality of life [276]. Disease severity, sleep disorders, and hospitalization can also affect the quality of life [277,278]. Also, Nardelli et al. showed that anxiety, alexithymia, and depression were common among cirrhotic

subjects and widely affect HRQOL (health-related quality of life)[279]. MHE patients had a reduction in psychological sub-score, total score, physical subscore, and all 12 SIP scales. Groenweg et al. reported compared to those not having MHE. An analysis showed that MHE was associated with a low SIP scale in the areas of social interaction, work, recreation, and vigilance [67]. Schomerus et al. reported that about half of MHE patients could not work [280]. Also, loss of appetite and MHE among cirrhotic patients can negatively affect HRQOL [69].

The question now is whether a certain therapy for MHE could improve HRQOL or not [67,276,281]. The prevalence of sleep disorders among cirrhotic patients varies from 26% to 70%, which greatly affects the health and quality of life [72,282]. Also, sleep disorders can badly affect the liver function and cognitive level [283]. Melatonin clearance is decreased due to the affected liver (hepatic clearance), so the level increases daily. Also, defects in the circadian rhythm of melatonin with a delayed nocturnal peak in plasma can likely occur due to decreased sensitivity to light [71]. However, other mechanisms, such as thermoregulatory and neuromuscular alteration, may contribute to this [284].

Cirrhotic patients have a very high risk for falls [285]. The possible causes may be sleep problems, changes in body composition such as myosteatosis and sarcopenia, malnutrition, antidepressant medications, cognitive dysfunction, and endocrine disorders such as hypogonadism. These fractures usually lead to hospitalizations, fractures, high costs for health care, and thus bad HRQOL. The result is more serious among cirrhotic patients due to coagulopathy and the risk of operation [79].

Urios et al. reported that MHE patients have a higher risk for falls because of delayed movement onset, increased time for reaction, defective postural control, and decreased stability [286]. All these factors could contribute to bradykinesia among MHE patients [287]. Also, cirrhotic patients have very bad outcomes after accidents (traffic mainly) with long hospital stays, high costs for health care, and higher mortality rates [62]. Furthermore, the decreased ability to work among these patients puts an economic burden on them and their families, which may increase the indirect cost of this disease [77].

6.3. Continuum of Hepatic Encephalopathy from Minimal Hepatic Encephalopathy to Overted Hepatic Encephalopathy and Prognosis

MHE is a risk factor for OHE and also for mortality [288]. Within nearly three years, about 50% of patients suffer from OHE [275]. Hartmann et al. reported an increased risk of OHE among MHE patients after nearly 29 months and more attacks of OHE than those not having cognitive defects, with no difference in mortality risk between both groups [289]. Also, other studies proved that patients with MHE are at higher risk for developing OHE, especially those having high levels of ammonia and higher severity of the disease [163]. The incidence of OHE is higher among MHE patients with impaired function of the liver and those in the late stages of cirrhosis [275]. PHES of less than six and Child-Pugh score above seven were connected with higher mortality, as Dhiman et al. reported [89]. In multivariate analysis, Amodio et al. revealed that MHE had a prognostic effect on survival and disease severity [148].

6.4. Minimal Hepatic Encephalopathy Versus Hepatic Encephalopathy Stage I in Clinical Practice

HE is classified clinically into groups according to the West Haven criteria, which considers neuromuscular problems, changes in personality, and alteration in both intellectual function and consciousness [136]. Unfortunately, the diagnosis of grade 1 HE clinically according to this criteria is suggested to be operator-dependent; from this point, the expression of OHE appeared when at least flapping tremors or temporal disorientation occurred [136,290]. This flapping tremor is a negative myoclonus, not a true tremor. When grade 1 HE, in which the patient is symptomatic, is grouped with MHE, in which the patient has only abnormal tests with no clinical symptoms, the term Covert HE appears. However, this term made a huge debate as covert means hidden, although these patients are clinically symptomatic [181]. It was also noted that this condition has a different prognosis than MHE [291]. MHE diagnosis is very important as it is a very common condition and is associated with an increased risk of OHE and a worse prognosis [163,280]. In general, patients with both grade 1 HE and MHE are likely to have the worst prognosis among cirrhotic patients with no neuropsychiatric affection [292].

7. Future Perspectives and Current Trends

7.1. Development of Biomarkers

Identifying reliable biomarkers for MHE can significantly improve early diagnosis, intervention, and patient management. A study examined the role of S-100-beta and NSE in MHE patients undergoing treatment with L-ornithine-L-aspartate. However, these biomarkers did not significantly correlate with MHE severity [293]. Labenz et al. showed that higher serum levels of neurofilament light chains were independently associated with the presence of MHE, demonstrating reliable discriminative power for MHE detection [294].

Another promising biomarker for MHE is 3-nitro-tyrosine, which has high sensitivity and specificity in detecting MHE among cirrhotic patients [295]. Also, brain-derived neurotrophic factor (BDNF) serum results were twofold lower in liver cirrhosis compared to healthy subjects, its decrease due to a degree of liver insufficiency that may serve as a potential role as a diagnostic marker for MHE [296].

The progress of artificial intelligence in the field of medical imaging offers the opportunity to discover more efficient diagnostic biomarkers and enhance the predictive accuracy of MHE and, with a significant role of modern MRI techniques, have the potential to offer new perspectives for the future detection of MHE [297]. In addition, Luo et al. suggested that the intestinal microbiota compositions of MHE patients were shown to be changed, specifically in terms of the relative abundances of Salivarius and Veillonella. These changes were linked to sleep disorders, indicating that Salivarius and Veillonella could be used as diagnostic biomarkers [298]. Gairing et al. suggest that IL-6 could be useful for identifying individuals who should undergo further psychometric testing, thereby eliminating the necessity for such testing in around one-third of cases. Furthermore, when IL-6 serum levels reach or exceed seven pg/mL, it may be appropriate to consider starting anti-HE medication in patients unable to undertake psychometric testing [299]. Collectively, a variety of biomarkers are present, but the actual challenge is to ensure accuracy and reliability using larger population studies and making more effort to identify new biomarkers.

7.2. Development of Medical Calculators

Using the DFC-Dstrength metric, seven nodes were determined to be the most distinguishing characteristics for classifying MHE from the absence of HE (noHE). These nodes include the left inferior parietal lobule, left supramarginal gyrus, left calcarine, superior frontal gyrus, left cerebellum, right postcentral gyrus, and right insula. The distinguishing features of DFCs exhibit greater precision in accurately detecting MHE in patients with cirrhosis [300].

Another study suggests that cirrhotic individuals underwent eye testing with the OSCANN desk 100. The main features were derived from the memory-guided saccades, smooth pursuit, and antisaccades tests. An algorithm achieved a sensitivity of 93% and a specificity of 93%, exceeding the performance of the current gold standard, the PHES battery test [301].

7.3. Preventive Medicine

Based on the concept that HE refers to a range of cognitive and behavioral impairments that can occur as a complication of cirrhosis and have negative effects on outcomes. Ammonia is essential in its development. Rifaximin is a non-absorbable antibiotic that prevents the growth of bacteria that produce urease and decreases the intake of ammonia from food and bacteria. Rifaximin has the potential to both prevent and treat HE in individuals with cirrhosis. However, its efficacy is dependent on the specific state of the patient [302]. Furthermore, a combination of rifaximin and lactulose may be beneficial in preventing HE after TIPS placement, and most medications are ineffective alone [303].

Modern diagnostic tools such as PHES, CFF, and ANT are used to detect and grade MHE at the initial stages. This can help intervene in time and not let it go into the OHE stage. However, PHES is not usually used in clinical practice due to its time-consuming. Hence, it is necessary to create efficient diagnostic algorithms to advance screening and therapy [105]. In addition, Probiotics were more effective in reversing MHE and reducing serum ammonia levels in patients with MHE than placebo or no treatment. Still, they were less effective than lactulose or LOLA, considering highlighting their

role in preventive treatment strategies [304]. Utilizing comprehensive strategies such as the ideal transitions of care model can successfully reduce the risk of readmission in patients suffering from MHE, facilitating a smooth transition to outpatient care. Ongoing research is focused on developing innovative approaches to reduce readmissions for patients with HE and enhancing their quality of life [305]. Expanding upon the integrated approach in the optimal transitions of care framework, advancements in digital and technology can result in additional enhancements in healthcare delivery. An example of such a method is the utilization of electronic medical record (EMR) alerts and electronic checklists. A quality improvement study examined the effectiveness of a paper checklist vs an electronic checklist in managing different decompensations of cirrhosis, with a specific focus on HE [12].

8. Conclusion

MHE is a major challenge in the management of chronic liver disease since it affects a large number of patients and is often unrecognized because of subtle clinical presentation. In the present review, some interrelationships between factors involved in the pathogenesis of MHE were shed, from the central role of hyperammonemia and its neurotoxic effects to complex systemic inflammation, gut dysbiosis, and altered neurotransmission. While no single diagnostic test perfectly captures the multifaceted nature of MHE, a combination of psychometric assessments (Psychometric HE Score, PHES) with neurophysiological tools (electroencephalography, EEG; critical flicker frequency, CFF) testing, as outlined in this review, contributes to accurate detection. The reduction strategies for the ammonia burden are based on the management of MHE with nonabsorbable disaccharides, such as lactulose, and antibiotics like rifaximin. These are usually combined with nutritional therapies and probiotics. In selected cases, treatments may include embolization of portosystemic shunts or even liver transplantation. Looking ahead, the development of dependable biomarkers, AI-driven diagnostic algorithms, and preventive strategies, including gut microbiome modulation, will bring about a future in which MHE is diagnosed early to enhance the quality of life and long-term outcomes for patients with chronic liver disease.

Abbreviations

ALD	Alcohol-related liver disease
ANT	Animal Naming Test
AP	Astrocyte Population
AEPs	Auditory Evoked Potentials
BAEPs	Brainstem Auditory Evoked Potentials
BCAAs	Branched-Chain Amino Acids
BDNF	Brain-Derived Neurotrophic Factor
CFF	Critical Flicker Frequency
CNP	Cortical Neuron Population
CLD	Chronic Liver Disease
CHC	Chronic Hepatitis C Virus
CHB	Chronic Hepatitis B Virus
cGMP	Cyclase Guanylyl Monophosphate

CSF	Cerebrospinal Fluid
CNS	Central Nervous System
CTP	Child-Turcotte-Pugh
DFCs	Distinguishing Features of DFCs
DMN	Default Mode Network
EEG	Electroencephalography
HE	Hepatic Encephalopathy
HRQOL	Health-Related Quality of Life
ICT	Inhibitory Control Test
IL	Interleukin
ISHEN	International Society for Hepatic Encephalopathy and Nitrogen Metabolism
LOLA	L-Ornithine L-Aspartate
MHE	Minimal Hepatic Encephalopathy
MDF	Mean Dominant Frequency
Mn	Manganese
NAFLD	Nonalcoholic Fatty Liver Disease
NHP	Nottingham Health Profile
NOS	Newcastle-Ottawa Scale
NMDA	N-Methyl-D-Aspartic Acid
OHE	Overt Hepatic Encephalopathy
PHES	Psychometric Hepatic Encephalopathy Score
pVEPs	Pattern Visual Evoked Potentials
PPI	Proton Pump Inhibitors
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SIP	Sickness Impact Profile
TNF-alpha	Tumor Necrosis Factor-alpha
VEPs	Visual Evoked Potentials
WHC	West Haven Criteria

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