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Minimal hepatic encephalopathy: a hidden threat to quality of life in cirrhosis patients

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Abstract

Minimal hepatic encephalopathy (MHE) is often the least recognized form of hepatic encephalopathy, affecting up to 80% of people living with liver cirrhosis. While the signs can be quite subtle, MHE can seriously disrupt cognitive functions such as attention and memory. This disruption can impact daily life, potentially leading to an increased risk of accidents. Unfortunately, many health care providers might overlook the diagnosis because the symptoms can be vague, and identifying MHE usually requires specific tests like the psychometric hepatic encephalopathy score (PHES). Several factors contribute to MHE, including elevated ammonia levels, systemic inflammation, and issues with the gut-brain connection. It's crucial to identify and treat MHE quickly, as it can progress to overt hepatic encephalopathy (OHE), which presents much more severe symptoms and is associated with higher mortality rates. Current treatment approaches often include medications like lactulose and rifaximin, along with cognitive rehabilitation and dietary changes. Emerging treatments that focus on gut health, such as probiotics, are showing potential in helping to lower ammonia levels. This review brings together the latest research on MHE, pointing out significant gaps in how we diagnose it and the potential of new therapies like synbiotics. By looking at recent multicenter studies, we aim to offer practical insights that could help prevent the progression to OHE, ultimately improving patient outcomes.

Keywords

Minimal hepatic encephalopathy (MHE), liver cirrhosis, cognitive impairment, overt hepatic encephalopathy (OHE), probiotics, synbiotics, hyperammonemia

Introduction

Minimal hepatic encephalopathy (MHE) represents an early and relatively mild form of hepatic encephalopathy (HE), yet it introduces significant difficulties for individuals living with liver cirrhosis. The prevalence of MHE is variable, ranging from 20% to 80%, largely due to differences in diagnostic methods, such as the psychometric hepatic encephalopathy score (PHES) and imaging techniques, as well as

variability in study populations. A comprehensive meta-analysis has estimated a global prevalence of MHE at approximately 40.9% (95% CI: 38.3–43.5%), with studies utilizing PHES reporting rates between 35% and 64% [1, 2].

Though MHE may present with subtle symptoms, it is associated with significant cognitive impairments, affecting attention, working memory, visuospatial skills, and psychomotor speed, which are frequently overlooked during standard clinical evaluations [3, 4]. The implications of MHE extend well beyond cognitive difficulties; it can substantially impact day-to-day activities, work productivity, driving safety, and overall quality of life. If left unaddressed, MHE increases the risk of progression to overt hepatic encephalopathy (OHE), a more severe condition characterized by pronounced neurological symptoms and elevated mortality rates. The pathophysiology underlying MHE involves factors such as hyperammonemia, systemic inflammation, and disruptions in the gut-brain axis, highlighting the pressing need for early detection and focused interventions [5–7].

This review aims to consolidate knowledge regarding MHE, shedding light on its clinical importance, the challenges associated with its diagnosis, and promising emerging therapies. By raising awareness and improving management strategies, we hope to enhance patient outcomes and reduce the likelihood of transitioning to OHE.

Pathophysiology of MHE

In people with liver cirrhosis, the development and progression of MHE are strongly influenced by several factors, including ammonia levels, inflammation, and the connection between the gut and brain (Table 1) [8–10]. One of the main culprits in MHE is ammonia. When the liver is cirrhotic, it struggles to filter out ammonia effectively, leading to a buildup of this toxic substance in the bloodstream known as hyperammonemia, which correlates with portosystemic shunt severity, particularly in patients with esophageal varices and further exacerbating MHE risk. Ammonia primarily comes from bacteria in our gut, and when it reaches high levels, it can cross into the brain. This can cause problems like swelling of brain cells, interrupted communication between neurons, and difficulties with thinking and memory [9, 10].

Table 1. Pathophysiology of MHE [8–10]

Factor	Mechanism
Hyperammonemia	Impaired liver detoxification→ammonia crosses blood-brain barrier→neuronal dysfunction
Systemic inflammation	Gut dysbiosis→endotoxemia→elevated TNF-α/IL-6→neuroinflammation
Gut-brain axis	Dysbiosis→increased ammonia/endotoxins→systemic and brain inflammation

MHE: minimal hepatic encephalopathy

Inflammation can worsen the harmful effects of high ammonia levels in the body. When the gut's balance of bacteria is disrupted and the intestinal barrier becomes more permeable, it allows bacteria to pass into the bloodstream, which triggers inflammation throughout the body. This process can elevate certain inflammatory markers, like TNF-α and IL-6, associated with brain inflammation. As a result, cognitive functions and motor skills can suffer even more [10–12].

The gut-brain connection is crucial in understanding how MHE develops. When someone has cirrhosis, changes in the gut bacteria can lead to increased production of harmful substances like ammonia and endotoxins. These substances can then enter the bloodstream, especially because the gut barrier becomes compromised. This chain reaction contributes to inflammation throughout the body and the brain, ultimately impacting cognitive function. To tackle this issue, healthcare professionals are exploring various treatments that focus on the gut microbiome. Options like lactulose, rifaximin, and probiotics aim to help restore a healthier balance of gut bacteria, reduce ammonia levels, and calm inflammation, which can all help improve brain health and overall well-being [13, 14].

MHE and OHE are two distinct stages of hepatic encephalopathy (HE) seen in patients with liver cirrhosis, each presenting its own unique cognitive and neurological challenges.

MHE can be quite tricky because it often presents with subtle cognitive challenges that might not show up during regular check-ups. People with MHE might notice that they're having a harder time focusing, keeping track of things, or processing information as quickly as they used to. This can lead to everyday difficulties, such as problems completing tasks, declines in work performance, and even challenges while driving. Unfortunately, these cognitive changes can make individuals more prone to falls and can significantly impact their overall quality of life. It's important to acknowledge these struggles and seek specialized assessments to better understand and manage them [7, 15–17].

On the other hand, OHE tends to show more noticeable neurological and psychiatric symptoms. People affected by OHE can experience a wide range of manifestations, from mild confusion and disorientation to more severe states, such as stupor or even coma. It's not uncommon for those with OHE to undergo personality changes, have disturbed sleep patterns, and exhibit motor issues like increased muscle tone, exaggerated reflexes, and asterixis (which is that characteristic hand-flapping movement). In the most serious situations, this can escalate to coma. Typically, the shift from MHE to OHE is marked by the onset of disorientation or asterixis, indicating a decline in the patient's overall condition [7, 17].

Clinical presentation and challenges

MHE is a condition that brings about subtle changes in thinking and movement that often go unnoticed during regular check-ups. However, when people undergo specialized testing, these changes become clearer. Here are some key areas where individuals with MHE may experience difficulties [1, 3, 16]:

- Attention: Many patients struggle to focus and are easily distracted, making it hard for them to stay on task.
- Working memory: Keeping track of and manipulating information over short periods can be challenging, leading to frustration in everyday situations.
- Psychomotor speed: People often notice that their reaction times are slower, and they might have trouble coordinating their movements.
- Visuospatial abilities: Challenges can occur with understanding spatial relationships and tasks that require visual processing, like navigating familiar places.

These cognitive and physical challenges can have a noticeable impact on daily life, highlighting the importance of specialized assessments to help identify and address them. Unfortunately, MHE often goes underdiagnosed or is overlooked entirely for a variety of reasons, which can further exacerbate the challenges individuals face. MHE often flies under the radar because it doesn't show obvious symptoms like more severe forms of the condition. This makes it tough for doctors to catch during routine check-ups [18]. Diagnosing MHE is also tricky since it usually requires specialized tests, such as the PHES or measuring how quickly a flicker is perceived. These tests aren't always available or commonly performed in typical clinical settings [17]. Another challenge is that the symptoms associated with MHE can vary widely from one person to another. Because there's no single definitive test that can pinpoint all potential cognitive or motor issues, that further complicates the diagnosis [19].

On top of that, the resources needed for thorough testing can be both time-consuming and pricey, which can make it difficult to implement these tests regularly. As a result, organizations like the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recommend testing mainly for those who are experiencing quality-of-life concerns or are at risk of progressing to more serious HE [7]. Below is a table that compares MHE and OHE (Table 2) [17–19].

Table 2. Clinical presentation of MHE vs. OHE [17–19]

Clinical presentation	MHE	OHE
Symptoms	Subtle (attention deficits, slow processing)	Severe (confusion, asterixis, coma)
Diagnosis	Requires specialized tests (PHES, EEG)	Clinical signs + blood ammonia levels
Impact	Reduced quality of life, driving risks	High mortality, hospitalization needs

MHE: minimal hepatic encephalopathy; OHE: overt hepatic encephalopathy; PHES: psychometric hepatic encephalopathy score; EEG: electroencephalography

Diagnostic tools for MHE

The diagnosis MHE includes various psychometric tests, neuroimaging techniques, and new blood-based biomarkers.

Psychometric tests and digital apps

PHES

The PHES is considered the gold standard when it comes to diagnosing MHE. It includes a series of five straightforward paper-and-pencil tests: the number connection test-A (NCT-A), NCT-B, line tracing test, serial dotting test (SDT), and the digit symbol test. These tests evaluate different areas of cognitive function, including attention, psychomotor speed, and visuospatial skills. The PHES has been validated in several countries, and there is normative data available to help interpret results based on factors like age, education, and cultural background [20–22].

Stroop Test

The traditional Stroop Test is a well-known tool used to measure how flexible our thinking is, especially when it comes to tasks involving color and words that don't match up. A modern twist on this test is the EncephalApp, which makes it a lot easier to use by handling the scoring and timing automatically. It is quite effective, with studies indicating that it has an impressive sensitivity of 85–90% when it comes to diagnosing MHE. What's particularly neat about the EncephalApp is its user-friendly smartphone version. This app has been thoroughly tested and validated for diagnosing MHE. It operates in two modes: in the "off" state, users are presented with neutral stimuli, while in the "on" state, they encounter challenging, incongruent stimuli. This setup allows for a quick and reliable assessment, ensuring that it not only saves time but also provides accurate results with good sensitivity and specificity for diagnosing MHE [23, 24]. Additionally, it may also incorporate neurophysiological tests, including electroencephalography (EEG) and evoked potentials, for a comprehensive assessment [25].

Neurophysiological tests

EEG

EEG is an effective neurophysiological tool for identifying brain dysfunction in patients with MHE. Distinct EEG patterns, such as a shift from alpha (8–13 Hz) to theta (4–7 Hz) rhythms, indicate the severity of MHE, with a mean dominant frequency dropping below 7.5 Hz and achieving a sensitivity of 78%. Quantitative spectral analysis reveals increased relative theta power and decreased alpha and beta power in MHE patients, with a theta to alpha/beta ratio providing 85% diagnostic accuracy. These EEG findings correlate with clinical indicators like PHES and cognitive impairments. Cognitive evoked potentials show prolonged latency in many patients, correlating with deficits in working memory and attention. Abnormal evoked potential results may indicate a higher risk of OHE. Somatosensory evoked potentials also show prolonged latencies in many cases, linked to psychomotor slowing. Neurophysiological testing offers objective measures of brain dysfunction, less influenced by educational or language factors, making it valuable for monitoring treatment effectiveness and disease progression. However, practical limitations exist, including the need for specialized equipment and the time-consuming nature of testing. Integrating neurophysiological results with other diagnostic tools is vital for optimal patient care. Future developments could streamline EEG protocols and improve diagnostic accuracy through multicenter studies and

automated analysis methods. This comprehensive approach enhances the clinical evaluation of MHE and sheds light on the associated brain dysfunction [26].

Neuroimaging

Magnetic resonance imaging

Magnetic resonance imaging (MRI) scans give us a close-up view of the brain, helping to spot any structural changes linked to MHE. Using advanced techniques like T_2-relaxometry, researchers have found that T_2 values become elevated in different parts of the brain. This increase suggests that there's more free water and some swelling, or edema, in the brains of patients dealing with MHE [27].

Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a technique used to assess the health of white matter in the brain by observing how water molecules move. In the context of MHE, research has indicated that there are notable changes in white matter integrity. Specifically, people with MHE often show increased mean diffusivity (MD), which means that water molecules are moving more freely, and a decrease in fractional anisotropy (FA), indicating that the organized structure of white matter is disrupted. These changes are linked to cognitive issues that some individuals with MHE experience. As a result, these markers could potentially be used to help diagnose MHE more reliably [28–30].

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a valuable tool for examining brain chemistry, particularly in the context of MHE. Studies have shown that patients with MHE often exhibit higher levels of glutamine and glutamate (combined referred to as Glx), while the levels of myoinositol (mI) and choline (Cho) are found to be lower. These changes in brain metabolites can be linked to conditions like hyperammonemia (excess ammonia in the blood) and neuroinflammation, both of which can negatively impact cognitive abilities. Understanding these shifts helps shed light on the underlying biochemical processes that lead to cognitive challenges in affected individuals [28, 31–33].

Biomarkers

3-nitrotyrosine

There's a promising biomarker that could help identify MHE. Recent findings suggest that higher levels of 3-nitrotyrosine in the serum are associated with MHE. This biomarker shows strong sensitivity and specificity, meaning it can reliably detect this condition [34].

Cytokines

Recent research has pointed out that changes in certain cytokines, like CCL20, CX3CL1, CXCL13, IL-15, IL-22, and IL-6, seem to be linked to MHE. These cytokines play a vital role in our immune response and inflammation, both of which are important factors in the development of MHE. Understanding how these molecules interact can help shed light on the underlying processes of this condition [35].

Serum metabolites

Recent studies on metabolic profiling have uncovered several changes in serum metabolites in patients with MHE. Specifically, these patients have been found to have higher levels of substances like glucose, lactate, methionine, trimethylamine *N*-oxide (TMAO), and glycerol. On the flip side, there are lower levels of important compounds such as Cho, branched-chain amino acids, alanine, glycine, acetoacetate, and various types of lipids. These findings shed light on the metabolic shifts that occur in MHE, which could help in understanding the condition better [36].

Immune cell activation markers

Recent studies have shown that there's a noticeable increase in CD4 T-lymphocytes, especially a subset known as CD4-CD28 T cells. Along with this, we also see higher levels of serum IgG. These markers are

linked to MHE and suggest that inflammation in the body could play a significant role in how MHE develops. This highlights the importance of understanding the body's immune response to this condition [12].

While MRI is widely available, specialized techniques like DTI and MRS remain limited to tertiary centers due to cost and expertise requirements. PHES and EncephalApp are more feasible for routine use, though cultural adaptations of psychometric tests are needed for global applicability. Biomarkers (e.g., 3-nitrotyrosine) are promising but require further validation for clinical adoption.

Management strategies

Effectively managing MHE requires a comprehensive approach that combines medical treatment with lifestyle changes (Table 3) [36–41]. These collaborative efforts aim to restore balance and enhance the quality of life for individuals living with MHE.

Table 3. Management strategies for MHE [36–41]

Management strategies	Examples	Mechanism/Effect
Pharmacological	Lactulose (20–30 g/day)	Acidifies gut, reduces ammonia
	Rifaximin (550 mg BID)	Modulates gut microbiota
	L-ornithine *L*-aspartate (LOLA)	Enhances urea cycle
Non-pharmacological	Probiotics/synbiotics	Restores gut microbiota balance
	Cognitive rehabilitation	Improves attention/memory
	Plant-based diet	Lowers ammonia production

MHE: minimal hepatic encephalopathy; BID: per 12 hours a day

Pharmacological interventions

Lactulose

Lactulose is a type of sugar that your body doesn't absorb, and it can be really helpful for lowering ammonia levels in the body. It does this by making the gut more acidic, which helps turn ammonia into a form called ammonium that your body can get rid of more easily. This treatment can be effective in reversing MHE and preventing OHE. Typically, the starting dosage is around 20 to 30 grams a day, and it's usually adjusted to help achieve about 2 to 3 soft stools each day [37].

Rifaximin

Rifaximin is a special type of antibiotic that doesn't get absorbed into the bloodstream. Instead, it works directly in the gut, where it helps change the balance of bacteria to lower ammonia levels. This can be beneficial for people dealing with MHE, as it can help improve their symptoms and overall quality of life. Typically, it's taken in a dosage of 550 mg, twice a day [36].

L-ornithine *L*-aspartate

L-ornithine *L*-aspartate (LOLA) is beneficial for reducing ammonia levels in the body by enhancing the urea cycle and encouraging the production of glutamine. This mechanism makes it particularly effective in reversing MHE and in preventing the development of OHE [38].

Non-pharmacological interventions

Cognitive rehabilitation

Participating in cognitive training exercises can help improve attention, memory, and reaction times. This can be especially beneficial for individuals dealing with MHE, as these exercises target and alleviate some of the cognitive challenges they may face [37].

Physical exercise

Staying active is important for people dealing with MHE. Exercise can boost brain function and significantly enhance the quality of life. It doesn't just help cut down inflammation in the body; it's also great for building

muscle mass. This is especially helpful for those who have cirrhosis, as maintaining muscle strength can make a big difference in their overall health and well-being [37].

Dietary modifications

Eating more plant-based proteins and cutting down on animal proteins can be a smart way to lower ammonia levels in your body. Just make sure you're getting enough calories and try not to skip meals or fast for too long, since that can lead to muscle breakdown and increase ammonia. Also, it's a good idea to limit your alcohol intake. Taking these steps can help keep your body balanced [37].

Gut microbiota modulation

Probiotics, prebiotics, and synbiotics are important for keeping our gut health in check. They work by crowding out harmful bacteria and encouraging the growth of beneficial ones. This balance is particularly crucial for managing issues like MHE. By helping to lower ammonia levels and reduce inflammation in the body, these compounds play a key role in improving overall health. Notably, synbiotics, which are a blend of probiotics and prebiotics, have been especially effective in lowering blood ammonia levels and even reversing symptoms of MHE [39, 40].

Clinical outcomes and prognosis

The progression from MHE to OHE poses significant clinical challenges for patients dealing with liver cirrhosis. Research indicates that individuals with MHE have a markedly increased risk of developing OHE compared to those without this condition. A multicenter study highlighted that MHE can raise the likelihood of progressing to OHE by about 1.74 times (subdistribution hazard ratio 1.74, $p < 0.001$) [41]. Additionally, MHE is associated with poorer survival outcomes. This same research showed that patients with MHE face a 1.53-fold increased risk of decreased survival without liver transplantation (hazard ratio 1.53, $p < 0.001$). This indicates that not only does MHE increase the chances of requiring urgent care for OHE, but it also adversely affects the overall prognosis for these patients [41]. One particularly striking study found a significant difference in the incidence of OHE between MHE patients and those who are not affected: rates of 64% for MHE patients compared to just 25% for those without it ($p < 0.001$). Furthermore, survival rates were dramatically lower among MHE patients, with only 41% surviving compared to 81% for non-MHE individuals ($p < 0.001$). Such findings underscore the urgent need for early detection and effective management of MHE, which could help prevent progression to OHE and improve patient outcomes [42].

The presence of MHE in individuals with liver cirrhosis significantly increases the risk of developing OHE, jeopardizing not only neurological function but also overall survival rates. Therefore, timely diagnosis and intervention are critical in addressing these risks and enhancing patient care. It's particularly important to monitor patients who exhibit higher PHES scores, hyperammonemia (specifically, ammonia levels over 60 μmol/L), or elevated inflammatory markers like TNF-α and IL-6, as they are at the highest risk of progressing to OHE. Regularly tracking these biomarkers and cognitive assessments can help identify those who are most vulnerable, allowing for targeted interventions that can potentially mitigate their risk.

Future directions

Establishing clear diagnostic criteria and treatment guidelines for MHE is essential, as MHE significantly affects patients' quality of life and can lead to more severe issues like OHE. The lack of a unified approach to diagnosis and treatment makes it difficult for healthcare providers to manage the condition effectively. Recognizing this challenge, organizations like the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) are advocating for standardized testing and treatment protocols. Similarly, groups such as the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases are calling for the development of HE scales that employ a variety of psychometric tools.

Currently, research is focused on both discovering new therapies and improving existing treatments. Standardization of EEG criteria and development of portable evoked potential systems could significantly improve MHE detection in clinical practice. Medications like lactulose and rifaximin have shown success in reducing serum ammonia levels and enhancing cognitive function while also helping prevent the progression to OHE. People are also looking into newer treatments, such as LOLA and probiotics, which could help balance gut microbiota and reduce inflammation throughout the body. Beyond medications, researchers are examining non-drug interventions like cognitive rehabilitation, exercise, and dietary adjustments to improve cognitive function and overall well-being for those with MHE. There's also promising research into manipulating gut microbiota using probiotics, prebiotics, and synbiotics, as these therapies aim to correct gut dysbiosis, an important factor in the development of MHE. Studies suggest that these approaches can lower ammonia production and decrease systemic inflammation, which could ultimately lead to better outcomes for patients.

Conclusions

The early detection and management of MHE are crucial for preventing the escalation to OHE and enhancing patient survival rates. This review highlights the urgent need for standardized diagnostic tools, such as EncephalApp, and emphasizes the importance of personalized risk stratification. Furthermore, emerging therapies that target gut microbiota, like synbiotics, represent promising new treatment options. Since MHE can progress to OHE and is associated with higher mortality rates, healthcare professionals must act swiftly to mitigate these risks. Utilizing appropriate diagnostic methods and evidence-based therapies allows for effective management of MHE in patients suffering from liver cirrhosis. Moreover, raising awareness among clinicians and patients about the implications of MHE is essential. Understanding its impact on cognitive function, daily life, and long-term survival can empower both patients and providers. By fostering education around MHE, healthcare practitioners can better equip patients with the knowledge they need to avoid disease progression and maintain their overall well-being. Lastly, cultivating a collaborative environment that includes patients, their families, and healthcare teams can significantly improve the recognition and management of MHE. This teamwork is crucial for enhancing patient outcomes and alleviating the overall burden on healthcare systems.

Abbreviations

Cho: choline

DTI: diffusion tensor imaging

EEG: electroencephalography

HE: hepatic encephalopathy

LOLA: *L*-ornithine *L*-aspartate

MHE: minimal hepatic encephalopathy

MRI: magnetic resonance imaging

MRS: magnetic resonance spectroscopy

NCT-A: number connection test-A

OHE: overt hepatic encephalopathy

PHES: psychometric hepatic encephalopathy score

TMAO: trimethylamine *N*-oxide

Declarations

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MG: Conceptualization, Writing—original draft, Writing—review & editing. The author has read and approved the final version of the manuscript.

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