Hepatic encephalopathy: From novel pathogenesis mechanism to emerging treatments

Chon Kit Pun[a,b,d], Hui-Chun Huang[a,b,d], Ching-Chih Chang[a,c], Shao-Jung Hsu[a,b,d,*], Yi-Hsiang Huang[a,b], Ming-Chih Hou[a,b,d], Fa-Yauh Lee[a,b,d]

[a]Faculty of Medicine, National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan, ROC; [b]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [c]Division of Holistic and Multidisciplinary Medicine, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Therapeutic and Research Center of Liver Cirrhosis and Portal Hypertension, Taipei Veterans General Hospital, Taipei, Taiwan, ROC

Abstract

Hepatic encephalopathy (HE) is one of the major complications of liver disease and significantly affects the quality of life (QOL) of patients. HE is common and frequently relapses in cirrhotic patients. The management of HE is supportive, and precipitating conditions should be eliminated. Most drugs used to treat HE are conventional and include nonabsorbable disaccharides such as lactulose, and antibiotics such as rifaximin. However, their therapeutic efficacy is still suboptimal, and novel therapeutic agents are urgently needed. In addition, the optimal management and diagnosis of minimal HE/covert HE are under debate. In this review, we focus on novel pathogenetic mechanisms such as central nervous system clearance, and emerging therapeutic targets of HE, such as fecal material transplantation. We also discuss different classifications and etiologies of HE.

Keywords: Hepatic encephalopathy; Liver cirrhosis; Neuroinflammation; Portal hypertension

1. INTRODUCTION

Hepatic encephalopathy (HE) is a potentially lethal complication resulting from acute or chronic liver disease, and it most commonly occurs in cirrhotic patients with portal hypertension. The symptoms of HE range from mild neuropsychiatric disturbances to severe cognitive dysfunction such as coma.[1] HE is associated with a poor prognosis and significantly affects the quality of life (QOL) of cirrhotic patient. The severity of HE can be classified into four grades, and the concept of minimal HE has been proposed.[1] It has been reported that 60% to 80% of cirrhotic patients exhibit mild cognitive impairment due to minimal HE and that 20% of patients will develop overt HE.[2] In the pathogenesis of HE, ammonia and neuroinflammation play critical roles. Ammonia metabolism is disrupted in cirrhosis, and ammonia bypasses the liver through portosystemic shunting. As a result, ammonia accumulates in the brain and causes neuroinflammation via various mechanisms. This review addresses different aspects of HE from the incidence to management including novel pathogenetic mechanisms and emerging treatment strategies.

* *Address correspondence. Dr. Shao-Jung Hsu, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: sjhsu@vghtpe.gov.tw (S.-J. Hsu).*

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2. INCIDENCE AND PREVALENCE

The epidemiology of HE is not well established due to a variety of diagnostic criteria. In addition, because there is currently no WHO International Classification of Diseases (ICD) code for HE, it is difficult to recruit appropriate patients with either minimal or overt HE in epidemiological studies. A population-based cohort study in America reported that the overall incidence of HE was 11.6 per 100 patient-years,[3] and another study reported that 40% to 60% of cirrhotic patients developed minimal HE and 33% developed overt HE within 1 year.[4,5] In addition, 40% of cirrhotic patients with HE grade II have been reported to develop recurrent HE within 1 year.

3. RISK FACTORS

Various risk factors have been reported in many studies, and they can generally be stratified as precipitating factors and predisposing factors (Fig. 1). According to the study by Tapper et al,[3] risk factors include age, liver function, pathogenesis of liver cirrhosis (alcoholic, nonalcoholic), presence of portal hypertension, medication, renal function, genetic background, and underlying diseases.

Precipitating risk factors include decompensated liver cirrhosis-related complications such as acute-on-chronic liver failure, hepatorenal syndrome, and gastrointestinal bleeding. Other risk factors include infection, hypokalemia, hyponatremia, constipation, disruption of the gut-liver axis, and type 2 diabetes mellitus.[6,7] Some pharmacological agents also exacerbate HE, including opioids, proton-pump inhibitors, benzodiazepines, and other sedative drugs. The most common precipitating factor is infection, and the second common precipitating factor is electrolyte imbalance.[8]

Predisposing factors include levels of albumin and bilirubin, the presence of covert HE, and previous episodes of overt HE. A predictive model of overt HE developed by Riggio et al[9] suggested that an albumin level <3.5 g/dL was associated with a

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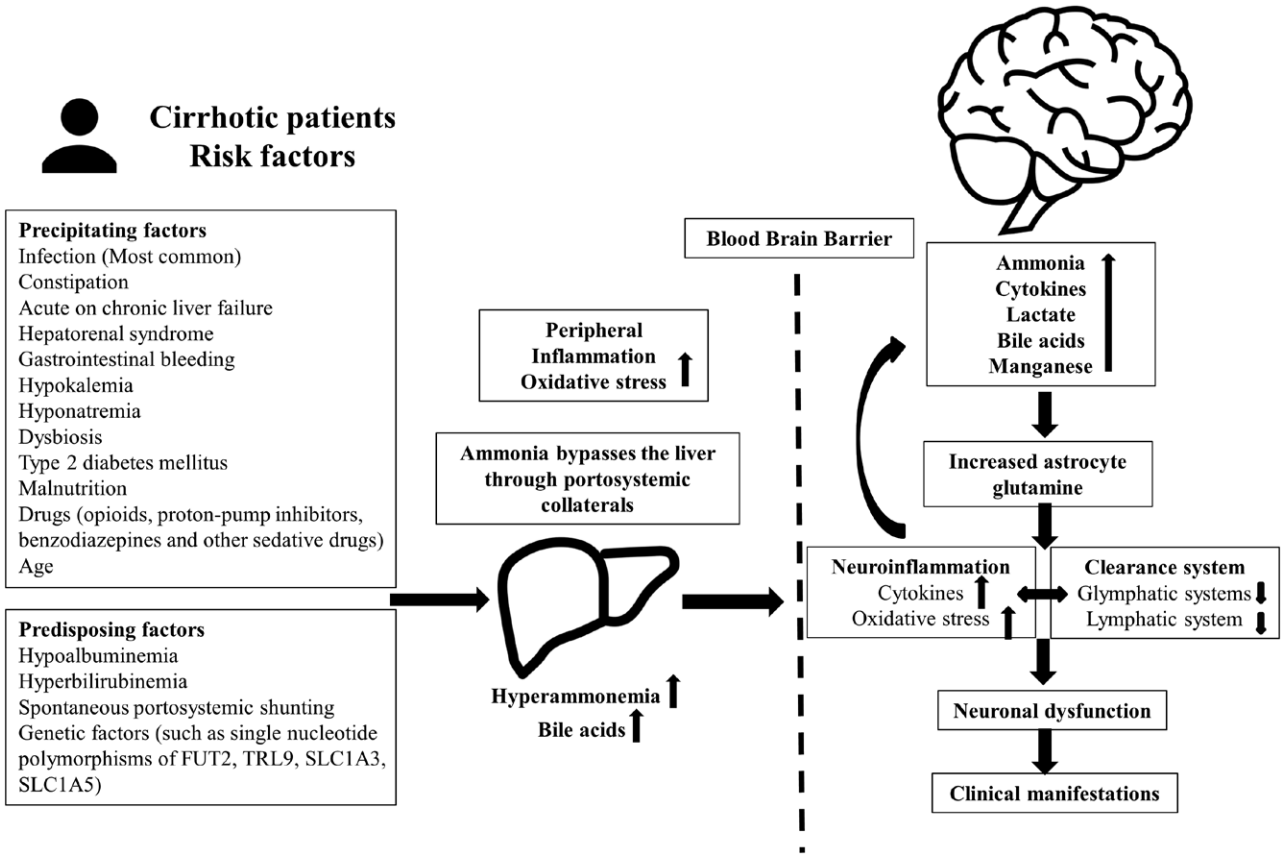

Fig. 1 Schematic figure of the pathogenesis and pathophysiology of hepatic encephalopathy.

higher risk of overt HE, whereas another study reported that a bilirubin level of ≥2.1 mg/dL was associated with a higher risk of overt HE.[10] Furthermore, the severity of portosystemic shunt has been positively correlated with a higher risk of overt HE, and one study found that cirrhotic patients with a total cross-sectional spontaneous portosystemic shunting area >83 mm^2 had a higher risk of overt HE.[11]

In cirrhotic patients, genetic risk factors such as single nucleotide polymorphisms of fucosyltransferase 2, toll-like receptor 9, solute carrier family 1 member 3, solute carrier family 1 member 5, and glutaminase microsatellite have been associated with a higher risk of overt HE. In addition, these genetic risk factors have also been shown to predict the severity of HE.[10]

4. PATHOPHYSIOLOGY

Fig. 1 shows a schematic figure of the pathogenesis and pathophysiology of HE. Dysregulation of noxious substances and metabolites such as ammonia and glutamate is mainly involved in the pathogenesis of HE. Ammonia is primarily generated in the gut by the microbiome and transported to the liver via the portal venous system. However, ammonia metabolism is impaired in cirrhosis due to impaired liver function. In addition, ammonia bypasses the liver and enters systemic circulation directly through portosystemic collaterals. Consequently, excessive ammonia reaches the brain through systemic circulation in liver cirrhosis. To maintain ammonia homeostasis, astrocytes in the brain eliminate ammonia by synthesizing glutamine through the amidation of glutamate by the enzyme glutamine synthetase.[12] In addition, manganese is a cofactor of glutamine synthetase. In end-stage liver disease, manganese excretion via a biliary route is impaired, which results in manganese deposition within the basal ganglia. The accumulation of glutamine induces instability of neurotransmitters and neuronal receptors,[13] and manganese deposition is associated with psychomotor impairment.[14] Moreover, hyperammonemia itself results in neuroinflammation.[15] Taken together, dysregulation of neurotransmitters and neuroinflammation lead to HE. Covert HE is regarded as the preclinical stage of overt HE, and it shares a similar pathogenesis to overt HE. The precise underlying mechanisms and the factors that determine the transition from covert to overt HE are still being investigated.

4.1. Oxidative stress in HE

In a cell culture study, nicotinamide adenine dinucleotide phosphate-oxidase was shown to be activated in response to hyperammonemia in astrocytes, resulting in increased oxidative stress.[16] Subsequently, various groups of reactive oxygen and nitrogen species form and induce modifications of RNA species and alterations in gene expressions and downstream signaling. Protein tyrosine nitration, and especially glutamine synthetase, is upregulated via formation of 8-hydroxyguanosin.[17] This pathophysiological mechanism has been identified in both an in vivo animal model and postmortem brain tissue in cirrhotic patients.[18] Such protein tyrosine nitration induces astrocyte swelling and changes between osmotic and oxidative stress.

4.2. Neuroinflammation and cytokines in HE

Inflammation is an important pathophysiological factor in HE, and hyperammonemia was shown to only induce HE in animal models with systemic inflammation.[12] In a human study of 84

cirrhotic patients, more severe minimal HE was shown to develop in those with significantly higher levels of inflammatory markers.[19] In patients with acute-on-chronic liver failure, sepsis has also been shown to be an important factor resulting in liver decompensation and HE.[20] Moreover, a human study of 4150 cirrhotic patients with HE demonstrated that systemic inflammation in HE was also correlated with mortality.[21] Taken together, these findings show that inflammation is significantly correlated with HE.

The role of neuroinflammation in HE is especially important. In a rat HE model induced by hyperammonemia, microglia activation, and neuroinflammation were observed. Interestingly, ibuprofen, an anti-inflammatory drug, restored cognitive function.[22] In addition, in rats receiving portocaval shunts, ibuprofen was shown to alleviate HE through a glutamate-nitric oxide-cGMP pathway.[23] Moreover, in rats with liver cirrhosis and HE, ibuprofen was shown to ameliorate abnormal microglia activation, an important marker of neuroinflammation, and improve functional disability.[15] Taken together, amelioration of neuroinflammation is an important strategy for HE treatment.

4.3. Cytokines participate in neuroinflammation

Several cytokines participate in neuroinflammation, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ. The activation of microglia releases inflammatory cytokines such as IL-1β, inducible nitric oxide synthase (iNOS), and prostaglandin E2 (PGE2). In 2015, a study proposed that impaired spatial learning and memory in rats with HE may be due to increased levels of IL-1β in the hippocampus.[24] Later in 2019, the same group found that increased IL-1β levels activated IL-1 receptors and downstream Src. In addition, they found a decreased expression of GluA1 (subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA] receptor) and increased expression of GluA2 (subunit of AMPA) membrane in the hippocampus, and that this pathway contributed to impaired spatial learning and memory in HE.[25]

Previous evidence also suggests that TNF-α is an important cytokine in neuroinflammation and HE. An animal study found that infliximab, an anti-TNF-α agent, reduced neuroinflammation and recovered spatial learning.[26] Another study confirmed that reducing peripheral inflammation with infliximab could prevent neuroinflammation. In that study, HE was induced in rats by feeding them with an ammonia-containing diet, and they were then treated with infliximab. The results showed that peripheral treatment with infliximab ameliorated peripheral inflammation and even neuroinflammation, indicating the role of TNF-α in HE. Furthermore, these findings imply that early treatment of peripheral inflammation could prevent the development of minimal HE.[27]

IFN-γ is another cytokine that is involved in neuroinflammation and HE. An elevated IFN-γ level has been found in both rats with HE and cirrhotic patients.[28] The plasma concentration of IFN-γ has also been strongly correlated with the severity of HE. Another study recruiting chronic hepatitis B-related cirrhotic patients also found an elevated IFN-γ level in patients with chronic HE.[29]

4.4. Relationship between central nervous system clearance and HE

In 2012, the glymphatic system was first defined as a brain-wide clearance system that provides a perivascular pathway for cerebrospinal fluid (CSF) and interstitial fluid (ISF) exchange. The glymphatic system facilitates efficient clearance of solutes and waste from the brain.[30] CSF in the perivascular space is transported into the interstitium by aquaporin-4 (AQP4) water channels on astrocytes membranes. The glymphatic system can clear noxious substances and metabolites in the brain including soluble amyloid β.[31]

In the past, it was believed that the central nerve system (CNS) lacked a classical lymphatic drainage system. In 2015, functional lymphatic vessels lining the dural sinuses of meninges were discovered,[32] and classical markers of lymphatic endothelial cells (LECs) such as vascular endothelial growth factor receptor 3 (VEGFR3) and prospero homeobox protein 1 (Prox1) were found to be expressed on these meningeal lymphatic vessels. These vessels can transport both fluid and immune cells from the CSF to the deep cervical lymph nodes. In 2018, Da Mesquita et al[33] further showed that the meningeal lymphatic system is significantly involved in CNS clearance.

In 2019, Hadjihambi et al[34] first described an association between HE and the glymphatic system. They found alterations of the glymphatic clearance system in a rat model with liver cirrhosis and HE, and magnetic resonance imaging (MRI) showed that the efficacy of glymphatic flow was decreased in the olfactory bulb and prefrontal cortex of cirrhotic rats, but increased in the hippocampus. This indicated that the glymphatic system was impaired in the cirrhotic rat model with HE. Although the whole picture of pathophysiological mechanisms of impaired glymphatic clearance system is unclear, a significantly lower AQP4 expression was found in both the olfactory bulb and prefrontal cortex of rats with bile duct ligation. This change has also been observed in other neurodegenerative disorders such as Alzheimer disease.[33]

Meningeal lymphatic vessels may also play a critical role in HE, as they have been shown to be the major route for draining brain waste materials and trafficking immune cells from the brain. A recent study demonstrated that the meningeal lymphatic system might fail to reduce harmful metabolites such as ammonia in the brain, but that meningeal lymphangiogenesis might enhance the ability to clear ammonia in cirrhotic rats.[35] The meningeal lymphatic system is therefore recognized to be a potential therapeutic target for HE, in addition to other neurodegenerative and neuroinflammatory disorders.

Several mechanisms may upregulate cytokine levels in the CNS, and noxious stimuli have been shown to induce cytokine production in the brain. In a model of Alzheimer disease, amyloid was shown to induce TNF, IL-6, and IL-1β production in microglia, the macrophages in CNS parenchyma.[36] On the other hand, cytokines released by meningeal immune cells in the CSF may diffuse into the brain. Cytokines can also come from the systemic circulation, and blood-borne cytokines can act on brain endothelial cells directly or reach the brain parenchyma. The circadian rhythm controls blood-brain barrier permeability, CSF production, and cytokine release.[37] The release of cytokines by different sources is regulated by the circadian rhythm via modulation of cytokine recirculation and exchange between the ISF and the CSF. Aging, impaired or diminished glymphatic and meningeal lymphatic functions can also affect cytokine efflux from the parenchymal ISF.[33] The meningeal lymphatic-lymphatic connection may be modulated by altered levels of cytokines in the brain parenchyma or CSF. Direct signaling on the cellular components within each system (eg, on astrocytes along the glymphatic route or on endothelial cells of the meningeal lymphatics) may play a crucial role in this effect.[38]

5. DIAGNOSIS

5.1. Classification

HE can be classified based on the underlying diseases contributing to its development, the severity of HE manifestation, the time course, and the existence of precipitating factors (Table 1).[1] According to the underlying conditions, HE is categorized as type A (resulting from acute liver failure), type B (primarily resulting from portosystemic shunts), and type C (resulting from liver cirrhosis).

Table 1

Various classifications of HE

According to the underlying disease	
Type A: resulting from acute liver failure	
Type B: primarily resulting from portosystemic shunts	
Type C: resulting from liver cirrhosis.	
According to the time course	
Episodic HE	
Recurrent HE	
Persistent HE	
According to the existence of precipitating factors	
Nonprecipitated	
Precipitated	
The West Haven criteria (based on the severity of HE)	
Covert HE	*Minimal*: abnormal alternations of psychometric or neuropsychological tests without significant clinical manifestation
	Grade I: alternations of behavior or cognitive function
Overt HE	*Grade II*: disorientation for time and lethargy. Flapping tremor (asterixis)
	Grade III: confused, with obvious personality changes
	Grade IV: coma

The West-Haven criteria are widely used to categorize HE based on the severity of HE.[39] In general, HE is subclassified into covert HE (minimal HE and West-Haven grade I HE) and overt HE (West-Haven grades II-IV HE). Minimal HE is defined as abnormal changes in psychometric or neuropsychological tests without significant clinical manifestations. Covert HE is often noticed by caregivers who are very familiar with the patient. Although clinical manifestations are not as prominent as in overt HE, covert HE significantly affects the patient's QOL, driving performance, and it is even associated with increased hospitalizations. Grade I HE is defined as changes in behavioral or cognitive function. Grade I HE is also often noticed by caregivers in patients who cannot pay attention or focus. Grade II HE is defined as disorientation in time and lethargy. A sign during a physical examination called flapping tremor (asterixis) has also been observed in patients with grade II HE. Grade III HE is defined as disorientation in space and confusion. Patients with grade III HE are often confused, with obvious personality changes. Grade IV HE is defined as patients who are comatose and unconscious.

According to the time course and presence of precipitating factors, HE can be classified as episodic, recurrent and persistent HE, and nonprecipitated and precipitated HE, respectively. Precipitating factors are often identified in patients with type C HE. Furthermore, some questionnaires are used for the staging of HE, for example, the Clinical HE Staging Scale (CHESS).

5.2. Diagnostic tools

Various neuropsychological and psychophysical tests are used to diagnose HE, including the Psychometric HE Score (PHES). The PHES consists of five sections: two number connection tests, a circle dotting test, Digit Symbol test, and line drawing test.[40] The PHES test has been widely used to identify minimal HE and quantify overt HE. Covert HE lacks significant clinical manifestations and is only detectable by using neuropsychological and psychophysical tests. Sharma et al[41] advocated critical flicker frequency to diagnose covert HE. In 2013, Bajaj et al[42] developed the smartphone application-based Stroop test to screen minimal HE. They found that the Stroop test was convenient and comparable to standard psychometric tests in the diagnosis of covert HE.[42] Electroencephalography (EEG), on the other hand, can demonstrate nonspecific features of cortical cerebral activity in patients with HE. For example, a significantly lower amplitude of peak frequency on EEG has been observed in HE patients.[43]

Serum ammonia level is the most frequently used biochemistry test in patients with different stages of HE. Importantly, no strong correlation has been identified between serum ammonia level and the severity of HE, and hyperammonemia alone cannot be used to diagnose HE. However, serum ammonia level can be a predictor of mortality and HE-related hospitalization. A serum ammonia level of ≥79.5 μmol/L has been associated with a higher mortality rate in patients with cirrhosis,[44] and cirrhotic patients with a fasting serum ammonia level of >1.5 × ULN have been reported to have a higher risk of recurrent HE and HE-related hospitalization.[45] Some limitations of the application of serum ammonia level have been suggested. First, standard values vary across different medical institutions, and there is a lack of standardization for blood sampling and the measurement of ammonia level. Second, venous blood for blood sampling is preferred as ammonia level in arterial blood tends to be higher than in venous blood. Third, fasting blood sampling is also preferred as the plasma ammonia measurement is more accurate in fasting status. Fourth, blood samples should be analyzed within 30 minutes after drawing, and the blood test tube should be placed on ice.

Some serum biomarkers for HE have been suggested in recent studies. Serum 3-nitrotyrosine level was found to be a useful biomarker to identify minimal HE in cirrhotic patients in a cohort study.[46] Another study suggested that serum IL-6 level may be a useful biomarker, as cirrhotic patients with minimal HE had more than twice the serum IL-6 level of patients without minimal HE.[47]

5.3. Brain imaging

Brain imaging techniques such as computed tomography and MRI play a role in the diagnosis of HE by excluding other neurological diseases. MRI techniques and positron emission tomography such as functional MRI, MRI with volumetric analysis, and diffusion tension imaging have also been applied. In patients with liver cirrhosis, greater activation of the bilateral parietal and prefrontal cortices has been observed.[48] Another study demonstrated reduced blood oxygen level-dependent signals in the right middle frontal gyrus and left posterior cingulate cortex.[49]

6. MANAGEMENT

The therapeutic strategy and goals are distinct according to the type of HE, such as type A and type B, due to their different pathophysiology. In cirrhotic patients with HE, treatment is always necessary for overt HE but not routinely for minimal HE. In general, treatment goals are based on the severity of HE. Liver transplantation is a definitive therapy for cirrhotic patients with HE. Table 2 shows various conventional therapies and novel treatment strategies for HE.

6.1. Therapy for overt HE in cirrhotic patients

In patients with high grade HE (grade III-IV), supportive measurements should be monitored closely. Airway protection is mandatory in patients with grade IV HE. Other blood tests such as renal function, arterial blood gas analysis, and electrolytes are also crucial in the management of acute HE. Nonabsorbable disaccharides such as lactulose are widely used in the treatment of acute episodes of overt HE.[39] The mechanism of lactulose in HE therapy is unclear, however, it is assumed that its acidification of the colon and prebiotic effects are beneficial for HE.

Table 2

Conventional therapies and novel treatment strategies of HE

Type of HE	Conventional treatments	Novel treatment strategies (undergoing pre-clinical investigations, still not approved)	
Covert HE	1. Nonabsorbable disaccharides (such as lactulose, polyethylene glycol)	Fecal Material Transplantation	Ongoing randomized control trial ClinicalTrials.gov: NCT03439982
	2. Albumin infusion	Activated carbon microspheres	Positive result in animal model. Early phase of clinical trial ClinicalTrials.gov: NCT03202498
Overt HE	1. Nonabsorbable disaccharides (such as lactulose, polyethylene glycol)	Golexanolone (a GABA receptor antagonist)	Positive result in a pilot study. Further clinical trial planned
	2. Rifaximin	Glutamine synthetase replacement	Under pre-clinical animal studies
	3. Albumin as an add-on to lactulose	Engineered bacteria	Under pre-clinical animal studies
	4. Oral branched-chain amino acid (BCAA) supplements, l-ornithine l-aspartate (LOLA)	DIALIVE liver dialysis	Small RCT done. Further larger clinical trial planned
	5. Liver transplantation (recurrent or persistent HE)		

Polyethylene glycol is an alternative for lactulose, and a randomized controlled trial (RCT) suggested that polyethylene glycol might be superior to standard lactulose therapy in patients with cirrhosis hospitalized for acute HE.[50] Antibiotics such as rifaximin are also used for HE treatment, and a study showed that rifaximin had beneficial effects on HE and suggested a definite role in the management of HE.[51] Other therapies such as oral branched-chain amino acid (BCAA) supplements and l-ornithine l-aspartate (LOLA) have been investigated in several studies and demonstrated to improve HE. Albumin as an add-on therapy to lactulose has been reported to be more effective than lactulose alone in the treatment of overt HE.[52] Nutritional support is critical in the management of HE, and malnutrition is common in cirrhotic patients with HE. A low protein diet or chronic protein restriction was suggested in the past; however, it is now considered to be detrimental in cirrhotic patients with HE, because sarcopenia has been proven to be a poor prognostic factor in cirrhotic patients.[53] Guidelines for the clinical management of HE by the American Association for the Study of Liver Diseases (AASLD) recommend a daily energy intake of 35 to 40 kcal/kg ideal body weight and daily protein intake of 1.2 to 1.5 g/kg/d.

6.2. Treatment for covert HE

Although treatment is not routinely needed for covert HE, some trials have demonstrated that treatments such as lactulose and probiotics may be beneficial in some patients with covert HE.[54] A recent double-blinded randomized control trial demonstrated that albumin infusion was beneficial for cirrhotic patients with prior HE and recurrent minimal HE.[55] Improved cognitive function and psychosocial QOL have also been reported. On the other hand, the diagnosis of covert HE remains challenging, and different trials have used different endpoints. Treatment decision should therefore be discussed case by case.

6.3. Prevention

Primary prophylaxis can prevent the first episode of overt HE in cirrhotic patients, and lactulose has been shown to have a beneficial role in primary prophylaxis.[56] Appropriate dosage adjustment is needed based on the patient's tolerability to side effects such as flatulence and diarrhea. Secondary prophylaxis can prevent recurrent episodes of HE after the initial episode. A RCT demonstrated that lactulose was effective for the prevention of recurrent HE in cirrhotic patients,[57] and another study showed that lactulose could also prevent HE in cirrhotic patients with acute variceal bleeding.[58] Guidelines for the clinical management of HE by the European Association for the Study of the Liver (EASL) recommend lactulose for secondary prevention after the initial episode, and rifaximin as an adjunct to lactulose for prevention after the second episode.[59] Probiotics have also been shown to be effective for the secondary prevention of HE and to reduce the risk of hospitalization for HE.[60,61] HE treatment is also routinely applied for patients after receiving a transjugular intrahepatic portosystemic shunt (TIPS) to prevent post-TIPS HE. Nevertheless, a study showed that neither lactulose nor rifaximin could prevent HE after TIPS.[62] Therefore, routine prophylactic therapy is not recommended for the prevention of post-TIPS HE according to the AASLD guidelines.

7. NOVEL TREATMENT STRATEGIES

Recent evidence has indicated that gut dysbiosis may play a pivotal role in ammonia metabolism, and that it may be involved in the pathophysiology of HE. In addition, gut dysbiosis may worsen portal hypertension,[63,64] and progression of portal hypertension could exacerbate HE. Therefore, an increasing number of clinical studies have demonstrated that fecal material transplantation (FMT) may be a novel and promising treatment for overt HE. The first open-label randomized trial evaluating the role of FMT from a single stool donor in cirrhotic patients with recurrent HE showed its effectiveness in a high-risk population.[65] A recent study also showed that microbiota transplantation could alleviate splanchnic hyperdynamic circulation by improving vascular responsiveness and decreasing mesenteric angiogenesis.[66] A larger open-label randomized trial of FMT from various stool donors in cirrhotic patients with recurrent episodes of HE despite maintenance therapy with lactulose or antibiotics is still ongoing (ClinicalTrials.gov: NCT03439982).

The aforementioned brain clearance systems such as the glymphatic system and meningeal lymphatic system may play a pivotal role in the pathogenesis of HE. An animal study demonstrated that promoting meningeal lymphangiogenesis ameliorated HE.[38] Modulation of brain clearance systems may be a novel strategy in the treatment of HE. Other novel strategies to reduce ammonia level are still being investigated in in preclinical studies, including activated carbon microspheres,[67] extracorporeal albumin dialysis,[68] engineered bacteria,[69] and glutamine synthetase replacement.[70]

In conclusion, HE is one of the main complications of liver disease and portal hypertension. Considering the suboptimal efficacy of traditional nonabsorbable disaccharides such as lactulose and antibiotics such as rifaximin, the exploration of novel therapies is anticipated. FMT may be promising because recent RCTs have demonstrated its beneficial effects in high-risk populations. In addition, therapies directly targeting neurons and novel ammonia removal methods are undergoing preclinical studies. Furthermore, recent studies have identified that central

nervous system clearance, such as via the meningeal lymphatic system and glymphatic system, plays an important role in HE. Hopefully in the near future, clarification of the pathogenesis of HE will lead to further progress in the treatment of HE.

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REFERENCES

1. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology* 2014;60:715–35.
2. Weiss N, Barbier Saint Hilaire P, Colsch B, Isnard F, Attala S, Schaefer A, et al. Cerebrospinal fluid metabolomics highlights dysregulation of energy metabolism in overt hepatic encephalopathy. *J Hepatol* 2016;65:1120–30.
3. Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and risk factors for hepatic encephalopathy in a population-based cohort of Americans with cirrhosis. *Hepatol Commun* 2019;3:1510–9.
4. Lauridsen MM, Jepsen P, Vilstrup H. Critical flicker frequency and continuous reaction times for the diagnosis of minimal hepatic encephalopathy: a comparative study of 154 patients with liver disease. *Metab Brain Dis* 2011;26:135–9.
5. Rathi S, Chopra M, Chouduri G, Sharma P, Madan K, Chhabra M, et al. Prevalence of minimal hepatic encephalopathy in patients with liver cirrhosis: a cross-sectional, clinicoepidemiological, multicenter, nationwide study in India: the PREDICT study. *J Clin Exp Hepatol* 2019;9:476–83.
6. Jepsen P, Watson H, Andersen PK, Vilstrup H. Diabetes as a risk factor for hepatic encephalopathy in cirrhosis patients. *J Hepatol* 2015;63:1133–8.
7. Guevara M, Baccaro ME, Torre A, Gómez-Ansón B, Ríos J, Torres F, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: a prospective study with time-dependent analysis. *Am J Gastroenterol* 2009;104:1382–9.
8. Poudyal NS, Chaudhary S, Kc S, Paudel BN, Basnet BK, Mandal A, et al. Precipitating factors and treatment outcomes of hepatic encephalopathy in liver cirrhosis. *Cureus* 2019;11:e4363.
9. Riggio O, Amodio P, Farcomeni A, Merli M, Nardelli S, Pasquale C, et al. A model for predicting development of overt hepatic encephalopathy in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2015;13:1346–52.
10. Gil-Gómez A, Ampuero J, Rojas A, Gallego-Durán R, Muñoz-Hernández R, Rico MC, et al. Development and validation of a clinical-genetic risk score to predict hepatic encephalopathy in patients with liver cirrhosis. *Am J Gastroenterol* 2021;116:1238–47.
11. Praktiknjo M, Simón-Talero M, Römer J, Roccarina D, Martínez J, Lampichler K, et al; Baveno VI-SPSS Group of the Baveno Cooperation. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. *J Hepatol* 2020;72:1140–50.
12. Shawcross DL, Shabbir SS, Taylor NJ, Hughes RD. Ammonia and the neutrophil in the pathogenesis of hepatic encephalopathy in cirrhosis. *Hepatology* 2010;51:1062–9.
13. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 2010;140:918–34.
14. Rose C, Butterworth RF, Zayed J, Normandin L, Todd K, Michalak A, et al. Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction. *Gastroenterology* 1999;117:640–4.
15. Rodrigo R, Cauli O, Gomez-Pinedo U, Agusti A, Hernandez-Rabaza V, Garcia-Verdugo JM, et al. Hyperammonemia induces neuroinflammation that contributes to cognitive impairment in rats with hepatic encephalopathy. *Gastroenterology* 2010;139:675–84.
16. Reinehr R, Görg B, Becker S, Qvartskhava N, Bidmon HJ, Selbach O, et al. Hypoosmotic swelling and ammonia increase oxidative stress by NADPH oxidase in cultured astrocytes and vital brain slices. *Glia* 2007;55:758–71.
17. Görg B, Qvartskhava N, Keitel V, Bidmon HJ, Selbach O, Schliess F, et al. Ammonia induces RNA oxidation in cultured astrocytes and brain in vivo. *Hepatology* 2008;48:567–79.
18. Görg B, Qvartskhava N, Bidmon HJ, Palomero-Gallagher N, Kircheis G, Zilles K, et al. Oxidative stress markers in the brain of patients with cirrhosis and hepatic encephalopathy. *Hepatology* 2010;52:256–65.
19. Shawcross DL, Wright G, Olde Damink SW, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. *Metab Brain Dis* 2007;22:125–38.
20. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. *Nat Rev Gastroenterol Hepatol* 2010;7:515–25.
21. Hung TH, Lay CJ, Chang CM, Tsai JJ, Tsai CC, Tsai CC. The effect of infections on the mortality of cirrhotic patients with hepatic encephalopathy. *Epidemiol Infect* 2013;141:2671–8.
22. Cauli O, Rodrigo R, Piedrafita B, Llansola M, Mansouri MT, Felipo V. Neuroinflammation contributes to hypokinesia in rats with hepatic encephalopathy: ibuprofen restores its motor activity. *J Neurosci Res* 2009;87:1369–74.
23. Cauli O, Rodrigo R, Piedrafita B, Boix J, Felipo V. Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with portacaval shunts. *Hepatology* 2007;46:514–9.
24. Hernandez-Rabaza V, Agusti A, Cabrera-Pastor A, Fustero S, Delgado O, Taoro-Gonzalez L, et al. Sildenafil reduces neuroinflammation and restores spatial learning in rats with hepatic encephalopathy: underlying mechanisms. *J Neuroinflammation* 2015;12:195.
25. Lucas T-G, Yaiza MA, Andrea C-P, Vicente F. Hyperammonemia alters membrane expression of GluA1 and GluA2 subunits of AMPA receptors in hippocampus by enhancing activation of the IL-1 receptor: underlying mechanisms. *J Neuroinflammation* 2018;15:36.
26. Dadsetan S, Balzano T, Forteza J, Cabrera-Pastor A, Taoro-Gonzalez L, Hernandez-Rabaza V, et al. Reducing peripheral inflammation with infliximab reduces neuroinflammation and improves cognition in rats with hepatic encephalopathy. *Front Mol Neurosci* 2016;9:106.
27. Balzano T, Dadsetan S, Forteza J, Cabrera-Pastor A, Taoro-Gonzalez L, Malaguarnera M, et al. Chronic hyperammonemia induces peripheral inflammation that leads to cognitive impairment in rats: reversal by anti-TNF-α treatment. *J Hepatol* 2020;73:582–92.
28. Manzhalii E, Virchenko O, Falalyeyeva T, Moiseienko V, Nykula T, Kondratiuk V, et al. Hepatic encephalopathy aggravated by systemic inflammation. *Dig Dis* 2019;37:509–17.
29. Li W, Li N, Wang R, Li Q, Wu H. Interferon gamma, interleukin-6, and -17a levels were correlated with minimal hepatic encephalopathy in HBV patients. *Hepatol Int* 2015;9:218–23.
30. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest* 2013;123:1299–309.
31. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med* 2012;4:147ra116.
32. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, et al. Structural and functional features of central nervous system lymphatic vessels. *Nature* 2015;523:337–41.
33. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* 2018;560:185–91.
34. Hadjihambi A, Harrison IF, Costas-Rodríguez M, Vanhaecke F, Arias N, Gallego-Durán R, et al. Impaired brain glymphatic flow in experimental hepatic encephalopathy. *J Hepatol* 2019;70:40–9.
35. Hsu SJ, Zhang C, Jeong J, Lee SI, McConnell M, Utsumi T, et al. Enhanced meningeal lymphatic drainage ameliorates neuroinflammation and hepatic encephalopathy in cirrhotic rats. *Gastroenterology* 2021;160:1315–29.e13.
36. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature* 2013;493:674–8.
37. Agorastos A, Hauger RL, Barkauskas DA, Moeller-Bertram T, Clopton PL, Haji U, et al. Circadian rhythmicity, variability and correlation of interleukin-6 levels in plasma and cerebrospinal fluid of healthy men. *Psychoneuroendocrinology* 2014;44:71–82.
38. Scheiermann C, Gibbs J, Ince L, Loudon A. Clocking in to immunity. *Nat Rev Immunol* 2018;18:423–37.
39. Conn H, Lieberthal M. *The hepatic coma syndromes and lactulose*. Baltimore: Williams & Wilkins; 1979, p. 5–8.

40. Weissenborn K, Heidenreich S, Ennen J, Rückert N, Hecker H. Attention deficits in minimal hepatic encephalopathy. *Metab Brain Dis* 2001;16:13–9.
41. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: diagnostic tool for minimal hepatic encephalopathy. *J Hepatol* 2007;47:67–73.
42. Bajaj JS, Thacker LR, Heuman DM, Fuchs M, Sterling RK, Sanyal AJ, et al. The Stroop smartphone application is a short and valid method to screen for minimal hepatic encephalopathy. *Hepatology* 2013;58:1122–32.
43. Kullmann F, Hollerbach S, Lock G, Holstege A, Dierks T, Schölmerich J. Brain electrical activity mapping of EEG for the diagnosis of (sub)clinical hepatic encephalopathy in chronic liver disease. *Eur J Gastroenterol Hepatol* 2001;13:513–22.
44. Shalimar, Sheikh MF, Mookerjee RP, Agarwal B, Acharya SK, Jalan R. Prognostic role of ammonia in patients with cirrhosis. *Hepatology* 2019;70:982–94.
45. Vierling JM, Mokhtarani M, Brown RS, Jr, Mantry P, Rockey DC, Ghabril M, et al. Fasting blood ammonia predicts risk and frequency of hepatic encephalopathy episodes in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2016;14:903–06.
46. Montoliu C, Cauli O, Urios A, ElMlili N, Serra MA, Giner-Duran R, et al. 3-nitro-tyrosine as a peripheral biomarker of minimal hepatic encephalopathy in patients with liver cirrhosis. *Am J Gastroenterol* 201;106:1629–37.
47. Gairing SJ, Anders J, Kaps L, Nagel M, Michel M, Kremer WM, et al. Evaluation of IL-6 for stepwise diagnosis of minimal hepatic encephalopathy in patients with liver cirrhosis. *Hepatol Commun* 2022;6:1113–22.
48. Zhang LJ, Yang G, Yin J, Liu Y, Qi J. Neural mechanism of cognitive control impairment in patients with hepatic cirrhosis: a functional magnetic resonance imaging study. *Acta Radiol* 2007;48:577–87.
49. Liao LM, Zhou LX, Le HB, Yin JJ, Ma SH. Spatial working memory dysfunction in minimal hepatic encephalopathy: an ethology and BOLD-fMRI study. *Brain Res* 2012;22:62–72.
50. Rahimi RS, Singal AG, Cuthbert JA, Rockey DC. Lactulose vs polyethylene glycol 3350—electrolyte solution for treatment of overt hepatic encephalopathy: the HELP randomized clinical trial. *JAMA Intern Med* 2014;174:1727–33.
51. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–81.
52. Sharma BC, Singh J, Srivastava S, Sangam A, Mantri AK, Trehanpati N, et al. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. *J Gastroenterol Hepatol* 2017;32:1234–9.
53. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol* 2012;10:166–73.
54. Luo M, Li L, Lu CZ, Cao WK. Clinical efficacy and safety of lactulose for minimal hepatic encephalopathy: a meta-analysis. *Eur J Gastroenterol Hepatol* 2011;23:1250–7.
55. Fagan A, Gavis EA, Gallagher ML, Mousel T, Davis B, Puri P, et al. A double-blind randomized placebo-controlled trial of albumin in outpatients with hepatic encephalopathy: HEAL study. *J Hepatol* 2023;78:312–21.
56. Sharma P, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labeled randomized controlled trial of lactulose versus no lactulose. *J Gastroenterol Hepatol* 2012;27:1329–35.
57. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. *Gastroenterology* 2009;137:885–91.
58. Sharma P, Agrawal A, Sharma BC, Sarin SK. Prophylaxis of hepatic encephalopathy in acute variceal bleed: a randomized controlled trial of lactulose versus no lactulose. *J Gastroenterol Hepatol* 2011;26:996–1003.
59. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of hepatic encephalopathy. *J Hepatol* 2022;77:807–24.
60. Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, et al. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014;147:1327–37.e3.
61. Agrawal A, Sharma BC, Sharma P, Sarin SK. Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy. *Am J Gastroenterol* 2012;107:1043–50.
62. Riggio O, Masini A, Efrati C, Nicolao F, Angeloni S, Salvatori FM, et al. Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study. *J Hepatol* 2005;42:674–9.
63. García-Lezana T, Raurell I, Bravo M, Torres-Arauz M, Salcedo MT, Santiago A, et al. Restoration of a healthy intestinal microbiota normalizes portal hypertension in a rat model of nonalcoholic steatohepatitis. *Hepatology* 2018;67:1485–98.
64. Yokoyama K, Tsuchiya N, Yamauchi R, Miyayama T, Uchida Y, Shibata K, et al. Exploratory research on the relationship between human gut microbiota and portal hypertension. *Intern Med* 2020;59:2089–94.
65. Bajaj JS, Kassam Z, Fagan A, Gavis EA, Liu E, Cox IJ, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: a randomized clinical trial. *Hepatology* 2017;66:1727–38.
66. Huang HC, Tsai MH, Chang CC, Pun CK, Huang YH, Hou MC, et al. Microbiota transplants from feces or gut content attenuated portal hypertension and portosystemic collaterals in cirrhotic rats. *Clin Sci (Lond)* 2021;135:2709–28.
67. Bosoi CR, Parent-Robitaille C, Anderson K, Tremblay M, Rose CF. AST-120 (spherical carbon adsorbent) lowers ammonia levels and attenuates brain edema in bile duct-ligated rats. *Hepatology* 2011;53:1995–2002.
68. Agarwal B, Cañizares RB, Saliba F, Ballester MP, Tomescu DR, Martin D, et al. Randomized, controlled clinical trial of the DIALIVE liver dialysis device versus standard of care in patients with acute-on- chronic liver failure. *J Hepatol* 2023;79:79–92.
69. Kurtz CB, Millet YA, Puurunen MK, Perreault M, Charbonneau MR, Isabella VM, et al. An engineered E coli Nissle improves hyperammonemia and survival in mice and shows dose-dependent exposure in healthy humans. *Sci Transl Med* 2019;11:eaau7975.
70. Song G, Kerbert A, Jones H, Arias N, Davies N, Andreola F, et al. PS-149-Recombinant glutamine synthetase: a novel strategy for the treatment of hyperammonemia and consequent hepatic encephalopathy in rodent model of cirrhosis and urea cycle enzyme deficiency. *J Hepatol* 2019;70:e93–4.