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Current Management of Hepatic Encephalopathy: A Review Article

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ABSTRACT

Hepatic encephalopathy, a neuropsychiatric syndrome stemming from liver failure, manifests in acute and chronic cases. The prevailing cause behind its development involves the neurotoxicity resulting from elevated ammonia levels in the brain, which can occur due to increased ammonia production or impaired ammonia excretion. The main objective in treating hepatic encephalopathy is to decrease ammonia levels. The detoxification of ammonia in this condition is regulated by two enzymes: glutaminase and glutamine synthetase. Numerous drugs, such as lactulose, rifaximin, BCAA, LOLA, glycerol phenylbutyrate, and zinc, have been utilized to treat hepatic encephalopathy. In terms of future research, experimental treatment options like fecal microbiota transplant, probiotics, bromocriptine, minocycline, indomethacin, ibuprofen, and flumazenil warrant investigation. Furthermore, albumin infusions have been shown to enhance cognitive function and improve the psychosocial quality of life, possibly by alleviating endothelial dysfunction in patients with minimal hepatic encephalopathy or previous episodes of hepatic encephalopathy. This review article offers a comprehensive overview of the current management strategies for hepatic encephalopathy.

Keywords- Encephalopathy, Neurotoxicity, Ammonia, Albumin.

I. INTRODUCTION

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome associated with acute and chronic liver disease resulting from liver insufficiency or portosystemic shunting. However, accurately determining the incidence and prevalence of HE poses challenges due to the variability in disease severity, underlying causes, and the distinction between minimum and overt HE[1]. This review aims to provide a comprehensive overview of HE by examining its classification, clinical features, pathophysiology, diagnosis, and treatment options. Notably, decompensated cirrhosis patients exhibit an overt HE prevalence of 16-21%, while those who have undergone transjugular portosystemic shunt (TIPS) procedures demonstrate a prevalence range of 10-50%. Additionally, approximately 80% of patients with liver cirrhosis experience minimal HE [1,2]. Understanding the multifaceted aspects of HE is crucial for its proper management and improved patient outcomes.

II. CLASSIFICATION

HE can be classified into three main types based on the underlying causes: Type A, observed in acute liver failure patients; Type B, arising from portosystemic bypass without intrinsic liver disease; and Type C,

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associated with cirrhosis. HE can also be classified based on time courses and precipitating factors. According to time courses, HE is categorized into episodic, recurrent, and persistent types. Recurrent HE occurs when HE episodes arise within intervals of less than six months. On the other hand, persistent HE is characterized by neuropsychiatric symptoms that are continually present for more than six months[3,4,5]. The classification of HE based on severity is presented in Table 1.

Table1. Classification of Hepatic encephalopathy

Classification of HE	**Underlying causes**	**Classification of Type C HE**	**Classification of persistent and episodic HE**
Type A	Acute liver failure	-	-
Type B	Portosystemic shunt and no intrinsic hepatocellular disease		-
Type C	Cirrhosis of the liver or, portal hypertension, or portosystemic shunts	Minimal Hepatic encephalopathy	-
-	-	Persistent Hepatic encephalopathy	Mild Severe Treatment dependent
-	-	Episodic Hepatic encephalopathy	Precipitated Spontaneous Recurrent

Several scoring systems are employed to assess the severity of HE. These include the West Haven Criteria (WHC), International Society for Hepatic Encephalopathy Criteria (ISHEN), Hepatic Encephalopathy Scoring Algorithm (HESA), and Clinical Hepatic Encephalopathy Scaling Scale (CHESS). These scoring systems help clinicians evaluate the severity of HE symptoms and determine appropriate treatment strategies[4,5]. Table 2 shows the West Haven criteria for grading the severity of hepatic encephalopathy.

Table 2: West Haven criteria for grading severity of hepatic encephalopathy

Grade	**Clinical features**
I	Trivial lack of awareness Euphoria or anxiety Shortened attention span Impairment of addition or subtraction
II	Lethargy or apathy Personality change Disorientation for time Inappropriate behavior
III	Somnolence to semi stupor Confusion Gross disorientation
IV	Coma

III. DIAGNOSIS

Clinical assessment serves as the primary method for diagnosing HE since no serological tests or imaging techniques can provide an accurate diagnosis or assess its severity. Although elevated ammonia levels are linked to the development of HE, they alone are insufficient for diagnosis and prognosis assessment, as other medical conditions can also cause elevated ammonia levels[6]. Instead, elevated serum ammonia levels, along with clinical features indicative of HE, are more reliable for diagnosis. Electroencephalograms (EEGs), combined with neurophysiological tests, are valuable in diagnosing HE when other neurological processes are absent. The sensitivity and specificity of an EEG depend on the method of data analysis and the severity of HE, typically ranging from 57% to 100% and 41% to 88%, respectively [7,8].

Neurophysiological tests include the Psychometric Hepatic Encephalopathy Score Test (PHES), Critical Flicker Frequency (CFF), Repeatable Battery for the Assessment of Neurological Status (RBANS), Scan Test, Continuous Reaction Time Test (CRT), Inhibitory Control Test (ICT), Cognitive Drug Research (CDR) Assessment Battery, Computer Aid Test, and others. These tests are useful in diagnosing minimal hepatic encephalopathy (MHE). Patients with MHE experience a reduced quality of life, including sleep disturbances, falls, diminished driving ability, and limitations in employment. The presence of MHE predicts the onset of overt HE and impacts the survival of individuals with cirrhosis. Despite their usefulness, these tests have limited utility due to the need for trained professionals and time constraints. Additionally, their

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use can be restricted by the age and educational background of patients[7,8,9]. CT and MRI scans of the brain usually do not provide specific indications for HE. However, PET scans can aid in understanding the pathogenesis of HE by evaluating blood flow, glucose metabolism, and ammonia metabolism, potentially offering prognostic value. Nevertheless, the widespread use of PET scans is limited due to their cost and limited availability [7].

IV. PATHOPHYSIOLOGY

The pathophysiology of hepatic encephalopathy (HE) is complex and not fully understood. It involves multiple factors that contribute to its development. These factors include elevated ammonia levels, neurotoxins, inflammation, oxidative stress, impaired blood-brain barrier permeability, and impaired energy metabolism in the brain. The neurotoxicity resulting from elevated ammonia levels in the brain is believed to be responsible for the development of HE. This can occur due to increased ammonia production or impaired ammonia excretion[10]. Ammonia detoxification in hepatic encephalopathy is regulated by two enzymes: glutaminase and glutamine synthetase. Glutaminase produces ammonia, while glutamine synthetase detoxifies it. Ammonia is produced in the small and large intestines (50%) as well as the kidneys (40%). In the gut, ammonia is generated through the breakdown of dietary protein by colonic urease-producing bacteria and the breakdown of glutamine by enterocyte glutaminase. In the kidneys, proximal tubular cells produce ammonia from glutamine and produce bicarbonate as a by-product. Various factors can alter the synthesis of ammonia in the gut and kidneys, including gastrointestinal bleeding, hypovolemia, excessive diuresis, hypokalemia, acidosis, and excessive protein intake [11, 12]. Table 3 shows the precipitating factors in hepatic encephalopathy.[13]

Table 3. Precipitating factors of hepatic encephalopathy

Infection
Electrolyte imbalance
Constipation
Dehydration
Gastrointestinal bleeding
Excessive dietary protein
Drugs (Sedatives, Diuretics, Narcotics)
Hypoglycaemia
Hypothyroidism
Hypoxia
Hepatoma
TIPSS, Surgical shunt
Vascular occlusion
Metabolic alkalosis
Anemia
Azotemia/Uremia

The liver converts ammonia into water-soluble urea through the urea cycle, which is then excreted via the intestine and urine. However, in patients with hepatic failure, the liver's ability to detoxify ammonia is reduced due to hepatocellular damage or shunting. Acid-base and potassium imbalances, increased protein intake, and dysregulations of glucocorticoid hormones can also decrease ammonia excretion through the kidneys. Skeletal muscle also plays a role in detoxifying ammonia by converting it into glutamine through glutamine synthetase [14]. When ammonia levels rise in the systemic circulation, it can cross the blood-brain barrier and be converted into glutamine by astrocytic glutamine synthetase. This leads to increased cerebral volume through osmosis. Acute liver failure with a rapid increase in ammonia can result in cerebral edema, which can be visualized through brain MRI[15.] Additionally, astrocytes can convert glutamine back into ammonia, causing direct oxidative damage. In chronic liver disease, ammonia acts as a neurotoxin, leading to decreased excitatory neurotransmission.

Apart from ammonia, other molecules such as serotonin, histamine, glutamine, dopamine, manganese, and gamma-aminobutyric acid can also contribute to the development of HE. The involvement of benzodiazepine receptors in HE is well-established. Manganese toxicity in patients with long-standing cirrhosis is another neurotoxic factor observed in the globus pallidus through T2-weighted MRI imaging [10,11,14]. In advanced liver disease patients, concurrent infections or sepsis can trigger a neuroinflammatory response, further worsening HE by increasing ammonia-induced neurotoxicity across the blood-brain barrier. Additionally, alterations in gut flora have been proposed as a pathological mechanism in developing HE. One hypothesis suggests that reduced bile acid synthesis can promote the growth of urease-producing bacteria in the gut, which produce ammonia. Studies have indicated an association between the microbiota and the development of HE. However, further research is required to fully understand the precise mechanisms underlying the pathogenesis of HE, which can ultimately improve the diagnosis and management of the disease [16,17].

V. MANAGEMENT

The primary objective in treating hepatic encephalopathy (HE) is to lower ammonia levels. Various medications have been utilized for this purpose, including lactulose, rifaximin, BCAA, LOLA, glycerol phenylbutyrate, and zinc. Lactulose and lactitol, both nonabsorbable disaccharides, function as osmotic laxatives that reduce the production and absorption of ammonia in the intestines by acidifying the colon and decreasing urease-producing bacteria. These disaccharides draw ammonia from the portal circulation to the colon and interfere with intestinal glutamine uptake. The recommended lactulose dosage ranges from

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30 to 80 grams daily and is adjusted to ensure the patient experiences at least two daily bowel movements. Lactulose offers benefits such as improved cognitive function, a decrease in the progression of overt HE, and cost-effectiveness. However, it may cause dehydration in severe cases of diarrhea. Lactulose and lactitol are considered first-line therapies for HE, with approximately 70% of cases showing symptomatic improvement. Clinical trials have demonstrated that lactitol is better tolerated and equally effective as lactulose for HE treatment[12, 18, 19].

Rifaximin, a synthetic antibiotic, reduces the growth of urease-producing bacteria, thereby lowering ammonia production. The recommended dose for rifaximin is 550 milligrams, taken twice daily. Its benefits include improved cognitive function, fewer HE-related hospitalizations, and modulation of gut flora. When comparing nonabsorbable antibiotics (rifaximin) to nonabsorbable disaccharides (lactitol/lactulose), no significant difference has been found in terms of improving HE grade[20, 21]. Branched chain amino acid (BCAA) promotes glutamine synthesis from ammonia in skeletal muscle but paradoxically may increase blood ammonia levels. It can be used in severely protein-intolerant patients. Studies have shown that oral BCAA improves HE manifestations but not overall mortality or nutritional status[22, 23]. L-Ornithine L-Aspartate (LOLA) is an ammonia scavenger that increases urea production in hepatocytes and activates glutamine synthase in hepatocytes and skeletal muscle. It decreases progression to overt HE, but further studies are needed to prove its efficacy[24].

Glycerol phenylbutyrate presents an alternative mechanism for eliminating ammonia and disposing of waste nitrogen. Research indicates that this medication effectively lowers ammonia levels and reduces the recurrence of hepatic encephalopathy (HE) or the need for re-hospitalization. However, the efficacy of co-administering it with rifaximin is still being investigated[25]. Zinc deficiency impairs the utilization of ammonia in the urea cycle. Supplementation with zinc has demonstrated improvements in cognitive tests, but no evidence supports its effectiveness in other outcomes. Several drawbacks are associated with zinc supplementation. Firstly, it diminishes the efficacy of ciprofloxacin. Secondly, the optimal dosage for maximum effectiveness has not been determined due to a lack of studies. Lastly, prolonged use of zinc supplements can lead to copper deficiency and dyspepsia [12,16].

5.1 Nutrition

It is crucial to maintain muscle mass as it plays a vital role in eliminating ammonia from the body. Malnutrition, conversely, has a contradictory impact as it raises ammonia levels while decreasing overall survival by affecting protein turnover. The recommendation for patients with hepatic encephalopathy (HE) is to follow the same diet as other patients with cirrhosis. There is no evidence suggesting that restricting dietary protein prevents episodes of HE. The daily calorie requirement falls within the range of 35 to 45 kcal/gm, while the protein requirement is recommended to be 1.2 to 1.5 gm/kg of body weight per day [26, 27].

5.2 Albumin

Albumin administration possesses antioxidant properties and has the ability to eliminate reactive oxygen species, thereby extending patient survival. However, it does not effectively reduce the severity of hepatic encephalopathy (HE). A clinical trial on outpatients with cirrhosis, previous HE, and current minimal hepatic encephalopathy (MHE) demonstrated that albumin infusions enhanced cognitive function and improved psychosocial quality of life. These improvements are likely attributed to the mitigation of endothelial dysfunction [28]. Furthermore, in patients with HE, the utilization of albumin dialysis through the Molecular Adsorbent Recirculating System (MARS) exhibited faster improvement compared to patients not subjected to this device [29].

VI. OTHER TREATMENT OPTIONS

Fecal microbiota transplant, a procedure that alters the gut microbiome, has demonstrated potential in enhancing the recurrence of HE. However, its current application is limited to recurrent cases of HE and necessitates additional research[15]. Another approach to improving HE involves embolic shunt occlusion, which benefits patients with sizable portosystemic shunts that bypass the liver, leading to hyperammonemia [30]. Furthermore, liver transplantation stands as the most efficacious treatment option for HE, albeit its high cost and limited availability in certain regions[16].

VII. FUTURE RESEARCH

Future research directions should focus on exploring various experimental treatment options for hepatic encephalopathy (HE). These options include probiotics, bromocriptine, minocycline, indomethacin, ibuprofen, and flumazenil. Probiotics show promise in reducing intestinal pH and plasma ammonia levels, although their ability to improve mortality has yet to be supported by evidence. Minocycline has demonstrated the potential to decrease plasma/cerebrospinal fluid ammonia levels by reducing the activation of microglial cells. Bromocriptine enhances dopamine neurotransmission, while indomethacin, ibuprofen, and phosphodiesterase inhibitors have exhibited the ability, in experimental models, to restore the function of the glutamate-nitric oxide-cyclic guanine monophosphate pathway in the cerebral cortex. Additionally, flumazenil, a benzodiazepine receptor antagonist, has shown promise in improving HE symptoms, possibly by reducing gamma-aminobutyric acidergic tone. However, further

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studies are necessary to determine the effectiveness of these treatments in improving HE outcomes [31,32].

VIII. CONCLUSION

Hepatic Encephalopathy (HE) plays a significant role as a prognostic factor in decompensated liver cirrhosis, and its inclusion in the Child-Turcotte-Pugh scoring system underscores its clinical relevance. The prognosis of HE is intricately linked to the degree of liver decompensation and the underlying cause of cirrhosis. Additionally, even subclinical HE, which may not manifest obvious symptoms, can profoundly impact a patient's daily activities and socioeconomic status, particularly affecting tasks like driving. It is important to note that patients diagnosed with subclinical HE are at risk of progressing to overt HE within a relatively short timeframe, ranging from 2 weeks to 2 years. The cumulative survival rate for patients who develop overt HE remains discouragingly low, with less than 50% survival rate at one year and less than 25% at three years [32,33]. These statistics emphasize the urgent need for improved management strategies and interventions for HE, especially in the context of cirrhosis. Early detection and appropriate therapeutic interventions are crucial in order to mitigate the detrimental impact of HE on patient outcomes and enhance their quality of life. Future research efforts should focus on elucidating the underlying mechanisms of HE and developing novel treatment approaches to improve patient prognosis and long-term survival.

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Conflict of interest

There is no conflict of interest.

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