Chapter

Pharmacotherapy of Hepatic Encephalopathy

Shatha Al-Muhaideb and Aziza A. Ajlan

Abstract

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is a serious neuropsychiatric disorder resulting from liver failure. It is one of the common complications of liver cirrhosis and portosystemic shunting (PSS). Ammonia accumulation is one of the well-established causes. Ammonia is a by-product of the intestinal bacteria as a result of the breakdown of dietary supplements. In the normal state of the liver, the peripheral hepatocyte contains glutaminase that converts glutamine into glutamate and ammonia; ammonia will be detoxified and converted into urea. The variant manifestations were linked to the severity of HE. A wide range of neurological and psychiatric signs have been reported. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) uses asterixis (i.e., flapping tremor) as the first clinical sign of HE. Four factors should be taken into consideration to classify and distinguish HE from other conditions: HE type, severity of manifestations following West-Haven Criteria (WHC), HE time course, and presence of precipitating factors. Nonabsorbable disaccharides (lactulose and lactitol) and rifaximin have been the standard of care as first- and second-line therapies, respectively. Non-pharmacological interventions had a crucial role in HE management. Liver transplantation is the ultimate management of hepatic cirrhosis.

Keywords: liver cirrhosis complications, hepatic encephalopathy, hepatic stupor, hepatic coma, portosystemic encephalopathy, hepato-cerebral encephalopathy, hyperammonemia, pharmacotherapy

1. Introduction

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is a serious neuropsychiatric disorder resulting from liver failure [1]. It is a state of abnormal neurological manifestations ranging from subclinical alterations to coma. It can be classified into three types based on underlying etiology. It is one of the common complications of liver cirrhosis and portosystemic shunting (PSS). HE accounts for 62% mortality rate among cirrhotic patients over 3 years [2]. A description of HE clinical state is as old as the Prognostics and Prosthetics of Hippocrates [3]. The association between jaundice and delirium was linked to cirrhosis as early as the seventeenth century [3]. In the absence of preexisting disease, acute, severe liver failure may cause the brain to swell, with patients becoming comatose and losing brain function altogether. Hepatic encephalopathy in patients with chronic liver disease is revocable and controllable, but new, acute (fulminant) hepatic

encephalopathy with speedily mounting blood ammonia values is harder to control due to the diffuse brain edema as well as structural brain-stem injury [4, 5].

Although HE is linked to liver cirrhosis, multifactorial complex pathogenesis is involved but not fully understood.

2. Epidemiology

Over a year, 5 to 7% of cirrhotic patients progress from a compensated state to decompensated stage [4]. The progression of the disease reduces survival by 10 years, with life expectancy around 12 years in patients with compensated liver cirrhosis that drop to 2 years in decompensated end-stage liver disease [4]. Mortality rate among patients in end-stage liver disease was 20% over 1 year. HE is one of the definitions of decompensated liver disease [5]. The incidence of overt HE ranges from 10 to 14% at the time of diagnosis and increases up to 21% at decompensated state and up to 50% in patients post transjugular intrahepatic portosystemic shunt (TIPS). Overall, up to 4% of cirrhotic patients will have HE state sometimes during the disease course. Once the patient develops the first episode of HE, the risk of recurrence increases up to 40% within a year from the first episode [5]. After the first episode of HE, the survival rate at 1 and 3 years was 73% and 38%, respectively [2].

3. Pathophysiology

The exact pathophysiology of HE has not been entirely understood with multiple mechanisms identified as pathological etiologies of HE. Ammonia accumulation is one of the well-described causes [6]. Ammonia is a by-product of the intestinal bacteria as a result of the breakdown of dietary supplements. In the normal state of the liver, the peripheral hepatocyte contains glutaminase that converts glutamine into glutamate and ammonia; ammonia will be detoxified and converted into urea, a product that is easily excreted by the kidneys. In case of liver cirrhosis, ammonia accumulates and is shifted into the systemic circulation leading to the activation of other detoxifying pathways (e.g., skeletal muscle, kidney, and brain). However, overtime ammonia will accumulate [6]. Neurotoxins that prevent the transmission of amino acids and electrolytes across the brain membrane is known [6]. The impact of ammonia on the neurons is directly linked to HE manifestations. This is one of the most targeted mechanisms for HE treatment. At high levels, ammonia will be able to penetrate the blood-brain barrier. Subsequently, glutamine is formed when astrocytic glutamine synthetase converts ammonia and glutamate. This in turn acts as an osmolyte and increases cerebral volume.

Nevertheless, other pathways have been identified including the gamma-aminobutyric acid (GABA), neurosteroids, inflammation, oxidative stress, manganese, zinc deficiency, and intestinal microflora [6]. Further research is needed to understand the magnitude of these factors in HE prognosis and the possibility of targeting those pathways in future therapies.

4. Clinical presentation

The variant manifestations were linked to the severity of HE. A wide range of neurological and psychiatric signs have been reported. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) uses asterixis

(i.e., flapping tremor) as the first clinical sign of HE [7]. The neurological symptoms might be mild to the extent of being undetectable to noticeable behavioral changes progressing to coma. HE may affect psychology, memory, visuospatial ability, and brain electrophysiology [8]. Hence, a series of manifestations are seen including but not limited to apathy, irritability, sleep-wake cycle disturbance, disorientation to time and place, hypertonia, and extrapyramidal dysfunction [9]. It is worth mentioning that none of these manifestations is HE pathognomonic finding.

5. Diagnosis and classification

The wide range of clinical manifestations necessitates a consensus diagnostic and classification criteria. Four factors should be taken into consideration to classify and distinguish HE from other conditions [5]: first, HE type (i.e., Type A resulting from acute liver failure, Type B resulting from PSS, and Type C resulting from liver cirrhosis); second, severity of manifestations where the most commonly used are West-Haven Criteria (WHC) with five grades (**Table 1** Minimal to Grade IV) and ISHEN criteria with two categories (covert and overt HE); third, HE time course: classified into episodic, recurrent (i.e., within 6 months or less), and persistent; and fourth, the presence of precipitating factors (e.g., infections, electrolyte disorder, gastrointestinal bleeding, transjugular intrahepatic portosystemic shunt). In clinical practice settings, WHC is the most useful tool to identify clinical description, but it should be correlated with the case scenario. Multiple neurological and psychometric clinical tests (e.g., portosystemic encephalopathy, critical flicker frequency, and inhibitory control test) have been developed to early identify minimal and covert HE (MHE and CHE), but it needs expert examiner to appropriately interpret results.

Ammonia level alone cannot be used as a sole diagnostic indicator, and it should be assessed within the clinical context. However, if the level is normal, the HE diagnosis is less likely [5]. Computed tomography (CT) scanning of the head could be performed to rule out structural considerations in the differential diagnosis, including intracranial hemorrhage. However, for patients with well-documented liver disease, it might not be necessary.

Grade	Criteria
Grade 0	Lack of detectable changes in personality or behavior, no asterixis
Grade 1	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition, and asterixis may present
Grade 2	Lethargy or apathy, minimal disorientation for time or place, inappropriate behavior, subtle personality, slurred speech, impaired performance of subtraction
Grade 3	Somnolence to semistupor but responsive to verbal stimuli, confusion, gross disorientation, and asterixis is usually absent
Grade 4	Coma (unresponsive to verbal or noxious stimuli)

Table 1.
West-Haven Criteria (WHC) [2, 5].

6. Management

The principle of HE management involves several steps. Those include airway protection (for patients presenting with coma), treat or prevent precipitating

factors, analyze and treat other causes of altered mental status (e.g., hyponatremia, diabetes, thiamin deficiency, intracranial bleeding), and provide pharmacological and non-pharmacological treatments. Different approaches are used to either treat or prevent HE.

6.1 Non-pharmacological treatment and prevention

6.1.1 Protein restrictions

Protein restriction is one of the components of managing patients with HE. As result, cirrhotic patients have higher prevalence of malnutrition [10]. During episodes of overt HE, protein restriction is advised. Once symptoms of HE are resolved, protein intake can be resumed: range 1–1.5 g/kg/day coupled with other therapies. This should be coupled with maintaining energy intakes at 35–40 kcal/kg ideal body weight daily [5].

Protein source may also play a role in management of HE. Vegetable protein with higher fiber content may be preferable to animal protein as it decreases colonic putrefaction [11, 12]. Animal protein contains high amounts of aromatic amino acids; those amino acids can work as substrates to neurotransmitter's tyramine and octopamine, are thought to inhibit dopaminergic neurotransmission, and worsen hepatic encephalopathy [11, 12].

6.1.2 Fecal transplant and probiotics

Fecal microbiota transplant was also reported to have beneficial outcomes reversing the intestinal microbial dysbiosis [13]. Additionally, probiotics have been used as secondary prophylaxis of HE, either as natural probiotics or in a pharmaceutical dosage form [14, 15].

6.1.3 Liver transplantation and artificial support system

Non-pharmacological interventions have a crucial role in HE management. Liver transplantation is the ultimate management of hepatic cirrhosis [5]. However, the complexity and challenges of such approach reduce the feasibility of transplantation. Other interventions may improve overall liver function, e.g., balloon-occluded retrograde transvenous obliteration, taking into consideration the applicability of each procedure on case-by-case manner [16]. Nevertheless, artificial liver support system was reported to have positive impact on overall liver cirrhosis complications, including HE [17, 18].

6.2 Pharmacological treatment and prevention

6.2.1 Non-absorbable disaccharides (lactulose and lactitol)

Lactulose is considered as the first-line therapy and has been in medical use since the 1950s. It is a form of synthesized fructose sugar containing galactose and lactose, while lactitol is a synthetic alcohol sugar consisting of lactose and sorbitol. It has been in the pharmaceutical market since 1987. As non-absorbable nutrients, the normal flora degradation of lactulose or lactitol leads to the reduction in PH toward acidic media in the colon. It will convert ammonia (NH_3) into ammonium (NH_4) that enhances a shift in NH_3 concentration and hence the movement from the blood to the intestine. This will reduce the ammonia level from dietary and endogenous source (**Table 2**). Nevertheless, they act as osmotic

Therapeutic agents*	Mechanism of action	Role in therapy
Nonabsorbable disaccharides (lactulose and lactitol)	Normal flora degradation of lactulose or lactitol leads to the reduction in PH toward acidic media in the colon. It will convert ammonia (NH_3) into ammonium (NH_4) that enhances a shift in NH_3 concentration and hence the movement from the blood to the intestine	First-line therapy
Rifaximin	Local action of rifaximin inhibits the bacteria protein synthesis via binding to RpoB inhibiting the function of DNA-dependent RNA polymerase	Add-on therapy

**Other therapies do not have a clear role in treatment and can be considered on a case-by-case basis.*

Table 2.
Recommended pharmacological treatment [5].

laxatives that increase water into the intestines and stimulate a bowel movement. Over the years, lactulose and lactitol are used to treat constipation and hyperammonemia. A systematic review assessing the impact of non-absorbable disaccharides on HE outcomes resulted in the inclusion of 22 randomized clinical trials (RCT) evaluating either lactulose or lactitol, neither showing significant difference in clinical outcomes including HE improvement and mortality [19]. Few years later, another systematic review was conducted. They included 38 RCT assessing the effect of either lactulose or lactitol in HE treatment and prevention. There was no significant difference between the two agents, but both of them had a beneficial effect on HE, including serious liver-related adverse events (e.g., variceal bleeding, serious infections, and hepatorenal syndrome), HE recurrence, and overall mortality [20]. The continuation on non-absorbable disaccharides beyond the treatment period had a positive impact on HE recurrence [21, 22]. Generally, both lactulose and lactitol have preferable safety profile and low burden from cost perspectives. However, non-favorable effects such as hypernatremia, hypokalemia, and gastrointestinal side effects have been reported. In lactose-intolerant patients, such side effects might be more pronounced. Polyethylene glycol (PEG) is a promising alternative, but further studies are needed to have robustness positive outcomes of PEG in HE management [23]. For all osmotic laxatives used in HE, two to four bowel motions per day as targeted outcome of therapy used to adjust doses and avoid side effects. Initial dose of 25 mL lactulose given orally every 1–2 hours until the patient has two bowel motions or loose stool can be adjusted accordingly [5]. Continuation on therapy reduces the risk of recurrent HE episode as long as the risk of lactulose overuse is monitored (e.g., dehydration, hypernatremia, severe perianal skin irritation, and even precipitating HE) [5]. No difference between oral and rectal as route of administration, however, based on the clinical context, one of them might be preferable over the other (e.g., comatose patient) [24].

6.2.2 Antibiotics

Antibiotics' role in HE management fills within the inhibition of ammonia-producing colonic bacteria. Rifaximin is a poorly absorbed bactericidal antibiotic (rifamycins). It is available in the market since 2004, and the Food and Drug Administration (FDA) approval for patients with liver disease was obtained in 2010. Rifaximin has a wide-spectrum antibacterial activity including anaerobic species. Local action of rifaximin inhibits the bacteria protein synthesis via binding to RpoB inhibiting the function of DNA-dependent RNA polymerase. At dose of 550 mg PO twice daily, it was effective in HE treatment and prevention of recurrent episode. However, it was used as add-on therapy where majority of participants

were using lactulose [25, 26] (**Table 2**). Different antibiotics have been used in HE management including neomycin, metronidazole, and vancomycin [27]. Neomycin is an aminoglycoside with controversy outcomes regarding its efficacy in HE. Antibacterial activity and glutaminase inhibition are the proposed mechanisms of neomycin effect in HE [27]. In attempt to find safer, effective, and more tolerable alternative, both metronidazole and vancomycin have been studied. Oral metronidazole is used with success, yet peripheral neuropathy may occur with long-term therapy. Limited studies were conducted in patients with poor response to lactulose monotherapy and showed improved response [27]. Although the FDA approved it, taking into consideration the safety profile of those agents (e.g., ototoxicity and neurotoxicity) and the risk of resistance development favors rifaximin over other antibiotics, although peripheral edema, central nervous system (CNS) side effects, and gastrointestinal intolerance have been reported with rifaximin. Published data on rifaximin cost-effectiveness showed that rifaximin alone was not cost-effective. Hence, it is not recommended as first-line therapy. However, in patients who are not responding to lactulose/lactitol, the addition of rifaximin may reduce hospitalization and prevent recurrence [28–30]. The availability of a generic rifaximin may change the cost-effectiveness outcomes.

6.2.3 L-ornithine-L-aspartate (LOLA)

The efficacy of intravenous L-ornithine L-aspartate (LOLA) as monotherapy in MHE was assessed in a RCT; it showed improved ammonia level and mental states [31]. In a meta-analysis of eight randomized trials with 646 patients in total, LOLA had a significant effect on improvement of hepatic encephalopathy total (RR, 1.49; 95% confidence interval [CI], 1.10 to 2.01) and overt HE (RR, 1.33; 95% CI, 1.04 to 1.69) [32]. LOLA has not been compared directly to active treatment (e.g., lactulose).

6.2.4 Glycerol phenylbutyrate (GPB)

Metabolic ammonia scavengers (e.g., benzoate, phenyl acetate, and glyceryl phenylbutyrate) have been used in genetic disorders involving urea cycle. Such disorders result in hyperammonemia, and such therapeutic agents may exert a possible treatment option [33]. In a randomized, double-blind, placebo-controlled phase II trial enrolling 178 patients with cirrhosis (including patients who were on lactulose ± rifaximin), GPB, dosed at 6 mL orally twice daily, significantly reduced the proportion of patients who experienced an HE event (21% versus 36%; $P = 0.02$), time to first event (hazard ratio [HR] = 0.56; $P < 0.05$), as well as total events (35 versus 57; $P = 0.04$) and was associated with fewer HE hospitalizations (13 versus 25; $P = 0.06$) [33]. Further trails are still required to validate the results. Moreover, the current cost of the drug may still be a barrier to its use at a larger scale.

6.2.5 Branched-chain amino acids (BCAA)

Branched-chain amino acids (BCAA) classified into proteinogenic (i.e., leucine, isoleucine, and valine) and non-proteinogenic (i.e., 2-aminoisobutyric acid) are essential amino acids. In limited clinical trials, BCAA had a beneficial impact on HE outcomes in addition to standard therapy. However, this positive effect was limited to oral dosage forms but not the intravenous formulation. BCAA had no impact on mortality, quality of life, or nutritional parameters; additional trials to evaluate such outcomes are needed [34–36].

6.2.6 Zinc supplementation

Zinc deficiency is common in cirrhotic patients. In case of documented deficiency, oral zinc supplementation can improve performance, but it did not affect the risk of recurrence [37]. Hyperammonemia could improve with zinc administration as it increases the activity of ornithine transcarbamylase, an enzyme in the urea cycle. Afterward, the increase in ureagenesis leads to the loss of ammonia ions. Further studies are needed to understand the possible role of micronutrient supplementation on long-term HE outcomes.

6.2.7 Flumazenil

Flumazenil is an antidote to reverse benzodiazepine toxicity by competitively binding to the benzodiazepine receptor site. Symptoms of benzodiazepine toxicity may overlap with HE (e.g., confusion, anxiety, and unresponsiveness). Flumazenil can be used as a diagnostic aid to differentiate between the two conditions [5].

6.2.8 Other therapies

Other therapies have not been assessed extensively in HE management (e.g., albumin and glutaminase inhibitors). Such alternatives had promising outcomes encouraging further research in this area. Albumin intravenous administration did not impact HE directly but improved survival post-discharge [38]. Glutaminase inhibition is a promising target of drug therapy in HE management. It could be a new era of research that may change HE management principle but nothing solid yet [39].

L-Carnitine was found to improve HE symptoms in several small studies of patients with cirrhosis. The exact mechanism remains unclear. One of the proposed mechanisms is that it may work by improving blood ammonia levels or centrally perhaps by decreasing brain ammonia uptake [40].

Dopamine agonists (e.g., levodopa or bromocriptine) are shown to result in improvement in clinical and electroencephalographic findings in anecdotal reports and small studies. If these results are confirmed at larger studies, it may lead to clinical recommendations.

7. Conclusion

HE is a reversible clinical syndrome with a wide range of manifestations, which will negatively impact patient quality of life if mismanaged. Different management approaches have been developed. The most appropriate treatment should be applied on case-by-case fashion.

Conflict of interest

The author declares no conflict of interest.

Author details

Shatha Al-Muhaideb and Aziza A. Ajlan*
King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

*Address all correspondence to: aajlan@kfshrc.edu.sa

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