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Definition, Classifications, Patho-physiology and Treatment of Hepatic Encephalopathy

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Abstract

Hepatic encephalopathy is an often-common complication of cirrhosis that is frequently demonstrated in consociation with severe hepatic insufficiency. Ammonia is a byproduct of protein metabolism, and a large portion is derived from the dietary ingestion of proteins. Bacteria present in the Gastrointestinal Tract (GIT) digest protein into polypeptides, amino acids, and ammonia. An increased ammonia level accelerates the amount of glutamine within astrocytes, resulting in cell swelling and finally brain oedema. Hyperammonemia has been displayed to lead to an escalated generation of the superoxide free radical and decline activities of several antioxidant enzymes in the brain. Nutritional management patients with hepatic encephalopathy should avoid extended periods of dietary protein restriction and take the maximum tolerable protein uptake, aiming at 1.2 g of protein/kg/day (range 1–1.5 g). Lactulose, used as standard therapy in hepatic encephalopathy, functions by changing gut flora to decrease ammonia secretion and absorption. Neomycin has activity against consummate gram-negative aerobes, excluding pseudomonas, and staphylococcal species. It prevents bacterial protein secretion is via attaching to the bacterial 30S ribosomal subunit and in certain narrates, has also been known to obviate intestinal glutaminase.

Keywords: Classifications; Definition; Hepatic Encephalopathy; Pathophysiology; Treatment

Introduction

Hepatic encephalopathy (HE) is defined as "brain malfunction caused by liver inadequacy and/or porto-systemic shunting manifesting as a broad spectrum of neurological or psychiatric deformity ranging from subclinical alters to coma" [1]. HE is an implicitly reversible, or progressive, neuropsychiatric syndrome described by changes in cognitive work, behavior, and personality, as well as by transient neurological symptoms and characteristic electrocardiogram (ECG) patterns consociated with acute and chronic liver failure. HE is an often-common complication of cirrhosis that is frequently demonstrated in consociation with severe hepatic inadequacy. The characteristic presentation is the advancement of acute encephalopathy with an abrupt decrease in the level of consciousness, manifested as confusion or coma. . Chronic encephalopathy can characterize as usually episodes of acute encephalopathy (chronic-recurrent encephalopathy) or with persistent neurological descriptions (chronic-persistent encephalopathy)

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[2-4]. Currently, an expert group on HE described a new classification for patients with the type of hepatic alteration that causes the condition, with three different types of encephalopathy being thought-out: Type A: acute liver failure; Type B: portal-systemic bypass without the innate hepato-cellular disease (the further frequent); Type C: cirrhosis and portal hypertension with portal- systemic shunts [5]. Hepatic encephalopathy (HE) remains a considerable clinical problem in patients with cirrhosis and is the feature that delineates the prognosis of patients with acute liver injury. In Acute Liver Failure (ALF) fast degeneration in consciousness level and increased intracranial pressure perhaps sequence in brain herniation and death. The manifestations of HE in cirrhosis seriously influence the quality of life (QOL) of patients and injury daily working in both the physical and psychological domains. When hepatic encephalopathy is solemn in cirrhosis, patients perhaps advance diversifying levels of confusion and coma [6].

Classification of Hepatic Encephalopathy

The West Haven Criteria classifies hepatic encephalopathy into four stages depending only on clinical criteria, and is frequently used arbitrarily and subjectively by clinicians in ordinary practice rather than considered all manifestations in a specific stage [7].

Grade	Clinical features
0	Lack of detectable changes in personality or behavior, asterixis absent.
I	A trivial dearth of awareness, euphoria or depression, shortened attention, hypersomnia, insomnia, or inversion of sleep pattern, asterixis can be detected, span impairment of addition or subtraction
II	Lethargy or apathy, slurred speech, obvious asterixis, personality change, disorientation for time, inappropriate behavior
III	Somnolence to semi-stupor, bizarre behavior, confusion, gross disorientation, asterixis generally absent.
IV	Coma

Table 1: West Haven criteria for grading severity of hepatic encephalopathy.

Pathophysiological Mechanisms of Hepatic Encephalopathy

Hepatic encephalopathy happens owing to a combination of distinct pathophysiological mechanisms such as inflammation [8], oxidative stress [9], impaired BBB permeability, neurotoxins, impaired energy metabolism of the brain [10] and more. Ammonia is a byproduct of protein metabolism, and a large portion is derived from the dietary ingestion of proteins. Bacteria present in the GIT digest protein into polypeptides, amino acids, and ammonia. These substances are then absorbed across the intestinal mucosa, where they are further metabolized, stored for later use, or used for the generation of new proteins. Ammonia is readily metabolized in the liver to urea, which is then renally eliminated. When blood flow and hepatic metabolism are injured by cirrhosis, serum and central nervous system (CNS) concentrations of ammonia are increased. The ammonia that enters the CNS combines with α-ketoglutarate to form glutamine. An increased ammonia level accelerates the amount of glutamine within astrocytes, resulting in cell swelling and finally brain edema [11]. Bile acids: The availability of more concentrations of bile acids was currently known to be available in the Cerebrospinal fluid (CSF) of cirrhotic patients with HE. Recently abnormal bile acid signalling has been indicated in the advancement of key features of HE due to ALF involving neuronal dysfunction, neuro-inflammation, and brain blood barriers permeability [12]. **Brain oedema and energy metabolism in ALF**: The lack of energy metabolism consociated with brain oedema has been fully characterized. This energy malfunction is

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considered to be owing to a compromised tricarboxylic acid cycle enzyme, a-ketoglutarate dehydrogenase activity, restrained anaplerotic flux and capacity of astrocytes to detoxify ammonium by glutamine synthesis increased lactate synthesis as well as mitochondrial permeability transition initiated by oxidative/nitrative stress [13, 14]. **Manganese accumulation:** Manganese deposits have been described as a cofactor in the advancement of hepatic encephalopathy. The observation that the reduction in brightness of the basal ganglia observed on magnetic resonance imaging rapidly ameliorates after liver transplantation is perhaps supportive of the manganese deposition hypothesis [15]. **Neurotransmission alterations:** Another pathogenic mechanism in hepatic encephalopathy consociated with energy disturbances are the alteration in neurotransmission systems, such as the glutamatergic and GABA-ergic systems, sequencing in neuronal disinhibition [16]. Glutamine synthesis happens within astrocytes and causes brain swelling. The level of brain swelling was displayed to compare with neuropsychological function and normalized after liver transplantation [17]. **Inflammation:** It is significant to highlight that brain cell detriment is not solely an effect of the advancement of hepatic encephalopathy but also a contributing factor. Under these situations, it has been known that astroglia releases TNF-a, pursued by a release of glutamate while also initiating microglia [18]. Nitric oxide that the free radical nitric oxide was implicated in the hyperdynamic circulation consociated with cirrhosis. Increased neuronal nitric oxide protein and mRNA were subsequently narrated in the brains of rats following portocaval anastomosis. Increased nitric oxide generation in the brain could be accountable for oxidative stress as well as the alterations of cerebral perfusion narrated in both humans and experimental animals with chronic liver failure. Hyperammonemia has been displayed to lead to increase the secretion of the superoxide free radical and decrease activities of several antioxidant enzymes in the brain [17].

Treatment of HE

Recent therapies for HE is depending upon ammonia lowering strategies. The pivotal of recent therapy of hepatic encephalopathy are non-absorbable antibiotics, lactulose and protein-restricted diets [19]. Treatment goals of hepatic encephalopathy are: 1) provision of supportive care: Adequate supportive care is critical during all stages of hepatic encephalopathy and perhaps enclose distinctive professionals in the provision of patient care; 2) identification and takeoff of precipitating factors: A vigorous search to distinguish and eliminate a precipitating factor or factors should be instantaneously instituted; 3) reduction of nitrogenous load from the gut measures to decrease the nitrogenous load from the gut should be implemented; 4) assessment of the requires for long term treatment of patients with cirrhosis are at pitfall of advancing fresh episodes of encephalopathy. At discharge, 3 factors necessitated to be considered: 1) control of potential chelating factors; 2) higher likelihood of recurrent encephalopathy; 3) assessment of the necessitated for liver transplantation [17].

Nutritional management patients with hepatic encephalopathy should avoid extended periods of dietary protein restriction and take the maximum tolerable protein uptake, aiming at 1.2 g of protein/kg/day (range 1–1.5 g) [19]. A free protein diet enhances the NH_3 concentration because of the diminished activity of the enzymes in the urea cycle. The protein diets cause a diminished urea generation. In chronic HE, protein restriction can have negative consequences on the patient, because the nutritional status is a parameter that ameliorates the prognosis of cirrhosis importantly. Also, ameliorate in nutritional status may be consociated with better control of HE. Elevate in muscle mass can facilitate the ammoniac metabolism by its conversion into glutamine. It is thought-out that a high protein diet is necessary (1.2 g/kg/day) to reach a stable nitrogen balance. Nutritional supplements rich in branch amino acids can be helpful in certain patients with chronic encephalopathy with meager tolerance to the diet proteins.

Vitamins and Nutrients: Cirrhosis also influences to scarceness of lipid-soluble vitamins, minerals, and micronutrients. For instance, Zinc is a cofactor in the urea cycle and also resulted in vesicles of highly glutamatergic presynaptic terminals thereby having a

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function in neurotransmission [20].

Glycaemic Control: Disturbed glycaemic and lipid control is ubiquitous in progressive liver disease and solely worsened by the stress reaction in hypercritically not well patients. Thereupon, once feeding has started, tight glycaemic control using insulin perhaps necessary to minimize oxidative stress (which triggers insulin resistance), limit mitochondrial liver injury, and ameliorate endothelial initiation (e.g., NO secretion), which will ameliorate blood flow, limits tissue damage, and ameliorate consequence [20].

Branched-chain amino acids: Branch amino acid supplements have certain anti-catabolic outcomes, perhaps because of their energetic outcomes in the muscle, with this mechanism capable to minimize the degree of ammonium. Malnutrition can lead a paradoxical increase in ammonia and decreased survival by influencing protein turnover, elevating susceptibility to infections, rupturing immuno competence and initiating malabsorption. It is believed that maintaining muscle mass in patients is significant, since it has the capability to takeoff ammonia from circulation, while patients administered with enough protein demonstrated a beneficial outcome in the treatment of hyperammonemia and HE. Administration of BCAAs is believed to support to ameliorate nutrition and perhaps effective in HE management. However, BCAA has paradoxically been seen to escalate blood ammonia levels [19, 21, 22].

Purgatives (Nonabsorbable disaccharides in the decrement of intestinal ammonia production and absorption): There are 2 forms: lactulose (β-galactosidase-fructose) and lactitol (β-galactosidase-sorbitol). Its mechanism is dependent on a diminution in the plasma concentration of NH_3, an indispensable factor in the advancement of encephalopathy. The exact mode of action by lactulose is considered to be the transformation to lactic acid and acetic acid resulting in acidification of the gut lumen. This favors transformation of NH_3 to ammonium (NH_4^+), which is comparatively membrane-impermeable; thereupon, less NH_3 is absorbed by the colon. Gut acidification obviates ammonia genic coliform bacteria, influencing to increased levels of non-ammonia genic lactobacilli. Nonabsorbable disaccharides also function as a cathartic, clearing the gut of ammonia before it can be absorbed [23, 24]. Lactulose, used as standard treatment in hepatic encephalopathy, functions by changing gut flora to reduce NH_3 secretion and absorption. Among the many actions of lactulose an indispensable one is its function as a “prebiotic”, antecedent escalated growth of endogenous bacteria that are implicitly beneficial to the host like Lactobacilli, thereby indirectly decreasing the strength of implicitly greater harmful urease secreting bacteria [25, 26]. Lactulose, an unabsorbed disaccharide (1:4, galactosidase-fructose) has been extensively used in the treatment of hepatic encephalopathy. `' Lactulose, however, is excessively sweet and consequently is unacceptable to certain patients. Lactitol (b-galactosidase-sorbitol), a disaccharide analogue of lactulose has currently been explained. This sugar is largely water soluble, less sweet than lactulose and is not absorbed in the human small intestine. It has seemed to us thereupon that lactitol might have a potential as an optional therapeutic agent to lactulose in the treatment of HE. The combination of neomycin and lactulose is still used in the treatment of HE despite the theoretical possibility that neomycin perhaps obviate the bacterial metabolism of lactulose [23, 27].

Modulation of gut microbiota ameliorates hepatic encephalopathy: Now that gut microbiota is implicated in the advancement of hepatic encephalopathy, their modulation by various agents provides an opportunity to treat covert and overt hepatic encephalopathy. Successful modulation of gut microbiota influencing to improvement in hepatic encephalopathy strengthens the belief that derangement in microbiota is certainly an indispensable factor in advancement of hepatic encephalopathy.

Prebiotics, probiotics and symbiotic: Prebiotics, probiotics and symbiotic modulate gut microbiota and perhaps exhibit efficacy in malignant haemangioendothelioma (MHE) and hepatic encephalopathy by various mechanisms involving decreased in counts of pathogenic bacteria, decreased bacterial urease activity and minimized ammonia

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absorption by decreasing luminal pH. They perhaps decline endotoxemia, inflammation and intake of toxins like indoles, oxindoles, phenols, mercaptans, etc. Despite several trials revealing the efficacy of prebiotics, probiotics and symbiotic, their function in the treatment of HE is inconclusive and, recently, they cannot be recommended. Probiotics is a medical therapy that attempts to alter colonic flora for a clinical benefit. Probiotics have been used to manage hepatic encephalopathy by declining urease-secreting bacteria and promoting growth of non-urease-secreting bacteria. Probiotics are considered to exert an outcome in hepatic encephalopathy by decreasing intestinal ammonia secretion by enterocyte glutaminase and minimize bacterial translocation, modulate proinflammatory responses, and modulate gut permeability. Additionally, probiotics bypass the small bowel and get fermented by colonic bacteria to form lactic, acetic, and butyric acids, and gas (chiefly hydrogen); any resultant intestinal hurry perhaps escalate the expulsion of ammonia genic bacteria [28, 29].

Medications and Devices Aimed at Elimination of Ammonia from Plasma or Modulators of Interorgan Ammonia Metabolism

L-Ornithine-L-aspartate: Ornithine-aspartate is a stable salt of two amino acids used for the management of hepatic encephalopathy, which is not yet applicable in the USA. Ornithine-aspartate is both enclosed in hepatic and muscle metabolism of NH_3, through urea cycle and glutamine secretion. Ornithine-aspartate is available in both enteral and parenteral forms and has been used to accelerate metabolic conversion of NH_3 through both pathways. Ornithine-aspartate is consummate ubiquitously used for decreasing of brain work in people with advanced liver disease or hepatic encephalopathy [23, 30].

L-ornithine phenylacetate: L-ornithine phenylacetate has been considered in the management of HE. L-ornithine would participate in the clearance of NH_3 in muscles and the liver through glutamine secretion and the phenylacetate would conjugate with glutamine (which contain nitrogen from NH3) to form phenylacetylglutamine. Phenylacetylglutamine is excreted by the kidneys by glomerular filtration and tubular secretion [23, 31]. L-Ornithine and L-aspartate (LOLA) are substrates for the urea cycle and can increase urea secretion in periportal hepatocytes. They also initiate glutamine secretion by activating glutamine synthetase in perivenous hepatocytes and skeletal muscles [32]. Additionally, although LOLA primarily lowers blood NH_3 levels, even in ESLD, its outcomes seem to be temporary as a rebound hyperammonemia is occasionally demonstrated on cessation of the medication [20, 33, 34].

Glycerol phenylbutyrate (HPN-100): Glycerol phenylbutyrate (GPB) provides an optional pathway for NH_3 takeoff and waste nitrogen excretion in the form of phenylacetyl glutamine. These sequences in a lower net blood glutamine and, thereupon, NH3 secretion from the action of glutaminase [21, 35].

Sodium benzoate and/or sodium phenylacetate: Sodium benzoate and/or sodium phenylacetate are revealed to accelerate tissue metabolism of ammonia. Benzoate conjugates with glycine (which contain nitrogen from NH3) to form hippuric acid and phenylacetate conjugates with glutamine (which contain nitrogen from NH_3) to form phenylacetylglutamine [23, 36].

L-Carnitine: L-Carnitine is revealed to enliven the urea cycle and a delayed onset of hepatic encephalopathy in hyperammonemia mice [23, 37]. The consequent increase in glutamine secretion sequences in a net decrease of plasma ammonia. Ultimately, to obviate the 'rebound effect' of glutaminase, glutamine is conjugated with phenylacetate to form phenylacetylglutamine, a molecule that cannot be metabolized and is harmlessly excreted in the urine [21, 32].

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Nonabsorbable Antibiotics (Antibiotics in the Reduction of Intestinal NH3 Production)

Bacterial infections are important precipitants of overt hepatic encephalopathy, particularly spontaneous bacterial peritonitis, and in conditions where bacterial translocation is elevated such as an upper gastrointestinal bleeding episode. Antibiotics specifically for hepatic encephalopathy are gut specific and are not effective for treating potential infections during the acute episode [31]. Neomycin and other antibiotics (metronidazole, vancomycin, rifaximin) are an optional for patient's intolerant to non-absorbable disaccharides, or in patients that are unresponsive to them. Lowering systemic ammonia and decrement of inflammation and endotoxemia can be achieved through antimicrobials [30].

Neomycin: Neomycin has an activity against further gram-negative aerobes, except pseudomonas, and staphylococcal species. It suppresses bacterial protein production via attaching to the bacterial 30S ribosomal subunit and in certain narrates, has also been revealed to suppress intestinal glutaminase [36]. Neomycin is FDA-confirmed for the management of acute hepatic encephalopathy, but not chronic HE. Neomycin has been used clinically for multiple years to treat HE, yet no restrained surveys are resulting in it to be as effective as lactulose [23].

Metronidazole, vancomycin and paromomycin: There have been limited surveys on the efficacy of metronidazole and vancomycin in the treatment of HE [30]. Oral vancomycin, on the other hand, perhaps safer for the treatment for an acute hepatic encephalopathy episode, and has been studied in a limited group of hepatic encephalopathy patients who were resistant to lactulose [38]. Metronidazole, paromomycin and vancomycin are not FDA confirmed for treatment of overt hepatic encephalopathy.

Rifaximin: Rifaximin, a poorly absorbable synthetic antibiotic, modulates gut microbiota, is safe, is consociated with low peril of bacterial resistance and is effective in both covert and overt hepatic encephalopathy [25, 26]**.** Rifaximin is an oral non-systemic antibiotic with < 0.4% absorption. It was granted an orphan drug designation by the USFDA for usage in HE [23]. It has a broad spectrum of activity against both gram-positive and gram-negative organisms, and specifically against anaerobic enteric bacteria. It attaches to the b-subunit of the bacterial DNA dependent RNA polymerase and disrupts RNA synthesis [37]. It also has minimal outcomes on normal gut flora, though elevated doses were known to primarily decrease gastrointestinal flora such as *Enterococcus, Escherichia coli, Lactobacillus spp., Bacteroides spp., Bifidobacterium spp.* and *Clostridium perfringens* all of which returned to primary values after a wash-out period [39].

Nitazoxanide: Nitazoxanide is an oral agent indicated for the management of infectious diarrhoea caused by *Cryptosporidium parvum* and *Giardia lamblia*, the precipitating factors of HE [23, 40].

Medication Effects on Neurotransmission

Flumazenil: Flumazenil, a short-acting benzodiazepine receptor antagonist, has been used as a management for patients with HE. There is evidence of increase in benzodiazepine receptor initiation among cirrhotic patients with hepatic encephalopathy. Flumazenil and bromocriptine exert their outcomes directly on the brain. An increased GABA-ergic tone was postulated to contribute to the advancement of encephalopathy. It has been noted that "endogenous benzodiazepines" perhaps available in patients with hepatic encephalopathy and exert neuroinhibitory outcomes via attaching to the GABAA receptor. Antagonism of their effect with flumazenil has been tested in patients with acute encephalopathy and severe changes in mental state [23, 35].

Bromocriptine: Bromocriptine, which stimulates dopamine receptors, is approved for Parkinson's disease. A decrement in dopaminergic neurotransmission has been proposed as one of the underlying mechanisms for hepatic encephalopathy.

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Improvement of extrapyramidal symptoms has been observed when bromocriptine was added to further conventional therapies [41].

Zinc: Zinc deficiency is ubiquitous among cirrhotic patients, particularly with alcohol-induced liver damage. Zinc supplementation has been revealed to decline serum ammonia levels and altering neurotransmitters like gamma-aminobutyric acid and norepinephrine in the brain [42].

Acarbose: Acarbose is an FDA-approved medication for the management of T2DM. It inhibits alpha-glucosidase activity in the intestine and delays digestion of ingested carbohydrates and also exerts its beneficial effects on hepatic encephalopathy by promoting the proliferation of intestinal saccharolytic bacterial flora at the expense of proteolytic bacterial flora, thereby decreasing substrate for ammonia secretion [41].

Manganese: Manganese deposition in many cirrhotic brains (globus pallidus) has been ascertained by magnetic resonance imaging (MRI), which disappears after liver transplantation and hepatic encephalopathy [42].

N-methyl-D-aspartate: N-methyl-D-aspartate (NMDA) receptors can interact with glutamate in the brain to activate many enzymes, including nitric oxide synthetase. Nitric oxide can induce distinctive pathways important to cerebral processes such as circadian rhythms, memory and learning. Hyperammonemia accelerates glutamatergic activity and overstimulation of NMDA receptors in the brain [23].

Conclusion

Hepatic encephalopathy (HE) is defined as ‘‘brain malfunction caused by liver inadequacy and/or porto-systemic shunting manifesting as a broad spectrum of neurological or psychiatric deformity ranging from subclinical changes to coma’’. When blood flow and hepatic metabolism are injured by cirrhosis, serum and CNS concentrations of ammonia are increased.

The ammonia that enters the CNS combines with α-ketoglutarate to form glutamine. An elevated ammonia level accelerates the amount of glutamine within astrocytes, resulting in cell swelling and finally brain edema. Among the multiplex actions of lactulose an indispensable one is its function as a “prebiotic”, causing escalated growth of endogenous bacteria that are implicitly beneficial to the host like lactobacilli, thereby indirectly decreasing the strength of potentially more harmful urease generating bacteria. Acarbose obviates alpha-glucosidase activity in the intestine and delays digestion of ingested carbohydrates and also exerts its beneficial consequences on hepatic encephalopathy by promoting the proliferation of intestinal saccharolytic bacterial flora at the expense of proteolytic bacterial flora.

Abbreviations

ALF: Acute liver failure; BCAAs: Branched-chain amino acids; CNS: Central nervous system; GIT: Gastrointestinal tract; HE: Hepatic encephalopathy; NH_3: Ammonia; NO: Nitric oxide

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Conflict of Interests

The author has no financial or proprietary interest in any of material discussed in this article.

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