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Hepatic encephalopathy: An updated approach from pathogenesis to treatment

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Summary

One of the most serious complications of chronic or fulminant liver failure is hepatic encephalopathy (HE), associated most commonly with cirrhosis. In the presence of chronic liver disease, HE is a sign of decompensation, while in fulminant liver failure its development represents a worrying sign and usually indicates that transplantation will be required. Despite the significance of HE in the course of liver disease, the progress in development of new therapeutic options has been unremarkable over the last 20 years. An up-to-date review regarding HE, including both research and review articles. HE is a serious and progressive, but potentially reversible, disorder with a wide spectrum of neuropsychiatric abnormalities and motor disturbances that ranges from mild alteration of cognitive and motor function to coma and death. Although a clear pathogenesis is yet to be determined, elevated ammonia in serum and the central nervous system is the mainstay for pathogenesis and treatment of HE. Management includes early diagnosis and prompt treatment of precipitating factors. Clinical trials and extensive clinical experience have established the efficacy of diverse substances in HE treatment. Novel therapies with clinical promise include: L-ornithine L-aspartate, sodium benzoate, phenylacetate, AST-120, and the molecular adsorbent recirculating system. Eventually, liver transplantation is often the most successful long-term therapy for HE.

key words: **hepatic encephalopathy • hyperammonemia • minimal hepatic encephalopathy • pathophysiology • treatment**

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Background

Hepatic encephalopathy (HE) or portosystemic encephalopathy (PSE) is one of the most serious complications of liver failure, either chronic or fulminant. HE refers to a complex and potentially reversible or progressive syndrome of cerebral dysfunction, which consists of neuropsychiatric, cognitive and motor components, characterized by a broad etiological spectrum. It is observed in cirrhotic patients and those with acute liver failure (ALF) in the absence of other known brain disease, as a result of decompensated liver function [1,2]. Five years after the diagnosis of cirrhosis, there is 26% probability for developing at least one episode of HE [3]. HE is also a common problem after insertion of a transjugular intrahepatic portosystemic shunt (TIPS) [4,5]. Despite the impressive advances in our understanding of the several pathophysiological mechanisms which are involved in HE, the treatment options remain an unmet clinical need, accompanied by considerably high mortality rates. After the first clinical manifestation of HE, the patients' prognosis is very poor; probability of five-year survival is 16% to 22%, compared with that of 55% to 70% in cirrhotic patients without HE [3,6]. The pathophysiology of chronic HE is apparently multifactorial, with several circulating neurotoxins being involved. The systemic accumulation of ammonia neurotoxic concentrations seems to be the most prominent factor [7,8], while the interorgan ammonia and amino acid metabolism is of pivotal importance in the pathogenesis of HE. Since Nencki and Pavlov described meat intoxification in portacaval shunted dogs over 100 years ago [9], ammonia has been considered as a central factor to the pathogenesis of HE [10]. The clinical importance of hyperammonemia's role in patients with liver failure is no more evident than in the observation that ammonia levels of >150 μmol/L predict brain herniation, coma and death in patients with ALF [11]. Several treatment agents such as lactitol, lactulose, L-ornithine-L-asparate and rifaximin aim to lower blood and cerebral ammonia levels and thereby attenuate its toxic effects.

Ôhe aim of this review is to summarize the current knowledge related to the pathophysiology leading to HE, as well as the subsequent therapeutic options and advances that have primarily arisen out of understanding the progression of HE.

Clinical Hepatic Encephalopathy

Patients with HE, according to the West Haven Criteria, display a variety of neuropsychiatric abnormalities characterized by four degrees of severity, ranging from disturbances affecting quality of life (abnormal sleep patterns, lack of awareness, increased reaction times, impairments in cognitive and mental function, behavior and personality alteration, disturbances in attention and coordination), to transient neurological symptoms, (asterixis or flapping tremor, combined with characteristic electroencephalographic abnormalities) [12–15]. With advanced disease, cerebral edema develops secondary to astrocyte swelling and leads to altered states of consciousness, varying degrees of confusion, stupor, coma and death [16–19] (Table 1).

Multiple HE episodes are common, being associated with precipitating factors [20] such as excessive protein intake, gastrointestinal hemorrhage, constipation, febrile episode or sedative use (Table 2). The HE symptoms are generally reversible, suggesting a metabolic etiology. The heterogeneity of HE manifestations between different cirrhotic patients, as well as within the same patient over time, make the diagnosis, assessment and classification of this condition difficult. HE also causes mortality in patients with ALF, especially when rapid deterioration in consciousness coexists with increased intracranial pressure, resulting in brain herniation and death. Therefore, prevention and effective treatment of HE may have important prognostic implications in patients with chronic and acute liver failure.

Minimal hepatic encephalopathy

Coma grade deeper than I is usually defined as overt encephalopathy and grade 0 or less as subclinical or minimal HE (MHE), which is the mildest form of HE spectrum. Patients with MHE have no recognizable clinical symptoms; a mild cognitive and psychomotor deficit are diagnosed under the result of various neuropsychological tests, such as the number correction test (NCT), digit-symbol test, line tracing test, serial-dotting and block design test [21]. Aside from neurophysiologic evaluations, electroencephalogram (EEG) and P3000 auditory evoked potentially are recommended [17]. Although these neurocognitive abnormalities are subtle, they primarily affect attention, speed of information processing, motor abilities and coordination, in a way that is not recognizable on standard neurological examination. These abnormalities are independent of sleep dysfunction or problems with overall intelligence [17,22,23]. The prevalence of MHE is high in patients with liver cirrhosis and varies between 30% and 84%, with higher prevalence in patients presenting poor liver function [24]. The diagnostic criteria for MHE have not been standardized, but are based on careful patient history and physical examination, normal mental status examination, demonstration of abnormalities in cognitive and/or neurophysiological functions and exclusion of concomitant neurological disorders. MHE is associated with impaired health-related quality of life, predicts the development of overt HE, and is associated with poor survival. Hence, screening all patients with cirrhosis for MHE using psychometric tests and treating those with MHE diagnosis has been recommended as a way of improving both quality of life and rate of survival.

Etiology of hyperammonemia

Ammonia is created primarily from nitrogenous products in the diet, bacterial metabolism of urea and proteins in the colon, as well as deamination of glutamine in the small intestine by glutaminase (EC 3.5.1.2) [25,26]. Ammonia is also produced by skeletal muscles, although the pattern of these metabolic pathways' contribution to HE pathogenesis is not yet thoroughly established. From the gut, ammonia enters the portal circulation and is converted to urea by the liver; urea is subsequently excreted by the kidneys [8]. Overall, the main causes of hyperammonemia are presented in Table 3 [27–30].

Vascular anatomic anomalies that result in blood flow bypassing the liver, as well as the existence of slow transit constipation, can both allow increased absorption of ammonia into the mesenteric blood supply, sufficient to overwhelm

Table 1. Degrees of severity and neuropsychiatric abnormalities in hepatic encephalopathy.

Hepatic encephalopathy	Consciousness	Intellectual function	Personality behavior	Neuromuscular abnormalities
Grade 0	No detectable changes	No detectable changes	No detectable changes	None
Grade I (mild)	Sleep disturbance, trivial lack of awareness	Shortened attention span, mildly impaired computations	Euphoria, depression, irritability	Muscular incoordination, impaired handwriting, asterixis may present
Grade II (moderate)	Lethargy, mild disorientation to time	Amnesia of recent events, grossly impaired computations	Overt change in personality, inappropriate behavior	Slurred speech, asterixis, hypoactive reflexes, ataxia
Grade III (severe)	Somnolence, confusion, Semistupor	Inability to compute, disorientation to place	Paranoia, bizarre behavior	Hyperactive reflexes, nystagmus, (+) Babinski's sign, clonus, rigidity
Grade IV (coma)	Stupor	None	None	Dilated pupils, opisthotonus, coma, lack of verbal, eye & oral response

Table 2. Precipitating factors for hepatic encephalopathy.

Increased nitrogen load	Electrolyte disorders	Drugs	Other
Gastrointestinal bleeding	Hyponatremia	Narcotics, tranquilizers, sedatives (Central nervous system acting drugs)	Infections (spontaneous bacterial peritonitis, urinary tract, skin, or pulmonary)
Excessive dietary protein	Hypokalemia		Surgery
Azotemia	Metabolic alkalosis/acidosis		Superimposed liver injury (acute hepatitis, drug-induced liver injury)
Constipation	Hypoxia		Progressive liver disease
	Hypovolemia		TIPS
	Dehydration		Renal failure
			Urinary obstruction
			Hepatocellular carcinoma
			Terminal liver disease

hepatic excretory pathways and therefore deteriorate into hyperammonemia. Aside from the most common form of decompensated liver disease, where the diagnosis is reasonably straightforward, less frequent causes of hyperammonemia can pose a certain clinical challenge, in the sense that they may present with an identical clinical syndrome. Although rare, some of these less frequent causes may be reversible or even curable with specific therapy, making prompt recognition potentially lifesaving [28].

Pathophysiology

Hyperammonemia is the pivotal biomarker of HE with normal blood ammonia levels being less than 50 μmol/*L*. The ammonia elevation is mainly caused by the inability of the liver to transform ammonia to urea via the urea cycle in periportal hepatocytes, the diminished glutamine synthesis in centrilobular hepatocytes and the portosystemic shunts. The contribution of each mechanism varies according to the underlying condition, which may be ALF, cirrhosis or total liver bypass. HE may be episodic, persistent or minimal and it is precipitated by constipation, infection, gastrointestinal hemorrhage, TIPS, electrolyte disorders, dehydration and drugs like benzodiazepines (Table 2).

The pathophysiology in most cases consists of several parallel mechanisms that must be considered; for instance, constipation can cause hyperammonemia due to delayed transit rate and subsequently increased absorption of ammonia, but the local pH and the composition of the colonic flora can effectively modulate absorption. It has been long supposed that the urease-producing colonic bacteria break down proteins, urea and possibly amino acids to ammonia, which is then absorbed into the portal circulation [31,32].

Table 3. Etiology of hyperammonemia.

Urea cycle deficiencies	Organic acidemias	ALF & CLD*	Fatty acid oxidation defects	Dibasic amino acid transport defect	Congenital lactic acidosis	Other
Ornithine transcarbamylase deficiency	Propionic acidemia	Viral infections (ALF)	Acyl-CoA dehydrogenase deficiency	Lysirunic protein intolerance	Pyruvate dehydrogenase deficiency	Gastrointestinal bleeding
Carbamoylphosphate synthetase-I deficiency	Isovaleric acidemia	Toxins (ALF)	Systemic carnitine deficiency	Hyperammonemia-hyperornithemia-homocitrullinuria	Pyruvate carboxylase deficiency	Valproate, 5-FU, Salicylates
N-acetylglutamine synthetase deficiency	Glutaric acidemia type II	Cystic fibrosis (CLD)			Mitochondrial diseases	Renal Diseases & infections, Reye's syndrome
Argininosuccinic synthetase deficiency	Multiple carboxylase deficiency	Wilson disease (CLD)				Parenteral hyperalimentation
Argininosuccinic acid lyase deficiency	Beta-ketothiolase deficiency	Biliary atresia (CLD)				Transient hyperammonemia of newborn
Argininase deficiency		A-1 antitrypsin deficiency (CLD)				Surgical creation of urinary diversion

* ALF – Acute Liver Failure; CLD – Chronic Liver Diseases.

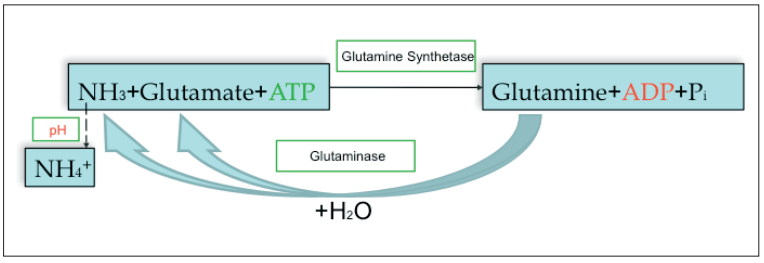

Figure 1. Glutaminase splits glutamine to ammonia and glutamate while glutamine synthetase has the opposite action. A molecule of ammonia can be ionized to an ammonium cation depending on the local pH. Acidification of the colonic lumen creates higher concentrations of ammonium cations, which are less likely to pass into the portal vascular bed.

Thus, given the insufficiency or bypass of the liver, ammonia is provided free entry to the systemic circulation. Moreover, recent studies suggest that the interorgan handling of ammonia is also of crucial importance in the pathogenesis of HE. Muscles, kidneys, gut and brain are at the forefront of this interplay between the enzymes glutamine synthetase (GS, EC 6.3.1.2) and glutaminase [33]. In the small intestine, glutaminase, which is abundant within enterocytes, splits glutamine to glutamate and ammonia, leading to increased ammonia levels. The glutamate-glutamine system plays a major role in the pathophysiology of HE (Figure 1).

When the liver fails to detoxify ammonia, it is the large mass of the skeletal muscular tissue which can take the role of converting it to glutamine with the utilization of GS. In this case, a satisfactory substrate supply is an essential requirement, since glutamate itself is not transported easily to the muscle cells, like its precursor, L-ornithine. Nevertheless, even with the help of L-ornithine administration as a therapeutic intervention, the ammonia-lowering effect seems to be transient. It may suggest that the subsequent high levels of glutamine, as a result of ammonia's detoxification, eventually lead to ammoniagenesis in peripheral tissues or organs with intact glutaminase activity, and therefore cause hyperammonemia rebounding [34,35].

The brain also hosts a glutamine-glutamate conversion buffer system, which has, however, a limited transforming capability and is situated at the astrocytes. Hence, ammonia can rise to neurotoxic levels in the brain despite the existence of this system. Ammonia can alter both excitatory and inhibitory neurotransmission, affecting the glutamatergic, γ-Aminobutyric acid (GABA)-ergic [36,37] and dopaminergic systems. Ámmonia can also affect energy metabolism, if accumulated at high concentrations [8].

Hyperammonemic encephalopathy in urea cycle disorders is compared with the encephalopathy of fulminant or chronic hepatic failure. Such a comparison reveals that the following features are shared by all three conditions: hyperammonemia; respiratory alkalosis; increased levels of glutamine in plasma, cerebrospinal fluid and brain; decreased brain levels of myo-inositol; and astrocyte swelling with few neuronal changes and brain functional changes [38].

High ammonia levels are not always related to the clinical severity of HE. Proton emission tomography (PET) studies have shown that there is an increased permeability of the blood-brain barrier (BBB) to ammonia in chronic liver failure, and it has also been shown that ammonia brain

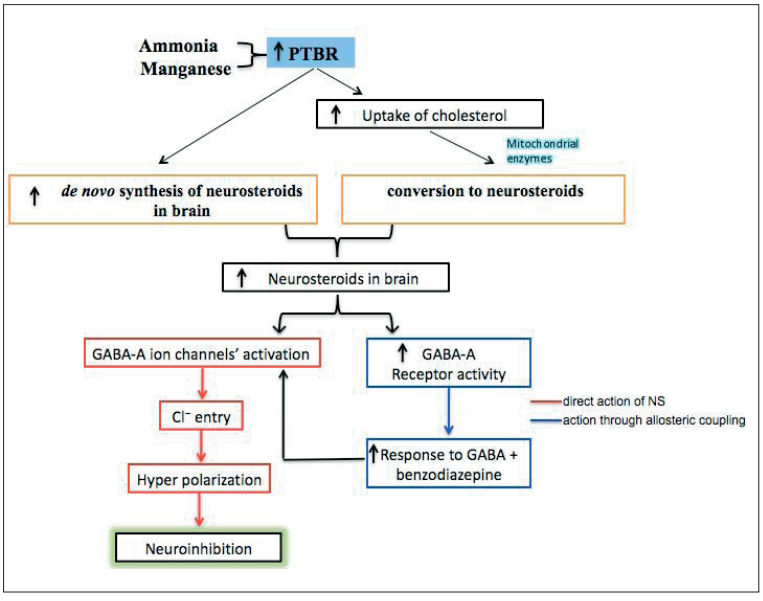

Figure 2. Interaction between Ammonia-PTBR-Neurosteroids-and GABA in pathogenesis of HE.

Table 4. Important points in pathogenesis of hepatic encephalopathy.

Hepatocellular insufficiency, portosystemic shunts in chronic cases
Up-regulation of Glutamine Synthetase in skeletal muscles
Increased uptake of ammonia in brain / altered permeability of BBB
Elevated levels of glutamine in plasma, brain and Cerebrospinal Fluid (CSF)
Accumulation of other neurotoxins in brain

uptake is significantly elevated in both chronic and acute liver failure, compared to normal values [12]. Another study showed that amiloride-sensitive non-selective cation channels, which are activated by lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF-α) and prostaglandin E2 (PGE2), allow ammonium cations to enter the brain [39]. Additionally, it has also been shown by another group that ammonia acts synergistically with LPS in rat brain, increasing cerebral blood flow (CBF) and intracranial pressure (ICP) [40], whereas endotoxemia seems to be a precipitant of HE in cirrhotic patients. It has also been proven that regional cerebral blood flow variations are associated with acute ammonia increase and cirrhosis [33]. In case of cirrhosis accompanied by ÌHE, changes in regional cerebral blood flow may be responsible for attention deficit disorder [41].

Despite the important role of ammonia in HE, it must not be ignored that other causative agents are also implicated in HE, such as manganese, mercaptans, phenols, aromatic aminoacids, proinflammatory cytokines and neuroactive medications administered in patients suffering from liver failure. These agents accumulate in the brain and induce neurotoxic actions, derailing normal brain function [42]. Magnetic resonance imaging (MRI) reveals bilateral signal hyper-intensities in the globus pallidus, which are caused by manganese accumulation and are more prominent in chronic liver failure. The dopaminergic neurons have a considerable sensitivity to the deleterious effects of manganese [42]. The role of inflammation and proinflammatory cytokines is highlighted in ALF patients where systemic inflammatory response, caused by hepatic inflammation and/or intercurrent sepsis, is driven by cytokines, such as interleukin (IL) 6, IL-1b and TNF-α [43]. Some of the important points in the pathogenesis of HE are depicted in Table 4.

Knowledge at the molecular level

Several studies have been performed in order to elucidate the molecular milestones in the pathogenesis of HE. As already pointed out, the skeletal muscle can detoxify ammonia with the activity of GS. Under normal circumstances the GS-activity is of small importance, but in the case of HE its gene expression and activity are up-regulated [35]. In ALF, genes that code glial glutamate transporter-1 (GLT-1), glucose transporter-1 (GLUT-1), glial fibrillary acidic protein (GFAP), peripheral type benzodiazepine receptor (PTBR) and aquaporin IV alter their expression in astrocytes when the liver fails [44].

The synthesis of neurosteroids, such as pregnenolone, progesterone, allopregnanolone and 3α-5α-tetra-dehydrodeoxycorticosterone (THDOC), takes place mainly in astrocytes and microglial cells, and it is driven by the up-regulation of PTBR by ammonia and manganese. The PTBR, a heteromeric complex of several subunits [isoquinoline binding protein (IBP), voltage-dependent anion channel (VDAC), adenine nucleotide carrier (ANC)] is localized in the outer and inner mitochondrial membranes, and its activation enhances the uptake of cholesterol, creating a channel, that allows significant cholesterol utilization and conversion to neurosteroids by mitochondrial enzymes. Moreover, *de novo* synthesis of neurosteroids is driven by PTBR upregulation. Increased expression of peripheral benzodiazepine binding sites (PBBS) has been shown *in vivo* in HE patients using the [^{11}C](R)-PK11195 ligand and PET. Brain regions such as the pallidum, right putamen and the right dorsolateral prefrontal region, showed increased radioisotope binding [45]. The neurosteroids positively modulate the activity of GABA-A receptor complex through the neurosteroid

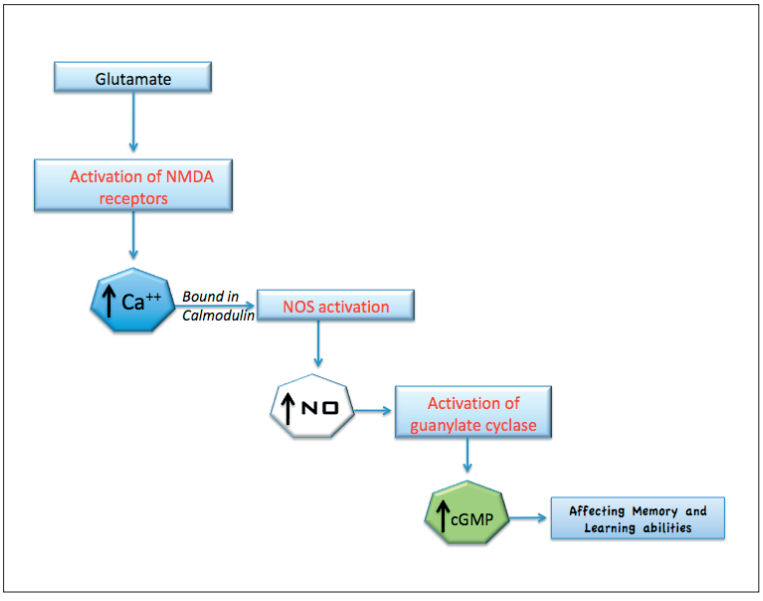

Figure 3. The glutamate-NO-cGMP pathway.

Table 5. Molecular mediators in hepatic encephalopathy.

Increased gene expression of GS in the skeletal muscle
Altered gene expression of MAO-A
Altered gene expression of Aquaporin IV
Increased cerebral mRNA levels of eNOS in ALF
Glutamate-NO-cGMP pathway
Affected gene expression of PTBR, Neurosteroid system (pregnenolone, THDOC etc), GABA-A receptor/ion channel GLUT-1, GLT-1, GFAP in ALF

binding site of the GABA-A receptor, and subsequently the GABA and the benzodiazepine recognition site, which are allosterically coupled. The increased GABA-ergic tone is a result of GABA-A ion channels activation by neuroinhibitory neurosteroids, which allow chloride to enter, hyper-polarize and eventually inhibit nerve cells (Figure 2).

It has also been shown that neurosteroids possess genomic actions that modulate gene expression through transcription in astrocytes [46] by various mechanisms, for example by altering the expression of Ìonoamine Ïxidase A (MAO-A) via the glucocorticoid receptors in humans [47] or Aquaporin IV via progesterone receptors in rats [48].

Several studies have been performed on the implication of NO in pathogenesis of HE. In ALF, vasodilation caused by NO is responsible for high cerebral blood flow, increased delivery of ammonia to the brain and edema. In rats with ALF due to hepatic devascularization, endothelial nitric oxide synthase (eNOS) mRNA exhibits increased expression in cerebral cortex compared to sham operated rats used as controls [49]. In the same study, mild hypothermia sufficient to prevent HE and brain edema in ALF rats normalized eNOS mRNA levels. However, eNOS did not correlate well with HE/edema in the early stages of ALF.

Another pathway impaired in chronic hyperammonemia is glutamate-NO-cGMP. Activation of the N-methyl-D-aspartic acid (NMDA) receptors leads to increased intracellular calcium that, bound in calmodulin, activates NOS, which subsequently produces NO. The synthesis of cGMP is mediated by the soluble guanylate cyclase (EC 4.6.1.2), which is activated by NO. The glutamate-NO-cGMP pathway has a role in learning and memory abilities, which are impaired, among along with other cognitive functions, in HE patients (Figure 3).

As mentioned before, the BBB permeability is altered in HE. An *in vitro* study on cultured mouse brain capillary endothelial cells revealed that, when exposed to ammonia, mRNA expression of taurine transporter (TAUT) and creatine transporter (CRT), both being BBB transporters, rises, as does their uptake [50,51]. On the other hand, mRNA expression of the tight junction protein claudin-12 was significantly suppressed, suggesting a partial explanation to BBB integrity changes seen in HE. The molecular mediators in HE are summarized in Table 5.

Treatment of hepatic encephalopathy

Treatment of HE consists of the following three goals: a) Dealing with precipitating factors of hyperammonemia and accumulation of toxic metabolites, b) Lowering blood and cerebral ammonia levels, and c) Dealing with the consequences of hyperammonemia and accumulation of toxic metabolites.

Dealing with precipitating factors of hyperammonemia and accumulation of toxic metabolites

One of the most important aspects of dealing with HE is the ability to potentially reverse its progress by prompt recognition and treatment of its precipitating factors before a decompensated liver function takes place. Fessel et al. demonstrated that HE is caused by reversible factors in over 80% of patients [52]. These common factors that can be reversed include dehydration, constipation, systematic infection,

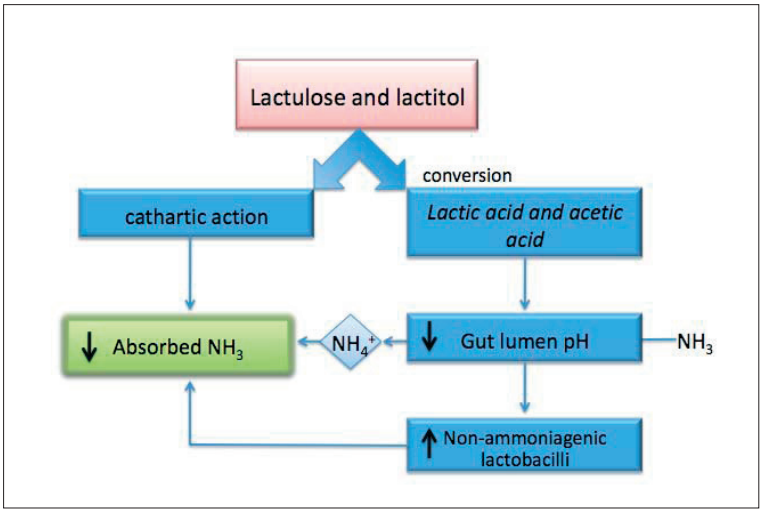

Figure 4. Non-absorbable disaccharides reduce the production and absorption of ammonia.

hypokalemia, gastrointestinal hemorrhage, protein overintake, sedatives and tranquilizers (Table 2). Addressing these factors in time has been proved to be crucial in effectively treating most patients with HE [53].

Gastrointestinal hemorrhage, renal failure, dehydration, constipation

Prompt treatment of upper or lower GI bleeding is essential. Acute renal failure as a result of dehydration and diuretics' effect may precipitate HE through hypokalaemia, hypoglycaemia and metabolic alkalosis. Intravenous thiamine replacement should be promptly initiated in nutritionally depleted and alcoholic patients. The assessment of recent bowel habits is crucial. Adequate defecation is essential and measures to produce it should be taken [54].

Infection

Culture from all appropriate body fluids should be received. A diagnostic paracentesis should be performed in all patients with ascites. In patients with hepatic coma, or pending culture results, a short course of empirical antibiotics should be considered [53].

Drugs

The use of psychoactive medications such as benzodiazepines and narcotics should be evaluated and discontinued if possible. The toxicology of urine may be also necessary. Any condition suggesting the development of encephalopathy should result in total discontinuation of chlordiazepoxide and other sedatives, or in a limitation to minimum possible dosages in drowsy cirrhotic patients who are at risk of delirium tremens [50].

Acute brain injury and seizures

The possibility of focal neurological injury must be excluded by a careful history and neurological examination. In case of any doubt, CT brain imaging should be performed. EEG analysis will exclude seizure activity, or may confirm the presence of typical slow, triphasic waveforms in the frontal lobes, which are associated with HE [54].

Lowering blood and cerebral ammonia levels

Dietary regulations

It has been demonstrated that dietary protein restriction in cirrhotic patients does not ameliorate or reverse the course of HE [55]. As a result, a daily protein intake of 1–1.5 g/kg of body weight can be safely administrated to a patient with HE, as a positive nitrogen balance is necessary to promote liver regeneration and increase capacity of skeletal muscles to remove ammonia in the form of glutamine [56]. However, it has been proven that the source of the protein intake may be of importance in controlling HE, with vegetable proteins being superior to animal-derived ones [57], although the hypothesis that branched -chain amino acids (BCAAs) can improve HE has failed to be proven. On the other hand, a high fiber intake diet seems to ameliorate HE by increasing the food transit rate through the gastroenteric system and therefore reducing the absorption of ammonia into the mesenteric blood supply [58,59].

Pharmacological approach

Reducing the production and absorption of ammonia

Lactulose (beta-galactosidofructose) and lactitol (beta-galactosidosorbitol) are two non-absorbable disaccharides that are converted into lactic and acetic acids inside the gut lumen, leading to a decrease in endolumen pH and therefore to the conversion of ammonia (NH3) to ammonium ($NH4^+$), which is more membrane impermeable. As a result, less ammonia is absorbed by the colon. Moreover, the acidification of gut lumen makes the enteric environment less suitable for ammoniagenic coliform bacteria and leads to increased levels of non-ammoniagenic lactobacilli. Additionally, lactulose and lactitol demonstrate a cathartic action, clearing the gut of ammonia before it can be absorbed and thus contributing to the improvement of HE via a secondary pathway (Figure 4). Both lactulose and lactitol have been proven to improve the clinical condition of patients with HE, although lactitol seems to be more tolerable and produces fewer side effects [60–63].

Mannitol may also be effective, but requires adequate kidney function. The antibiotics rifaximin [64], neomycin [65],

metronidazole [66] and nitazoxanide [67] have been used in the treatment of HE, either as a replacement of, or in conjunction with, non-absorbable disaccharides. Their effectiveness, although it has not yet been conclusively proven by larger studies, is considered to be equal to that of non-absorbable disaccharides; however, their side effects are generally more diverse and severe [68].

Probiotics may have a beneficial effect on the course of HE through alteration of colonic flora in favor of nonurease-producing bacteria. Their action results in a decrease of ammonia production in the gastroenteric system [69]. Colonic cleansing reduces the luminal ammonia content and lowers blood ammonia in cirrhotic patients [31].

Removing the ammonia from plasma

L-ornithine-L-aspartate (LOLA) is a stable salt of two amino acids, which administered to a hyperammonemic patient effectively lowers the blood and brain ammonia levels [70]. This is achieved by precipitating ammonia metabolism both in liver and muscles, through the urea cycle (stimulating hepatic urea and glutamate synthesis by offering more substrates), and glutamine synthesis (stimulating glutamine synthetase within the muscle), respectively. Moreover, ornithine is able to cross the BBB and increase the cerebral ammonia disposal. Oral LOLA has been proven to be a safe, well tolerated treatment with a good compliance rate and a beneficial therapeutic effect in patients with cirrhosis and stable, overt, chronic HE [71]. Nonetheless, according to a recent meta-analysis, the use of LOLA for patients with MHE does not seem to produce beneficial results [72]. Moreover, LOLA infusion was found to be ineffective in reducing ammonia levels in ALF patients [73], as well as having a decreased ability to ameliorate the psychometric function of TIPS patients, possibly due to enhanced portosystemic shunting [74].

Sodium benzoate can enhance the tissue ammonia metabolism, as it conjugates with glycine, created through tissue ammonia metabolism, to form hippuric acid. This is in turn excreted into the urine by the kidney.

Phenylacetate is considered to have a synergistic action with both LOLA and sodium benzoate, as it conjugates with glutamine, which is created and stored in the muscles, to form phenylacetylglutamine, which in turn is excreted by the kidney through glomerular filtration and tubular secretion. Therefore, the final effect is the net removal of excess blood ammonia into the urine by a two-step procedure, [75] and the elimination of possible rebound hyperammonemia. This possibility was observed in patients treated with LOLA after conversion of muscle glutamine back into glutamate and ammonia, by the presence of phosphate-activated glutaminase enzyme in the gut, kidneys and liver [33,34,76]. This proposed synergistic action between L-ornithine and phenylacetate has been confirmed in studies with cirrhotic rats and ALF pigs [77].

Both L-carnitine and its acetylated form, acetyl-L-carnitine, have been shown to stimulate the urea cycle, but their effectiveness in the treatment of HE has not yet been solidly established [78].

Novel approaches and strategies under development

The spherical adsorptive carbon AST-120, which is used in the treatment of patients with kidney failure in order to reduce the absorption of uremic toxins, was able to reduce ammonia levels in experimental animal models [79]. HPN-100 is a pro-drug of phenylbutryrate and a pre-pro-drug of phenylacetic acid, which, although not yet tested on patients with liver disease, is thought to ameliorate the clinical condition of HE by inducing the same metabolic pathway as phenylacetate. Acarbose ($C_{25}H_{43}NO_{18}$) is an alpha-glucosidase intestine inhibitor, which reduces digestion of carbohydrates and therefore decreases colonic proteolytic flora, affecting metabolism of dietary nitrogen and thereby reducing production of ammonia [80].

Genetically engineered bacteria with the ability to metabolize ammonia at an increased rate have been used in experimental animal models in order to reduce its ammonia levels [81].

Dealing with the consequences of hyperammonemia and the accumulation of toxic metabolites

Regulating neurotransmission in the brain

Branched-chain amino acids, benzodiazepine antagonists such as flumazenil [82,83], dopamine receptor stimulators such as bromocriptine [84], NMDA receptor antagonists and zinc [85] have been tested as supplementary medication for the treatment of HE-related neurological symptomatology. Their effectiveness however, needs to be more thoroughly proven before they can be systematically introduced into the treatment of HE, given the fact that they can also present considerable side effects in the nervous system.

Invasive treatments

Molecular adsorbent recirculating system (MARS)

Molecular adsorbent recirculating system (MARS) is a blood detoxification system that removes both protein-bound and water-soluble toxins by means of hemodiadsorption, a combination of hemodialysis and adsorption by the use of albumin [86]. This system, which can be generally beneficial for patients with liver failure, has been additionally proven to improve the condition of HE patients [42,87,88].

Surgical treatments

The obliteration of any large spontaneous portosystemic anastomoses, surgical shunts, or TIPS, usually by the insertion of a reduction stent, [89] balloon-occluded retrograde transvenous obliteration (BRTO), [90] or by surgical eradication of shunt vein, should be considered in cases of chronic HE. Nonetheless, the risk of bleeding and hepatic decompensation should be considered before such an invasive technique is used. In cases of chronic HE that persists even after continued therapy, splenic artery embolization or total colectomy could be of some therapeutic value, depending on the patient's specific medical profile [41,91].

Liver transplantation (LT) is the ultimate treatment for curing liver disease, obliterating HE. In cases of ALF, when the

onset of HE and coagulopathy occurred within 26 weeks of jaundice in a patient without preexisting liver disease, LT is currently the best therapeutic option [92]. The first episode of overt encephalopathy, because of its poor prognosis, is the trigger for including the patient in a transplantation list [93]. Before the availability of liver transplantation, ALF was associated with 80% to 90% mortality, especially in patients who progressed to grade 3 or 4 of HE [94]. However, with successful LT more than 90% of patients survive one year and 75% of them survive five years post-transplant, with most of patients having an excellent quality of life [95]. Early referral to an LT center is essential, since deterioration in a patient's health status can occur suddenly, the chance of receiving a liver transplant increases with early placement on the waiting list, the prediction of which patients will recover spontaneously is quite difficult, and once brainstem herniation has occurred patients cannot be saved by any means, including LT [96].

Another option in surgical treatment of HE, from the LT point of view, is live-donor LT [94]. This option produces excellent recipient results with a low risk of donor morbidity and mortality, while also at the same time decreasing waiting list mortality.

More recently hepatocytes transplantation has been successfully used to treat certain liver-based metabolic disorders, even when associated with HE [97]. Results from individual patients are promising, but the lack of controlled trials makes interpretation of the findings difficult [98]. Moreover, the limited supply of donor organs that can provide good quality cells, and the number of cryopreserved hepatocytes required to achieve therapeutic purpose, are the main limitations of this approach.

Novel approaches and strategies under development

Endocannabinoids have been used in animal studies in order to alleviate the symptoms of cerebral dysfunction, by activating the AMP-activated protein kinase [99]. In addition, continuous intracerebral administration of cGMP, or zaprinast (a cGMP-degrading phospho-diesterase inhibitor that does not cross the BBB), have been proven to enhance the learning ability of hyperammonemic rats [100]. Therefore sildenafil, an inhibitor of cGMP-degrading phospho-diesterase with ability of BBB crossing, has been used in order to improve the cerebral function of patients with HE by increasing the levels of extracellular cGMP [101]. The contribution of glutamatergic transmission in cerebral dysfunction symptoms presenting in HE patients provides the opportunity of a pharmacological approach by means of blocking the metabotropic glutamate receptor 1 [102]. According to current evidence, inflammatory mediators play an important role in inducing the neurophysiological brain alterations observed in patients with HE [103]. Based on this observation, experimental studies have been conducted on animal models, proving the ability of indomethacin [104] and ibuprofen [105] to ameliorate the cerebral symptoms observed in HE patients. L-methinine S-sulfoximine (MSO), an irreversible inhibitor of GS, can prove of therapeutic value for patients with HE, given the fact that it can lower brain glutamine levels and therefore prevent astrocyte swelling and cerebral edema [106]. Oxidative stress, causing mitochondrial permeability transition (mPT), could lead to astrocyte swelling and cerebral edema [107]. Taking this into account, mPT inhibitors, such as pyruvate, minocycline, magnesium and TFP, have been tested as a possible treatment for cerebral manifestations of HE [16]. Moreover, the use of manganese-chelating agents [108], as well as application of moderate hypothermia [109] could aid in alleviating brain symptoms in patients with HE, although their effectiveness remains to be solidly proven.

Conclusions

Hepatic or porto-systemic encephalopathy (HE) is one of the most serious complications of chronic or fulminant liver failure, associated most commonly with cirrhosis, and encompasses a spectrum of neuropsychiatric symptoms and signs. Due to differences in etiology and severity, as well as heterogeneity of manifestations, the diagnosis and management of HE remain a difficult challenge for physicians and medical professionals. Since HE does not clinically differ from encephalopathies of different etiologies, its diagnosis requires the presence of liver disease or a portosystemic shunt. Several factors have been implicated in pathogenesis, with ammonia considered to have a central role, thus prompt recognition of the cause of hyperammonemia can be potentially lifesaving. Identification and correction of precipitating factors remains the cornerstone of treatment, while morbidity and mortality can be decreased by timely intervention. Overall, treatment of HE consists of the following three directions: modifying factors precipitating hyperammonemia and accumulation of toxic metabolites; decreasing blood and cerebral ammonia levels; and addressing the consequences of hyperammonemia and accumulation of toxic metabolites. Screening all patients with cirrhosis for MHE and treating those with MHE diagnosis has been recommended to improve quality of life and rate of survival. Finally, liver transplantation is often the most successful long-term therapy for HE.

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