Journal of Advanced Biomedical and Pharmaceutical Sciences

Journal Homepage: http://jabps.journals.ekb.eg

Overview on Hepatic Encephalopathy

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Received: March 14, 2019; revised: May 12, 2019; accepted: May 29, 2019

Abstract

Hepatic encephalopathy (HE) has appeared in the last years as serious, life threatening and debilitating complication of both persistent and episodic liver diseases. This review explores HE definition, pathogenesis, diagnosis and available treatment options. Overt HE is a major cause for hospitalization, readmission and even death in cirrhotic patients, while covert HE can affect negatively on patient quality of life, ability of driving and survival. Clinical manifestations of HE include cognitive function impairment and deteriorated psychometric motor functions. Diagnostic options for HE are varied and depend on the impairment degree and the acuity of clinical presentations of HE. Pathogenesis of HE is sophisticated and depends on several factors, however, ammonia is considered to play a critical role in HE pathophysiology. Management options of HE include controlling of precipitating factors, medical treatment and liver transplantation. Standard medical treatment of HE comprises non-absorbable disaccharides as lactulose and some antibiotics as rifaximin. Newer drugs that act on serum ammonia level have a vital role in management of HE, such as l-ornithine-l-aspartate, sodium phenylbutyrate and sodium benzoate.

Key words
hepatic encephalopathy, ammonia, hyperammonemia

1. Introduction and definition

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that results in a reversible impairment of brain function which occurs in patients of advanced liver disorders as a result of hepatic malfunction [1]. The case is assorted as overt if it is clinically obvious or minimal if only manifest through psychometric testing [2].

In cirrhosis, HE generally combined with several neuropsychiatric disturbances (e.g. psychomotor impairment, deteriorated memory, shortened reaction time, declined awareness, sensory abnormalities and weakened concentration) [3]. HE is also accompanied by personality features changes, intellectual deterioration, and a diminished consciousness [4]. The etiology behind HE could be attributed to the presence of neurotoxic substances in case of cirrhosis and portal hypertension [5]. Inflammation, modulation of cerebral blood circulation autoregulation and presence of ammonia are fundamental to the progress of HE, and so they have become essential therapeutic targets in the treatment of HE [6].

About 70 % of cirrhotic patients are positive for signs of HE [7]. Several reports estimated that 30 – 45 % of cirrhotic patients undergo overt and clinically evident forms of HE [8], while minimal HE or covert HE occurs in 20 – 80 % of patients with cirrhosis [9].

Development of HE is usually associated with higher rates of mortality and its occurrence may be serious enough to cause hospitalization. The survival possibility of HE is 23 % at three years and 42 % at one year of follow-up. Moreover, about (30 %) of patients who died due to end-stage liver disease undergo prominent encephalopathy, reaching to coma [10].

2. Classification of hepatic encephalopathy

Categorization of HE is usually categorized according to all of the following factors [1]:

i. Underlying disease: type A (due to acute liver injury), type B (due to portosystemic shunting without intrinsic liver disease), and type C (due to cirrhosis).
ii. Severity of manifestations (**Table 1**) [11].
iii. Time course of HE: episodic, recurrent or persistent HE.
iv. Presence of precipitating factors: non precipitated or precipitated HE.

3. Clinical Presentation of Hepatic Encephalopathy

Hepatic encephalopathy produce a several nonspecific neurological and psychiatric symptoms [12]. Initially, HE alters psychometric tests orientated toward, working memory, awareness, visuospatial capability and psychomotor speed [13, 14]. With the progress of HE, personality changes begin to appear such as apathy, irritability, disinhibition, and obvious alterations in consciousness occur. Disturbances of the sleep-wake round with extreme daytime sleepiness are frequent [15]. Time and place confusion, inappropriate behavior, sudden confusional condition with agitation, stupor, and coma may be developed [16]. The initial and middle stages of HE may have asterixis or “flapping tremor” preceding stupor or coma [13].

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However, asterixis is not characteristic of HE because it can be detected in other diseases (e.g., uremia) [17].

Table (1): West-Haven criteria (WHC) grading system for hepatic encephalopathy and clinical description [11].

WHC	Description
Minimal	Psychometric or neurophysiological changes of tests investigating psychomotor functions or neurophysiological variations without clinical proof of mental alteration
Grade I	slight insufficiency of awareness Euphoria or nervousness Shortened attention period Impairment of addition or subtraction Altered sleep cycle
Grade II	Lethargy or apathy Disorientation for time Clear personality changes Inappropriate behavior Asterixis
Grade III	Somnolence to semistupor reactive to stimuli Confused large disorientation strange behavior
Grade IV	Coma

4. Pathophysiology of hepatic encephalopathy

Pathogenesis of HE is a complex process with multiple substances causing malfunction of neuronal cells and ammonia has been considered the fundamental pathophysiologic mechanism of HE [18].

Ammonia (NH_3) is an intestine-originated nitrogenous toxin created by bacterial metabolism of urea resulting from proteins that are found in diet [19]. Ammonia metabolism takes place in the liver then it is subsequently cleared via kidneys, and to a slighter degree through the muscles **(Figure 1)** [8].

In cirrhotic patients, liver malfunction reduces hepatic metabolism of NH_3 and portal hypertension leads to shunting of portal blood rich in NH_3 to the systemic circulation without undergoing any detoxification in the liver [20]. In the brain, NH_3 crosses the blood-brain barrier and is metabolized in the astrocytes by glutamine synthetase, which converts NH_3 and glutamate to glutamine [19]. Glutamine accumulation in astrocytes produce an osmotic gradient, which results in swelling of astrocytes and creation of reactive oxygen species, that in turn participating in the cerebral impairment seen in HE [20]. Oxidative stress that results as a by-product of ammonia induced increase in glutamine, contributes also to the pathophysiology of HE [21]. Oxidative stress results from inefficient removal of reactive oxygen species (ROS) and free radicals from astrocytes, leading to major damage of cells and finally cell death [22]. Oxidative stress is directly related to malfunction of astrocytes, which is responsible for deterioration in cognitive performance of patients with cirrhosis and HE [23].

5. Diagnosis and testing of HE

The suitable testing and diagnostic tools for HE vary according to the acuteness of the clinical manifestations and the grade of impairment [24].

Diagnosis of overt HE depends on a clinical assessment and a clinical decision, several clinical scales are used for evaluating its severity, the 'gold standard' clinical scale is the West-Haven criteria (WHC) grading system **(Table 1)** [25]. Other scales include Clinical Hepatic Encephalopathy Staging Scale (CHESS) **(Table 2)** and Glasgow Coma Scale (GCS) [1, 26].

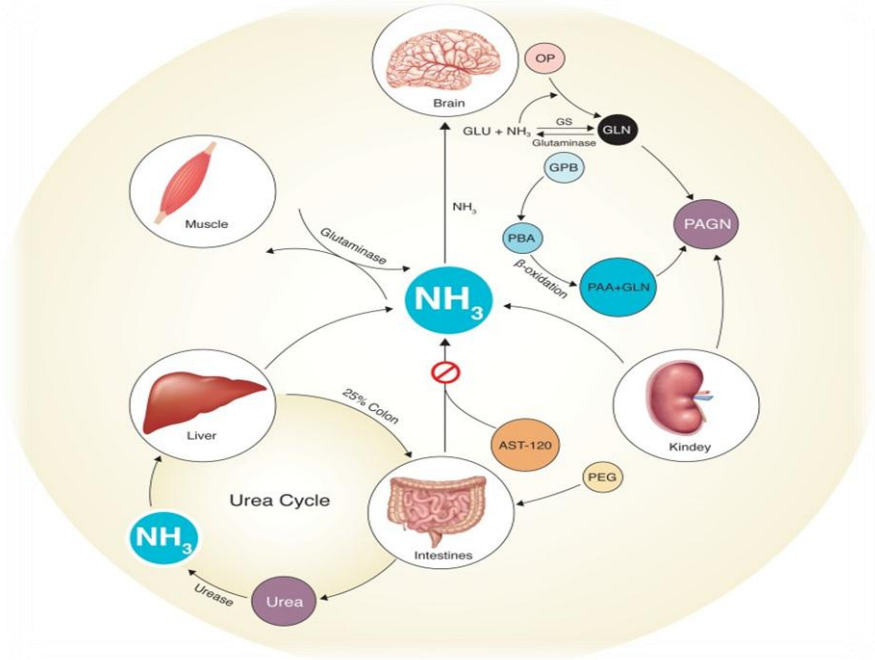

Figure (1): Different organs ammonia pathways with definite ammonia level reducing medications used in cirrhotic patients, ammonia (NH_3), glutamate (GLU), glutamine (GLN), glutamine synthetase (GS), ornithine phenylacetate (OP), glycerol phenylbutyrate (GPB) and polyethylene glycol (PEG) [8].

Table (2): Clinical Hepatic Encephalopathy Staging Scale (CHESS) [26].

Patient name:……..... Date:……....

			SCORE	
			0	**1**
1	Does the patient recognize which month he/she is in (i.e. : January, February)?	Yes No or he/she does not speak		
2	Does the patient identify which day of the week he/she is in (i.e. : Thursday, Friday)?	Yes No or he/she does not speak		
3	Can he/she count backwards from 10 to 1 without making mistakes or stopping? (the patient is asked between item 2 and 3 to count forward from 1 to 10 and is helped if necessary)	Yes No or he/she does not speak		
4	If asked to do so, does he/she lift his/her arms?	Yes No		
5	Does he/she understand what you are telling him/her? (based on the answers to questions 1 to 4)	Yes No or he/she does not speak		
6	Is the patient aware and attentive?	Yes No, he/she is sleepy or quick asleep		
7	Is the patient quick asleep, and is it hard to wake him/her up?	Yes No		
8	Can he/she speak?	Yes He/she does not speak		
9	Can he/she speak appropriately? In other words, can you understand all he/she says, and he/she doesn't stutter?	Yes No or he/she does not speak or does not speak appropriately		
		Total		

The testing options of covert HE is based on psychometric neurophysiological tests (the term 'covert' comprises minimal and Grade 1 HE) [27]. In the absence of clear physical examination signs of HE, neuropsychometric tests may be used to distinguish disruption in concentration, working memory, visuospatial abilities and normal motor skills [28]. Psychometric tests used to identify minimal HE include Electroencephalograph (EEG), Continuous Reaction Time (CRT) test, number connection tests and Psychometric Hepatic Encephalopathy Score (PHES) [29, 30].

6. Management of hepatic encephalopathy

6.1. Providing of Supportive Care

All stages of HE require sufficient supportive care, that is essential for HE patients and may encompass other professional members in the provision of patient care [12]. The advanced grades of HE patients who are at danger or incapable to protect their airways require additional intensive monitoring and are preferably managed in an intensive-care units [31].

6.2. Identification and Removal of Precipitating Factors

Correction of precipitating factors has vital importance in the treatment of HE, as about 90 % of patients can be cured only by adjustment of the causative precipitating factor [1].

6.3. Standared treatment

6.3.1. Diet

About 75 % of HE patients undergo moderate to severe malnutrition of protein-calories associated with reduced muscle mass and energy stores [32]. Proteins restriction in HE patients increases muscles catabolism and amino acids release, resulting in raising the serum level of ammonia and deterioration of HE [33]. Diets rich in vegetable proteins seem to be preferable than diets containing animal proteins, mainly red meats proteins. Malnourished patients are advised to add nutritional supplements as commercially available liquid to their diet and patients who display dietary protein intolerance may be treated with formulations rich in branched-chain amino acids either orally or enterally [33, 34].

6.3.2. Cathartics

Lactulose is known to be the first-line agent in the treatment of HE [35]. Lactulose has laxative effect, moreover nonabsorbable disaccharides as lactulose decrease the production and uptake of ammonia through lowering the colon pH [36]. But overuse of lactulose causing complications like dehydration, abdominal bloating, flatulence, aspiration, hypernatremia and serious perianal skin irritation, it also can precipitate HE [37].

6.3.3. Antibiotics

Neomycin and other antibiotics as metronidazole are used for HE patients in an attempt to reduce the colonic content of ammonia producing bacteria, but the aminoglycosides side effects on long term as ototoxicity and nephrotoxicity limit their clinical use [38, 39]. Rifaximin is a nonabsorbable derivative of rifampin, it is effective antibiotic in the management of HE [40].

6.3.4. Probiotics

Probiotics represent an interesting therapeutic options in the management plan of HE. They are live microorganisms which are able to prevent or treat some illness. They are natural agents that are considered as complementary medicine, they are comparatively well tolerated even in patients with cirrhosis [41]. Probiotics are beneficial in HE pathogenesis via different mechanisms as they reduce ammonia level in portal blood by decreasing ammonia absorption and the activity of urease-producing bacteria. They also reducing inflammation and oxidative stress in the hepatocytes results in increasing ammonia clearance [42].

6.4. Treatments to Increase Ammonia Clearance

6.4.1. L-Ornithine L-aspartate (LOLA)

L-Ornithine L-aspartate, ornithine and aspartate are substrates of the urea cycle [43]. LOLA reduces serum ammonia levels via enhancing of hepatic urea cycle activity and stimulating glutamine synthesis [44].

6.4.2. Zinc

Zinc is a critical cofactor in ammonia metabolism, zinc deficiency is associated with the down-regulation of muscle glutamine synthetase, which leads to hyperammonemia, zinc administration has the possibility to improve hyperammonemia [45].

6.4.3. Sodium benzoate, sodium phenylbutyrate, sodium phenylacetate

Sodium benzoate (SB) is metabolized in liver to benzoyl CoA that conjugates with glycine to form hippurate, which is rapidly excreted in urine, thus SB raises ammonia ions' renal excretion [46]. SB has exposed to be as efficient as lactulose and it resembles inexpensive alternative in episodic HE. It is also used in the management of congenital errors of urea synthesis [42].

Sodium phenylbutyrate is metabolized to phenylacetate which reacts with glutamine giving phenylacetyl glutamine, that is consequently excreted in the urine. Excretion of phenylacetyl glutamine results in loss of ammonia ions [47].

6.4.4. Metabolic ammonia scavengers

These drugs have been utilized in management of urea cycle inborn errors for many years. Several agents are available and currently available as promised investigational agents. *Ornithine phenylacetate* has been studied for HE patients but additional clinical information is awaited [48]. *Glyceryl phenylbutyrate* (GPB) that is a prodrug of sodium phenylbutyrate with much lower therapeutic doses needed [49].

6.5. Surgical treatment

Liver transplantation has been shown to improve the brain activity and cognitive function of patients suffering from cirrhosis with or without HE and it improves survival in patients with significant hepatic dysfunction, but the presence of neurologic deficits may result in remarkable morbidity and even death [50].

Conclusion

Development of standard treatment options and addition of newer agents for HE are required due to its negative impact on patient's quality of life, finances and employment. Management of hyperammonemia is essential for treatment of HE, standard treatment with rifaximin and lactulose is effective in reducing ammonia level and improving the condition of HE patient. However, some certain patients cannot withstand the adverse events of these drugs, unable to afford their costs or not responsive to them. In these cases, newer additional agents may be used as effective adjunctive to improve the patient's response.

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