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Hepatic Encephalopathy

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1. Introduction

The liver is the most important organ for the well-functioning of other organs because of its vital role in nutrition, metabolism and secretion. Any disturbance in normal homeostasis of liver as it happens in acute liver failure (ALF) and chronic liver disease (cirrhosis) will lead to extra hepatic manifestations of liver disease, among them one is encephalopathy. And this encephalopathy caused by liver abnormality is known as Hepatic encephalopathy (HE).(1) HE occurs in 50-70% of patients with chronic liver disease and this is one of the sign of decompensated chronic liver disease. Occurrence of HE associated with poor prognosis with survival of approximately 42% at 1 year.(2)

1.1 Definition

Hepatic encephalopathy(HE) is defined as a reversible and metabolically induced neuropsychiatric complication, most commonly associated with cirrhosis, but may also be a complication of acute or chronic liver disease.(3) The affected patients exhibit alterations in psychomotor functions, personality changes, cognitive impairment and disturbed sleep pattern. Although, precise pathophysiologic mechanisms are not well understood, severe liver damage or the presence of Porto-systemic shunts are thought to be the major mechanisms involved.(4)

According to the classification proposed by the working party in 1998, HE can be graded into 3 types:

1. Type A HE (associated with acute liver failure);
2. Type B HE (observed in patients with Porto-systemic bypass and no intrinsic hepato-cellular disease);
3. Type C HE (associated with cirrhosis or portal-hypertension or Porto-systemic shunt).

   Type C HE can be further divided into three categories:

   i. Episodic HE (Spontaneous; recurrent; precipitated)
   ii. Persistent HE (Mild; Severe; Treatment dependent)
   iii. Minimal or Overt HE(3)

Overt HE (OHE) is a syndrome of neuropsychiatric abnormalities that can be detected by bedside clinical tests in contrast to minimal HE (MHE) that requires specific psychometric tests for detection.(5) Defining type-C HE into minimal or overt, episodic or persistent and

precipitated or spontaneous is clinically relevant since the management of each category is very different. Nowadays MHE has been recognized as the major factor in impairing the health related quality of life (HRQOL) in patients with cirrhosis.(6, 7) And MHE has prognostic significance because it predicts the occurrence of overt HE and is not useful predictor for mortality in cirrhosis.(8)

2. Pathophysiology

The pathophysiology of hepatic encephalopathy is intricate and exact mechanisms leading to HE are not clearly understood. Hepatic encephalopathy pathogenesis has many components which include ammonia, inflammatory cytokines, benzodiazepine like compounds and manganese like substances which impair neuronal function.(9) The role of ammonia has dominated explanations for the pathogenesis of HE but it cannot single handedly explain all the neurological changes seen in HE. Evidence regarding other concurrent factors has emerged over the years and it is thought that these factors either work alone or in synergy to cause astrocytes to swell and fluid to accumulate in brain which causes the symptoms of HE(10). Some factors and conditions also appear to precipitate HE (Box A).

2.1 The ammonia theory

Ammonia is produced predominantly from dietary nitrogenous components, bacterial metabolism of these nitrogenous products in the colon and in small intestine from glutamine by glutaminase enzyme.(11) Eventually this ammonia from gastrointestinal tract enters portal circulation for its final destination of urea cycle in the liver to be converted as urea which will subsequently be excreted by kidneys.(12) Under normal conditions, ammonia is eliminated through urea formation in the liver but in patients with acute liver failure, brain and muscle cells are also involved in the metabolism. Elevated levels of ammonia may cause severe toxicity so it must be removed from the body.(13) Because of liver disease and portosystemic collaterals in cirrhosis, ammonia concentration in blood rises hence crosses the blood brain barrier.(14) In Brain, astrocytes are the only cells capable of metabolizing ammonia and express the enzyme glutamine synthase for the conversion of ammonia into glutamine. So, ammonia detoxification in astrocytes leads to accumulation of glutamine which being an osmolyte, causes movement of water inside the astrocyte and causes cerebral edema i-e 'Trojan horse' hypothesis(14-16). Some of the studies had shown the ammonia induced expression of aquaporin water channel on astrocytes. (17)

This has been seen in autopsies of patients with cirrhosis in which brain tissue had shown swollen astrocytes with enlarged nuclei along with displacement of chromatin to the perimeter of the cell, this condition is known as Alzheimer type II astrocytosis.(18) Acute insult of ammonia leads to calcium dependent glutamate release from astrocytes, which causes increased neuronal activity (as seen in Type A HE). A prolonged exposure to ammonia leads to glutamine induced osmotic stress, which causes compensatory release of myoinositol and taurine from the astrocytes, which may lead to down regulation of glutamate receptors and neuroinhibitory state of HE (as seen in Type C HE). Elevated intracellular ammonia levels also results in altered neurotransmission by agonizing GABA tone.(19)

Hyper ammonia lead to abnormal cerebral blood flow and glucose metabolism and this had been seen in studies of single photon emission tomographic (SPECT) in which redistribution of blood flow form cerebral cortex to subcortical regions had been demonstrated. This abnormality lead to different HE features.(17, 20)

2.2 Inflammation

The partial credit also goes to the inflammation because majority of the cirrhotic patients in the presence of infection develop the HE. This association of markers of inflammatory response in state of systemic inflammatory response (SIRS) and HE, has been demonstrated in different studies.(21, 22) In one of the clinical study, it has been seen that HE or neuropsychological dysfunction improves after the resolution of SIRS.(23) Despite this exact mechanism of inflammation leading to HE is still not known as yet, but possibly it is hypothesized that cytokine mediated changes in blood brain barrier (BBB) permeability, altered glutamate uptake by astrocyte and altered expression of GABA receptors.(23)

TNF released in response to inflammation has been correlated to the symptoms of HE. It causes Astrocytes to release inflammatory cytokines (i-e IL-1, IL-6) which impairs the endothelial Blood-Brain barrier and increases ammonia diffusion into astrocytes. (24)

2.3 Neurosteroids and GABA/Benzodiazepine receptor complex theory

Neurosteroids are mainly produced by myelinating glial cells in response to increased expression of peripheral type benzodiazepine receptor (Trasnslocator proteins), which are activated by ammonia, inflammation and manganese. Neurosteroids increase chloride influx and thereby enhance GABAergic tone, causing symptoms in patients with Type C HE.(25, 26)

GABA mediates its action through GABA-receptor complex (GRC) and acts as an inhibitory neurotransmitter. Increased sensitivity of the trasnslocator proteins also enhances the activation of GABA-GRC complex, hence causing inhibition of neurotransmission.(14, 27) Increased GABAergic tone has been associated with the pathogenesis of HE and this was proved by the reports which had revealed the beneficial effects of benzodiazepine antagonist (Flumazenil).(28) There is an excess of benzodiazepine like compounds in HE that are derived from synthesis by intestinal flora, dietary vegetables and medications.(29, 30) Moreover natural benzodiazepines also accumulate in brain and furthermore cirrhotic patients have the poor capability of clearing the benzodiazepine like compounds.(31) These compounds bind to GABA receptor complex inducing GABA release and neuro-inhibition. A study by Stewart et al group had shown that ammonia itself bind to the GABA receptor complex.(32) It may also potentiate benzodiazepines by up regulating expression of peripheral type benzodiazepine receptor that trigger synthesis of neuro-steroids, which are strong GABA agonists.(33)

Hence GABAergic tone is more likely attributed to elevated levels of benzodiazepines like compounds in patients with cirrhosis.

BCCA and false neurotransmitter theory: Brain neurotransmission is regulated by CNS concentration of amino acids and their precursor. In cirrhotic patients, plasma concentrations of aromatic amino acids (tryptophan, tyrosine, and phenalanine) are elevated and branch

chain amino acids (Leucine, isoleucine and valine) concentration are reduced. Aromatic as well as branch chain amino acids share a common transport mechanism into the CNS and as a consequence of increased of aromatic amino acids, neuronal levels may be increased leading to the production of false neurotransmitter subsequently leading to HE.(34)

Serotonin theory: Serotonin, a neurotransmitter which is widely distributed in CNS, has been implicated in the pathogenesis of HE. In cirrhotic patients it has been seen that serotonin metabolism is altered hence leading to serotonergic synaptic deficit. Serotonergic pathway in brain is important for regulation of sleep, locomotion and circadian rhythmicity.(35) Serotonin metabolism is intricately and selectively sensitive to the degree of portosystemic shunting and hyperammonaemia, therefore suggesting a role for serotonin in early neuropsychiatric symptoms of HE.(36)

Zinc theory: Zinc (Zn) element is a component/substrate of urea cycle enzymes. It is assumed that this element is reduced in patients with liver cirrhosis. Zn supplementation increases activities of ornithine transcarbamalyse increasing excretion of ammonia ions. Interestingly till now there is conflicting evidence for this hypothesis of Zn supplementation in He patients.(37, 38)

2.4 Oxidative and nitrosative stress

Exposure of astrocytes to ammonia, inflammatory cytokines, hyponatremia and benzodiazepines leads to enhanced production of RNS & ROS via the Calcium dependent N-methyl-D-aspartate (NMDA) pathway. RNS and ROS cause tyrosine nitration, leading to altered BBB permeability and astrocyte swelling. (39, 40)

2.5 Manganese theory

In normal healthy individuals, Maganese is cleared by liver and excreted into the bile. Manganese is known to stimulate the Translocator proteins located on astrocytes, leading to enhanced neurosteroid synthesis. In cirrhotic patients, it accumulates in the basal ganglia because of decreased excretion of Maganese due to portosystemic shunting and promotes formation of Alzheimer's type 2 astrocytes.(41) Brain magnetic resonance imaging (MRI) in cirrhotic patients has shown changes which are due to accumulation of Maganese in basal ganglia particularly in the palladium, putamen and caudate nucleus.(41)

3. Precipitating factors: (Box A)

The Most of HE episodes are precipitated by an event rather than spontaneous, with infection anywhere in body being the common, though its frequency is decreasing. Hence careful history and examination are necessary to identify the precipitating or contributing factors for HE, most of the time these factors are evident.(42)

Gastrointestinal bleeding commonly precipitates the HE even if it is controlled or stopped bleeding. Sometimes occult chronic gastrointestinal blood loss can also lead to HE, which needs to be evaluated and treated accordingly.(42)

Dehydration is again a very common precipitating factor in cirrhotic patients leading to HE because some of the patients ascites, are diuretics. And aggressive diuresis do induce dehydration leading to metabolic alkalosis and electrolyte imbalances.

• GI Bleeding	• Constipation
• Electrolyte imbalance	• Hypovolemia
• Trauma	• Dehydration
• Infection	• Medications (sedatives, diuretics, psychotropic,)
• Sepsis	• Uremia
• Dietary protein Overload	

Box A. Precipitating Factors for HE

It has also been seen that transjuglar intrahepatic portosystemic shunt (TIPS) in some of the cases can lead to HE. Few other precipitating factors which can sometimes lead to HE, need to be looked into by taking careful history and examination and shown in Box (A)

4. Clinical features

The clinical signs and symptoms of HE may range from mild cognitive impairment to profound coma. These include forgetfulness, alteration in sleep-wake cycle, changes in personality and emotions, hyperreflexia and drowsiness. In more severe cases disorientation, constructional apraxia , asterixis, seizures and eventually coma may develop.(43) It is very important to exclude other causes of altered mental status or encephalopathy (Box B) in suspected patients for appropriate management of HE.

- Subdural Hematoma
- Drug or alcohol intoxication
- Wilson's disease
- Hypoglycemia
- Wernicke's encephalopathy
- CNS Sepsis
- Postictal Confusion

Box B. Differential Diagnosis for HE

Clinically, the most commonly employed criteria used for grading is the West Haven criteria (Table 1) which defines HE semi quantitatively into four grades, based on the presence of specific clinical signs and symptoms and their severity. Further classification of comastose or unconscious patients can be done by using Glasgow Coma Scale which provides a more objective assessment of the conscious state of the patient.(4)

5. Diagnosis

Checking for Elevated Blood ammonia levels is the most commonly used parameter for assessment, but they may also be elevated due to other possible causes (i-e tourniquet use, delayed processing and cooling of sample, disorders related to ammonia and proline metabolism). In acute liver failure, arterial ammonia levels >150 mg/dl may be predictive of brain edema and herniation. However, measurement of arterial ammonia over venous ammonia offers no advantage in Chronic liver disease.(3, 44)

Grade	Intellectual function	Neuromuscular function
0	Normal	Minor abnormalities
1	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination
2	Changes in sleep-wake cycle, cognitive dysfunction, lethargy, behavioral changes	Asterixis, Speech abnormalities, Ataxic gait
3	Disorientation, unconsciousness, amnesia	Nystagmus, Clonus, Muscular rigidity
4	Stupor and Coma	Unresponsiveness to noxious stimuli, Oculocephalic reflex

Table 1. West Haven classification for grading of HE(1)

Neuropsychometric evaluation usually is done via 'paper and pencil tests' and 'computerized tests'. The routinely used paper and pencil tests include psychometric HE scores (PHES) and The Repeatable Battery for the Assessment of neurological status (RBANS). PHES has been endorsed as a 'gold standard' for diagnosis of MHE and is used to diagnose the cognitive changes that characterize MHE. RBANS in addition to diagnosing the cognitive issues, also scores patient's memory.(45) Some computerized psychometric tests like 'The inhibitory control test' and 'CDR computerized assessment system' are gaining popularity as promising diagnostic tests due to their effectiveness and convenience(46). However, the value of these psychometric tests is limited by methodological problems, training and education, demographic dependence and lack of standardization.(43)

Neurophysiological assessment is done via Electroencephalography (EEG) and the Critical flicker frequency test (CFF). EEG is associated with decreased electrical activity and shows diffuse slowing of alpha waves with eventual development of delta waves.(47) CCF, a light based test, is used for a rapid and reliable quantification of HE. Based on the principle of hepatic retinopathy, it represents the frequency at which discrete light pulses are first perceived by the patient. A CCF of below 39 Hz is diagnostic for MHE and the test results are not dependent on sex, occupation and education level.(48)

Imaging Modalities include different Magnetic resonance techniques(T1-weighted imaging, proton spectroscopy, magnetic transfer ratio, T2- weighted FLAIR sequence and diffusion weighted imaging) to measure cerebral edema, changes in brain activity and concentration of different substances(i-e glutamine, choline). A CT scan can be used to exclude subdural hematoma or other cerebrovascular events that may mimic HE.(48)

6. Treatment

HE treatment has evolved over the last 5 decades and medical science had seen many breakthroughs during this tenure. Treatment can be tailored around multiple key management principles which parallel the pathophysiology of the disease and these principles are:(42)

Management of precipitating factors,

Reduction of ammonia

Modulation intestinal flora

Modulation of neurotransmission

Correction of nutritional deficiencies

Reduction of inflammation/infection

Many treatment options are available for the treatment of HE with the mainstay to eliminate the underlying factors that precipitate HE. It is recommended that all patients should receive the empiric therapy (Box C) for HE, based on the principle of reducing the production and absorption of ammonia. Some strategies that are commonly applied to stop precipitating events are the following:

1. in patients with HE induced by gastrointestinal hemorrhage, stop the bleeding with vasoactive drugs, an endoscopic therapy or an angiographic shunt (TIPS), correct the anemia with a blood transfusion and use a nasogastric tube to facilitate upper gastrointestinal cleansing;
2. Promptly start Antibiotics therapy for infections;
3. Resolve constipation by cathartic and/or bowel enema, electrolyte abnormalities by discontinuing diuretics and correct hypo- or hyperkalemia;
4. Correct deterioration of renal function by stopping diuretics, treating dehydration and discontinuing nephrotoxic drugs
5. if HE is precipitated by the administration of exogenous sedatives, discontinue benzodiazepines and start flumazenil.(49)

- Lactulose (15-30ml orally, twice daily)
- Rifaximin (550mg orally, twice daily)
- Neomycin (500mg orally, four times daily)
- Metronidazole (250mg orally, four times daily)
- Vancomycin (250mg orally, four times daily)
- Sodium Benzoate(5 mg orally, twice daily)
- Flumazenil (1-3 mg IV)

Box C. Empiric Treatment for Hepatic encephalopathy(48)

7. Reduction of ammonia and modulation of neurotransmission

7.1 Nonadsorable disaccharides

Nonadsorable disaccharides (Lacutlose and Lactitol) especially Lactulose are considered the first line therapy for HE despite lack of well-designed randomized controlled trial. They are metabolized by the colonic bacteria and form by products that reduce the colonic PH, hence interfering with mucosal uptake of glutamine and reducing the synthesis and absorption of ammonia. There are other proposed mechanism of lactulose in HE such as lactulose modifies the colonic flora which in turn results in shift of urease containing bacteria with lactobacillus, fourfold increased fecal nitrogen excretion due to increase stool volume and it

also helps in reduction of formation potentially toxic short chain fatty acids e.g propionate or butyrate.(50-53)

Lactulose can also be administered orally through a nasogastric tube to unresponsive patients as well as rectally through enemas.

The most common side effects associated with over use include dehydration, electrolyte imbalance and abdominal cramping. Previously it is known to cause no improvement in psychometric test performance and mortality(54). Few years back a study conducted in India had shown significant improvement and health related quality of life and psychometric improvement in patients with HE especially with minimal HE.(7)

The lactulose has got some role in preventing recurrent episodes of HE. It was proved by an open label RCT study from India by Sarin group, which suggested that lactulose is also effective in preventing recurrent episodes of HE.(55)

The recommended dose of lactulose is about 15-30ml given twice a day. Lactitol, an alternative to lactulose is considered equally effective and is used in patients intolerant of lactulose, but it is not available in some countries.(56, 57)

7.2 Antibiotics

Patients intolerant to nonabsorable disaccharides are generally treated with antibiotics, to suppress the bacteria involved in ammonia genesis. There are few antibiotics which have been used for the treatment of HE which had shown limited benefit, which include neomycin, metronidazole, oral vancomycin and very recently Rifaximin.(54)

In fact neomycin was used for treatment of HE for many years based on earlier studies then in early 1990's a double blind randomized controlled trial had no improvement in HE. And also because of its limited systemic absorption which would lead to ototoxicity and nephrotoxicity has lost its use in HE in liver cirrhosis. (58)

Rifaximin, a minimally absorbed oral antibiotic has been approved by FDA for the treatment of chronic HE, on the basis of results of a multicenter, randomized, controlled trials and met analysis.(59) Recently a RCT had shown benefit in prevention of recurrent hepatic encephalopathy over period of 6 months follow up. Subsequently further studies had also shown role of Rifaximin in improving the health related quality of life in patients with HE similarly improvement in Psychometric tests and simulated driving tests.(60-62) The use of this antibiotic is increasing due to few adverse effects and no known drug interactions. The recommended adult daily dose is 1200 mg/day, usually in three divided doses.

Some small studies have also reported the effectiveness of vancomycin and metronidazole, but the data to support their use is not enough.(54)

7.3 Other agents

Acarbose; a hypoglycemic agent and an intestinal a-glucosidase inhibitor which causes decrease in blood ammonia levels and improves mild HE in patients with cirrhosis.(63) It has also been hypothesized that Acarbose promotes the proliferation of intestinal

saccharolytic bacterial flora while reducing proteolytic flora that produce mercaptans, benzodiazepine like substances and ammonia as well. This theory was answered in a randomized cross over trial by Gentile S et al group in Italy.(63)

Probiotics and synbiotics modify the gut bacterial flora and reduce ammonia levels. Their use however is still being investigated.(64)

7.4 Agents causing alteration in ammonia metabolism (L-Ornithine L-Aspartate and benzyl benzoate)

Urea cycle plays a key role in ammonia metabolism and its excretion by forming urea in periportal hepatocytes or synthesis of glutamine in perivenous hepatocytes. But in cirrhosis, the activities of carbamyl phosphate synthetase enzyme (Urea synthesis) and of glutamine synthesis (glutamine synthesis) are impaired hence as compensation glutamine increased which in turn lead to increased level of ammonia. Therefore ornithine aspartate and benzoate has been used for reducing the ammonia levels by increasing the metabolism to glutamine and hippurate respectively.

L-ornithine-L-aspartate (LOLA) activates urea cycle and enhances ammonia clearance. LOLA induces an increase of liver and muscle ammonia metabolism, leading to decreased blood levels, and is able to cross the blood-brain barrier, increasing the cerebral ammonia disposal.(65) One or two sachets of LOLA should be administered three times daily.(4)

Other ammonia excretors like sodium benzoate, sodium phenyl acetate and sodium phenyl butyrate are also reported to show improvement but clear efficacy has not been established yet. Sodium phenyl acetate and Ammonal are the only drugs approved by the Food and Drug Administration for the treatment of acute hyperammonemia and associated encephalopathy in patients with urea cycle disorders.(66)

7.5 Agents used in neurotransmission hypothesis

Branch chain amino acids (BCCA): As it has been hypothesized that in liver cirrhosis, there has been reversal of aromatic amino acids (AAA) to BCCA which could lead to encephalopathy in patients with cirrhosis. Encephalopathy is presumably caused by increase in levels of AAA for monoamine neurotransmission which lead to transformed neuronal excitability and causing HE. Hence numbers of studies have been done to evaluate the effects of BCCA on HE. BCCA can be given orally as well as in infusion form.(67, 68)

Agents used for GABA hypothesis pathway: GABA receptor complex is the principal inhibitory network in nervous system and seems to be a contributor to neuronal inhibition in HE. This GABA receptor complex contains barbiturates and benzodiazepine receptor sites, chloride channels and a GABA binding site. In cirrhosis, there is an evidence for increase in benzodiazepine receptor ligands in subjects with HE, therefore effects of benzodiazepine receptor antagonist have been evaluated.(69, 70)

Flumazenil, a $GABA_A$ receptor antagonist also improves the symptoms in patients with grade 3 or 4 HE but its use is limited due to adverse effects(71). It has been seen that response to treatment with flumazenil is rapid onset with few minutes and then with few hours, more than half of these patients deteriorated with 2-3 hours.(72, 73) Because of its

short duration effect and variable results of different studies, flumazenil cannot be recommended as routine therapy.

7.6 Other treatment options

7.6.1 Nutritional intervention

In the past, dietary protein restriction was considered an important component of the treatment of HE. Recent evidence however suggests that excessive restriction can raise serum ammonia levels, as a result of reduced muscular ammonia metabolism.(74) It has also been seen that majority of the patients with advanced liver disease had severe protein calorie malnutrition due to multifactorial reasons including the decreased oral intake, catabolic state etc.(75)

A high-protein diet is therefore recommended for improving the symptoms of HE. The European society for Parenteral and Enteral nutrition recommended an energy intake of 35/40 kcal/kg body weight per day and that patients must eat at least 1.2g/kg of protein daily along with Branched-chain amino acids (BCAA's) and vegetable-based protein.(76) Vegetable and dairy based proteins are preferred to animal proteins because of a high calorie-to-nitrogen ratio. Vegetable based proteins increase colonic motility and enhances intestinal nitrogen clearance. They also reduce colonic PH, which prevents ammonia absorption into gut.(77)

Zinc increases the activity of ornithine transcarbamylase (an enzyme in urea cycle) so zinc supplementation is also recommended for HE especially in patients who don't show any response to lactulose or neomycin.(38)

7.6.2 Prognosis once recovered from HE

Patients who recovered from HE can have persistent and cumulative neurologic deficits despite achieving normal mental status after receiving medical therapy. Study for North America had shown that patients with overt HE had persistent deficits in working memory, response inhibition and learning when assessed by psychometric tests. Recurrent episodes are associated with severity of underlying disease.(78, 79)

Conclusion: HE includes variety of neuropsychiatric symptoms and signs among patients with CLD leading to liver failure. Occurrence of HE indicates worse prognosis and should be kept on liver transplant list wherever it is available. Initial treatment includes the identification and correction of precipitating factors such as electrolyte imbalances, GI bleeding, medications, and sepsis. The main treatment modalities include the nonabsorbable disaccharide, principally lactulose and antibiotics like metronidazole or Rifaximin nowadays.

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