Hepatic encephalopathy (HE) in end-stage liver disease (ESLD) such as cirrhosis of the liver is a reversible and recurrent disorder of neurological function. It is caused by liver disease portosystemic shunting of blood or both.

Common causes of ESLD in the USA are alcohol abuse, chronic hepatitis C, B and metabolic liver disease. The main clinical features of HE, namely deterioration of intellectual function, sleep disorders and asterixis are described. Histological changes, and commonly incriminated toxins in pathogenesis of HE are discussed.

Factors which precipitate HE, their mechanism of action and importance of their prevention and correction in the management of HE are emphasized. Principles in the treatment of HE and the role of liver transplantation in the treatment of HE in ESLD are pointed out. Controversial therapeutic modalities, such as bioartificial liver (MARS) system, etc., are briefly dealt with.

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is a commonly encountered disorder because end-stage liver disease (ESLD) is quite prevalent. The overall incidence of (ESLD) cirrhosis in the United States is approximately 360 per 100,000 population. Common causes of ESLD in the USA are alcohol abuse, chronic hepatitis C, B and metabolic liver diseases (Hemochromatosis, Wilson’s disease, nonalcoholic fatty liver disease, etc.).

A patient with HE not only becomes a nonproductive member for his or her family but also becomes a burden on his family and society. The survival probability in a cirrhotic patient after the first episode of HE is 42% at one year and 23% at 3 years (1). The liver performs a large number of vital metabolic and biochemical functions. In ESLD (cirrhosis) a number of these functions are deranged and these result in multiorgan dysfunction. Hepatic encephalopathy (HE) is the consequence of these abnormalities.

**CLINICAL FEATURES OF HE**
The main clinical features of hepatic encephalopathy (HE) are as follows:

**The Four Grades of HE**
Grade 1 is the mildest form and it is characterized by mild intellectual deterioration (mental confusion, memory and concentration loss). In grades 2 and 3 intellectual function deteriorates further; and in grade 4 (HE) the patient is comatose.

Another grade of (HE) is minimal or subclinical encephalopathy. These patients have apparently normal intellectual function but exhibit abnormalities on psychomotor testing. Up to 5%–15% of patients with cirrhosis have abnormal number connection test or abnormal EEG (2–5).

**Sleep Disorder**
Disturbances in sleep are quite common in cirrhosis (ESLD). Some of these patients are drowsy and others have altered sleep rhythm (they sleep during the day and keep awake at night). These disturbances have been attributed to abnormalities in melatonin metabolism (6). Melatonin is said to modulate sleep rhythm. Serum melatonin levels are high during the day in HE when they should be low and relatively high at night (6).

**Personality Changes**
Patients with HE may be mentally slow, confused and may exhibit inappropriate behavior. At times they may become violent.

**Asterixis**
Asterixis is a flapping tremor of outstretched and dorsiflexed hands. It is quite suggestive but not diagnostic of HE. Asterixis can be seen in other disorders such as respiratory failure, uremia and hypoglycemia.

**Hyperventilation**
Noxious substances such as ammonia, mercaptans, etc. escape detoxification in liver and reach the brain through portosystemic shunts and cause hyperventilation and respiratory alkalosis.

**HISTOLOGICAL CHANGES IN HE (PSE)**
Swelling of astrocytes is present frequently in HE (PSE). It plays an important role in the development of HE. This swelling of astrocytes is due to an increase in osmolarity of intracellular fluid of astrocytes and it is caused by the metabolism of ammonia to glutamine (7).

**PATHOGENESIS OF HE (PSE)**
A large number of toxins have been incriminated in the pathogenesis of HE. The extent of their role alone or in combination is not clear. The list of toxins discussed in the following paragraphs is by no means comprehensive. The most common incriminating toxins and their role in HE is as follows:

1. Ammonia is one of the most frequently accused toxins (8). Most of the ammonia is produced by action of bacteria on undigested proteins and secreted urea in the gastrointestinal tract (9). H. pylori may metabolize urea in the stomach and produce ammonia in infected
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persons (10). Ammonia is also produced in the kidney by the action of glutaminase on glutamine. In hypokalemia the ammonia production in nephrons is increased and its concentration is increased in renal veins (11,12). Hypokalemia and hypokalemic alkalosis is common in decompensated cirrhosis because of overzealous use of diuretics such as furosemide, thiazides, and secondary hyperaldosteronism. The above mentioned factors and muscle wasting which is common in cirrhics increase blood ammonia level. Evidence favoring ammonia as a pathogenetic factor in PSE is the fact that it is increased in 80%–90% of patients with decompensated cirrhosis and HE. Coma and HE are seen in patients with urea cycle enzyme level abnormalities. These patients have high blood ammonia levels. Evidence against ammonia is that it is not elevated in all patients with PSE and there is no exact relationship between arterial blood ammonia concentration and the level of coma, but the blood ammonia levels should be interpreted in light of the acid base status of the patient. In hypokalemic alkalosis the ammonia is transferred from blood and extracellular fluid to the intracellular fluid where it exerts its harmful effects.

2. Mercaptans are methionine derivatives. They are formed in the gut by the action of bacteria on undigested proteins. Mercaptans are absorbed and escape detoxification in the liver due to portosystemic shunting of blood (13–15).

3. Other noxious agents which accumulate in the body in end-stage liver disease (cirrhosis) and are believed to induce HE are short chain fatty acids, phenols, serotonin, melatonin, and manganese. Accumulation of manganese causes hyperintensity of globus pallidus on MRI (6,13,16).

4. Hypoglycemia: The brain uses mainly glucose for its energy need. The liver provides glucose through glycogenolysis and gluconeogenesis. A cirrhotic liver may not be able to perform these processes adequately and hypoglycemia may result. Hypoglycemia occurs more frequently in acute fulminant hepatic failure than in cirrhosis.

5. Abnormalities of some areas of brain perfusion occur through activation of nitric oxide synthetase and synthesis of nitric oxide in cirrhics with HE. Nitric oxide causes vasodilation.

6. Role of false neurotransmitters in HE: Increase in concentration of aromatic amino acids (tryptophan, tyrosine and phenyl alanine) and decrease in the concentration of branched chain amino acids (leucine, isoleucine and valine) in blood and brain results in the formation of false neurotransmitter amines such as octopamine. These false neurotransmitters replace the true neurotransmitters (dopamine and norepinephrine). False neurotransmitters are not efficient and when they replace true neurotransmitters neurological dysfunction (17) results.

7. Gamma Aminobutyric Acid (GABA)/Benzodiazepine (BZ)/Chloride Channel Complex: This is a glycoprotein complex and it plays a key role in the causation of HE (15,9). This complex is located in the postsynaptic membrane. It is subdivided into a GABA receptor unit, Benzodiazepine (BZ) receptor unit and chloride channel. GABA is an inhibitory neurotransmitter in the brain. GABA and BZ are produced in the gut by the action of bacteria on unabsorbed proteins (18) and some of these neuronal inhibitors are absorbed into the blood. Exogenous benzodiazepines taken by cirrhics also precipitate HE. Attachment of GABA and benzodiazepines to their respective receptor units increases neuronal membrane permeability to chloride by opening chloride channels. Chloride enters the neuron causing membrane hyperpolarization. This is the mechanism of GABA-ergic inhibition of neurotransmission.

Factors Which Precipitate HE (PSE)

It is very important to consider the role of precipitating factors when a stable and compensated cirrhotic develops HE (PSE). If you prevent these precipitating factors you shall prevent HE (PSE) in the majority of compensated cirrhics.

The following factors commonly precipitate HE in stable cirrhics (19):

1. Azotemia: 25%–30% episodes of HE in cirrhics are precipitated by azotemia. Azotemia in cirrhics is produced frequently by overzealous use of potent diuretics such as furosemide. These agents as well as vomiting and diarrhea cause contraction of effective circulatory volume, secondary hyperaldos-
It cannot be over emphasized that if a stable cirrhotic develops HE for no obvious reason please have a high index of suspicion for the following:

- Azotemia (perhaps caused by overzealous use of diuretics)
- Use of tranquilizers or analgesics such as benzodiazepines and opiates
- GI hemorrhage
- Infection
- Hypovolemia
- Hypokalemic alkalosis

These are all potentially correctable causes. If you correct them promptly you will reverse HE in most cases.

**ROLE OF CT AND MR IMAGING OF BRAIN IN HE**

- CT and MRI are helpful in ruling out intracranial lesions such as bleeding or abscess. These lesions may produce signs and symptoms similar to those of HE.
- MRI often demonstrates hyperintensity of globus pallidus which is probably due to increased manganese level.
- MR spectroscopy detects neurometabolic changes and may be used as a measure of lactulose effect.

**ELECTROENCEPHLOGRAM (EEG) IN HE**

- EEG shows slowing of waves from 8-13 cycles per second to 4 cycles per second. These changes are nonspecific and are also seen in metabolic disorders such as uremia and hypoglycemia.

**PRINCIPLES IN THE TREATMENT OF HE (PSE)**

1. General and supportive measures are extremely important in the management of HE.
2. Treatment of precipitating factors as already discussed is of paramount importance.
3. Correct fluid and electrolyte imbalance. These measures include management of hypovolemia, hypokalemia, severe hyponatremia, significant hypophosphatemia.
4. Correct hypoglycemia, with IV glucose if necessary.
5. Avoid sedatives, tranquilizers and opiate anal-

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gesics if possible. If the use of these agents becomes necessary for example, in a patient who is violent or convulsing then these agents should be used only in the smallest possible dose and for the smallest possible period and choose a tranquilizer which is minimally affected by liver disease such as oxazepam or lorazepam.

6. Treat GI bleeding. Endoscopic therapy of upper GI bleeding is quite effective. Bleeding varices are treated with band ligation or sclerotherapy and IV octreotide infusion. Peptic ulcer bleeding is treated with injection of 1:10,000 epinephrine into the margins of the bleeding ulcer and ulcer crater with a sclerotherapy needle. These patients frequently have coagulopathy and thrombocytopenia. These coagulation abnormalities should be promptly corrected with IV infusion of platelets and fresh frozen plasma. Recurrent upper GI bleeding from portal hypertensive gastropathy is controlled with oral propranolol and argon plasma coagulator therapy.

7. Infection is a commonly overlooked precipitant of HE and its early detection and treatment reverses HE in a large percentage of cases. Spontaneous bacterial peritonitis (SBP) and urinary tract infection are common culprits, helicobacter infection has also been a suspect. When a cirrhotic with ascites and HE is seen, an urgent diagnostic paracentesis, neutrophil count and culture of ascetic fluid is mandatory. If the ascetic fluid neutrophil count is 250/mL or more, treatment with a third generation cephalosporin such as cefotaxime is started immediately.

8. A low protein diet of 20 gm a day is recommended in severe HE. The role of protein as a precipitant of HE has already been discussed (19); vegetable proteins are preferred because they produce less ammonia (20). Cirrhotics have decreased muscle mass and muscles metabolize ammonia (21). Therefore protein restriction in HE should be temporary. As soon as HE improves, the protein intake should be gradually increased to 0.8–1 gm/kg body weight daily (22) in order to avoid further decrease in muscle mass.

9. Lactulose: It is a nonabsorbable synthetic disaccharide. It is the mainstay of therapy in HE although it has not yet passed the test of evidence-based medicine. The dose is 45–90 mL by mouth per day to produce 2–4 loose stools a day. Lactulose is broken down by colonic bacteria into lactic acid and acetic acid. These acids lower the stool pH to 5 or less and convert the absorbable NH$_3$ into unabsorbable NH$_4$. Lactulose also causes osmotic diarrhea and the unabsorbed ammonia in NH$_4$ form is eliminated in diarrheal stool. This lowers blood ammonia level. Lactulose also alters colonic flora by replacing urease producing bacteria with lactobacillus (23,24). Lactulose 300 mL plus tap water 700 mL have also been used as a retention enema in HE with good results. Lactitol is another compound similar to lactulose; it is used in HE and is more palatable.

10. Zinc: Zinc deficiency is common in cirrhotics due to loss of zinc in urine (25) and it enhances conversion of amino acid into urea (26). Zinc sulfate 600mg by mouth daily for several weeks is beneficial in these patients (22).

FORMS OF THERAPY NOT WELL ESTABLISHED IN HE

- L-dopa (dopamine precursor).
- Bromocriptine (dopamine agonist).
- L-ornithine/L-aspartate (It stimulates ureagenesis and reduces blood ammonia level (27).
- Sodium Benzoate combines with NH$_3$ and forms Hippurate (This lowers blood ammonia and is helpful in HE).
- Benzodiazepine Antagonists (useful in cases where exogenous benzodiazepines have been ingested).

ANTIBIOTICS

Matronidazole 250mg orally every 8 hours is also quite helpful but it should only be given for a short time (7–10 days). A short oral course of oral neomycin is also effective. Prolonged use of neomycin carries a risk of ototoxicity and nephrotoxicity.

LIVER TRANSPLANTATION

It is the final solution in refractory HE (PSE). It is expensive and donor organs are in short supply.

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A study of usefulness of the molecular absorbent recirculation system (MARS) in refractory HE is being carried out in the USA (29).

References

There isn’t a physician who hasn’t at least one
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