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# Identification, Prevention and Management of Risks Associated With Hepatic Encephalopathy -A Review

Hina Yasmeen*, Wafa Batool Shah*, Khawaja Tahir Mehmood**

* Department Of Pharmacy, Lahore College For Women University.
** Drug Testing Lab, Lahore

**Abstract:**
Hepatic encephalopathy (HE) is a neuropsychiatric complication of either acute or chronic hepatic insufficiency. Aim was to analyze the precipitating factors of hepatic encephalopathy and to determine therapeutic approach for treatment of HE. A retrospective study was carried out in Sir Ganga Raam Hospital, Mayo Hospital and Jinnah Hospital Lahore from 15 June 2010 to 15 July 2010. 30 admitted patients having hepatic encephalopathy were probed into for precipitating factors, based on history, clinical examination and laboratory methods. Upper GI Bleeding (90%), Constipation (86.67%) and Infection (83.33%) stood out as the most common risk factors. Other common associations were hepatic disorder (80%), Ascites (46.67%), Electrolyte imbalance (80%), renal disorder (76.67%), and high mortality rate (63.33%).11 patients recovered and were discharged while 19 patients expired. Majority of patients expired were in Grade III and IV of Hepatic encephalopathy. Prophylactic use of beta-blockers and nitrates along with prompt control of infection and prevention of constipation by laxatives needs to be given importance. Sedatives and diuretics should be use carefully. There is a definite need for health education in patients with cirrhosis regarding the risk of HE and its precipitating factors and a proper advice to them that can be best delivered by the Pharmacist.

**Key Words:** *Hepatic Encephalopathy, Precipitating factors, Constipation.*

## Introduction

Hepatic encephalopathy (sometimes portosystemic encephalopathy) is the occurrence of confusion, altered level of consciousness and coma as a result of liver failure. In the advanced stages it is called hepatic coma. It may be triggered by an alcohol binge, a drug, or another stress in people who have a long-standing liver disorder. Doctors base the diagnosis on results of a physical examination, electroencephalography, and blood tests. Eliminating the trigger and reducing protein in the diet may help symptoms resolve.

## Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome characterized by neuronal inhibition and damage probably by chronic accumulation of endotoxins. The production of tumor necrosis factor-a (TNF-a) is of the earliest events in hepatocyte injury, which trigger cytokine production, damage hepatocytes and Kupffer cells release transforming growth factor b which initiate fibrogenesis as the healing response [1].

Hepatic encephalopathy is a syndrome of neuropsychiatric dysfunction caused by Porto systemic venous shunting with or without the presence of intrinsic liver disease. Clinical presentations are variable ranging from an abnormal sleep pattern to somnolence and deep coma. Decerebrate and decorticate posturing, have been rarely reported with hepatic encephalopathy. The physician should be aware that decerebration and decortication posture can occur with hepatic encephalopathy and can be reversible [2]. It can be divided into two primary components: overt HE (OHE) and minimal HE (MHE). OHE can be diagnosed clinically through a constellation of signs and symptoms, whereas MHE requires specialized testing. MHE is manifested by impairment in specialized testing and is considered by most of the clinicians to be a preclinical stage of OHE [3]. It includes the spectrum of potentially reversible neuropsychiatric abnormalities such as personality changes, intellectual impairment, and a depressed level of consciousness seen in patients with liver dysfunction after exclusion of unrelated neurological and/or metabolic abnormalities [4].

**Signs and symptoms**

More severe forms of hepatic encephalopathy lead to a worsening level of consciousness, from lethargy to somnolence and eventually coma. In the intermediate stages, a characteristic jerking movement of the limbs is observed (asterixis); this disappears as the somnolence worsens. There is disorientation and amnesia, and uninhibited behavior may occur. Coma and seizures represent the most advanced stage; cerebral edema (swelling of the brain tissue) leads to death [5]. Encephalopathy often occurs together with other symptoms and signs of liver failure. These may include jaundice (yellow discoloration of the skin and the whites of the eyes), ascites (fluid accumulation in the abdominal cavity), and peripheral edema (swelling of the legs due to fluid build-up in the skin). The tendon reflexes may be exaggerated, and in severe encephalopathy the plantar reflex may be abnormal (extensor plantars or Babinksi's sign). A particular smell (*foetor hepaticus*) may be detected [7]. The symptoms of hepatic encephalopathy may also derive from other conditions, such as cerebral hemorrhage and seizures (both of which are more common in chronic liver disease). A CT scan of the brain may be required to exclude hemorrhage, and if seizure activity is suspected an electroencephalograph (EEG) study may be performed [5].

**Pathophysiology**

Hepatic encephalopathy is a syndrome whose pathophysiology is poorly understood, for which we lack high-quality diagnostic tests and markers, and whose treatment has improved only slightly over the last several decades. Serum ammonia levels remain the diagnostic gold standard [6]. There are various explanations why liver dysfunction or portosystemic shunting might lead to encephalopathy. In healthy subjects, nitrogen-containing compounds from the intestine, generated by gut bacteria from food, are transported by the portal vein to the liver, where 80–90% is metabolized and/or excreted immediately. This process is impaired in all subtypes of hepatic encephalopathy, either because the hepatocytes (liver cells) are incapable of metabolizing the waste products or because portal venous blood bypasses the liver through collateral circulation or a medically constructed shunt. Nitrogenous waste products accumulate in the systemic circulation. The most important waste product is ammonia ($NH_3$). This small molecule crosses the blood-brain barrier and is absorbed and metabolized by the astrocytes, a population of cells in the brain that constitutes 30% of the cerebral cortex. Astrocytes become swollen, there is increased activity of the inhibitory γ-aminobutyric acid (GABA) system, and the energy supply to other brain cells is decreased. Despite numerous studies demonstrating the central role of ammonia, ammonia levels don't always correlate with the severity of the encephalopathy; it is suspected that this means that more ammonia has already been absorbed into the brain in those with severe symptoms whose serum levels are relatively low [5, 7]. GABA is the main inhibitory neurotransmitter in humans and acts through binding to the GAB receptor complex (GRC). Elevated levels of endogenous benzodiazepines as well as other neurosteroids lead to inhibition of neurotransmission. Changes in the GRC as well as cerebral GABA levels have also been reported in HE [32]

**Diagnosis**

The diagnosis of hepatic encephalopathy requires the presence of a liver problem and the exclusion of an alternative explanation for the symptoms. Blood tests (ammonia levels) may assist in the diagnosis. Often, attacks are precipitated by an intercurrent problem, such as infection or constipation [7]. Diagnostic techniques for hepatic encephalopathy range from simple scales to sophisticated tools. Techniques for the clinical, psychometric and neurophysiologic evaluation of hepatic encephalopathy are psychometric tests (PSE-syndrome test), neurophysiologic tests (EEG, Critical flicker frequency, CFF) and computerized tests (Inhibitory control test, ICT). However, there is no single test that can

capture the entire spectrum of cognitive impairment. Treatment options and goals depend on the acuity of hepatic encephalopathy [8]. There are at least two levels of cognitive function in patients with HE that need to be specifically investigated.

i. Deterioration in psychometric or neurophysiological function
ii. Deterioration in mental status

The existence of these two levels of functioning is important to acknowledge, as only mental status changes can be diagnosed by clinical interview and examination. Mental status testing can be achieved by evaluation of alertness and orientation using clinical judgment. Specific questionnaires such as clinical hepatic encephalopathy staging scale (CHESS) have been used in a small study but require further analysis [9]

**Differential diagnoses of encephalopathy**

Distinguishing hepatic encephalopathy from other acute and chronic causes of altered mental status may be difficult in patients with cirrhosis. A decision to perform additional neurologic studies should be based on the severity of the patient's mental dysfunction, the presence of focal neurologic findings (observed infrequently in patients with hepatic encephalopathy), and the patient's responsiveness to an empiric trial with cathartic agents. Even patients with severe hepatic encephalopathy should demonstrate steady improvement in mental dysfunction after an initiation of treatment with lactulose or cathartics derived from polyethylene glycol (PEG) [10]

- Intracranial lesions, such as subdural hematoma, intracranial bleeding, stroke, tumor, and abscess
- Infections, such as meningitis, encephalitis, and intracranial abscess
- Metabolic encephalopathy, such as hypoglycemia, electrolyte imbalance, anoxia, hypercarbia, and uremia
- Hyperammonemia from other causes, such as secondary to ureterosigmoidostomy and inherited urea cycle disorders
- Toxic encephalopathy from alcohol intake, such as acute intoxication, alcohol withdrawal, and Wernicke encephalopathy
- Toxic encephalopathy from drugs, such as sedative hypnotics, antidepressants, antipsychotic agents, and salicylates
- Organic brain syndrome
- Post seizure encephalopathy [11].

**Precipitating Factors**

The leading causes are gastrointestinal bleeding, sepsis and dehydration resulting from diuretics, diarrhea or vomiting. Also important are hyponatraemia, surgical intervention, transjugular intra-hepatic porto-systemic shunting (TIPS), constipation and the use of sedative and narcotic drugs [12]. There are different factors which play a key role in precipitating hepatic encephalopathy. Among these factors, infection, constipation and gastrointestinal bleeding are predominant. There is a definite need for health education and proper counseling in patients who were diagnosed as liver cirrhosis in relation to hepatic encephalopathy [13].

Nitrogenous substances derived from the gut adversely affect the cerebral function. The main substance implicated is ammonia. The astrocyte, which accounts for 30% of cortical mass, is the only cerebral cell capable of metabolizing ammonia and is considered to be the cellular basis of the majority of changes in HE [14]. Ammonia toxicity is a major factor in the pathogenesis of hepatic encephalopathy associated with subacute and chronic liver disease. Ammonia levels in patients with severe liver disease are frequently found to be elevated both in blood and cerebrospinal fluid (CSF). Hepatic encephalopathy results in neuropathological damage of a similar nature (Alzheimer type II astrocytosis) to that found in patients with congenital Hyperammonemia resulting from inherited defects of urea cycle enzymes [15].

**Treatment goals:**

Treatment goals for Hepatic Encephalopathy are providing supportive care, identifying and removing precipitating factors, reducing

nitrogenous load, and assessing long-term therapy needs. Newer, nonabsorbed agents, such as rifaximin, alone or in conjunction with lactulose, may enhance compliance and adherence with therapy, and provide better treatment outcomes [16].

**Treatment options:**

Cirrhotic individuals during an overt HE episode require careful management, focusing on precipitant factors as well as metabolic and hemodynamic derangements. Intestinal ammonia genesis requires flora modification by antibiotics, prebiotics and probiotics; glutaminase inhibition as well as antibiotics to pre-empt systemic inflammation. Hemodynamic/fluid support is essential. Nutritional support is crucial and hypoproteinemic diets should be avoided. Blocking benzodiazepine-like compounds by the use of flumazenil could be useful in patients with severe, benzodiazepine-induced HE. Long-term rifaximin is well tolerated, does not promote resistance and could decrease overt HE bouts in patients with previous episodes of overt HE. Lactulose is better than no treatment in improving quality of life in patients with minimal HE; it also acts as secondary prophylaxis following overt HE [17]. The treatment of chronic portal-systemic encephalopathy (PSE) was approached in a new manner by feeding the non absorbable disaccharide lactulose (1-4-beta-galactosido-fructose) in doses sufficiently large to produce a mild artificial disaccharide malabsorption syndrome. Control treatment with laxatives and neomycin eliminated the possibility of a nonspecific effect. Protein tolerance increased during lactulose administration. Diarrhea, the major side effect, was not a problem when the administered doses were adjusted to each individual patient [18].

HE could be precipitated by zolpidem in a similar manner to benzodiazepine hypnotics. Caution should be taken with the use of this drug in patients with advanced CLD because its half life could be severely prolonged with liver failure. It is notable that flumazenil is also an antagonist of non-benzodiazepine hypnotics, such as zolpidem, and could be efficaciously used to reverse HE induced by this class of drugs. Zolpidem tartrate is a non-benzodiazepine imidazopiridine hypnotic with fast onset of action used to treat transient insomnia in doses averaging 5 to 10 mg per day [19]. Rifaximin was effective in improving behavioral, laboratory, mental status, and intellectual abnormalities associated with hepatic encephalopathy. Some studies demonstrated superior and more rapid improvement in signs or symptoms of encephalopathy during treatment with rifaximin compared with non absorbable disaccharides (lactulose, lactitol). Patients treated with rifaximin also required less hospitalization, had shorter duration of hospitalization, and lower hospital charges compared with lactulose. Adverse effects of rifaximin were mostly minor gastrointestinal complaints; however, rifaximin was better tolerated than other pharmacologic treatments [20].

Flumazenil improves symptoms of hepatic encephalopathy in some patients with chronic liver disease and a highly favorable prognosis. However, there is not enough information to assess if the effect of flumazenil lasts after the end of treatment or can lead to full recovery or survival. Future trials should use a parallel design and assess if treatment with flumazenil leads to a sustained improvement or increased recovery and survival [21]. Compared with placebo or no intervention, non-absorbable disaccharides had no significant effect on mortality in Hepatic Encephalopathy. Antibiotics were superior to non-absorbable disaccharides in improving hepatic encephalopathy, but it is unclear whether this difference is clinically important. Non-absorbable disaccharides should not serve as comparator in randomized trials [22].

Hepatic encephalopathy (HE) is a significant cause of morbidity and mortality in patients with advanced chronic liver disease. Current therapies are associated with inconvenient side-effects, high cost, and incomplete efficacy. The quaternary ammonium compound L-acyl-carnitine has been suggested as a potent, low-

cost, and safe alternative therapy for patients with cirrhosis and HE. Analysis of the selected carnitine trials compared to currently accepted therapies suggests that L-acyl-carnitine is promising as a safe and effective treatment for HE, and further trials of this drug are warranted [23]

Antibiotics with activity against urease-producing bacteria, such as neomycin or metronidazole, also reduce the production of intestinal ammonia and have proved value [24, 25, 26]

**Vegetable-protein diet**

A vegetable-protein diet resulted in overall clinical improvement, decreased hepatic encephalopathy index scores, decreased arterial ammonia levels, improved performance on intellectual tasks, and in one case, markedly improved protein tolerance. Further, the beneficial effects of a vegetable-protein diet were enhanced by the use of the synthetic disaccharide, lactulose. These studies do not provide a clear-cut definition of the mechanism for the observed beneficial effects of vegetable protein in chronic hepatic encephalopathy. However, the most plausible explanation is that vegetable-protein diets contain lower amounts of certain amino acids and other putative materials which may be important in the pathogenesis of hepatic encephalopathy [27]

**Standard supportive therapy**

A characteristic feature of the neuropsychiatric changes in hepatic encephalopathy (HE) is the potential for a complete recovery in the majority of patients by Providing standard supportive therapy for patients with an altered mental status including administration of parenteral fluids and nutrition, care of vascular and bladder catheters, control of self-injurious activities, and instituting aspiration precautions [29]. Patients with acute liver failure and grade 3 or 4 hepatic encephalopathy should undergo elective ventilation, sedation with fentanyl, and paralysis with atracurium both to protect the airway and to facilitate the management of cerebral edema by preventing surges in intracranial pressure related to psychomotor agitation. Monitoring of extradural pressure is of value in these patients but carries some risk [30].

**Liver Transplantation**

Hepatic encephalopathy is associated with short survival in cirrhotic patients. Although these patients can be classified into several groups with a different prognosis, the survival probability in every group is lower than that currently expected after liver transplantation. Therefore, cirrhotic patients developing a first episode of acute hepatic encephalopathy should be considered as potential candidates for this therapeutic procedure [28]. Orthotopic liver transplantation is increasingly being used in the treatment of patients with end-stage cirrhosis, even older patients, many of whom have hepatic encephalopathy along with other manifestations of severe hepatic decompensation. Liver transplantation is also indicated in the small group of patients with severe, refractory hepatic encephalopathy, including such syndromes as dementia, spastic paraparesis, cerebellar degeneration, and extrapyramidal disorders, even when hepatic encephalopathy is the sole manifestation of hepatic decompensation [31]

Hepatic encephalopathy is rarely encountered with carcinoid syndrome, but massive hepatic replacement by carcinoid tumor can cause neuropsychiatric alterations. Extensive replacement of liver parenchyma by carcinoid tumors can lead to hepatic dysfunction as circulating levels of unmetabolised ammonia rise secondary to Porto systemic shunting [33]

**Conclusion and Recommendations:**

Hepatic encephalopathy (HE) is a challenging clinical complication of liver dysfunction with a wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function and consciousness to coma and death. Most cases of hepatic encephalopathy had an identifiable precipitating factor. Upper GI Bleed, infections, diuretics/electrolyte imbalance and constipation were the most common precipitating factors. Prophylactic use of beta-blockers and nitrates along with prompt control of infection and prevention of constipation by

laxatives needs to be given importance. Sedatives and diuretics should be used judiciously. Caution must be exercised in putting cirrhotic patients on diuretics. Prophylactic use of beta-blockers and nitrates along with prompt control of infection and prevention of constipation by laxatives needs to be given importance. Consistent use of lactulose and fiber should be encouraged to prevent constipation. More and more endoscopic facilities should be made available nationwide for prompt control of gastrointestinal bleeding, and most importantly, a more committed effort is the need to control increasing incidence of hepatitis C. Early and effective infection control and better hygienic conditions in government hospitals are needed to be maintained. Routine follow up should be done to prevent the re emergence of any complication.

Special considerations required for Grade III to IV hepatic encephalopathy patients:

a. Usually no oral nutrition
b. Upon improvement, individual protein tolerance can be titrated by gradually increasing oral protein intake every three to five days from a baseline of 40 g/day
c. Oral protein not to exceed 70 g/day if pt has hepatic encephalopathy.
d. Below 70 g/day rarely necessary, minimum intake should not be lower than 40 g/day to avoid negative nitrogen balance

Proper dietary advice must be an integral part of all counseling protocols to chronic liver disease patients. Nutritional measures should be taken place in patient with acute HE

1. Sufficient caloric supply
    a. 30 k cal /kg body weight /day
2. Restriction of dietary protein
    a. Day 1-5 20-30 g/day
    b. Then 1-2 g/kg body weight /day
3. Increased of glucose (lipid) calories
    a. 10% glucose 1-2 l/day
4. Branched chained amino acid (bcaa)
    a. 0.2-1.2 g/kg body weight i.v/day
5. Replacement of vitamins and trace elements
    a. Vitamin b complex
    b. Vitamin k
    c. Zinc

New updated practice guidelines need to be developed for hepatic encephalopathy, along with treatment algorithms for patients with both minimal hepatic encephalopathy and overt hepatic encephalopathy. The future challenge is to evaluate cognitive function as a continuum with clinically relevant outcomes and to develop well-tolerated and inexpensive treatments for hepatic encephalopathy.

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