Hepatic Encephalopathy: High Lights
Gadour M O EH¹, Al kalaefa M S²

Introduction

Hepatic encephalopathy (HE) remains a challenge to hepatologists. It is defined as a protein spectrum of potentially reversible neuropsychiatric abnormalities developing in patients with hepatic dysfunction and/or portal hypertension after exclusion of brain disease and/or unrelated metabolic abnormalities. Considerable difficulties arise when applying this definition to patients whose basic disease affects the brain as well as the liver e.g. Wilson's and ethanol induced liver disease. Overt HE is common, and is reported to affect 30-45% of cirrhotic patients.¹,²

HE is characterized by disturbances of personality, intelligence, level of consciousness, extrapyramidal and motor activity. Diversion of the blood -loaded with neurotoxic substances- away from the detoxifying hepatocytes either through spontaneous or induced shunts or because of paucity of normal hepatocytes is a corner stone in the development of HE. However, neither the presence nor the severity of the liver disease (Child's classification) or portal hypertension has a strong or consistent relationship with the development of this disease. This highlights the essential role of other factors in the pathogenesis of HE.

A lot of research was done to explore the nature of the disease and many hypotheses came out. Nevertheless, the exact mechanisms underlying the development of the clinical symptoms of HE remain far from precise identification³.⁴. This added to the difficulties in evaluation and management of these patients.

Clinical manifestations

Beside the clinical features of the underlying liver disease and/or portal hypertension, patients with HE usually have cognitive, extra pyramidal and motor dysfunction. HE is considered to be the hallmark of fulminant hepatic failure (FHF) when it is associated with an acute elevation of liver enzymes.

Depending on chronicity and/or the presence of portal hypertension the 11th World Congresses of Gastroenterology typed HE as follows⁵,⁶:

Type A: HE associated with acute liver failure.

Type B: HE associated with portosystemic bypass (non-cirrhotic).

Type C: HE associated with chronic liver disease/cirrhosis. This was further sub-classified to:

Episodic HE: Single or recurrent.
Persistent HE: Mild or severe.
Minimal HE(MHE): Formerly called subclinical or latent.
Any of these types may present with different features denoting degrees of severity which is the bases for staging the HE into five stages. (The table)⁷.

These features if present together will justify staging, otherwise they are neither specific nor diagnostic of the stage and on many occasions they may overlap. Disturbances in the diurnal sleep pattern usually precede overt HE. Flapping tremors which are commonly tested for are not pathogenic of the disease and can be seen in almost all end stage organ failures. Some features including restlessness, agitation, irritability, lethargy, forgetfulness, apraxia, incoordination and others may be present with variable degrees.

Patients with HE may present with focal neurological signs especially hemiplegia.⁸. Diffuse or focal seizures can unmask HE. Their incidence is unknown. On rare occasions patients with HE may present with status epilepticus.⁹,¹²

It was initially believed that cerebral function is normal in the interval between episodes of HE; this turned to be incorrect when more sensitive diagnostic tests such as the new psychometric and neurophysiological assessment were applied. Also before the first episode of overt HE, cerebral function may be abnormal. This evidence supports the existence of minimal HE.¹³,¹⁷

Unlike minimal HE, stages 1-4 are usually overt and pauses no diagnostic difficulties
Table: Some of the common features of each stage of HE (Adapted from Riordan S M and Williams R)\textsuperscript{7}.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Level of consciousness</th>
<th>Intellect</th>
<th>Neuro. signs</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal psychometric tests</td>
<td>Triphasic waves</td>
</tr>
<tr>
<td>1</td>
<td>Inverted sleep pattern</td>
<td>* Forgetfulness</td>
<td>Flapping tremors, impaired handwriting</td>
<td>Triphasic waves</td>
</tr>
<tr>
<td>2</td>
<td>* Slow response</td>
<td>* Disorientation for time</td>
<td>Hypotonia, hyporeflexia</td>
<td>Triphasic waves</td>
</tr>
<tr>
<td>3</td>
<td>* Somnolence, confusion</td>
<td>* Disorientation for place</td>
<td>Rigidly, hyper-reflexia, Babinski sign</td>
<td>Triphasic waves</td>
</tr>
<tr>
<td>4</td>
<td>coma</td>
<td>none</td>
<td>Decerebration</td>
<td>Delta waves</td>
</tr>
</tbody>
</table>

* in addition to the features of previous stage
0 Abnormal other neuroelectrical tests

Currently hepatologists are giving more weight to MHE as it has therapeutic and prognostic value. Its prevalence in patients with hepatic cirrhosis ranges between 30-84\%. This wide range reflects the difficulties in identifying the exact clinical and investigational parameters for diagnosis of this entity. MHE refers to the disturbances in cognitive function, fine concentration requiring motor skills, psychomotor speed, tracking, visuospatial, electrophysiological parameters, cerebral neurochemical/neurotransmitter homeostasis, cerebral blood flow and fluid homeostasis that may be observed in patients with cirrhosis and/or portal hypertension who have no clinical evidence of hepatic encephalopathy. The frequently used paper-pencil tests are not sensitive enough to diagnose MHE but critical flicker frequency is giving promising results. The psychometric hepatic encephalopathy score has been recommended as the "gold standard" in the diagnosis of MHE. Interestingly, the verbal memory skills are relatively well preserved in these patients\textsuperscript{6, 13, 16–24}.

Pathogenesis

The pathogenesis of HE is not well known. There is a consensus that HE is a multifactorial metabolic encephalopathy.\textsuperscript{25}. Some theories exist to explain the condition. The most popular ones are related to ammonia, gamma-aminobutyric acid (GABA), false neurotransmitters and others. Overt brain edema and increased intracranial pressure although characteristic of FHF, are also reported to occur in patients with liver cirrhosis. Astrocyte swelling is a characteristic pathological finding in HE and is thought of as the major structural marker of the disease.

However, other factors including gene disturbance, putative neurotoxins including short-chain fatty acids, mercaptans, manganese, hyponatremia, glutamate and ligands of the peripheral benzodiazepine receptor may have a synergistic effect on the event. On the other hand, reactive nitrogen and oxidant compounds are considered to play a major role in HE. Contradicting opinions exist regarding the role of nitric oxide and tumor necrosis factor alpha. There is growing evidence that osmotic and oxidative stresses are closely interrelated. It was suggested recently that inflammation and its modulators may play a synergistic role with ammonia in the pathogenesis of hepatic encephalopathy.\textsuperscript{26–30}

Ammonia

About 10\% of patients with significant encephalopathy have normal serum ammonia levels and some patients with significant elevation of ammonia have no evidence of HE. This questions the theory of ammonia. Despite this debate ammonia remains to be the major suspect as the injurious substance to the brain. Glutamine is reported to play a crucial role in transferring ammonia from the cytoplasm to the mitochondria of the astrocyte. This glutamine-derived ammonia within mitochondria is thought of as responsible for triggering excessive production of free radicals and induction of the mitochondrial permeability transition leading to astrocyte swelling and dysfunction\textsuperscript{31}. The gastrointestinal tract is a major source of ammonia mainly via production by enterocytes from glutamine and only partially by colonic bacterial catabolism of nitrogenous sources in the gut. This is usually detoxified by the liver and the muscles and excreted through the kidneys\textsuperscript{29}.

Increased ammonia production

Excess dietary protein intake, gastrointestinal hemorrhage, constipation, increased muscle catabolism due to reduced intake, infections, septicemia, blood transfusion, surgical intervention and hypokalemia augment
the production of ammonia. Although skeletal muscles remove more ammonia from the circulation than the cirrhotic liver and incorporate it in the formation of glutamine, they counteract that by releasing the glutamine in the circulation which is taken by the entocytes and kidneys to reproduce ammonia. Renal ammoniagenesis seems to have an appreciable role in the pathogenesis of HE\textsuperscript{32}.

**Reduced ammonia metabolism**

Patients with liver cirrhosis have no adequate viable and functioning hepatocytes to deal with the ammonia coming through the portal system. At the same time these patients have reduced muscle bulk so the other major detoxifying organ is defective. Arterial hypotension, anemia, hypoxemia, fluid restriction, fluid loss through diuretics or diarrhea result in hepatic hypoxemia and so contribute tremendously to the reduction of ammonia removal. Ammonia may bypass the liver though spontaneous or surgical shunts including transjugular intrahepatic portosystemic shunt. A normal ammonia load in these patients will therefore cause significant rise of its level in the circulation.

**Increased diffusion of ammonia across blood–brain barrier**

Hypokalemia and systemic extracellular alkalosis with intracellular acidosis which are commonly seen in patients with liver cirrhosis disturb the blood brain barrier and increase its permeability to ammonia\textsuperscript{33}.

**GABA- benzodiazepine**

Gamm-aminobutyric acid (GABA) is a neuroinhibitory substance produced in the gastrointestinal tract. Under the effect of ammonia the levels of some neurosteroids -which are potent GABA agonists- are increased\textsuperscript{26}. Alterations of GABAergic neurotransmission and tone are observed in HE. It is suggested that the increased brain concentration of endogenous ligands on GABA-A receptors rather than disturbance of the integrity of the receptors is responsible for this effect\textsuperscript{34}.

Patients with HE were found to have altered benzodiazepine metabolism with hypersensitivity and increased tone of the benzodiazepine receptors. Increased benzodiazepine receptor ligands may also participate in the increased GABAergic receptors tone\textsuperscript{55}.

**False-neurotransmitter hypothesis**

Other neurotransmitters including histamine 1 receptor agonist were shown in animal trials to participate in the onset of HE. False neurotransmitters such as tyramine, octopamine, and beta-phenylethanolamines were considered to induce HE in appropriate settings\textsuperscript{36}.

**Others**

**Nitric Oxide**

Nitric oxide (NO) is a neurotransmitter and neuromodulator that is found in different body tissues. It dilates the cerebral vasculature and is found to affect the blood brain barrier permeability\textsuperscript{37},\textsuperscript{38}. Its existence and regulatory effect in the mitochondria of different brain regions was observed. Mitochondrial dysfunction with decreased nitric oxide activity and expression were reported in animals with hepatic encephalopathy. Clear participation of NO in the pathogenic process of HE was reported in animal models\textsuperscript{39},\textsuperscript{40}. Because NO facilitates the systemic hypotension, some believe that by so doing NO will augment hepatic hypoperfusion and hepatocyte hypoxic damage. However, trials on animals to inhibit NO contradict this hypothesis\textsuperscript{41}.

**Zinc and manganese**

The extrapyramidal manifestation of HE were attributed to the impaired neuronal oxidative metabolism induced by manganese deposition in the basal ganglia. This is supported by the T1-weighted magnetic resonance imaging (MRI) in cirrhotic patients\textsuperscript{42},\textsuperscript{43}.

Zinc is an essential trace element which has an antioxidant effect. Its deficiency is commonly seen in patients with liver cirrhosis and on occasions is associated with GABAergic receptor disorder\textsuperscript{44}.

**Diabetes and Endotoxins**

It had been noted that diabetic patients who have liver cirrhosis have more severe HE without obvious precipitating factors, and if the diabetes is associated with HCV infection, the patient will be prone to express severe HE at an earlier stages of biochemical decompensation. The gastroparesis, intestinal dysmotility and autonomic disturbances associated with diabetes may enhance enteric bacterial overgrowth, increased ammonia production and hence explain the increased severity of HE in these patients\textsuperscript{45},\textsuperscript{46}. Although it was claimed that endotoxins play significant role in HE the data to support this is scanty and there is no published work to show the effect of endotoxin neutralization on HE. In fact recent reports refute this\textsuperscript{47}.

**Diagnosis**

Diagnosis and staging of overt HE is generally a clinical procedure. Simple blood
testing and radiological examination may be helpful in determining the presence and severity of liver disease and/or portal hypertension, unveiling some of the precipitating factors and planning the management program. However, they play no role in the diagnosis of HE.

Determination of ammonia level is needed in only few conditions as it is not required for screening or the diagnosis of HE. It is not an indicator of severity and has no prognostic value. Serial ammonia measurements are inferior to clinical assessment in follow up of patient under therapy for hepatic encephalopathy. Venous and arterial blood ammonia levels are different. However, this has no clinical implication. Only gaseous ammonia which is readily diffusible through the blood-brain barrier is useful for clinical studies and its testing is not available for routine clinical use.48

**Electrophysiologic tests** –

Neurophysiologic measures like visual and automatic electroencephalogram (EEG) analysis and spectral EEG49 may add to the staging of HE, whereas, checker board and flash visual evoked potentials, brainstem auditory-evoked potentials, somatosensory-evoked potentials, 50 and Critical flicker frequency (CFF) 51 are part of the diagnostic tool for MHE.

Alteration in the CFF threshold was reported to serve as a diagnostic marker for hepatic encephalopathy.51, 52

These neuropsychometric tests may not readily return to normal after improvement of HE and even after liver transplant. This raises the possibility that these tests may be assessing different components of HE. 51.

Conventional Computed tomography and magnetic resonance imaging of the brain are of use if the diagnosis of HE is questionable and for determination of other related brain complications. T1 mapping with partial inversion recovery may be helpful in determining HE severity.54

**Treatment**

**General measures:**

Because it is reversible and on occasions episodic, spontaneous recovery is expected in a high percentage of patients. However, those who do not have this favorable outcome usually require in hospital management. Correction of the precipitating factor- if possible- is the most important measure. Those with stage three and four HE have to be treated in intermediate or intensive care units. Because of the systemic hypotension and hypoxemia seen in these patients oxygen supplementation should be given. Close observation for the three common killers in HE-hypoglycemia, cerebral edema and infection- and prompt treatment of them is of utmost importance. Also it is important to observe for the significant unpleasant side effects of the classical treatment of HE which may include diarrhea, renal failure, neuropathy and other gastrointestinal disturbances. Sedatives should be avoided whenever possible.53, 54

**Special measures**

**Diet**

Patients with liver cirrhosis have reduced stores of vitamins and glycogen and are prone to hypoglycemia. On the other hand liver content of iron is usually high. Diet rich in carbohydrates and vitamins is advocated. Restriction of protein intake especially animal proteins was the rule in the treatment of HE for quite a long time. This had gradually changed as catabolization of the patients' own proteins and worsening of their condition were noticed. Recently a lot of debate came out questioning the validity of protein restriction and some advocate diet with normal protein content to patients with HE especially those who have the episodic type. Proteins have to be calculated and administered in a precise way that will neither lead to over load nor augment internal catabolism. Diets with high vegetable proteins were shown to have favorable impact on patients with HE.57-60

**Disaccharides**

Despite being a constant item in the treatment of HE; the use of oral non-absorbable disaccharides like lactulose and lactitol was also recently questioned. Review of randomized trials neither supported nor refuted their usage. However, lactulose enema was proved effective in treatment of HE.61

**Antibiotics**

Antibiotics are essential for treatment of precipitating or co-existing infection in patients with HE. Oral antibiotics "to sterilize the bowel" were found to be superior to oral disaccharides in treatment of the encephalopathy. Rifaximin is reported to be more effective and safe alternative to some of the currently used oral drugs especially in patients with impaired renal function. Interestingly some studies claimed that eradication of H. pylori may be helpful for prevention and treatment of HE.62-64

**Dialysis**

Continuous venovenous hemodiafiltration, intermittent dialysis and plasmapheresis were found to be helpful in ameliorating the impact of
rapid fluid shifts and remove some neurotoxins from the circulation. Some types of albumin dialysis had shown promising results regarding survival in FHF and other types of HE. Because of their inherently limited role, these measures were suggested as supportive therapy options in combination with standard treatment in HE.65-67

Others

Elevation of the head of the bed to 30 degrees to improve venous drainage and use of intravenous mannitol may help to reduce cerebral edema.68

Trails on animals had shown that induced hypothyroidism and marginal hypothermia via reduction of metabolism and amelioration of the hydrodynamic circulation in patients with liver cirrhosis may reduce oxidative liver injury and be beneficial in treatment of HE.69

By improving antioxidant defenses, C-Phycocyanin is potentially effective in patients with HE.70 L-ornithine and L-aspartate were found to stimulate and increase the activity of glutamine synthetase and hence reduce ammonia level in patients with liver cirrhosis.71

Symbiotics, fermentable fiber and L-Acetylcarnitine were reported to improve the clinical picture in some patients. On the other hand flumazenil which had gained initially a lot of enthusiasm in treatment of HE was reported later to be effective in only a small minority of patients 72-74

None responders:

Patients who show no response or an unexpected sub-optimal response to treatments should be reviewed. Special considerasion for hidden complications is important. These include occult infection, trace mineral deficiency, bowel ischemia and large spontaneous portosystemic shunts and others which are potentially amenable to treatment.75

Intermittent therapy with an extracorporeal liver support system seemed to sufficiently replace hepatic detoxification on a long-term basis in some patients and may be a good tool to bridge the time period until liver transplantation which so far remains to be the gold standard treatment for HE.75

Prognosis

Development of HE is an independent poor prognostic factor in patients with liver cirrhosis with 1-year mortality rate of about 60%. Elevated liver enzymes, low serum albumin, evidence of renal failure are independent risk factors for poor prognosis.55,76

References


25. Jones EA. Ammonia, the GABA neurotransmitter system, and hepatic encephalopathy. Metab Brain Dis. 2002 Dec; 17(4):275-81


