An evidence-based update on hepatic encephalopathy

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Abstract

Hepatic encephalopathy (HE) is a disturbance of the central nervous system (CNS) function secondary to porto-systemic shunting. It usually occurs in the setting of advanced liver cirrhosis or acute fulminant hepatic failure. An extensive Medline search was undertaken and all relevant papers found were critically examined. Special emphasis was paid to clinical trials and meta-analyses. All guidelines and conference proceedings related to hepatic encephalopathy were also examined. HE presents with a spectrum of neuropsychiatric manifestations that may be quite subtle (minimal HE) or overt, ranging from disturbance of the sleep pattern to deep hepatic coma. Most patients with HE may be diagnosed on clinical grounds only after excluding other causes of neurological disease, but a wide variety of neuropsychological, neurophysiological, and neuroradiological tests may be utilized. The first step in the management of patients with HE should be supportive care. Following that, a significant effort must be exerted to find and correct possible exacerbating factors which may include: renal impairment, infection, constipation, drugs, gastrointestinal bleeding and other factors. Medications used to treat patients with encephalopathy aim to reduce toxin production, increase toxin elimination, and protect the brain from the harmful effects of these toxins. A critical analysis of the evidence concerning most of the available management modalities is presented. Ultimately, all patients with HE must be considered for liver transplantation. It is concluded that early recognition, positive diagnosis, and a multi-target management plan constitutes appropriate management of patients with HE.

Key Words: Hepatic encephalopathy, liver cirrhosis

Hepatic encephalopathy (HE) may be defined as a disturbance of the central nervous system (CNS) function secondary to porto-systemic shunting. It represents a wide spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known neurological diseases.(1)

Clinical setting

HE usually develops in three clinical scenarios(2);

1. Overt HE in a patient with liver cirrhosis

This is by far the most common clinical scenario seen in clinical practice. It is most commonly seen in patients with advanced liver cirrhosis secondary to significant porto-systemic shunting and severe hepatocellular dysfunction.

2. Minimal hepatic encephalopathy in patients with liver cirrhosis

Patients with stable advanced liver disease may develop subtle cognitive abnormalities that are not clinically apparent that represent a “low grade” HE. These symptoms are otherwise unexplained and are only detectable on psychometric or neurophysiological testing in the absence of overt HE.

3. HE in patients with acute liver failure

HE is the cardinal feature of fulminant hepatic failure.

Classification

The working party at the 11th World Congress of Gastroenterology, Vienna, 1998 proposed a multi-axial definition of HE with a very encompassing classification that is quite useful clinically (table 1) (1). In this classification they talk about the same clinical scenarios discussed above, but add encephalopathy associated with porto-systemic shunts that are not associated with intrinsic liver disease, such as congenital and spontaneous shunts, which are quite rare.

This consensus conference discouraged some commonly used
terms to describe clinical features in HE such as subclinical, acute, and chronic HE.

### Clinical features

**Overt HE**

When HE presents acutely (whether in a cirrhotic patient or one with fulminant liver failure) the patient may have a wide spectrum of neurological and psychomotor abnormalities. These typically include: impaired mental status, neuromuscular abnormalities, fetor hepaticus, and hyperventilation. An important feature of HE is its fluctuating nature ranging from mild neurological impairment that can progress to deep coma in hours and resolve again in hours. The CNS manifestation of HE usually starts in a subtle way with personality changes or disturbances in the circadian rhythm of sleep (insomnia at night and sleeping on day time). This usually progresses to inappropriate behavior, disorientation, confusion, slurred speech and, finally, coma. Flapping tremor (astrixis) is characteristic for HE and represents failure to actively maintain posture or position. Once the acute episode of HE resolves the patient will then either have a relapsing type of recurrent acute attacks of HE or may develop persistent neurological features called chronic HE. In a minority of patients the so called “hepatic dementia” happens, which is usually fluctuating. In other patients features similar to Parkinson disease may be seen, and, in a few, symmetric progressive spastic paraparesis named “hepatic myelopathy”.

**Minimal HE**

In patients with minimal HE there are no detectable neurological findings, but there may be subtle cognitive changes that are brought up by neuropsychologic and neurophysiologic testing. The prevalence of minimal HE in cirrhotic patients is variable, but is expected to be high as shown by many studies. Patients who develop minimal HE tend to be older, have more severe liver disease, and more often have esophageal and fundal varices. Many studies have shown that these patients have impaired quality of life, and disturbed sleep and daily life activities.

One major concern is car driving as one study showed that at least 44% of patients with well compensated cirrhosis and features of minimal HE are not actually fit to drive. Patients with minimal HE may improve, remain the same or, more often, deteriorate and go on to develop overt recurrent HE.

### Precipitating factors for HE

Any factor that increases the generation of toxins, further impairs liver function, or enhances the effects of toxins on the CNS may precipitate HE in patients with liver cirrhosis (table 2).

### Pathogenesis

A full understanding of the pathophysiologic mechanisms causing hepatic encephalopathy is lacking, but is under extensive research. In its simplest form, most think of the cause of encephalopathy as the accumulation of toxic substances that are, under normal circumstances, metabolized by the liver. These substances bypass the liver due to the porto-systemic shunting and decreased hepatic clearance. These “toxins” then lead to neurochemical changes in the...
CNS resulting in disturbance of its function leading to HE. In this review we will discuss some of the well established theories regarding the possible toxins leading to HE.

Ammonia

Historically, ammonia has been regarded as the most important factor in the development of HE. The main source of ammonia production in humans is the nitrogenous compounds in the colon which include ingested proteins and secreted urea. Under normal physiological conditions, ammonia enters the portal tract in high concentrations (5-10 times greater than in mixed venous blood) from the gastrointestinal tract derived from colonic bacteria and from glutamine in the small intestine. In the liver, ammonia is transformed in the periportal hepatocytes into urea and in the centrovenular hepatocytes into glutamine. Urea is then eliminated through the urine. Circulating urea diffuses into the intestine where it is transformed back into ammonia by colonic bacteria.

Clinical studies show that in 60-80% of patients with HE, arterial blood samples show increased ammonia levels suggesting an important role of ammonia accumulation in the pathogenesises of HE. Even more convincing, although arterial blood levels of ammonia are not universally high, there is an increased diffusion of ammonia into the brain. The problem has always been the lack of correlation between the levels of ammonia and the clinical stage of HE.

When high levels of ammonia are reached in the brain numerous neurochemical changes have been observed. These may include: blockage of chloride channels, increase in the transport of neural amino acids and cerebral tryptophan, decrease in the activity of alfa ketoglutarate dehydrogenase, enhancement of the synthesis of neurosteroids, modulation of GABA receptors, up-regulation of the peripheral benzodiazepine receptors, and increased brain glutamine.

In summary, ammonia seems to be an integral component of the neurotoxins affecting the CNS in HE but is unable to explain the entire picture.

Gamma-Aminobutyric Acid (GABA) Receptor Complex

GABA receptor complex localized in post-synaptic membranes constitutes the principal inhibitory network within the CNS and has been shown to be a key contributor to neuronal inhibition in HE. This complex consists of a GABA-binding site, a chloride selective pore that opens in response to GABA binding to permit influx of chloride and produce membrane hyperpolarization, and a closely associated barbiturate and benzodiazepine receptor site that potentiates the effect of GABA.

The liver contains high concentrations of GABA and GABA transaminase and, due to that, liver injury may disrupt the GABA hemostatic mechanisms, which may contribute to HE.

In addition, ammonia combines with alfa ketoglutarate in the central nervous system to form glutamate which increases the production of GABA. Other mechanisms in the relation of ammonia to the GABA receptor have been explored.

Endogenous Benzodiazepine Receptor Ligands

Benzodiazepine receptor ligands (BRL) are a group of substrates that are sometime called “natural benzodiazepines”, which are able to bind to the benzodiazepine site of the GABA receptor complex and act as agonists or antagonists. The exact effect of these ligands on the CNS is unclear but they are found to induce amelioration and increase in benzodiazepine activity in CSF, blood, and post mortem brain tissue. Animal studies have shown that HE is associated with increased benzodiazepine receptor ligands, which may bind to GABA receptors in the CNS and cause neurological inhibitory effect. Alternatively, BRL may bind to peripheral benzodiazepine receptors in the mitochondria, which may lead to synthesis of neurosteroids within the astrocytes affecting GABA receptors.

This role of BRL in the pathogenesis of HE is supported by the observed partial response of patients with HE to benzodiazepine receptor antagonists, such as flumazenil, an issue that will be discussed in the treatment section in detail.

Pathological brain abnormalities

The astrocyte seems to be the brain cell that is mostly affected in patients with HE. This has been consistently shown in both patients with fulminant liver failure and in patients with liver cirrhosis (in that setting called Alzheimer 2 astrocytes). On electron microscopy, the astrocytes are characterized by a swollen cellular nucleus, with its chromatin displaced to the periphery. It is thought that these structural abnormalities may lead to abnormal interaction between the altered astrocyte and other cellular elements in the brain and this may lead to HE.

Diagnosis

Clinical

The diagnosis of HE is usually based on the presence of typical clinical features in the right clinical context. Rarely does one need more sophisticated tests to diagnose HE. It is important initially to rule out other possible causes of abnormal neurological symptoms in a patient with advanced liver disease. These include metabolic abnormalities, sepsis, stroke, brain tumor, Wernicke-Korsakoff encephalopathy, and seizures.

Neuropsychiatric/Neurophysiology testing

In cases of minimal HE many neuropsychiatric tests have been developed to try to detect early subtle changes that may lead to the diagnosis. One should use standardized tests that...
test across different neuropsychological domains as to detect subtle changes. One such battery of tests is the porto-systemic encephalopathy-syndrome-test\(^{(23)}\). This is a standardized battery of tests including the number connection test A and B, the line-tracing, the serial dotting, and the digit-symbol tests. These paper and pencil tests combined are expected to examine motor speed and accuracy, visual perception, visual-spatial orientation, visual construction, concentration, attention, and memory. This test has been shown to have a high specificity for HE\(^{(23)}\), and has been recommended to be used in the diagnosis of minimal HE by the working party of the World Congress of Gastroenterology\(^{(1)}\).

EEG typically shows non specific changes that are often seen in other causes of metabolic encephalopathy like high voltage low frequency changes\(^{(3)}\).

**Neuroimaging**

Brain imaging is rarely required to diagnose HE. CT scan of the brain should be obtained if the diagnosis of HE is in doubt to rule out other causes of the neurological abnormalities. If MRI is obtained, the most consistent finding in patients with chronic liver failure is bilateral, symmetrical hyperintensities in the globus pallidus on T1-weighted imaging\(^{(3)}\). Most studies indicate that these abnormalities are probably secondary to increased manganese deposition in this area of the brain which has been confirmed in autopsy samples in patients who died of hepatic coma\(^{(24)}\). Although these MRI abnormalities have not been shown to directly relate to the stage of encephalopathy, they are reversible after liver transplantation\(^{(25)}\). Proton magnetic resonance spectroscopy allows the assessment of several brain metabolites (glutamine, glutamate, myo-inositol).

Studies using sufficiently high magnetic field strengths reveal increase in resonance assigned to the protons of the glutamine molecule\(^{(26)}\) and a reduction in the muo-inositol\(^{(27)}\).

On the other hand, there is little agreement on the abnormalities detected by the 31P studies. Using position emission tomography (PET) several investigators have shown alterations in local cerebral glucose utilization in brains of cirrhotic patients with mild HE\(^{(27)}\).

In addition, other investigators have found an increase in the cerebral metabolic rate for ammonia coupled with an increase in the permeability surface area of the blood brain barrier to ammonia\(^{(28)}\).

In spite of these promising findings, neither magnetic resonance spectroscopy nor PET scanning is ready for clinical use up to date\(^{(1)}\).

**Management**

The management of a patient with HE is usually directed to the management of the underlying liver disease in addition to some specific HE directed treatments (table 3).

### Supportive measures

Intravascular volume status needs to be evaluated and replaced in all patients regardless of the presence of ascites or edema. Diuretics should be stopped. If sepsis is suspected broad spectrum antibiotics should be started. Beyond that, supportive measures of the patient depend on the level of consciousness. If the patient is comatose ICU care may become necessary.

### Identification and management of precipitating factors

As discussed above, HE can be precipitated by many factors. A detailed history and physical examination must be undertaken looking for these precipitant factors. Subtle sepsis is a commonly missed precipitant especially spontaneous bacterial peritonitis\(^{(29)}\). We recommend full septic screen
including blood and urine cultures, chest x-ray and a diagnostic aseptic tap in every cirrhotic patient admitted with hepatic encephalopathy.

**Decreasing nitrogenous load from the gut**

**Dietary management**

For many years, most clinicians used to restrict protein from patients with HE in an effort to reduce the amount of nitrogenous products production. In addition to the fact that this recommendation is not evidence based, it is potentially harmful, as most patients with HE are malnourished to start with and this is one of the important factors in their high mortality. In addition, a positive nitrogenous balance may help hepatic regeneration and help maintain muscle mass which is useful in detoxifying ammonia. For these reasons, most authorities do not support protein restriction in patients with hepatic encephalopathy and rather recommend a 25-35 kcal/Kg per day and 1-1.5 g/Kg/day of protein\(^{(30)}\). The protein content may be increase as the patient improves.

**Non-absorbable disaccharides**

Lactulose is considered to be standard therapy for HE\(^{(2,3)}\). Although its mechanism of action is not completely understood it is postulated that, when lactulose is ingested, it reached the cecum unchanged, where it is metabolized by enteric bacteria to lactate and acetate which causes a drop in the colonic pH. This acidification favors the passage of NH\(_3\) into the colonic lumen where bacteria utilize ammonia as a metabolic substrate which increases fecal nitrogen excretion that eventually leads to a reduction in the amount of nitrogen that reaches the portal blood\(^{(31)}\) leading to a reduction in the plasma ammonia level. Other possible mechanism of action of lactulose have been proposed including the fact that lactic acid production may promote lactobacillus and other saccharolytic bacteria that suppress proteolytic and urealytic bacteria, and the fact that lactulose may serve as an energy source altering the metabolism of facultative urealytic and proteolytic bacteria\(^{(32)}\).

Lactulose should be administered initially in a high dose (30-50 ml every 1-2 hours) until catharsis occurs and then it should be adjusted according to the bowel movements aiming to get two to three loose bowel movements per day. Alternatively, lactulose may be given as an enema (300 ml in 1-3 L of water) with the patient in the reverse Trendelenburg position for 1 hour and then adjusted according to the bowel movements. In a recent very provocative Cochrane systematic review, 10 trials were found assessing lactulose or lactitol vs. placebo or no treatment randomizing 280 patients with a median number of patients in each trial of only 26\(^{(33)}\). Overall, including patients with acute and chronic HE, lactulose or lactitol appeared to reduce the risk of “no improvement” (RR 0.62 (0.46-0.84), but when only high quality trials were included (2 trials only) a significant effect could not be demonstrated. When examined separately, there was no statistically significant effect of lactulose or lactitol on acute (RR0.27 (0.02-3.28)) and chronic HE (1.33 (0.41-4.33). In the same Cochrane review, they found eight trials comparing lactulose vs. lactitol\(^{(33)}\).

No statistically significant difference was found between the two. In some comparative trials, lactitol was found to be more palatable but similar in efficacy to lactulose\(^{(34,35)}\). From the above data, we find that the actual evidence for the efficacy of lactulose and lactitol in HE is quite weak, most likely secondary to the poor design and small number of patients in most of the trial rather than the lack of an actual effect.

**Neomycin**

The exact mechanism of action of neomycin is unknown. Similar to Lactulose it leads to reduction in the amount of ammonia absorbed from the intestine, probably by reducing the activity of glutaminase in the small bowel decreasing the generation of ammonia from glutamine\(^{(36)}\). When treating acute HE, 3-6 g/day in divided doses needs to be given. Although less than 4% of it is actually absorbed there are concerns regarding its potential nephrotoxicity and ototoxicity especially with prolonged use. Given the potential side effects is considered second line therapy for HE\(^{(2)}\).

The evidence regarding the efficacy of neomycin in HE is contradicting. On one hand neomycin has not shown any significant benefit when compared to placebo in acute HE, and on the other hand it showed equivalent effectiveness to lactulose in chronic HE\(^{(3)}\). We believe that neomycin is probably effective in chronic HE as two larger trials found that the effectiveness of neomycin and lactulose were comparable\(^{(37,38)}\).

Although metronidazole is often used in treatment of HE, there is only one trial suggesting that it as effective as neomycin in treating chronic HE\(^{(39)}\). There has also been one trial using vancomycin in 12 patients with lactulose resistant chronic HE showing a very significant improvement in symptoms\(^{(40)}\).

**Synbiotic modulation of gut flora**

Further trials to reduce ammonia production from the gut and by that help in treating HE includes the use of probiotics. In a recent trial involving a total of 97 consecutive outpatients with hepatic cirrhosis but no HE, 60% were found to have evidence of minimal HE on further testing with psychometric and neurophysiology studies\(^{(41)}\). Fifty five of these patients have been randomized to receive a synbiotic preparation, fermentable fiber alone, or placebo for 30 days. There was a significant reduction in the ammonia levels in the group receiving synbiotics with more than 50% of them showing
Improving extraintestinal elimination of ammonia

L-ornithine-L-aspartate (LOLA)

This product provides substrate for ureagenesis and for glutamine syntheses and by that is considered an ammonia lowering treatment. In a randomized clinical trial involving 126 patients, LOLA infusion for 7 days was found to be better than placebo in acute HE\(^{(41)}\). In another placebo-controlled double-blind study by the same group using oral dosing for 14 consecutive days in a dose of 18 g per day, LOLA was found to be superior to placebo in group of 66 patients with mixed overt and minimal HE\(^{(42)}\). In another interesting study, performed on stable cirrhotic patients without HE who were challenged with an oral glutamine load, LOLA was found after a double-blind randomized comparison to be able to ameliorate the deleterious psychometric effects of glutamine in these patients\(^{(43)}\). Based on the above evidence, we consider this drug to be promising and required further confirmatory trials.

Zinc

Zinc is another ureagenic co-factor that has been reported to be low in patients with HE\(^{(44)}\). Five trials have been published to date using zinc in HE, one of them published in abstract form only\(^{(45)}\). In a more recent prospective non randomized Italian study zinc was shown to be associated with improvement in psychometric studies and in the Child-Pugh score when used for 3 months\(^{(46)}\). The preparations that are usually used are zinc acetate or zinc sulfate in daily doses of 200mg to 600 mg. The evidence for significant beneficial effect of this therapy in patients with HE is not convincing in our opinion and required further study.

Artificial and bioartificial support systems

Since liver transplantation is not available for many patients with fulminant hepatic failure, multiple artificial and bioartificial liver support systems have been developed to “bridge” the patient to either transplantation or complete recovery. A recent Cochrane database systematic review found 12 randomized trials comparing various models of these systems with standard medical care\(^{(47)}\). In the primary meta-analyses, support systems did not seem to affect mortality. In further subgroup analyses, it was found that these support systems reduce mortality in patients with acute on chronic liver failure only and not in patients with acute liver failure. This area of management of acute fulminant liver failure is still in its early stages and much hope is put on it.

Minimizing the effect of toxins on the CNS

Flumazenil

The mechanism of action of flumazenil is by antagonizing the benzodiazepine receptors leading to the amelioration of its effects on the GABA complex in the CNS. Multiple clinical trials have been performed to test the clinical efficacy of flumazenil. Most studies show a modest clinical effect. In one randomized trial, there was a suggestion that patients with HE and gastrointestinal bleeding were more likely to respond than patients without bleeding\(^{(48)}\). It was also noticed that, if a response was not seen in the first six hours, it will be unlikely to occur later on.

In a meta-analyses including six randomized trials involving 641 patients, flumazenil has shown clinical improvement in 27% of patients compared to 3% with placebo, a difference that was statistically significant\(^{(49)}\). Flumazenil has also shown statistically significant improvement in EEG findings. In a more recent Cochrane database review including 13 trials involving 805 patients, it was found that flumazenil had a significant beneficial effect on improvement of HE at the end of treatment, but no significant effect or recovery from encephalopathy or on survival\(^{(50)}\). This means that flumazenil may help some patients to wake up but doesn’t seem to really change the actual course and complications of the disease. Moreover, in the majority of studies, the effect of flumazenil was short lived leading to no difference in efficacy compared to placebo at 24 hours after administration.

Treatment of the underlying liver disease

Attention should be paid to the cause of portal hypertension and underlying liver disease and every effort to halt or reverse the progression of the liver disease should be done. The effect of such strategy is variable. While some liver disease are unlikely to respond to specific treatment once advanced cirrhosis is established such as primary biliary cirrhosis, other types of liver disease may respond favorably such as hepatitis B, Wilson disease, and auto-immune hepatitis. For instance, in a recent trial involving 651 patients with advanced liver
Liver transplantation

HE is one of the signs of decompensation in a stable patient with compensated cirrhosis and is one of the minimal listing criteria for liver transplantation\(^1\). For this reason, every patient who develops HE must be considered for liver transplantation. The results of liver transplantation for HE depends on the whether its for acute fulminant liver failure or for chronic liver disease. It also depends on the cause of the liver disease in the first place.

Conclusion

From the above review we find that hepatic encephalopathy has multiple clinical presentations that must be recognized early. Although the diagnosis is primarily clinical, multiple other tests may be helpful in diagnosing more subtle cases. When diagnosed, every effort must be exhausted to identify exacerbating factors and correct them. The management after that should be initiated at multiple intervention levels. All patients with chronic liver disease presenting with HE must be referred for possible liver transplantation.

References


