INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 20, No. 6, p. 45-64, 2022

REVIEW PAPER OPEN ACCESS

Hepatic encephalopathy and its management

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Key words: Hepatic, Encephalopathy, Causes, Diagnosis, Treatment.

http://dx.doi.org/10.12692/ijb/20.6.45-64 Article published on June 14, 2022

Abstract

Hepatic encephalopathy (HE) is a symptom of decompensated cirrhosis that affects up to half of all individuals with the disease. Approximately 23,000 inpatients are diagnosed with (HE) each year, and internists and subspecialists are frequently responsible for their care. In recent years, the treatment of hospitalized HE patients has evolved. Induction and maintenance of remission are two aspects of treatment. Infection, gastrointestinal bleeding, medicines, or other factors trigger the majority of instances of serious HE. Secondary triggers should be considered in all cases and in most individuals, treatment should begin with a non-absorbable disaccharide. In patients who do not respond to lactulose, rifaximin might be used. Because of its side effects, neomycin is a less preferable option to rifaximin. For patients who do not respond to disaccharides or non-absorbable antibiotics, other therapy such as zinc, l-ornithine–l-aspartate, and branched-chain amino acids can be considered.

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Introduction

Hepatic encephalopathy is a syndrome observed in patients with cirrhosis. Hepatic encephalopathy is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of brain disease. Hepatic encephalopathy is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. An important prerequisite for the syndrome is a diversion of portal blood into the systemic circulation through portosystemic collateral vessels (Riggio *et al.*, 2005).

Hepatic encephalopathy is also described in patients without cirrhosis with either spontaneous or surgically created portosystemic shunts. The development of hepatic encephalopathy is explained, to some extent, by the effect of neurotoxic substances, which occurs in the setting of cirrhosis and portal hypertension (Riggio *et al.*, 2005). Subtle signs of hepatic encephalopathy are observed in nearly 70% of patients with cirrhosis. Symptoms may be debilitating in a significant number of patients. Overt hepatic encephalopathy occurs in about 30-45% of patients with cirrhosis. It is observed in 24-53% of patients who undergo portosystemic shunt surgery (Poordad, 2007).

The development of hepatic encephalopathy negatively impacts patient survival. The occurrence of encephalopathy severe enough to lead to hospitalization is associated with a survival probability of 42% at 1 year of follow-up and 23% at 3 years (Bustamante *et al.*, 1999). Approximately 30% of patients dying of end-stage liver disease experience significant encephalopathy, approaching coma (Ferenci *et al.*, 1995). The economic burden of hepatic encephalopathy is substantial. After ascites, hepatic encephalopathy is the second most common reason for hospitalization of cirrhotic patients in the United States (Bajaj *et al.*, 2007). Hepatic encephalopathy is also the most common, possibly preventable, cause of readmission (Volk *et al.*, 2012). The US national charges related to hospitalizations for hepatic encephalopathy have been estimated to range from about $1 billion per year to upwards of $7 billion per year (Poordad, 2007; Stepanova *et al.*, 2012). These costs may underestimate the true economic burden of hepatic encephalopathy in terms of the condition's negative impact on the employment and finances of patients and their caregivers (Bajaj *et al.*, 2011). Hepatic encephalopathy, accompanying the acute onset of severe hepatic synthetic dysfunction, is the hallmark of acute liver failure (ALF). Symptoms of encephalopathy in ALF are graded using the same scale used to assess encephalopathy symptoms in cirrhosis (Stepanova *et al.*, 2012).

The encephalopathy of cirrhosis and ALF share many of the same pathogenic mechanisms. However, brain edema plays a much more prominent role in ALF than in cirrhosis. The brain edema of ALF is attributed to increased permeability of the blood-brain barrier, impaired osmoregulation within the brain, and increased cerebral blood flow. The resulting brain cell swelling and brain edema are potentially fatal. In contrast, brain edema is rarely reported in patients with cirrhosis. The encephalopathy of ALF is not covered in this article but is addressed in Acute Liver Failure (Poordad, 2007).

Classification of hepatic encephalopathy

Nomenclature has been proposed for categorizing hepatic encephalopathy (Ferenci *et al.*, 1998).

Type A: Type A hepatic encephalopathy describes encephalopathy associated with acute liver failure.

Type B: Type B hepatic encephalopathy describes encephalopathy associated with portal-systemic Bypass and no intrinsic hepatocellular disease.

Type C: Type C hepatic encephalopathy describes encephalopathy associated with Cirrhosis and portal hypertension or portal-systemic shunts. Type C hepatic encephalopathy is, in turn, subcategorized as episodic, persistent, or minimal. In cirrhotic patients, episodic and persistent hepatic encephalopathy is less

prevalent; however, a minimal type of hepatic encephalopathy presents in more than two-thirds of patients population with cirrhosis (Butterworth, 2011). The subject of minimal hepatic encephalopathy, also known as covert hepatic encephalopathy, has attracted increasing attention. Minimal hepatic encephalopathy describes a state of low-level cognitive dysfunction that is present in as many as 70% of patients with cirrhosis (Butterworth, 2011).

It may be marked by decreased attention and executive function, as well as depressed psychomotor speed and visuomotor activity. Typically, the patient and those around the patient, including physicians, are not aware that the condition is present. Minimal hepatic encephalopathy is detected through psychometric testing (e.g., the number connection test, the digit symbol test, the block design test, reaction times to light or sound, and the reaction time to interference in a task) (Weissenborn *et al.*, 2001; Bajaj *et al.*, 2008; Bajaj *et al.*, 2013).

Minimal hepatic encephalopathy is most likely the result of hyperammonemia. Elevated ammonia levels are detected in most patients. Similarly, the subtle neurological changes of minimal hepatic encephalopathy can be improved by the administration of lactulose (Watanabe *et al.*, 1997). Minimal hepatic encephalopathy is an important diagnostic consideration in patients with cirrhosis. It is associated with a diminished quality of life (Groeneweg *et al.*, 1998), an increased risk of falls (Román *et al.*, 2011), and impaired ability to operate a motor vehicle (Bajaj *et al.*, 2007; Kircheis *et al.*, 2009).

For this reason, a number of authors have raised concern that the term "minimal" may trivialize the condition and have proposed that this disease stage be renamed covert encephalopathy (Kappus and Bajaj, 2012). Two articles have noted that rifaximin can be helpful in patients with minimal hepatic encephalopathy. Sidhu *et al.* (2011) found that rifaximin treatment led to improved health-related quality of life. Bajaj *et al.* (2011) noted that rifaximin led to decreased driving errors compared with placebo when patients with minimal hepatic encephalopathy operated a driving simulator.

At this time, no guidelines address the testing and treatment of minimal hepatic encephalopathy in patients with cirrhosis. The neuropsychometric tests typically used to diagnose minimal hepatic encephalopathy can be time-consuming and cumbersome to perform in the busy physician's office. Similarly, no consensus has been reached on how physicians should approach the issue of the fitness of patients with minimal hepatic encephalopathy to drive automobiles (Cohen *et al.*, 2011).

Pathogenesis of hepatic encephalopathy

A number of theories have been proposed to explain the development of hepatic encephalopathy in patients with cirrhosis. Some investigators contend that hepatic encephalopathy is a disorder of astrocyte function. Astrocytes account for about one-third of cortical volume. They play a key role in the regulation of the blood-brain barrier. They are involved in maintaining electrolyte homeostasis and in providing nutrients and neurotransmitter precursors to neurons. They also play a role in the detoxification of a number of chemicals, including ammonia (Brusilow *et al.*, 2002).

It is theorized that neurotoxic substances, including ammonia and manganese, may gain entry into the brain in the setting of liver failure. These neurotoxic substances may then contribute to morphologic changes in astrocytes. In cirrhosis, astrocytes may undergo Alzheimer's type II astrocytosis. Here, astrocytes become swollen. They may develop a large pale nucleus, a prominent nucleolus, and a margination of chromatin (Bajaj *et al.*, 2007). In ALF, astrocytes may also become swollen. The changes in Alzheimer's type II astrocytosis are not seen in ALF. But, in contrast to cirrhosis, astrocyte swelling in ALF may be so marked as to produce brain edema. This may lead to increased intracranial pressure and, potentially, brain herniation (Bajaj *et al.*, 2011).

In the late 1990s, authors from the University of Nebraska, using epidural catheters to measure intracranial pressure (ICP), reported elevated ICP in 12 patients with advanced cirrhosis and grade 4 hepatic coma over a 6-year period (Donovan *et al.*, 1998). Cerebral edema was reported on CT scan of the brain in 9 of the 12 patients. Several of the patients transiently responded to treatments that are typically associated with the management of cerebral edema in patients with ALF. Interventions included elevation of the head of the bed, hyperventilation, intravenous Mannitol, and phenobarbital-induced coma (Cohen *et al.*, 2011).

In many investigators' opinion, patients with worsening encephalopathy should undergo a head CT scan to rule out the possibility of an intracranial lesion, including hemorrhage (Butterworth, 2003). Certainly, cerebral edema, if discovered, should be aggressively managed. The true incidence of elevated ICP in patients with cirrhosis and severe hepatic encephalopathy remains to be determined (Kircheis *et al.*, 2009). Work focused on changes in gene expression in the brain has been conducted. The genes coding for a wide array of transport proteins may be up-regulated or down-regulated in cirrhosis and ALF. As an example, the gene coding for the peripheral-type benzodiazepine receptor is up-regulated in both cirrhosis and ALF. Such alterations in gene expression may ultimately result in impaired neurotransmission (Chatauret and Butterworth, 2004)

Hepatic encephalopathy may also be thought of as a disorder that is the end result of accumulated neurotoxic substances in the brain. Putative neurotoxins include short-chain fatty acids; mercaptans; false neurotransmitters, such as tyramine, octopamine, and beta-phenylethanolamines; manganese; ammonia; and gamma-aminobutyric acid (GABA) (Butterworth, 2003).

Ammonia hypothesis

Ammonia is produced in the gastrointestinal tract by bacterial degradation of amines, amino acids, purines, and urea. Enterocytes also converts glutamine to glutamate and ammonia by the activity of glutaminase (Stahl, 1993). Normally, ammonia is detoxified in the liver by conversion to urea by the Krebs-Henseleit cycle. Ammonia is also consumed in the conversion of glutamate to glutamine, a reaction that depends upon the activity of glutamine synthetase. Two factors contribute to the hyperammonemia that is seen in cirrhosis. First, there is a decreased mass of functioning hepatocytes, resulting in fewer opportunities for ammonia to be detoxified by the above processes. Secondly, portosystemic shunting may divert ammonia-containing blood away from the liver to the systemic circulation (Chatauret and Butterworth, 2004).

Normal skeletal muscle cells do not possess the enzymatic machinery of the urea cycle but do contain glutamine synthetase. Glutamine synthetase activity in muscle actually increases in the setting of cirrhosis and portosystemic shunting. Thus, skeletal muscle is an important site for ammonia metabolism in cirrhosis. However, the muscle wasting that is observed in patients with advanced cirrhosis may potentiate hyperammonemia (Groeneweg *et al.*, 1998). The kidneys express glutaminase and, to some extent, play a role in ammonia production. However, the kidneys also express glutamine synthetase and play a key role in ammonia metabolism and excretion (Stahl, 1993).

Brain astrocytes also possess glutamine synthetase. However, the brain is not able to increase glutamine synthetase activity in the setting of hyperammonemia. Thus, the brain remains vulnerable to the effects of hyperammonemia (Sidhu *et al.*, 2011). Ammonia has multiple neurotoxic effects. It can alter the transit of amino acids, water, and electrolytes across astrocytes and neurons. It can impair amino acid metabolism and energy utilization in the brain. Ammonia can also inhibit the generation of excitatory and inhibitory postsynaptic potentials (Weissenborn *et al.*, 2001). Additional support for the ammonia hypothesis comes from the clinical observation that treatments that decrease blood

ammonia levels can improve hepatic encephalopathy symptoms (Schafer and Jones, 1982). One argument against the ammonia hypothesis is the observation that approximately 10% of patients with significant encephalopathy have normal serum ammonia levels. Furthermore, many patients with cirrhosis have elevated ammonia levels without evidence of encephalopathy. Also, ammonia does not induce the classic electroencephalographic (EEG) changes associated with hepatic encephalopathy when it is administered to patients with cirrhosis (Stahl, 1963).

GABA hypothesis

GABA is a neuro inhibitory substance produced in the gastrointestinal tract. Of all brain nerve endings, 24-45% may be GABAergic. For 20 years, it was postulated that hepatic encephalopathy was the result of increased GABAergic tone in the brain (Ahboucha and Butterworth, 2004). However, experimental work is changing perceptions regarding the activity of the GABA receptor complex in cirrhosis (Butterworth, 2000).

The GABA receptor complex contains binding sites for GABA, benzodiazepines, and barbiturates. It was believed that there were increased levels of GABA and endogenous benzodiazepines in plasma. These chemicals would then cross an extra permeable blood-brain barrier. The binding of GABA and benzodiazepines to a supersensitive neuronal GABA receptor complex permitted the influx of chloride ions into the postsynaptic neurons, leading to the generation of an inhibitory postsynaptic potential (Ahboucha and Butterworth, 2004). However, experimental work has demonstrated that there is no change in brain GABA or benzodiazepine levels. Similarly, there is no change in the sensitivity of the receptors of the GABA receptor complex (Ahboucha *et al*., 2006).

Previously, it was believed that the administration of flumazenil, a benzodiazepine receptor antagonist, could improve mental function in patients with hepatic encephalopathy. It now appears that flumazenil improves mental function in only a small percentage of patients with cirrhosis (Schafer and Jones, 1982).

The neuronal GABA receptor complex contains a binding site for neurosteroids. Today, some investigators contend that neurosteroids play a key role in hepatic encephalopathy. In experimental models, neurotoxins, like ammonia and manganese, increase the production of the peripheral-type benzodiazepine receptor (PTBR) in astrocytes. PTBR, in turn, stimulates the conversion of cholesterol to pregnenolone to neurosteroids. Neuro steroids are then released from the astrocyte. They are capable of binding to their receptor within the neuronal GABA receptor complex and can increase inhibitory neurotransmission (Bajaj *et al*., 2010).

One study compared the levels of various chemicals in autopsied brain tissue from patients with cirrhosis who either died in a hepatic coma or died without evidence of hepatic encephalopathy. Elevated levels of allopregnanolone, the neuroactive metabolite of pregnenolone, were found in the brain tissue of patients who died in hepatic coma. Brain levels of benzodiazepine receptor ligands were not significantly elevated in patients with or without coma. This work further bolsters the role of neurosteroids in hepatic encephalopathy (Sotil *et al*., 2009).

Reversibility of hepatic encephalopathy

Classically, hepatic encephalopathy was regarded as a reversible condition. Patients appeared to improve with either drug therapy (e.g., lactulose or rifaximin) or liver transplantation. However, a recent study assessed cirrhotic patients who had apparently recovered from an episode of overt hepatic encephalopathy. After careful psychometric testing, it was discovered that these clinically improved patients had residual cognitive impairment compared with cirrhotic patients with either minimal hepatic encephalopathy or no encephalopathy (Garcia-Martinez *et al*., 2011). Sotil *et al.* (2009) evaluated 39 patients who had undergone liver transplantation about 1.5 years before the study. The 25 patients who

had hepatic encephalopathy prior to transplantation, on the whole, performed worse on psychometric testing than the 14 patients with no history of overt encephalopathy prior to transplantation (Blei and Córdoba, 2001).

In 2011, Garcia-Martinez *et al.* assessed cognitive function in 52 patients who had undergone liver transplantation. Global cognitive function after transplantation was worse in patients with a history of alcohol-induced cirrhosis, patients with diabetes, and patients with a history of hepatic encephalopathy prior to transplantation. Furthermore, brain volume (as assessed by MRI) after transplantation was smaller in patients with a history of hepatic encephalopathy prior to transplantation than in patients with no overt encephalopathy. These are provocative findings that require additional investigation (Kappus and Bajaj, 2012).

Clinical presentation

Grading of the symptoms of hepatic encephalopathy is performed according to the so-called West Haven classification system (Munoz, 2007).

Grade 0: Minimal hepatic encephalopathy (also known as covert hepatic encephalopathy (Ferenci *et al.*, 2002) and previously known as subclinical hepatic encephalopathy); lack of detectable changes in personality or behavior; minimal changes in memory, concentration, intellectual function, and coordination; asterixis is absent.

Grade 1: Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks.

Grade 2: Lethargy or apathy; disorientation; inappropriate behavior; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in the ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time.

Grade 3: Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech.

Grade 4: Coma with or without response to painful stimuli.

With minimal hepatic encephalopathy, patients may have normal abilities in the areas of memory, language, construction, and pure motor skills. However, patients with minimal hepatic encephalopathy demonstrate impaired complex and sustained attention. They may have delays in choice reaction time. They may even have impaired fitness to drive (Bajaj *et al.*, 2008; Bajaj *et al.*, 2009). Typically, patients with minimal hepatic encephalopathy have a normal function on standard mental status testing but abnormal psychometric testing. Neurophysiologic tests in common use are the number connection test, the digit symbol test, the block design test, and tests of reaction times to light or sound (e.g., the critical flicker test) (Bajaj *et al.*, 2008).

Patients with grade 1 hepatic encephalopathy typically demonstrate decreased short-term memory and concentration on mental status testing. However, grade 1 hepatic encephalopathy may be difficult to diagnose. The presence of disorientation and asterixis are characteristic of grade 2 hepatic encephalopathy (Bajaj *et al.*, 2011). The borderline between covert and overt hepatic encephalopathy is being redrawn. Until recently, the term "overt" hepatic encephalopathy was applied to patients with grades 1 through 4 encephalopathy. Now, patients with grades 0 and 1 hepatic encephalopathy are said to be "covert"; patients with grades 2 through 4 hepatic encephalopathy are said to be "overt". (Burkhard *et al.*, 2003).

In terms of the physical examination finding of asterixis, it must be emphasized that this flapping tremor of the extremities is also observed in patients with uremia, pulmonary insufficiency, and barbiturate toxicity (Bajaj *et al.*, 2011). Some patients

with hepatic encephalopathy show evidence of fetor hepaticus, a sweet, musty aroma of the breath believed to be secondary to the exhalation of mercaptans (Bajaj *et al.*, 2009). Other potential physical examination findings include hyperventilation and decreased body temperature. Extrapyramidal symptoms including tremor, bradykinesia, cog-wheel rigidity, and shuffling gait have been described in patients with portosystemic shunting (Kok *et al.*, 2003; Caldwell *et al.*, 2010).

These symptoms may or may not be associated with hyperammonemia. It is postulated that manganese deposition in the basal ganglia may predispose patients to develop these symptoms (Bustamante *et al.*, 1999). However, some patients with the "Parkinsonian phenotype of hepatic encephalopathy" may respond to treatment with rifaximin (Conn *et al.*, 2006). Another neurologic condition that may be seen in the setting of portosystemic shunting is hepatic myelopathy. It is a rare condition that has been described in patients with cirrhosis of varying degrees of severity, patients who have undergone portosystemic shunt surgery, or the creation of a transjugular intrahepatic portosystemic shunt (TIPS), and noncirrhotic patients with portosystemic shunts. Patients may present with lower extremity weakness, difficulty walking, spastic paraparesis, and hyperreflexia (Singhal *et al.*, 2009).

Although patients typically have concomitant hepatic encephalopathy, this is not invariable (Hartmann *et al.*, 2000). Symptoms may be rapidly progressive in some patients. Neurologic deficits do not typically respond to standard medical therapies for hepatic encephalopathy. Neurologic improvement has been described after TIPS closure and after liver transplantation (Kulisevsky *et al.*, 1992; Stewart *et al.*, 2005). An elevated blood ammonia level is the classic laboratory abnormality reported in patients with hepatic encephalopathy.

This finding may aid in correctly diagnosing patients with cirrhosis who present with altered mental status (Bajaj *et al.*, 2008). However, serial ammonia measurements are inferior to clinical assessment in gauging improvement or deterioration in a patient under therapy for hepatic encephalopathy. Checking the ammonia level in a patient with cirrhosis who does not have hepatic encephalopathy has no utility. Only arterial or free venous blood specimens must be assayed when checking the ammonia level. Blood drawn from an extremity to which a tourniquet has been applied may provide a falsely elevated ammonia level when analyzed. Classic EEG changes associated with hepatic encephalopathy are high-amplitude, low-frequency waves and triphasic waves. However, these findings are not specific to hepatic encephalopathy. When seizure activity must be ruled out, an EEG may be helpful in the initial workup of a patient with cirrhosis and altered mental status. Visual evoked responses also demonstrate classic patterns associated with hepatic encephalopathy. However, this test is not in common clinical use. Computed tomography (CT) and magnetic resonance imaging (MRI) studies of the brain may be important in ruling out intracranial lesions when the diagnosis of hepatic encephalopathy is in question (Ferenci *et al.*, 2002).

MRI has the additional advantage of being able to demonstrate hyperintensity of the globus pallidus on T1-weighted images, a finding that is commonly described in hepatic encephalopathy (*Polson and Lee, 2005*; Poordad, 2006). This finding may correlate with increased manganese deposition within this portion of the brain (*Polson and Lee*, 2005).

Precipitating factors of hepatic encephalopathy

Some patients with a history of hepatic encephalopathy may have normal mental status while under treatment. Others have chronic memory impairment in spite of medical management. Both groups of patients are subject to episodes of worsened encephalopathy. Common precipitating factors are as follows (*Bajaj, 2010*).

Renal failure

Renal failure leads to decreased clearance of urea, ammonia, and other nitrogenous compounds (Garcia-Martinez *et al.*, 2011).

Gastrointestinal bleeding

The presence of blood in the upper gastrointestinal tract results in increased ammonia and nitrogen absorption from the gut. Bleeding may predispose to kidney hypoperfusion and impaired renal function. Blood transfusions may result in mild hemolysis, with resulting elevated blood ammonia levels.

Infection

Infection may predispose to impaired renal function and to increased tissue catabolism, both of which increase blood ammonia levels (Bajaj *et al.*, 2011).

Constipation

Constipation increases intestinal production and absorption of ammonia.

Medications

Drugs that act upon the central nervous system, such as opiates, benzodiazepines, antidepressants, and antipsychotic agents, may worsen hepatic encephalopathy (Garcia-Martinez *et al.*, 2011).

Diuretic therapy

Decreased serum potassium levels and alkalosis may facilitate the conversion of NH_4^+ to NH_3. At the author's institution, diuretic-induced hypovolemia is the most common reason for patients with previously well-controlled hepatic encephalopathy to present to the emergency room with worsening mental function (Poordad, 2006).

Dietary protein overload

This is one of the infrequent causes of hepatic encephalopathy; however, it can rarely present (Poordad, 2006).

Epidemiology of hepatic encephalopathy

In patients with cirrhosis, the risk of developing hepatic encephalopathy is 20% per year, and at any time, about 30–45% of people with cirrhosis exhibit evidence of overt encephalopathy.

The prevalence of minimal hepatic encephalopathy detectable on formal neuropsychological testing is 60–80%; this increases the likelihood of developing overt encephalopathy in the future (Bell, 2009). Once hepatic encephalopathy has developed, the prognosis is determined largely by other markers of liver failure, such as the levels of albumin (a protein produced by the liver), the prothrombin time (a test of coagulation, which relies on proteins produced in the liver), the presence of ascites and the level of bilirubin (a breakdown product of hemoglobin which is conjugated and excreted by the liver) (Kappus *et al.*, 2012).

Together with the severity of encephalopathy, these markers have been incorporated into the Child-Pugh score; this score determines the one- and two-year survival and may assist in a decision to offer liver transplantation (Davis *et al.*, 2003). In acute liver failure, the development of severe encephalopathy strongly predicts short-term mortality and is almost as important as the nature of the underlying cause of the liver failure in determining the prognosis. Historically, widely used criteria for offering liver transplantation, such as King's College Criteria, are of limited use and recent guidelines discourage excessive reliance on these criteria. The occurrence of hepatic encephalopathy in patients with Wilson's disease (hereditary copper accumulation) and mushroom poisoning indicates an urgent need for a liver transplant (Bustamante *et al.*, 1999).

HE occurs as a complication of advanced liver disease, either chronic or acute (Bajaj *et al.*, 2007). It is difficult to accurately assess the disease burden of chronic liver disease (CLD) since liver disease frequently has an insidious onset and a long latency period. Most patients, therefore, do not seek medical attention until late in the clinical course of the disease when complications develop (Singhal, 2009). The prevalence of CLD in the United States is approximately between 7 and 11 million cases (Mullen, 2006). Approximately 150,000 individuals are newly diagnosed with CLD each year by gastroenterologists, and, of these, approximately 30,000 (20%) present with cirrhosis (Blei and Córdoba, 2001).

While the prevalence of hepatitis C is decreasing, complications including cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, and death in the large cohort of patients infected in the 1980s and early 1990s are expected to increase significantly through 2030 as the disease progresses (Hartmann *et al.*, 2000). As with CLD in general, accurate data about the incidence and prevalence of HE is lacking. It is thought that most patients with cirrhosis will develop some degree of (HE) at some point during the course of the disease.

Current estimates are that MHE occurs in up to 80% of cirrhotic patients, while OHE occurs in up to 45% of cirrhotic patients and up to 50% of patients with trans jugular intrahepatic portosystemic shunts (TIPS) (Bajaj, 2008). Patients with MHE have a higher likelihood of developing OHE than those with no symptoms. OHE is associated with a poor prognosis. Following the first episode of OHE, one study found that survival probability was 42% at 1 year and 23% at 3 years (Mullen, 2007). OHE also occurs as a complication of acute liver failure (Ferenci *et al.*, 1998).

Diagnosis of hepatic encephalopathy

The nomenclature for characterizing the various forms of HE according to cause, duration, and characteristics has been standardized and has been generally accepted (Romero-Gómez *et al.*, 2007). For OHE, the characteristic neurologic features, the existence of the acute or chronic liver disease, the exclusion of other etiologies of neuropsychiatric symptomatology, and the identification of a precipitating factor are essential for establishing a diagnosis (Bajaj *et al.*, 2008). neuropsychologic and/or neurophysiologic testing is required to detect mental impairment that precedes clinical HE since altered mental state and neurologic abnormalities are not clinically apparent in patients with MHE (Bajaj *et al.*, 2007).

No universally accepted standardized methods have been established for the diagnosis of MHE. Cirrhotic patients who are ambulatory and capable of living independently are the ones most affected by MHE and should be tested (Bajaj *et al.*, 2007). 16 Patients who do not have MHE should be tested every 6 months to 1 year or after events that can precipitate OHE (Bajaj *et al.*, 2007). A summary of current diagnostic methods along with the advantages and limitations of each is presented (Cordoba *et al.*, 2004). Neuropsychologic psychometric "pencil-and-paper" tests are the tests most commonly utilized in clinical studies for assessing cognitive and motor abnormalities in patients without clinical evidence of HE (Romero-Gómez *et al.*, 2007). The 4 tests utilized most frequently are the number connection test A (NCT A), the number connection test B (NCT B), the digit symbol test (DST), and the block design test (BDT). Another battery of tests that is used frequently is referred to as the PSE-Syndrome Test and includes the NCT A, NCT B, DST, line-tracing, and serial-dotting tests. The results of the 5 tests are reported as the psychometric hepatic encephalopathy score (PHES) (Als-Nielsen *et al.*, 2004; Mas *et al.*, 2003).

A patient is considered to have MHE if they fall more than 2 standard deviations from normal on at least 2 psychometric tests (Miglio *et al.*, 1997). Administration of psychometric tests can take from one-half to 1 hour depending on the tests utilized (Bass *et al.*, 2010). Although psychometric tests can be administered in the office setting, it is probably best to have the tests performed in a psychology testing laboratory where the staff is experienced in administering and interpreting the tests (Sidhu *et al.*, 2011).

A recent survey of American Association for the Study of Liver Diseases members found that, while 84% of those surveyed thought that MHE was a significant problem and 74% thought that it should be tested for, 34% tested less than 50% of their at-risk patients and 38% never tested for MHE (Bass *et al.*, 2010). Among reasons given for not testing were that testing adds time to the clinic visit (cited by 85% of those who did not test) and that testing was difficult and expensive and required trained personnel (cited by 75% of those who did not test) (Kircheis *et al.*, 1997).

Recently developed computer-based tests may improve testing rates. The Critical Flicker Frequency (CFF) test and the Inhibitory Control Test (ICT) are 2 such tests. To administer the CFF, a portable, battery-powered analyzer (Hepatonorm Analyzer) evokes pulses of light. The initial frequency of the pulse is 60 Hz which gives the impression of a steady light (Sidhu *et al.*, 2011). The frequency is gradually reduced, and the patient identifies the frequency at which the steady light changes to a flicker by pressing a switch. In a recent clinical study, 35 patients with cirrhosis and MHE (diagnosed by PHES) had a lower mean CFF (35.6±4.1 Hz) compared with 79 patients with cirrhosis without MHE (40.5±3.7) or compared with 103 healthy controls (42.7±3.6) (Pinterspersed with the letters X and Y (Bass *et al.*, 2010).

The patient is instructed to respond only when X and Y are alternating (called targets) and to refrain from responding when X and Y are not alternating (called lures). The test consists of a training run and 6 test runs of approximately 2 minutes each. The 6 test runs contain 40 lures, 212 targets, and 1728 random letters. The lure and target response rates and the lure and target reaction times are automatically calculated. Lower lure response rates, higher target response rates, and shorter lure and target response times are indicative of good psychometric performance (Sidhu *et al.*, 2011; Bass *et al.*, 2010). A recent trial compared ICT lure and target response rates and lure and target reaction times in cirrhotic patients diagnosed as MHE+ (n=87) or MHE– (n=48) by NCT A, BDT, and DST. Using a cut-off of >5 lures per person to diagnose MHE, of the 87 patients identified as MHE + by psychometric testing, 76 had >5 lures. Of the 48 patients identified as MHE– by psychometric testing, 37 had < 5 lures. ICT testing was performed on a subpopulation of patients (n=10) tested prior to (26±5 days) and after (35±8 days) transvenous intrahepatic portosystemic shunting (TIPS) placement. Mean ICT lure response increased significantly from 5.2±3.8 to 9.4±4.6 (P=0.02). Conversely, a subgroup of patients (n=17) placed on a 60-day probiotic yogurt supplemental diet had a significant decrease in lure response from 10±5 prior to the diet to 5±3 after 60 days of yogurt supplementation (P=0.002). The ICT appears to be a sensitive, reliable, and valid test for both the diagnosis of MHE and for monitoring changes in clinical status (Delcker *et al.*, 2000).

Differential diagnosis

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 initiation of treatment with lactulose (Delcker *et al.*, 2000).

Differential diagnoses of encephalopathy are as follows (Marchesini *et al.*, 1996):

Intracranial lesions, such as subdural hematoma, intracranial bleeding, stroke, tumor, and abscess.

Infections, such as meningitis, encephalitis, and intracranial abscess.

Metabolic encephalopathies, 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 intakes, 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.

Management of hepatic encephalopathy

Approach considerations

The approach to the patient with hepatic encephalopathy depends upon the severity of mental status changes and upon the certainty of the diagnosis. As an example, a patient with known cirrhosis and mild complaints of decreased concentration might be served best by an empiric trial of rifaximin or lactulose and a follow-up office visit to check its effect. However, the patient presenting to the emergency department with severe hepatic encephalopathy requires a different approach. General management recommendations include the following:

Exclude non-hepatic causes of altered mental function.

Consider checking an arterial ammonia level in the initial assessment of a hospitalized patient with cirrhosis and with impaired mental function. Ammonia levels have less use in a stable outpatient.

Precipitants of hepatic encephalopathies, such as hypovolemia, metabolic disturbances, gastrointestinal bleeding, infection, and constipation, should be corrected.

Avoid medications that depress central nervous system function, especially benzodiazepines. Patients with severe agitation and hepatic encephalopathy may receive haloperidol as a sedative. Treating patients who present with coexisting alcohol withdrawal and hepatic encephalopathy is particularly challenging. These patients may require therapy with benzodiazepines in conjunction with lactulose and other medical therapies for hepatic encephalopathy.

Patients with severe encephalopathy (i.e., grade 3 or 4) who are at risk for aspiration should undergo prophylactic endotracheal intubation. They are optimally managed in the intensive care unit.

Most current therapies are designed to treat hyperammonemia which is a hallmark of most cases of hepatic encephalopathy (Sidhu *et al.*, 2011).

Treatments to decrease intestinal ammonia production

Diet

In the late 19th century, it was recognized that the feeding of a high-protein to dogs that had undergone portosystemic shunt surgery could produce symptoms of abnormal coordination and stupor in the treated animals. In the 20th century, low-protein diets were routinely recommended for patients with cirrhosis, in hopes of decreasing intestinal ammonia production and preventing exacerbations of hepatic encephalopathy. An obvious consequence was the worsening of preexisting protein-energy malnutrition. Protein restriction may be appropriate in some patients immediately following a severe flare of symptoms (i.e., episodic hepatic encephalopathy). However, protein restriction is rarely justified in patients with cirrhosis and persistent hepatic encephalopathy. Indeed, malnutrition is a more serious clinical problem than hepatic encephalopathy for many of these patients (Miglio *et al.*, 1997).

According to previous experience, it is the infrequent patient who is intolerant of a diet high in protein. Most patients with mild chronic hepatic encephalopathy tolerate more than 60-80 g of protein per day. Furthermore, one study administered a protein-rich diet (>1.2 g/kg/d) to patients with advanced disease awaiting liver transplantation without inducing a flare of encephalopathy symptoms (Bresci *et al.*, 1996). In another randomized study, patients with severe episodic encephalopathy to either a low-protein diet or a high-protein diet administered via nasogastric tube (Sushma *et al.*, 1992). All patients received the same regimen of neomycin per nasogastric tube. Mental function improved at the same rate in both treatment groups. Importantly, patients receiving the low-protein diet had evidence

of increased protein breakdown during the duration of the study (Marchesini *et al*., 1996).

Diets containing vegetable proteins appear to be better tolerated than diets rich in animal protein, especially proteins derived from red meats. This may be because of increased content of dietary fiber, a natural cathartic, and decreased levels of aromatic amino acids. Aromatic amino acids, as precursors of the false neurotransmitters tyramine and octopamine, are thought to inhibit dopaminergic neurotransmission and worsen hepatic encephalopathy (Cordoba *et al*., 2004).

The author recommends that patients consume well-cooked chicken and fish in addition to vegetable proteins. Malnourished patients are encouraged to add commercially available liquid nutritional supplements to their diet. Patients infrequently require specialized treatment with oral or enteral supplements rich in branched-chain amino acids (Bajaj *et al*., 2008).

Cathartics

Lactulose (beta-galactosidofructose) and lactilol (beta-galactosidosorbitol) are non-absorbable disaccharides that have been in common clinical use since the early 1970s (the latter is not available in the United States). They are degraded by intestinal bacteria to lactic acid and other organic acids (Bass *et al*., 2010).

Antibiotics

Neomycin and other antibiotics, such as metronidazole, oral vancomycin, paromomycin, and oral quinolones, are administered in an effort to decrease the colonic concentration of ammonia genic bacteria. Initial neomycin dosing is 250 mg orally 2-4 times a day. Doses as high as 4000 mg/d may be administered. Neomycin is usually reserved as a second-line agent after the initiation of treatment with lactulose. Long-term treatment with this oral aminoglycoside runs the risk of inducing ototoxicity and nephrotoxicity because of some systemic absorption.

Rifaximin (Xifaxan, Salix Pharmaceuticals, Inc, Morrisville, NC), a non-absorbable derivative of rifampin, has been used in Europe for more than 20 years for a wide variety of gastrointestinal indications. Multiple clinical trials demonstrated that rifaximin at a dose of 400 mg taken orally 3 times a day was as effective as lactulose or lactitol at improving hepatic encephalopathy symptoms (Batshaw *et al*., 2001; Ghabril *et al*., 2013). Similarly, rifaximin was as effective as neomycin and paromomycin. Rifaximin had a tolerability profile comparable to a placebo. It was better tolerated than both the cathartics and the other non-absorbable antibiotics (Batshaw *et al*., 2001).

In 2004, rifaximin received approval by the FDA in the United States for the treatment of travelers' diarrhea. In 2005, it received orphan drug status as a treatment for hepatic encephalopathy. In March 2010, rifaximin was approved by the FDA to reduce the recurrence of hepatic encephalopathy. The approval was based on phase 3 clinical trial conducted by (Malaguarnera *et al*., 2005).

Bass *et al*., (2010) evaluated rifaximin's ability to reduce the risk of recurrent hepatic encephalopathy (HE) (Prasad *et al*., 2007). In this double-blind, placebo-controlled, multinational, phase 3 clinical trial, 299 patients received either rifaximin 550 mg or placebo BID. Each group also received lactulose. Breakthrough episodes of HE occurred in 22% of patients treated with rifaximin and 46% of patients with placebo ($P < 0.001$). HE-related hospitalization occurred in 14% of patients treated with rifaximin and 23% of patients treated with placebo ($P = 0.01$) (Ghabril *et al*., 2013).

Peripheral edema and nausea are described in some rifaximin-treated patients. There are also questions about whether long-term treatment with rifaximin can induce microbial resistance. Thus far, microbial resistance has not been reported in patients using the medication. It remains unclear whether diarrhea caused by *Clostridium difficile* occurs at a higher rate in rifaximin-treated patients than in untreated

patients. In the study by Bass *et al.*,(2010) 2 rifaximin-treated patients and no placebo-treated patients developed C. difficile infection (Therrien *et al.*, 1997).

Rifaximin was also examined in patients with minimal hepatic encephalopathy. In a large study by Sidhu *et al.*, rifaximin was more effective than placebo in terms of improving patient performance on psychometric testing and in terms of improving health-related quality of life (Spahr *et al.*, 2007).

Treatments to increase ammonia clearance

L-ornithine L-aspartate (LOLA)

LOLA (Hepa-Merz, Merz Pharmaceuticals GmbH, and Frankfurt am Main, Germany) is available in Europe in both intravenous formulations and oral formulations. It is not available in the United States. LOLA is a stable salt of the 2 constituent amino acids. L-ornithine stimulates the urea cycle, resulting loss of ammonia. Both l-ornithine and l-aspartate are substrates for glutamate transaminase.

Their administration results in increased glutamate levels. Ammonia is subsequently used in the conversion of glutamate to glutamine by glutamine synthetase. LOLA was found to be effective in treating hepatic encephalopathy in a number of European trials (Fanelli *et al.*, 2009; Prasad *et al.*, 2007).

Zinc

Zinc deficiency is common in cirrhosis. Even in patients who are not zinc deficient, zinc administration has the potential to improve hyperammonemia by increasing the activity of ornithine transcarbamylase, an enzyme in the urea cycle.

The subsequent increase in ureagenesis results in the loss of ammonia ions. Zinc sulfate and zinc acetate have been used at a dose of 600 mg orally every day in clinical trials. Hepatic encephalopathy improved in 2 studies (Sharma *et al.*, 2012); there was no improvement in mental function in 2 other studies (Mittal *et al.*, 2011).

Sodium benzoate, sodium phenylbutyrate, sodium phenylacetate, glycerol phenylbutyrate

Sodium benzoate interacts with glycine to form hippurate. The subsequent renal excretion of hippurate results in the loss of ammonia ions. Dosing sodium benzoate at 5 g orally twice a day can effectively control hepatic encephalopathy (Sharma *et al.*, 2009). The use of the medication is limited by the risk of salt overload and by its unpleasant taste.

The medication, also used as a food preservative, is available through many specialty chemical manufacturers throughout the United States. The author has limited its use to patients with severe encephalopathy symptoms. However, in the author's opinion, doses of sodium benzoate as low as 2.5 g orally three times per week significantly improved mental function in outpatients who had persistent encephalopathy symptoms despite co-therapy with lactulose and rifaximin (Sharma *et al.*, 2009).

Sodium phenylbutyrate is converted to phenylacetate. Phenylacetate, in turn, reacts with glutamine to form phenylacetylglutamine. This chemical is subsequently excreted in the urine with a loss of ammonia ions. Sodium phenylbutyrate (Buphenyl, Ucyclyd Pharma, Scottsdale, Ariz), intravenous sodium phenylacetate in combination with sodium benzoate (Ammonul, Ucyclyd Pharma, Scottsdale, Ariz), and glycerol phenylbutyrate (Ravicti, Hyperion Therapeutics, San Francisco, Calif) are approved by the FDA for the treatment of hyperammonemia associated with urea cycle disorders(Agrawal *et al.*, 2012). The latter is currently in clinical trials in cirrhotic patients with hepatic encephalopathy (Sharma *et al.*, 2012).

L-carnitine

L-carnitine improved hepatic encephalopathy symptoms in several small studies of patients with cirrhosis (Gluud *et al.*, 2013).

Whether the medication works by improving blood ammonia levels or whether it works centrally, perhaps by decreasing brain ammonia uptake, remains unclear (Mittal *et al.*, 2011).

Treatments to improve sleep disturbances

Sleep disturbances are more common in patients with cirrhosis than in control subjects. Whether or not this relates to hepatic encephalopathy is unclear. A trial compared the histamine H1 blocker hydroxyzine to placebo in patients with cirrhosis and minimal hepatic encephalopathy (Therrien *et al*., 1997). Sleep efficiency and the patients' subjective quality of sleep improved in patients receiving hydroxyzine (25 mg) at bedtime. However, there was no accompanying improvement in cognition, as measured by neurophysiologic tests. The authors urged caution when prescribing hydroxyzine, on account of the risk of worsening encephalopathy in some patients.

Post-TIPS hepatic encephalopathy

Hepatic encephalopathy is seen in about 1 in 3 patients who undergo the creation of a Tran's jugular intrahepatic portosystemic shunt (TIPS). Typically, post-TIPS encephalopathy symptoms are well controlled with the use of rifaximin or lactulose. However, post-TIPS encephalopathy symptoms can be profound in some instances. In a study by Fanelli *et al*., (2009) 12 of 189 patients undergoing TIPS developed encephalopathy that was refractory to conventional therapy with lactulose. These patients subsequently underwent placement of an hourglass-shaped balloon-expandable polytetrafluoroethylene (ePTFE) stent-graft inside the original shunt. Encephalopathy symptoms resolved in all of the patients over the next 18-26 hours.

It is sure that such a procedure is not expected to improve a patient's overall condition. At the end of a mean of 74 weeks of follow-up, only 5 of the 12 patients remained alive and in good clinical condition.

Lactulose therapy in hepatic encephalopathy

Lactulose appears to inhibit intestinal ammonia production by a number of mechanisms. The conversion of lactulose to lactic acid results in acidification of the gut lumen. This favors the conversion of NH_4^+ to NH_3 and the passage of NH_3 from tissues into the lumen. Gut acidification inhibits ammonia genic coliform bacteria, leading to increased levels of non-ammonia genic lactobacilli. Lactulose also works as a cathartic, reducing colonic bacterial load. Initial lactulose dosing is 30 mL orally, daily, or twice daily. The dose may be increased as tolerated. Patients should be instructed to reduce lactulose dosing in the event of diarrhea, abdominal cramping, or bloating. Patients should take sufficient lactulose so as to have 2-4 loose stools per day. Great care must be taken when prescribing lactulose. Overdosage can result in ileus, severe diarrhea, electrolyte disturbances, and hypovolemia. Hypovolemia may be sufficiently severe as to actually induce a flare of encephalopathy symptoms. High doses of lactulose (e.g., 30 mL q2-4h) may be administered orally or by nasogastric tube to patients hospitalized with severe hepatic encephalopathy. Lactulose may be administered as an enema to patients who are comatose and unable to take the medication by mouth. The recommended dosing is 300 mL lactulose plus 700 mL water, administered as a retention enema every 4 hours as needed. Lactulose has been the subject of dozens of clinical trials over almost 4 decades. Many small trials demonstrated the medication's efficacy in the treatment of hepatic encephalopathy. A controversial meta-analysis published in 2004 contradicted these trials and most physicians' clinical experiences.

When assessing high-quality randomized trials, lactulose was no more effective than placebo at improving encephalopathy symptoms. In trials comparing lactulose to an antibiotic (e.g., neomycin, rifaximin), lactulose was actually inferior to antibiotic therapy. In subsequent years, multiple randomized trials have reinvestigated the efficacy of lactulose. In patients with minimal hepatic encephalopathy, lactulose was more effective than placebo in terms of improving patient performance on psychometric testing. Lactulose was studied in large randomized trials as secondary prevention against recurrent overt encephalopathy. In the study by Sharma *et al*. (2009), patients who were recovering from hepatic encephalopathy were randomized to receive lactulose (n = 61) or placebo (n = 64). Over a median follow-up

of 14 months, 12 patients (19.6%) in the lactulose group developed overt hepatic encephalopathy as compared with 30 patients (46.8%) in the placebo group (P = .001). The authors concluded that lactulose effectively prevented the recurrence of overt hepatic encephalopathy in patients with cirrhosis (Malaguarnera *et al*., 2005).

Lactulose also appeared to be effective as primary prophylaxis against the development of overt hepatic encephalopathy, although few physicians in the United States would advocate the use of lactulose for this indication. An updated meta-analysis published in 2013 included these studies and affirmed the utility of lactulose in the management of hepatic encephalopathy (Gluud *et al*., 2013).

Conclusion

Supportive care, identification and treatment of any precipitating events, a decrease of nitrogenous load in the gut, and assessment of the need for long-term therapy and liver transplant evaluation should all be included in the treatment of acute overt hepatic encephalopathy. For the treatment of acute hepatic encephalopathy, lactulose should be utilized as the first line of treatment. For people who do not respond well to lactulose, rifaximin might be added to the mix. Drug therapy, as well as the prevention or avoidance of triggering variables, such as potentially sedating drugs, are used to prevent repeat hepatic encephalopathy or treat persistent hepatic encephalopathy. As a general rule, protein restriction should be avoided because it can exacerbate hepatic encephalopathy. Cirrhotic should consume 1.2 to 1.5 grams of protein per kilogram of body weight every day. Once a diagnosis of overt hepatic encephalopathy is made, a liver transplant evaluation should be considered ineligible individuals. Persons with liver failure and repeated intractable overt hepatic encephalopathy should consider liver transplantation.

Acknowledgment

This study pays special thanks to the Director China Study Center University of Balochistan for his support, advice, and guidance.

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