

Clinical Management of Hepatic Encephalopathy

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The number of patients with cirrhosis in the United States continues to rise, and 30–45% of these patients are expected to develop hepatic encephalopathy. A broad spectrum of clinical manifestations is seen with the disorder, including mental or personality changes, asterixis, decreased energy level, impaired cognition, impaired sleep-wake cycle, decreased hand-eye coordination, psychomotor retardation, and incessant talking. Hepatic encephalopathy is a clinical diagnosis, and several scoring systems have been used to determine the severity of hepatic encephalopathy. The West Haven Criteria appear to be the scoring system most frequently used. Minimal hepatic encephalopathy has been reported to affect 60–70% of patients with cirrhosis and is predictive of the development of overt hepatic encephalopathy. An estimated 10–50% of patients who have undergone a transjugular intrahepatic portosystemic shunt for variceal bleeding develop hepatic encephalopathy. A great amount of attention has centered on the role of ammonia in hepatic encephalopathy, but that role is still largely hypothetical. Lactulose has been used for many years to minimize the effects of hepatic encephalopathy; however, noncompliance with lactulose is a common cause of rehospitalization. The pathophysiology of hepatic encephalopathy is extremely complex, and formal treatment guidelines are grossly outdated. The survival rate after 3 years among patients with hepatic encephalopathy is only 25%.

Key Words: ammonia, asterixis, cirrhosis, coma, hepatitis, hyponatremia, lactulose, transjugular intrahepatic portosystemic shunt, TIPS, West Haven criteria.

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The number of patients with cirrhosis in the United States is expected to increase exponentially in the near future, and the need for liver transplantation will also continue to increase. Several reasons can be attributed to these trends. More patients are developing cirrhosis and

nonalcoholic steatohepatitis (NASH) resulting from obesity.¹ Hepatitis C and related hepatocellular carcinoma also appear to be reaching epidemic proportions, both in the United States and abroad.^{2,3} The frequency of liver transplantation is increasing in patients with hepatitis C. The number one cause of death in patients with human immunodeficiency virus infection is liver disease.⁴ Finally, the U.S. population is aging, which allows for more time for patients to develop clinical sequelae as consequences of their liver diseases. Hepatic encephalopathy is one of the many complications of cirrhosis, and it is estimated that hepatic encephalopathy is present in 30–45% of patients with cirrhosis.⁵ This article provides a brief overview of current opinions concerning the diagnosis and management of hepatic encephalopathy.

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Defining Hepatic Encephalopathy

A wide spectrum of potentially reversible neuropsychiatric abnormalities exists in patients with liver disease^{6,7} or portosystemic shunting.⁸ Hepatic encephalopathy can lead to a variety of disturbances, including impaired social and work functioning at one extreme, and coma and death at the other.⁷ The patient's family or friends may report mental or personality changes since patients are typically unaware of any behavioral changes.⁷ Asterixis, decreased energy level, an impaired sleep-wake cycle, and impaired cognition or motor function are also part of the spectrum of clinical manifestations.⁹

Hepatic encephalopathy is a clinical diagnosis, and medical history and physical examination are important elements in the diagnosis. Decreased hand-eye coordination and subtle psychomotor retardation are present. Incessant talking, associated with perseveration, is a common symptom. Knowledge of existing liver disease and precipitating factors is essential.^{6,7} Several conditions that mimic hepatic encephalopathy must be taken into consideration in the differential diagnosis. These include toxic-metabolic causes (i.e., drug overdose), ischemic or structural brain injury, central nervous system infection or neoplasm, acute or chronic alcohol injury, postictal state, dementia, and psychiatric disorders. When the diagnosis is in doubt, measurement of ammonia levels may be supportive.⁷

Scoring Systems for Hepatic Encephalopathy

Several scoring systems have been used to determine the severity of hepatic encephalopathy. The Glasgow Coma Scale may be used to grade mental status. The Portosystemic Encephalopathy score and index may be used to grade overall severity of hepatic encephalopathy. This scoring system is composed of five elements: mental status, electroencephalogram abnormalities, blood ammonia concentration, intellectual function, and severity of asterixis. Mental status, intellectual function, and severity of asterixis are all subjective assessments. A simple test for reduced intellectual function is to have the patient connect 25 consecutively numbered circles with the time (in seconds) noted. Electroencephalogram abnormalities display subtle slowing in stage 1 hepatic encephalopathy, slow rhythms and triphasic waves at frontal regions in stages 2 and 3, and severe slowing with theta and delta waves in stage 4.

The West Haven Criteria are used by many

Table 1. West Haven Criteria

| Grade | Symptoms |
|----------------|---|
| 0 (minimal) | Mild confusion |
| 1 | Euphoria or anxiety Impaired performance of addition Shortened attention span Trivial lack of awareness |
| 2 | Disorientation to time or place Inappropriate behavior Impaired performance of subtraction Lethargy or apathy Subtle personality change |
| 3 | Confusion Gross disorientation Somnolence (may respond to verbal stimuli) |
| 4 | Coma (no response to verbal or noxious stimuli) |

hepatologists (Table 1). These criteria include an assessment of mental status and a severity assignment (grades 0–4) based on observed symptoms, many of which are subjective determinations. Grade 0 is defined as minimal hepatic encephalopathy (MHE), indicated by mild confusion, and the diagnosis is determined through psychometric or more complicated testing. Grade 4 is coma, indicated by no response to stimuli. Clearly this scoring system is quite good at differentiating hepatic encephalopathy between grades 0 and 4, but in between there are a number of gray areas that overlap.

All scoring systems for determining the severity of hepatic encephalopathy have inherent weaknesses, since several, if not all, aspects of scoring criteria are highly subjective. For this reason, our institution does not employ scoring systems alone to assess the severity of hepatic encephalopathy, and we rely largely on clinical diagnoses.

Overt Hepatic Encephalopathy

At our institution, we define overt hepatic encephalopathy as the presence of West Haven Criteria grade 1 or higher and typically diagnose its presence through clinical observation. Hepatic encephalopathy has been observed in 30–45% of patients with cirrhosis^{10,11} and in 10–50% of patients with a transjugular intrahepatic portosystemic shunt (TIPS).¹⁰ Quality of life is significantly affected in these patients.¹² There is a 50% survival rate after the first year after diagnosis and a 25% survival rate after 3 years.¹³ The 1-year survival rate is less than 50%

for patients with severe hepatic encephalopathy who are hospitalized in intensive care units.¹⁴

Overt hepatic encephalopathy is associated with a poor prognosis. In a retrospective review of 1611 patients with chronic liver disease, patients with hepatic encephalopathy had a higher 1-year mortality rate than those without hepatic encephalopathy ($p < 0.001$).¹⁵ The authors noted that hepatic encephalopathy was an independent predictor of mortality at 1 year (hazard ratio 2.16) and at the end of the entire follow-up period (hazard ratio 1.96).

Minimal Hepatic Encephalopathy

Minimal hepatic encephalopathy is defined as the presence of West Haven grade 0 and cannot be diagnosed solely through clinical observation.⁷ It affects approximately 70% of patients with cirrhosis.¹⁶ The presence of MHE significantly diminishes quality of life, including job functioning and the ability to drive an automobile.^{17, 18} As MHE increases in severity, quality of life further decreases. Assessment of quality of life in patients with MHE can be performed with a short, easy-to-administer questionnaire that measures physical functioning (8 items), psychological well-being (7 items), symptoms and adverse effects (7 items), social functioning (4 items), and general health (4 items).¹⁸

The importance of diagnosing MHE cannot be understated because it can be identified in such a large number of patients with cirrhosis.⁵ Minimal hepatic encephalopathy significantly diminishes quality of life^{17, 19} as well as working and earning capacity.⁵ Minimal hepatic encephalopathy is also predictive of the development of overt hepatic encephalopathy.²⁰ Motor vehicle driving on structured driving tests is impaired, leading to an increased risk of traffic accidents and violations.²¹⁻²³

Stages of Hepatic Encephalopathy

At the Mount Sinai Medical Center, we try to equate physical signs with the stages of hepatic encephalopathy when making a clinical assessment (Table 2). The earliest sign we see is inverted sleep-wake cycles, which is a major issue in patients with cirrhosis. Handwriting changes and aggressiveness are often reported by a spouse or partner and can also be indicative of hepatic encephalopathy. As the disease progresses, asterixis (a hand-flapping tremor), ataxia, and dysarthria may be noted. A word of caution is that asterixis has also been reported in

patients with chronic renal failure, chronic obstructive pulmonary disease, and myxedema. Gross disorientation, slurred speech, and somnolence, when accompanied by hyperreflexia and muscle rigidity, are indicative of disease progression to the third stage. Coma marks the final stage of the disease.

Neurologic Manifestations of Hepatic Encephalopathy

Common clinical signs of hepatic encephalopathy are confusion or coma, asterixis, loss of fine motor skills, hyperreflexia, cognitive deficits detected by special testing, and slow, monotonous speech. Infrequent neurologic manifestations are a positive Babinski sign, extrapyramidal-type movement disorders, clonus, decerebrate posturing, hyperventilation, and seizures.

Pathogenesis of Hepatic Encephalopathy

The pathogenesis of hepatic encephalopathy is extremely complex. An elevated ammonia level seems to play a role, but the specific role has yet to be elucidated. For instance, a comatose patient with a normal ammonia level probably does not have hepatic encephalopathy. Even an elevated ammonia level in a comatose or noncomatose patient may not be predictive of hepatic encephalopathy. Monitoring ammonia levels also plays only a minor role in managing patients with hepatic encephalopathy. Hyperammonemia, whether direct or indirect, affects changes in the plasma levels of amino acids. Toxic metabolites of ammonia are generated, which cause patients to become encephalopathic, and these metabolites result in an upregulation of γ -receptors. Certain benzodiazepine receptors also appear to be upregulated in the presence of ammonia.

A hypothesis concerning the importance of ammonia in hepatic encephalopathy begins with an alteration in the metabolism of ammonia. Half of the ammonia is produced in the portal-drained viscera, and half is produced in the colon. Hepatocytes generally remove ammonia as either urea or glutamine, but with hepatic dysfunction, this capability is markedly decreased, and sometimes even lost. In patients with chronic liver disease, skeletal muscle becomes a major organ for ammonia removal; unfortunately, these patients are muscle wasted. Ammonia has direct effects on excitatory and inhibitory neurotransmission, although the complex interplay of these effects has not been

Table 2. Stages of Hepatic Encephalopathy

| Stage | Symptoms | Physical Signs |
|-------|--|--|
| 1 | Mild confusion | Lack of coordination, limited attention span, irritability, inverted sleep-wake cycles, tremor, impaired handwriting |
| 2 | Drowsiness, personality changes, intermittent disorientation | Asterixis, ataxia, dysarthria |
| 3 | Somnolence, gross disorientation, marked confusion, slurred speech | Hyperreflexia, muscle rigidity, positive Babinski sign |
| 4 | Coma | No response to pain, decerebrate posture |

well established. Advances in molecular biology may help clarify the role of ammonia in the pathogenesis of hepatic encephalopathy; however, at present, that role is largely hypothetical.

Precipitating Factors of Hepatic Encephalopathy

A primary component of the treatment process for hepatic encephalopathy is the identification of precipitating factors. A major issue is infection, including sepsis. Inflammatory cytokines present during infection may affect ammonia levels. Sedative-hypnotic or narcotic drug use can be a factor. Many patients with hepatic encephalopathy have some degree of dehydration, particularly if they are taking lactulose; even if they are edematous or have ascites, it is our practice to hydrate them. Electrolyte disturbances, particularly hyponatremia, can be an issue, especially in patients with chronic liver disease. Acute gastrointestinal bleeding is a common presenting condition, and when there is a significant amount of blood in the intestines, ammonia levels are elevated. Head trauma is another precipitating factor, as patients with hepatic encephalopathy often fall, both before or after a hospitalization. Excess protein intake, diuretic use, and acidosis can also be precipitating factors. All these factors contain components that induce astrocyte swelling and increase oxidative stress.²⁴ Other precipitating factors include anemia, renal failure, presence of TIPS and other portosystemic shunts, and constipation. A common cause of rehospitalization in patients with hepatic encephalopathy is non-compliance with lactulose; compliance, therefore, has to be continually stressed.

Complications of Hepatic Encephalopathy

Several severe sequelae are observed in patients undergoing treatment for hepatic encephalopathy. One is an increased risk of aspiration. This

situation can be seen in a pre-coma patient with a nasogastric tube who has significant ascites and is administered lactulose, resulting in gaseous distension. Trauma resulting from an unsteady gait followed by a fall may also occur. Secondary infections, glucose intolerance, malnutrition, and renal failure are all major issues that we observe in patients with hepatic encephalopathy. These patients are usually receiving drug therapy for other conditions, so any attendant complications arising from their use are considerations. Finally, due to impaired mental functioning, decreased quality of life is almost always bound to occur. This is particularly evident in social interactions and in the ability to operate a motor vehicle.

Conclusion

Hepatic encephalopathy occurs commonly in cirrhotic patients and results in significant morbidity. There is a broad differential diagnosis, but hepatic encephalopathy is mostly a clinical diagnosis. The lack of a standardized scoring system has a large impact on studies of treatment intervention. The pathophysiology of hepatic encephalopathy is extremely complex, and formal treatment guidelines are outdated. Identification, prevention, and treatment of precipitating factors early in the course of the disease are essential. Minimal hepatic encephalopathy will probably be the focus of this disease in the future.

Participants' Discussion

After the live presentation that was the basis for this article, pharmacists participated in a panel discussion.

1. What concerns do you have about automobile driving?

Automobile driving engendered discussion because taking away driving privileges often

leads to depression from a loss of independence. When Dr. Schiano asked if any of the participants cautioned or restricted driving privileges when dispensing drugs, there was a negative response. It was pointed out that driving is less of an issue among city dwellers than among those who live in suburban or rural areas, where entire livelihoods depend on driving. It was agreed that certain patients with MHE should not be allowed to drive, such as those who drive public transportation vehicles. On the other hand, if patients are fairly compliant and have good family support, they will probably not endanger themselves or others driving short distances. An opinion was offered that MHE impacts most tellingly on blue-collar workers who drive for a living or work with their hands because the disease affects their earning capacity.

2. What is the best scoring system for assessing hepatic encephalopathy?

Dr. Schiano replied that he had never seen a provider use only a scoring system to diagnose hepatic encephalopathy. In his practice, a patient is usually assessed for asterixis and given a portion of the Mini-Mental State Examination.

3. Do you order ammonia levels to aid in the diagnosis of hepatic encephalopathy?

Dr. Schiano replied that they were not useful, but that his house staff would routinely question what the target ammonia levels should be in the management of hepatic encephalopathy. He went on to say that ammonia levels have been used as markers for improvement in some clinical trials. Ideally, an ammonia level should be collected without a tourniquet, because with a tourniquet, blood drawn distal to it can result in a falsely elevated reading. In addition, an ammonia level should be measured within 30 minutes of testing and kept on ice until that time. In most institutions, such a procedure is probably not very practical. Dr. Schiano stated that a lot of misinformation about the utility of ammonia levels exists.

4. What is a TIPS procedure?

Dr. Schiano explained that a TIPS procedure is a shunt that is placed inside the liver, typically for patients who have had variceal bleeding. It is a shunt that interventional radiologists typically insert between the hepatic vein and the portal vein within the

liver. The procedure decreases portal pressure. However, it results in blood bypassing all of the hepatic sites that generally metabolize some of the nitrogenous waste products. The procedure can often be life saving for patients with variceal bleeding, but older patients with renal dysfunction are going to have significant problems with hepatic encephalopathy. A participant questioned whether there was any mention in the literature that distinguished treatment options based on pre-TIPS or post-TIPS hepatic encephalopathy. Another participant responded that a very small study (but not a "formal" study) reported that this is an age-related problem. An older patient in the 60–70-year age range with bleeding that requires a TIPS has a much higher risk of having post-TIPS encephalopathy versus a younger patient. The diameter of the shunt and how much the pressure is reduced are additional variables that make it difficult to demonstrate statistical significance, even in the same clinical setting, so formal studies are difficult to design.

5. Should acetaminophen be ordered if a patient with hepatic encephalopathy has pain?

The participant went on to point out that acetaminophen is the number one drug-induced cause of liver disease in the United States. Dr. Schiano replied that pretransplant patients with cirrhosis should not be given nonsteroidal antiinflammatory drugs or acetaminophen with codeine or other opiates. He stated that acetaminophen 2 g/day can probably be given safely for analgesia.

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