Management of Overt Hepatic Encephalopathy

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KEYWORDS

• Hepatic encephalopathy • Liver disease • Cirrhosis
• Overt hepatic encephalopathy

Hepatic encephalopathy (HE) is a potentially reversible state of impaired cognitive function or altered consciousness in patients with liver disease or portosystemic shunting.[1] It represents a continuum of transient and reversible neurologic and psychiatric dysfunction, varying from subtly altered mental status to deep coma. It can be categorized into 3 types: type A, which occurs in acute liver failure; type B, which occurs in patients with bypass shunts; and type C, which occurs in patients with chronic liver disease.[2,3] Type C HE is of importance given the increasing burden of cirrhosis in the United States and the world. Approximately 5.5 million people in the United States have hepatic cirrhosis.[4] It is difficult to estimate the true incidence of HE, but the majority of patients with cirrhosis develop a degree of encephalopathy at some point during their disease. Overt HE (OHE) occurs in at least 30% to 45% of cirrhotic patients and 10% to 50% of patients with transjugular intrahepatic portosystemic shunt (TIPS).[5,6]

HE imposes a significant burden on patients, their families, and health care resources.[4,7] A recent 104-patient cross-sectional study in 2 transplant centers revealed that previous HE and cognitive dysfunction are associated with worse employment, financial status, and caregiver burden. Patients with previous HE had 87.5% unemployment versus 19% in those without previous HE ($P = .00001$). Patients with previous episodes of HE also had lower financial status and posed a higher caregiver burden than those who had not experienced HE.[8] Cognitive performance and Model for End-Stage Liver Disease (MELD) scores were significantly correlated with employment and caregiver burden.[8] Based on the Zarit short form, caregivers

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are at similar stress levels compared with caregivers of patients with Alzheimer disease (score 15 ± 10) and patients with advanced cancer (score 12 ± 8.5) but at lower stress levels compared with caregivers of patients with acute brain injury (score 21.7 ± 10.1).[9]

OHE is a particularly pressing problem. Episodes can occur without warning and often require inpatient hospitalization. In 2005, more than 50,000 patients required hospitalization for HE.[7] Increases in the frequency and severity of episodes of HE predict an increased risk of death.[10,11] Data presented at the 2010 annual meeting of the American Association for the Study of Liver Diseases and at the 2011 annual meeting of the European Association for the Study of the Liver (EASL) by Bajaj and colleagues[13] showed that deficits in working memory, psychomotor speed, attention, and response inhibition increase with the number and severity of episodes of OHE. It is possible that the metabolic derangements that produce OHE cause chronic neurologic injury that is not readily reversible.[12,13] For patients with severe HE who are hospitalized, 1-year and 3-year survival rates are less than 50% and less than 25%, respectively.[14]

DIAGNOSIS OF HE

OHE is diagnosed clinically, based on 2 types of symptoms: impaired mental status, as defined by the West Haven criteria (Conn score), and impaired neuromotor function.[4,15,16] The Working Party on Hepatic Encephalopathy recommends the Conn score for assessment of OHE in clinical trials.[3] More recently, the Hepatic Encephalopathy Scoring Algorithm has been used.[17] Examples of neuromotor impairment include hyperreflexia, rigidity, myoclonus, and asterixis.[16,18,19] OHE can be further subdivided into episodic or persistent and precipitated or spontaneously occurring.

THERAPY OF OVERT HE

The burden of OHE is great and the diagnosis simple. Clinicians must ensure that a patient has OHE, treat precipitating factors if necessary, triage the patient to an ICU versus floor bed, decide if intubation is necessary to protect the airway, and treat with appropriate pharmacotherapy. After an episode of OHE, prophylactic therapy with lactulose or rifaximin is recommended for an indefinite period of time or until liver transplantation. Currently available treatment strategies for OHE are presented in **Table 1**.

Clinical guidelines for OHE were published 10 years ago, and many physicians have developed comfort with older therapies.[20] As new therapies are discovered, practice patterns should change. The first step in treatment is identifying and treating precipitating causes, including but not limited to hypovolemia, gastrointestinal (GI) bleeding, infection, dehydration secondary to diuretic use, diarrhea, vomiting, hyponatremia, hypokalemia or hyperkalemia, alkalosis, surgery, renal failure, TIPS, constipation, benzodiazepine use, narcotic use, hypoxemia, hepatoma, and noncompliance with lactulose therapy.[21]

Therapy is generally focused on treating episodes after they occur. Many agents currently available reduce the nitrogenous load in the gut to reduce the accumulation of ammonia.[7,22] The 2 key therapies used to reduce circulating ammonia are nonabsorbable disaccharides and oral antibiotics. Both reduce intestinal production and absorption of ammonium ions (NH_4^+).[23] The standard of care has been nonabsorbable disaccharides (lactitol or lactulose), which decrease the absorption of ammonia through cathartic effects and by altering colonic pH.[20] Oral antibiotics have also proved useful in reducing ammonia-producing enteric bacteria.[20,24,25] The long-term use of some oral