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The diagnosis of hepatic encephalopathy is predominantly clinical, and the tests available assist in the diagnosis only by excluding other causes. Covert hepatic encephalopathy, which is defined as abnormal performance on psychometric tests when standard neurologic examination is completely normal, has gained widespread attention in recent years due to its effect on quality of life. This review focuses on the tests available to aid in the diagnosis of this significant complication of liver disease, and discusses the complex pathophysiologic mechanisms identified through new imaging techniques and their significance toward development of new therapeutic targets for this condition.

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Hepatic encephalopathy (HE) shows a wide spectrum of neuropsychiatric manifestations. A combined effort with neuropsychological and psychometric evaluation has to be performed to recognize the syndrome, whereas minimal HE (MHE) is largely under-recognized. Subtle symptoms of MHE can only be diagnosed through specialized neuropsychiatric testing. Early diagnosis and treatment may drastically improve the quality of life for many cirrhotic patients. Further research to gain better insight into the pathophysiology and diagnostic accuracy of HE will help determine future management strategies.

**Covert Hepatic Encephalopathy: Who Should Be Tested and Treated?**  473  
Steven L. Flamm

Covert hepatic encephalopathy is a common problem in cirrhosis, affecting up to 80% of patients. It is defined as test-dependent brain dysfunction with clinical consequences in the setting of cirrhosis in patients who are not disoriented. Because it is not apparent clinically, and diagnostic testing has not been standardized, the issue has often been ignored in clinical practice. Yet, the clinical consequences are notable, including impaired quality of life, diminished work productivity, and poor driving skills.

**Should We Treat Minimal/Covert Hepatic Encephalopathy, and with What?**  487  
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Hepatic encephalopathy exists along a continuum from abnormal neuropsychiatric testing in the absence of clinical findings to varying
degrees of detectable clinical findings. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism has endorsed the term “covert” to encompass minimal hepatic encephalopathy and grade I overt hepatic encephalopathy. Covert hepatic encephalopathy has been associated with poor quality of life, decreased employment, increased falls, and increased traffic accidents that significantly impact quality of life and health care expenditures. Probiotics, nonabsorbable disaccharides, rifaximin, and L-ornithine-L-aspartate have been evaluated with varying levels of success. Because of the lack of universally accepted diagnostic tools, optimal timing of testing and treatment remains controversial.

Diets in Encephalopathy
George G. Abdelsayed

As many as 80% of patients with end-stage liver disease and hepatic encephalopathy have significant protein-calorie malnutrition. Because of the severe hypercatabolic state of cirrhosis, the provision of liberal amounts of carbohydrate (at least 35 to 40 kcal/kg per day), and between 1.2 and 1.6 g/kg of protein is necessary. Protein restriction is not recommended. Branched-chain amino acid supplementation and vegetable protein are associated with improved outcomes. Dietary supplementation with vitamins, minerals (with the notable exception of zinc) and probiotics should be decided on a case-by-case basis.

The Role of Sarcopenia and Frailty in Hepatic Encephalopathy Management
Catherine Lucero and Elizabeth C. Verna

Normal regulation of total body and circulating ammonia requires a delicate interplay in ammonia formation and breakdown between several organ systems. In the setting of cirrhosis and portal hypertension, the decreased hepatic clearance of ammonia leads to significant dependence on skeletal muscle for ammonia detoxification; however, cirrhosis is also associated with muscle depletion and decreased functional muscle mass. Thus, patients with diminished muscle mass and sarcopenia may have a decreased ability to compensate for hepatic insufficiency and a higher likelihood of developing physiologically significant hyperammonemia and hepatic encephalopathy.

Ammonia and Its Role in the Pathogenesis of Hepatic Encephalopathy
Parth J. Parekh and Luis A. Balart

Hepatic encephalopathy (HE) is a commonly encountered sequela of chronic liver disease and cirrhosis with significant associated morbidity and mortality. Although ammonia is implicated in the pathogenesis of HE, the exact underlying mechanisms still remain poorly understood. Its role in the urea cycle, astrocyte swelling, and glutamine and gamma-aminobutyric acid systems suggests that the pathogenesis is multifaceted. Greater understanding in its underlying mechanism may offer more targeted therapeutic options in the future, and thus further research is necessary to fully understand the pathogenesis of HE.
Novel Ammonia-Lowering Agents for Hepatic Encephalopathy

Robert S. Rahimi and Don C. Rockey

Hepatic encephalopathy (HE) is a common complication of cirrhosis, leading to frequent hospitalizations. Because ammonia is thought to play an important role in the pathogenesis of HE, therapies specifically aimed at reducing ammonia levels have been developed for conditions causing hyperammonemia, including HE. Ammonia scavengers have been used in HE patients, leading to improvements in symptoms. Bowel cleansing with polyethylene glycol has also been studied recently, resulting in more rapid improvement in acute HE compared with lactulose. Extracorporeal devices have been used in cases of refractory HE but currently are used primarily in research settings and not approved for clinical management for HE.

Treatment of Overt Hepatic Encephalopathy

Norman L. Sussman

Hepatic encephalopathy (HE) is defined by an altered mental status in the setting of portosystemic shunting, with or without cirrhosis. The basis of HE is probably multi-factorial, but increased ammonia delivery to the brain is thought to play a pivotal role. Medical therapies have typically focused on reducing blood ammonia concentrations. These measures are moderately effective, but further improvements will require identification of new therapeutic targets. Two medications, lactulose and rifaximin, are currently approved for the treatment of HE in the USA - new compounds are available off-label, and are in clinical trials. The presence of HE is associated with a higher risk of death in cirrhotic patients. Liver transplantation typically cures HE, but HE does not increase the MELD score, and therefore does not contribute to the likelihood of liver transplantation.

Diagnosis and Management of Hepatic Encephalopathy in Fulminant Hepatic Failure

Sudha Kodali and Brendan M. McGuire

Hepatic encephalopathy (HE) is associated with cerebral edema (CE), increased intracranial pressure (ICP), and subsequent neurologic complications; it is the most important cause of morbidity and mortality in fulminant hepatic failure. The goal of therapy should be early diagnosis and treatment of HE with measures to reduce CE. A combination of clinical examination and diagnostic modalities can aid in prompt diagnosis. ICP monitoring and transcranial Doppler help diagnose and monitor response to treatment. Transfer to a transplant center and intensive care unit admission with airway management and reduction of CE with hypertonic saline, mannitol, hypothermia, and sedation are recommended as a bridge to liver transplantation.

Legal Responsibilities of Physicians When They Diagnose Hepatic Encephalopathy

John M. Vierling

Both covert hepatic encephalopathy (CHE) and overt hepatic encephalopathy (OHE) impair the ability to operate machinery. The legal responsibilities of US physicians who diagnose and treat patients with hepatic...
encephalopathy vary among states. It is imperative that physicians know the laws regarding reporting in their state. OHE represents a neuropsychiatric impairment that meets general reporting criteria. The medical advisory boards of the states have not identified OHE as a reportable condition. In the absence of validated diagnostic guidelines, physicians are not obligated to perform tests for CHE. There is a need for explicit guidance from professional associations regarding this issue.