Would you recognize this 'invisible' encephalopathy?

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Mr. Z, an obese adult with a history of portal hypertension and cirrhosis from alcoholism, visits your clinic because he is having difficulty sleeping and concentrating at work. He recently reduced his alcohol use and has improved support from his spouse. He walks into your office with an unremarkable gait before stopping to jot down a note in crisp, neat handwriting. He sits facing you, making good eye contact and exhibiting no involuntary movements. As has been the case at previous visits, Mr. Z is fully oriented to person, place, and time. You can follow one another's train of thought and collaborate on treatment decisions. You've ruled out hepatic encephalopathy. Could you be missing something?

Hepatic encephalopathy is a neuropsychiatric condition caused by metabolic changes secondary to liver dysfunction and/or by blood flow bypassing the portal venous system. Signs and symptoms of hepatic encephalopathy range from subtle changes in cognition and affect to coma. Pathophysiologic mechanisms involved in hepatic encephalopathy include inflammation, neurotoxins, oxidative stress, permeability changes in the blood-brain barrier, and impaired brain energy metabolism.[1]

Patients with poor liver function commonly have psychometrically detectable cognitive and psychomotor deficits that can substantially affect their lives. When such deficits are undetectable by routine physical and mental status examinations, the condition is called minimal hepatic encephalopathy (MHE), or latent hepatic encephalopathy. Minimal hepatic encephalopathy is associated with a reduced quality of life, sleep disturbances, fall risk, impaired ability to work and/or drive, and a risk of developing overt hepatic encephalopathy.[1]

Approximately 22% to 74% of patients with liver dysfunction develop MHE.[2] Prevalence estimates vary widely because of the poor standardization of diagnostic criteria and potential underdiagnosis due to a lack of obvious symptoms.[2]

How is MHE diagnosed?

The most commonly administered psychometric test to assess for MHE is the Psychometric Hepatic Encephalopathy Score, a written test that measures motor speed and accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction, and memory.[3,4] Other methods for evaluating MHE, including EEG, MRI, single-photon emission CT, positron emission tomography, and determining a patient's frequency threshold of perceiving a flickering light, have predictive power, but they do not have a well-defined, standardized role in the diagnosis of MHE.[2] Although ammonia levels can correlate with severity of impairment in episodic hepatic encepha-

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lopathy, they are not well correlated with the deficits in MHE, and often it is not feasible to properly measure ammonia concentrations in outpatient settings.[2]

Limited treatment options

Few studies have investigated interventions specifically for MHE. The best-studied treatments are lactulose[5] and rifaximin.[6] Lactulose reduces the formation of ammonia and the absorption of both ammonia and glutamine in the colonic lumen.[5] In addition to improving MHE, lactulose helps prevent the recurrence of episodic overt hepatic encephalopathy.[5] The antibiotic rifaximin kills ammonia-producing gut bacteria because it is minimally absorbed in the digestive system. No studies investigating rifaximin have observed antibiotic resistance, even with prolonged use. Rifaximin improves cognitive ability, driving ability, and quality of life in patients with MHE. Adding rifaximin to a treatment regimen that includes lactulose also can reduce the recurrence of overt hepatic encephalopathy.[6] Branched chain amino acids, L-carnitine, L-ornithine aspartate, treating a comorbid zinc deficiency, probiotics, and increasing vegetable protein intake relative to animal protein intake may also have roles in treating MHE.[2]

The best-studied treatments for minimal hepatic encephalopathy are lactulose and rifaximin

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