

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Diagnosis and Treatment of Hepatic Encephalopathy



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G&H What is hepatic encephalopathy, and how is the severity of this condition currently being graded?

JB Hepatic encephalopathy (HE) is a neuropsychiatric abnormality in patients who have a liver disease such as cirrhosis or in those with portosystemic shunting. HE ranges from subclinical manifestations all the way to coma. HE that is clinically apparent is referred to as overt HE, whereas HE that is difficult to define clinically is referred to as covert HE. Patients with covert HE can be completely asymptomatic and can have cognitive impairment. Covert HE includes patients with prior Grade 1 HE and those with minimal HE. Patients with minimal HE usually have never had overt HE before and currently do not have any type of behavioral problems, but when these patients undergo diagnostic testing, they have abnormal results compared with healthy controls who are age- and sex-matched but do not have cirrhosis. Grade 1 HE is difficult to diagnose unless the patient is being followed carefully. Patients with Grade 1 HE have some behavioral or sleep abnormalities, but are not disoriented and have no asterixis. Patients who are disoriented and/or have asterixis have Grade 2 HE and beyond, which is currently considered overt HE.

G&H Which patients should be tested for or suspected of having HE?

JB Overt HE is very straightforward. Patients with this condition are confused and disoriented. There is no specific test to rule in HE because it is a diagnosis of

exclusion. There are many tests to exclude HE, and the majority are related to determining whether there are any other causes for the patient's altered mental status, such as focal neurologic deficits, seizures, or psychoactive medicines (including alcohol).

As for covert HE, nearly all patients with cirrhosis who have issues with quality of life should be tested for this condition, especially if they are driving, working, and complaining about their quality of life. Those are the people who are likely to have covert HE and may benefit from treatment.

G&H Which tests have been used to diagnose HE, and what are their advantages and disadvantages?

JB Paper-and-pencil tests, neurophysiologic tests, and computerized tests can be used to diagnose covert HE. The gold standard paper-and-pencil test is the psychometric HE score (PHES). Norms are finally available in the United States, but had already been created for other countries. The PHES is a compendium of 5 tests that assess multiple levels of functioning in a patient. However, the patient has to be able to understand the tests, which can be quite complicated. Therefore, providers give a screening test, such as an animal naming test or the Mini-Mental State Examination, beforehand to make sure that the patient will be able to comprehend the tests to come.

The leading neurophysiologic tests are the Critical Flicker Frequency (CFF) test and the electroencephalogram (EEG). The CFF test is more user-friendly, but it

requires binocular vision and is quite expensive. The EEG is one of the gold standard neurophysiologic tests, but it requires a lot of infrastructure, is only available in specialized centers, and is difficult to perform.

There are multiple computerized tests that can be used. The EncephalApp Stroop test may be used as a first-line screening test because it can be done within 3 to 7 minutes on any Apple or Android device and is free to download. After the test is complete, it provides a score that can be entered on the application's website (www.encephalapp.com) to see whether the patient has minimal or covert HE.

G&H Is a single test sufficient, or is a combination of tests always needed?

JB According to the current guidelines, using a combination of tests is better to rule in covert HE when comparing patients from different centers because different types of tests evaluate different parts of the patient's brain function. The overlap between these tests is not as high as would be preferred. For example, a patient may have a positive result for the PHES but negative results for the other tests. Therefore, the guidelines state that having an abnormal PHES plus another abnormal test result makes for a more stable diagnosis and ensures impairment, especially if comparing patients from multiple centers. If patients are impaired in the PHES plus the EncephalApp Stroop test, EEG, or the CFF test, for example, it is much more likely that these patients will have covert HE than if only one test is used. However, using a combination of tests is not necessarily needed for single-center studies, where 1 test abnormality compared with norms is still considered sufficient to diagnose minimal HE.

G&H Should the patient's ammonia level be considered in the diagnostic process?

JB No. HE is a clinical diagnosis that does not rely on ammonia. There are many patients with advanced liver disease who are able to perform their daily activities who have high ammonia levels but do not have HE. Diagnosis should be guided by the patient's clinical symptoms, rather than a high ammonia level.

G&H What is the typical treatment course for covert HE?

JB Currently, treatment of covert HE is on an as-needed basis. First-line treatment is a 4- to 8-week trial of lactulose. If the patient improves, treatment can continue. Rifaximin has been studied in clinical trials for the

treatment of covert HE but is not usually used for this patient population due to logistic issues.

There is an interesting dichotomy between western and eastern populations in terms of the treatment of covert HE. Lactulose is more acceptable to eastern populations than to western populations. Therefore, it is important for providers who administer lactulose to adequately explain to patients and their family members that altered bowel movements and mental status changes need to be monitored regularly.

G&H How is overt HE typically treated?

JB For an acute episode of overt HE, the first step is to make sure that the patient's airway is safe and that the precipitating factors are corrected. The provider should make sure that there is no other issue that would explain the patient's faulty mental status. The patient should then be started on HE-specific empiric treatment. First-line treatment is lactulose, and second-line treatment is rifaximin as needed. Lactulose is used as the first-line treatment for overt HE because it has the longest history of use and it works as a laxative, which is one of the main needs of these patients.

Approximately 40% to 50% of patients with overt HE respond well to just lactulose. The rest of the patients have to be started on rifaximin with or without lactulose, based on patients' tolerance, to prevent the recurrence of HE. Rifaximin is very well tolerated, but is quite expensive at least in western countries, so its use is limited to patients who have either failed lactulose or who cannot tolerate the side effects of lactulose, which are mostly gastrointestinal. In clinical practice, most of the time lactulose is given, it is administered in combination with rifaximin.

G&H What research has been conducted on combining these treatments?

JB The pivotal trial for the prevention of overt HE recurrence was done with lactulose plus rifaximin, rather than lactulose alone, and the results were published in the *New England Journal of Medicine* in 2010. In this multicenter trial, patients who had 2 episodes of HE were randomized to rifaximin or placebo. The investigators found that the patients randomized to rifaximin, many of whom were already on lactulose, had a lower chance of breakthrough HE, as well as a lower chance of rehospitalization because of HE. A future analysis examined patients on placebo in this trial who developed an HE episode and then were given open-label rifaximin. When these patients were followed for 6 months, they had significantly fewer HE episodes. These findings showed that patients who had failed with placebo could be rescued with rifaximin.

G&H Overall, how safe are these treatments?

JB There are no significant safety issues overall. Lactulose can potentially be problematic because taking too little or too much of it can cause recurrence of HE due to nonadherence or dehydration, respectively. Therefore, the administration of lactulose should be accompanied by counseling and contact with the patient to prevent hospital readmissions that could have been avoided by more judicious use of lactulose. Rifaximin has no major side effects that should be considered apart from the usual antibiotic-related risk of *Clostridium difficile* infection.

In addition, clinical experience has shown that treatment with both lactulose and rifaximin is safe long term, as the current labels for both of these agents allow lifelong use until transplantation.

G&H Has there also been research on other agents, such as other antibiotics or probiotics?

JB Metronidazole and vancomycin have been studied, but have issues related to neurotoxicity and the emergence of resistance. There have been very few high-quality studies with probiotics. In addition, there have been issues with the reliability of the colony-forming units in the probiotics that are currently available over-the-counter in the United States, as probiotic formulations are not regulated by the US Food and Drug Administration.

G&H What research has been conducted on fecal microbiota transplantation in patients with HE?

JB Results from only 2 randomized trials have been published, with the rest of the research consisting of open-label studies. In the first trial, patients with HE who were already on lactulose and rifaximin were given antibiotics plus an enema of fecal microbiota transplantation (FMT) or standard of care, and, in the second trial, 15 capsules of FMT or placebo were given. In both trials, FMT was found to be safe and improved the gut microbial composition and brain function of the patients. More importantly, the improvements extended into fewer hospitalizations and HE episodes, and patients were followed for more than 5 months to 1 year after FMT was initiated. These are encouraging findings, but it is important to remember that these were only phase 1 studies and that FMT is an investigational therapy. Thus, there is not enough information at this time to recommend FMT for the treatment of HE.

G&H How common is HE recurrence?

JB There is a very high risk of recurrence (30%-50%). HE is the leading cause of hospital readmission in the United States and Canada over 90 days after discharge.

G&H What other considerations should be taken into account when managing patients with HE?

JB Providers should make sure that the patient has good nutrition and is able to exercise, both of which are proven to be beneficial. It is sometimes thought that a low-protein diet may be helpful. However, HE is a catabolic state in which muscles are broken down, and those muscles are needed for ammonia detoxification in the body. Therefore, patients should actually be given a high-protein diet, or at least not have restricted protein intake.

Last but not least, providers should consider liver transplantation in these patients when appropriate. After all, the liver has to be fixed before the brain can be fixed in HE. When patients continue to have multiple HE episodes, providers should look for a portosystemic shunt, especially a splenorenal shunt. If present, it can be embolized, and the patient may get better afterward. Because Model for End-Stage Liver Disease scores no longer consider HE, it is challenging for providers to bring these patients to within a transplantable range.

Dr Bajaj has received grants to his institution from Valeant, Grifols, Synlogic, and Mallinckrodt. He holds the copyright for the EncephalApp Stroop test, which is free to download.

Suggested Reading

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