

Hepatic encephalopathy: what the multidisciplinary team can do

Andy Liu¹
Eric R Yoo²
Osama Siddique³
Ryan B Perumpail⁴
George Cholankeril⁵
Aijaz Ahmed⁴

¹Department of Medicine, California Pacific Medical Center, San Francisco, CA, ²Department of Medicine, University of Illinois College of Medicine, Chicago, IL, ³Department of Medicine, Brown University, Providence, RI, ⁴Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, ⁵Division of Gastroenterology and Hepatology, University of Tennessee Health Sciences Center, Memphis, TN, USA

Abstract: Hepatic encephalopathy (HE) is a complex disease requiring a multidisciplinary approach among specialists, primary care team, family, and caregivers. HE is currently a diagnosis of exclusion, requiring an extensive workup to exclude other possible etiologies, including mental status changes, metabolic, infectious, traumatic, and iatrogenic causes. The categorization of HE encompasses a continuum, varying from the clinically silent minimal HE (MHE), which is only detectable using psychometric tests, to overt HE, which is further divided into four grades of severity. While there has been an increased effort to create fast and reliable methods for the detection of MHE, screening is still underperformed due to the lack of standardization and efficient methods of diagnosis. The management of HE requires consultation from various disciplines, including hepatology, primary care physicians, neurology, psychiatry, dietician/nutritionist, social workers, and other medical and surgical subspecialties based on clinical presentation and clear communication among these disciplines to best manage patients with HE throughout their course. The first-line therapy for HE is lactulose with or without rifaximin. Following the initial episode of overt HE, secondary prophylaxis with lactulose and/or rifaximin is indicated with the goal to prevent recurrent episodes and improve quality of life. Recent studies have demonstrated the negative impact of MHE on quality of life and clinical outcomes. In light of all this, we emphasize the importance of screening and treating MHE in patients with liver cirrhosis, particularly through a multidisciplinary team approach.

Keywords: multidisciplinary, hepatic encephalopathy, management, multidisciplinary team

Introduction

The management of hepatic encephalopathy (HE) is complex, requiring coordination and multidisciplinary effort among the patient, caretaker, and health professionals, including dietician/nutritionist, social work services, physical therapy, occupational therapy, pain management, palliative care, ophthalmology, psychiatry, neurology/neurosurgery, and subspecialists within Internal Medicine – infectious disease, endocrinology, nephrology, and sleep medicine. The family and support systems are often the first to recognize early changes in cognitive function and motor skills. Initial steps in the management of HE require workup to exclude other possible etiologies such as metabolic, neoplastic, infectious, traumatic, or drug-related processes that can be responsible for the altered mental status. First-line treatment is lactulose and studies have demonstrated benefits of adding rifaximin. Secondary prophylaxis with lactulose can be effective, although adherence to therapy is lower due to poor tolerability. Secondary prophylaxis with rifaximin is another option. The coordination among the various disciplines involved in the management of a patient with HE requires clear

Correspondence: Aijaz Ahmed
Division of Gastroenterology and Hepatology, Stanford University School of Medicine, 750 Welch Road, Suite # 210, Palo Alto, CA 94304, USA
Tel +1 650 498 5691
Fax +1 650 498 5692
Email aijazahmed@stanford.edu

communication and coordination of management plan at all levels. In this article, we aim to review clinically relevant information regarding HE and the role of a multidisciplinary team in the diagnosis and management of this condition.

Classifications of HE

A comprehensive understanding of how HE is classified and diagnosed is an important component of managing patients with HE, not only for the primary health care professional but also for consultants/specialists on the multidisciplinary team. As defined by the Working Party in 1998, HE is categorized into three types: type A is acute liver failure associated encephalopathy, type B is bypass-associated encephalopathy, and type C is cirrhosis-associated encephalopathy.¹ Type C is further categorized into episodic, persistent, and minimal HE (MHE). Episodic HE involves episodes of delirium with rapid onset and fluctuation in severity. Persistent HE and MHE describe the gradient in clinical status described by overt HE (OHE). OHE is stratified into four grades by the West Haven Criteria for Semiquantitative Grading of Mental State. Grade 1 OHE is characterized by trivial lack of awareness, euphoria or anxiety, shortened attention span, and impaired performance of addition. Grade 2 OHE is characterized by lethargy or apathy, minimal disorientation, subtle personality change and inappropriate behavior, and impaired ability to subtract. Grade 3 OHE is characterized by confusion, gross disorientation, and somnolence to semi-stupor, but responsiveness to verbal stimuli. Grade 4 OHE is characterized by coma. While OHE is clinically apparent, MHE encompasses cognitive impairment only discernible through additional dedicated neuropsychiatric testing.

Diagnosis of HE

The diagnosis for MHE is challenging. The traditional gold standards for psychometric testing have been the psychometric hepatic encephalopathy score (PHES) and inhibitory control tests (ICT).² However, the regular use of these tests has been limited by their time-intensive nature and lack of standardization. The original PHES consisted of seven tests: line tracing, serial dotting, digit symbol, digit span, canceling d-test, and number connection tests A and B. Comparing the test results of patients with MHE and healthy volunteers (excluding digit span and canceling d-tests for the interest of time), a study achieved a sensitivity of 96% and specificity of 100%.³ In 2014, a study examining 132 cirrhotic patients investigated the prognostic values of electroencephalogram (EEG), PHES, and critical flicker frequency (CFF) for OHE.⁴ Although the prevalence of abnormalities in EEG,

PHES, and CFF was significantly higher in patients with grade I OHE, only the abnormalities in EEG and PHES were predictive of later occurrence of OHE. Moreover, CFF was not found to be predictive. However, in another study, improvement or worsening in HE was reflected by changes in CFF frequency.⁵ CFF sensitivity and specificity were found to be 65% and 91%, respectively.⁶ The prevalence of EEG abnormalities is higher in patients with a history of OHE.⁴ EEG has also been shown to be predictive of OHE and mortality.⁷ A study of 296 cirrhotic patients who had undergone quantified EEG detected abnormalities in 38% of patients. In these patients, EEG abnormalities were prognostic for episodes of OHE and increased mortality. The use of spectral versus visual EEG is advocated as a simpler method to screen for MHE.⁸ In comparing cirrhotic patients to healthy controls, one study found changes in peak frequency, mean amplitude, and localization of beta-2 band to the frontocentral area of the cortex as a sensitive tool in 85% of cirrhotic patients without OHE.⁹ A more recent study published in 2016 found spectral EEG to be 96% sensitive and 84% specific for diagnosing MHE, when compared to the gold standard PHES.¹⁰ In this study, EEG changes also corresponded to improvement in MHE in patients who responded to treatment. In a survey sent to liver society members, the majority of the 137 survey responders believed that MHE requires screening, contributes to poor quality of life, and is a significant problem.¹¹ However, 72% of these responders reported testing for MHE in less than half of all their patients or never testing for MHE. The top three reasons cited for not testing for MHE were: adds time to clinic visit, difficult/expensive tests requiring trained personnel, and testing not standardized in the US. While this was only a survey conducted with relatively small sample size in a particular society, it does shed light on the possible factors influencing a clinician's decision to screen or test for possible MHE. One recent attempt for a faster and reliable diagnostic method is the Stroop test, a psychological test in which the color of the text is concordant or discordant with the denoted color of the text. This discordance interferes with the reaction time of a task. For example, the text "green" may be printed in green ink, red ink, or blue ink, therefore increasing the time required to name the color. In 2013, Bajaj et al sought to utilize the Stroop test by a smartphone application as a quick and reliable screening tool for MHE.¹² They studied 125 cirrhotic patients and 134 control patients, and found Stroop performance to be significantly lower in patients with MHE as diagnosed by standard psychometric test, ICT, and PHES. A recent follow-up study published in 2016 by the same

authors investigated the use of the application, EncephalApp, across three sites.¹² EncephalApp had a sensitivity of 80% and 70% compared with PHES and ICT, respectively. As the screening methods for MHE improve and become regulated, distribution of such knowledge among different disciplines would likely be beneficial. Because of the diagnostic nature of HE, it is important to rule out other disorders that may mimic HE using a multidisciplinary approach. Psychiatric consultation may be warranted in patients with cirrhosis and psychiatric disorders because psychiatric symptoms may overlap with clinical features of HE. Sleep clinic referral can differentiate HE-related sleep manifestations from other sleep disturbances. Gait and other motor changes may be due to muscle wasting and can be perceived as HE. Therefore, consultation with physical therapy may also be necessary. Reversible causes and other etiologies that may lead to symptoms mimicking HE include underlying infectious etiology (Infectious Disease), severe hyperglycemia and poorly controlled diabetes (Endocrinology), neuropsychiatric and visual disturbances due to Wilson's disease (Neurology and Ophthalmology), alcoholic liver disease and withdrawal (Psychiatry/Behavioral Medicine), advanced renal disease and uremia (Nephrology), and cerebrovascular accident or head trauma (Neurology and Neurosurgery). Palliative care may also be consulted to focus on patient-defined goals of care and to address the patient's and family's various sources of distress. It is important to understand that noncompliance is the most common reason for readmission; thus it is important for the multidisciplinary team, including the family and caretakers, to stay informed and communicate with one another.

The importance of recognizing MHE

Recent research has drawn to light the worse outcomes in patients with MHE and their decreased quality of life.¹³ Patients with MHE also have a higher risk of developing OHE, becoming hospitalized and dying or undergoing transplantation.¹⁴ Patidar et al followed 170 cirrhotic patients, of whom 56% were diagnosed with MHE using psychometric testing, and found that 30% of patients experienced an episode of OHE and 42% became hospitalized. Patients with MHE were more than twice as likely to develop OHE and undergo hospitalization. MHE poses not only an increased burden on the health care system, but also leads to a significant decline in quality of life. In one study, patients diagnosed with MHE through an abnormal psychometric test and abnormal EEG demonstrated significant impairment in all 12 categories of the Sickness Impact Profile, a questionnaire

that analyzes one's health status using behaviorally based measures.¹⁵ Other studies found an increase in incidence in falls in patients with MHE,¹⁶ impairments in driving,¹⁷ and increase in motor vehicle accidents.¹⁸ Thus, it may be pertinent to involve occupational therapists on a case-by-case basis to optimize the work environment of patients who may be more prone to these increased risks. Lastly, it is evident that underdetection of MHE has downstream effects on the patient, caretakers, and the health care system. In a survey of 451 questionnaires in India, the most common precipitants of HE were upper gastrointestinal bleed (47%), constipation (18%), and spontaneous bacterial peritonitis (12%).¹⁹ Educating family members and care providers to be vigilant for these precipitants and other clinical clues can lead to early diagnosis, prompt treatment of subclinical or MHE and their associated complications, and timely referral to various services that stem the progression of the condition and improve support for patients. Proper nutritional guidance can be guided by diet/nutrition consultation. Social work consultation can ensure adequate support system and proper housing. Pain management consultation can help patients with pain disorders avoid or minimize use of narcotics, sedatives, or other mind-altering medications that may precipitate HE.

Ammonia levels

In clinical practice, ammonia levels are not followed through the course of HE and clinical history remains the gold standard.²⁰ Ammonia is among the toxins implicated in HE, but its levels are not regarded as an effective screening test for MHE. Gundling et al compared ammonia blood levels in Emergency Department patients with the West Haven criteria and CFF and found misdiagnoses (including both false-positive and false-negative results) in 40.7% and 49.2%, respectively.²¹ Studies also disagree over the correlation in ammonia levels and disease severity. One study of 121 patients found ammonia levels correlating with severity of HE based on the West Haven criteria.²² Because gaseous ammonia is more likely to cross the blood brain barrier, Kramer et al studied the partial pressure of ammonia and its correlation with clinical grade, comparing this to total ammonia. While both measures correlated with clinical grade of HE, the results demonstrated that partial pressure of ammonia had a stronger correlation than total ammonia.²³ Subsequent studies of ammonia measurements in cirrhotic patients with and without HE found no significant advantage to utilizing partial pressure of ammonia compared with venous ammonia levels.^{22,24,25} Shawcross et al

in London studied the role of ammonia and inflammation in MHE. Their results found presence and severity of MHE to be independent of severity of liver disease and ammonia concentration.²⁶ However, in 73% of patients, induction of hyperammonemia impaired cognitive performance on psychometric testing. Researchers also found inflammatory markers to be significantly elevated in patients with MHE.

Management of OHE

The first-line therapies for OHE are nonabsorbable disaccharides, lactulose and lactitol. Dosed to achieve three to four bowel movements per day, lactulose therapy is the mainstay of treatment. A 2016 Cochrane review included 29 randomized clinical trials comparing nonabsorbable disaccharides against placebo or no intervention; patients receiving nonabsorbable disaccharides demonstrated significant improvements in mortality.²⁷ Patients receiving therapy also reported lower rates of serious complications of liver disease including liver failure, hepatorenal syndrome, and variceal bleeding. With regards to HE, therapy was shown to be effective in treating patients with HE and preventing the development of HE. Nine randomized clinical trials compared lactulose with lactitol, finding similar efficacy in both,^{28–30} with one trial noting patients on lactitol responded more quickly³¹ and another noting better palatability.³² A 2013 study by Sharma et al investigated the use of rifaximin in a double-blind, randomized controlled trial of 120 patients with OHE.³³ Comparing patients treated with rifaximin and lactulose therapy versus lactulose alone, the study found that 76% of patients in the rifaximin group experienced reversal of HE compared to 50.8% in the lactulose group. The results also showed a significant decrease in mortality in the rifaximin group when compared with the lactulose only group (23.8% versus 49.1%). Furthermore, the rifaximin group also reported a shorter hospital stay (5.8 versus 8.2 days). For the patient population awaiting liver transplantation, the management of HE is important and may have implications in post-liver transplantation outcomes. A retrospective study assessing posttransplant outcomes found that patients with grade 3 or grade 4 HE at the time of liver transplantation demonstrated poor outcomes.³⁴ These poor outcomes were associated with increased rates of infection. Alternatives to standard lactulose therapy have been studied as well. These include a reduction in oxidative stress with the theory that systemic inflammation and oxidative stress are implicated in the pathogenesis of HE.³⁵ In a study from Egypt, 58 cirrhotic patients diagnosed with MHE by psychometric testing were treated with lactulose alone or lactulose and zinc gluconate, vitamin A, vitamin C, and vitamin E.³⁶ Posttreatment, alanine transaminase and

aspartate transaminase levels were decreased and zinc level increased in the group with antioxidant, compared to the lactulose-only group.

Secondary prophylaxis of OHE

Following an episode of HE, the focus of care is prevention of recurrent episodes of HE. Lactulose has been established as an effective therapy in secondary prophylaxis for recurrent HE. Sharma et al randomized 140 patients who recovered from HE to lactulose or placebo and found that within 14 months, 19.6% of patients in the lactulose group experienced recurrent HE compared to 46.8% in the placebo group.³⁷ The beneficial effects of lactulose became apparent after 4 months of therapy. Bass et al studied the addition of rifaximin to lactulose therapy for secondary prophylaxis of HE and found that in comparison to lactulose therapy alone, addition of rifaximin therapy decreased breakthrough episodes (22.1% lactulose and rifaximin versus 45.9% lactulose only).³⁸ Furthermore, 13.6% of patients in the rifaximin group underwent hospitalization for HE, compared to 22.6% of patients in the lactulose group. Benefits to rifaximin were found 28 days after randomization. Bajaj et al performed a retrospective study identifying predictors for recurrent HE and found that that lactulose nonadherence and lactulose-associated dehydration were associated with almost 50% of all recurrent episodes.³⁹ As part of the multidisciplinary effort, patient and family education on correct lactulose dosing and the importance of hydration may reduce recurrent episodes of OHE.⁴⁰ Thus, it is important for health care providers – primary providers and consultants alike – to stay educated and relay the information to those who are also involved in caring for patients with HE. The benefits of secondary prophylaxis have been documented beyond reduction in recurrence of HE.

Primary prophylaxis of OHE

Episodes of OHE are associated with worsening quality of life and recurrent hospitalizations, which ultimately worsen the prognosis. In 2012, Sharma et al randomized patients to placebo or lactulose and followed them over a 12-month period.⁴¹ Eleven percentage of patients in the lactulose group and 28% of patients in the placebo group developed OHE during this study. Both groups had comparable numbers of patients with MHE, and lactulose was shown to effectively improve symptoms of MHE in 66% of patients. While lactulose therapy has been studied in patients with MHE, studies of empiric lactulose for cirrhotic patients with no prior episodes of OHE are lacking; future studies should look into this further.

The role of nutrition in HE

A complete diet/nutrition evaluation is an important component in the management of HE. While reduction in protein intake has not been found to be beneficial, supplementation with branched chain amino acids has been recommended for its benefit in patients with cirrhosis and has been shown to reduce recurrence in HE.⁴² If standard protein sources are not tolerable in patients, vegetarian protein sources as well as branched chain amino acid supplementation are recommended for patients. The branched chain amino acids are thought to stimulate hepatic protein synthesis and improve nutritional status.⁴³ Alterations in gut flora have also been documented in patients with decompensated cirrhosis. Because of this, probiotics have been studied for the management of HE. The role of gut flora in the acidification of gut and absorption of ammonia has led to the use of probiotics in an attempt to modify the gut microbiome.⁴⁴ A meta-analysis of six randomized clinical trials found that probiotic therapy may significantly reduce the development of OHE in patients with cirrhosis.⁴⁵ The results demonstrated no significant difference in mortality, serum ammonia levels, or constipation. Another study compared probiotic therapy with lactulose to lactulose therapy alone, specifically in patients with MHE.⁴⁶ While both groups demonstrated improvement in psychometric testing after 2 weeks of treatment, patients on probiotics and lactulose showed continued improvement at their 8-week follow-up. The authors performed a follow-up in which patients were treated with probiotics alone, finding this to be as effective as lactulose and probiotics; moreover, probiotics alone showed long-term effects at their 8-week follow-up. Another study, conducted by Sharma et al, treated 124 patients with MHE randomized to l-ornithine l-aspartate, rifaximin, and probiotics, and found improvement in 67.7%, 70.9%, and 50% of patients, respectively.⁴⁷ A more recent meta-analysis in 2016 reviewed the results of 14 studies of probiotics in the management of HE. The findings suggested probiotics to be effective in decreasing hospitalization, improving MHE, and preventing progression to OHE in cirrhotic patients with MHE.⁴⁸ These results were similar to those of lactulose and found no improvement in mortality. While probiotics may be used in MHE, their role in secondary prophylaxis requires additional studies. Agrawal et al randomized 360 patients who recovered from HE with lactulose, probiotics, or placebo, and found both interventions to be more effective at preventing recurrent episodes of OHE.⁴⁹ Although the proportion of those who developed HE was lower in the lactulose group compared with the probiotic group, the difference between the two was not statistically

significant. The importance of proper nutrition, including the likely benefits of probiotics, should be highlighted in patients with HE; therefore, a dietician/nutritionist consult is usually helpful. This multidisciplinary approach also adds an additional measure to prevent malnutrition, bone disorders, and/or vitamin/mineral deficiencies in patients with HE.

Conclusion

In summary, HE is a diagnosis of exclusion and its management can be optimized with a multidisciplinary approach. First and foremost, family members and care providers of patients with compensated cirrhosis should be educated to seek symptom-specific consultation that may prevent or delay the onset of HE and to identify clinical clues leading to early diagnosis and prompt treatment of subclinical, covert HE, or MHE and its associated complications. These referrals include proper nutritional guidance in consultation with a dietician/nutritionist to prevent malnutrition, bone disorders, and/or vitamin/mineral deficiencies; social work services evaluation to ensure adequate support system and housing is in place; psychological evaluation with periodic psychometric testing and if needed, addiction counseling; psychiatric consultation in patients with coexisting cirrhosis and psychiatric disorders, as psychiatric symptoms may overlap with HE clinical features; evaluation by Sleep Disorders clinic to differentiate HE-related sleep manifestations from other sleep disturbances (sleep reversal, insomnia, sleep apnea, narcolepsy, etc); consultation with physical therapist if there is any change in gait and other motor skills due to muscle wasting that may be perceived as HE; occupational therapy referral on a case-by-case basis to optimize the work environment of patients expected to perform heavy physical activities (construction, farming, lifting heavy objects, operating machines/cranes, driving trucks, etc); close collaboration with Pain Management service in patients with pain disorders, with recommendations to avoid or minimize the use of narcotics, sedatives, and other mind-altering medications that can precipitate an episode of HE; and palliative care consultation to focus on patient-defined goals of care and address the patient's and family's various sources of distress. Secondly, in patients with new diagnosis of HE, reversible causes and other disorders that may mimic HE should be ruled out with a multidisciplinary approach – for example, infectious workup in consultation with Infectious Disease team in patients suspected of underlying infectious etiology-based clinical features at presentation; Endocrinology consult in patients with severe hyperglycemia and poorly controlled diabetes; Nephrology input in patients with coexisting advance renal

disease and suspicion of uremia; Neurology and Ophthalmology consultations in patients with neuropsychiatric and visual disturbances due to Wilson's Disease; Psychiatry/Behavioral health input in patients with alcoholic liver disease and presenting with symptoms of withdrawal; and Neurology and Neurosurgery input in patients who are also suspected of cerebrovascular accident or present after head trauma. Finally, in patients with established diagnosis of HE, the most common reason for readmission is noncompliance. A well-coordinated multidisciplinary approach is vital to minimize such noncompliance, to successfully manage these patients, and to improve their prognosis.

Disclosure

The authors report no conflicts of interest in this work.

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