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Covert and Overt Hepatic Encephalopathy: Current Options for Diagnosis and Treatment

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Abstract Overt hepatic encephalopathy (OHE) and covert hepatic encephalopathy (CHE) are two clinically distinct entities that are at the end of the spectrum of cognitive impairment due to portal hypertension. They are fraught with diagnostic and treatment challenges, but both could result in serious complications if not intervened upon in a timely fashion. CHE has been recognized as a harbinger to OHE providing an opportunity to intervene. There are numerous diagnostic strategies for CHE, and most require specialized equipment, trained personnel, and time. Diagnosis of OHE is significantly easier compared to CHE. As such, the psychometric tests have been more favored due to less dependence on specialized equipment and personnel, and their ability to be equally reliable compared to neuropsychological tests. While we have learned more about the pathophysiology of hepatic encephalopathy, our treatment modalities have not evolved as much. A collaborative approach to management, with development of easier reliable tests, will help us combat this epidemic.

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Introduction

Hepatic encephalopathy (HE) is a widely prevalent [1] serious complication of decompensated chronic liver disease (CLD) representing the neurological and psychiatric manifestation of porto-systemic shunting (PSS). It has been defined as "A brain dysfunction caused by liver insufficiency and or porto-systemic shunting" by the 2014 practice guidelines of the AALSD and EASL [2••]. The commonly practiced classification system that is based on clinical manifestations and specialized testing divides HE into OHE, the more obvious and recognizable form, and CHE, the more prevalent but not readily diagnosable form [3, 4]. CHE includes grade 1 and minimal HE (MHE) on the West Haven Scale (WHS) for HE [5••]. The other common classification systems for HE is based on underlying etiology [6]. Another classification for HE defines it based on duration into episodic, recurrent with repeated bouts in a 6-month time frame, and persistent, which defines a baseline altered behavior with interspersed relapses of OHE [6]. Since grade 1 HE and MHE are often difficult to distinguish clinically and have the same diagnostic approach, we shall be talking about CHE in this article. HE, in general, has an unpredictable clinical course in terms of onset and response to therapy, and it is a well-known independent predictor of mortality in cirrhotics. The estimated incidence of OHE in cirrhotics is 30–40 % during their lifetime [7] and MHE/CHE occur in 20–80 % of cirrhotics [4, 8–10].

Given the complexities in diagnosing and grading OHE, in an attempt to standardize management, the recent AASLD/EASL guidelines suggest evaluating HE as a spectrum along four axes—Axis 1: underlying reason: could be acute liver failure (type A), porto-systemic by-pass (type B), and cirrhosis (type C); Axis 2: severity of

the current episode: covert (minimal+grade I), overt (grades II–IV of the West Haven Criteria); Axis 3: time course (episodic, one episode in 6 months; recurrent, >1 episodes within 6 months; and persistent, never resolved fully); and Axis 4: spontaneous or precipitated based on the identification of precipitating factors. Axes 3 and 4 only apply to those with overt HE.

Despite optimal lactulose treatment, OHE can recur in 40 % of patients in 6 months [11•]. No data regarding CHE recurrence has been documented so far. CHE has been explored by various groups over the past decade and is now a well-recognized clinical entity. The importance and urgency of diagnosis of MHE/CHE lie in the fact that it is a predictor of impending OHE [9, 12, 13]. Therefore, the epidemiological and clinical burden of MHE/CHE is equally important as that of OHE, and its diagnosis forebears a poor prognosis as it has been shown as an independent predictor of mortality in cirrhosis itself [14].

In this article, we shall be discussing the diagnosis of OHE based on current standards, the diagnostic challenges of MHE and CHE, and subsequently discuss the current therapeutic options for treating HE (Fig. 1).

OHE—Diagnosis and WHS Testing

Diagnosis

Diagnosis of OHE is primarily by clinical manifestations based on the WHS which grades impaired mental function and impaired neuromotor functions. The spectrum of impaired mental function varies from agitation to coma, while the presence of asterixis is commonly noted in early stages of OHE. As such, HE is a diagnosis of exclusion and hence clinicians need to perform a detailed history, examination, and pertinent laboratory investigations to exclude the extensive differentials of HE.

Biochemical Tests

HE is associated with upregulated neuro-inflammation and neurotoxicity related to hyperammonemia and other toxic metabolites. Elevated levels of interleukins have been documented in acute and chronic liver failure and MHE [15, 16], but do not really have any clinical significance for testing. Serum ammonia, on the other hand, is a widely accepted screening test for HE though it lacks specificity. Venous ammonia levels

Fig. 1 Algorithm to approach OHE and CHE
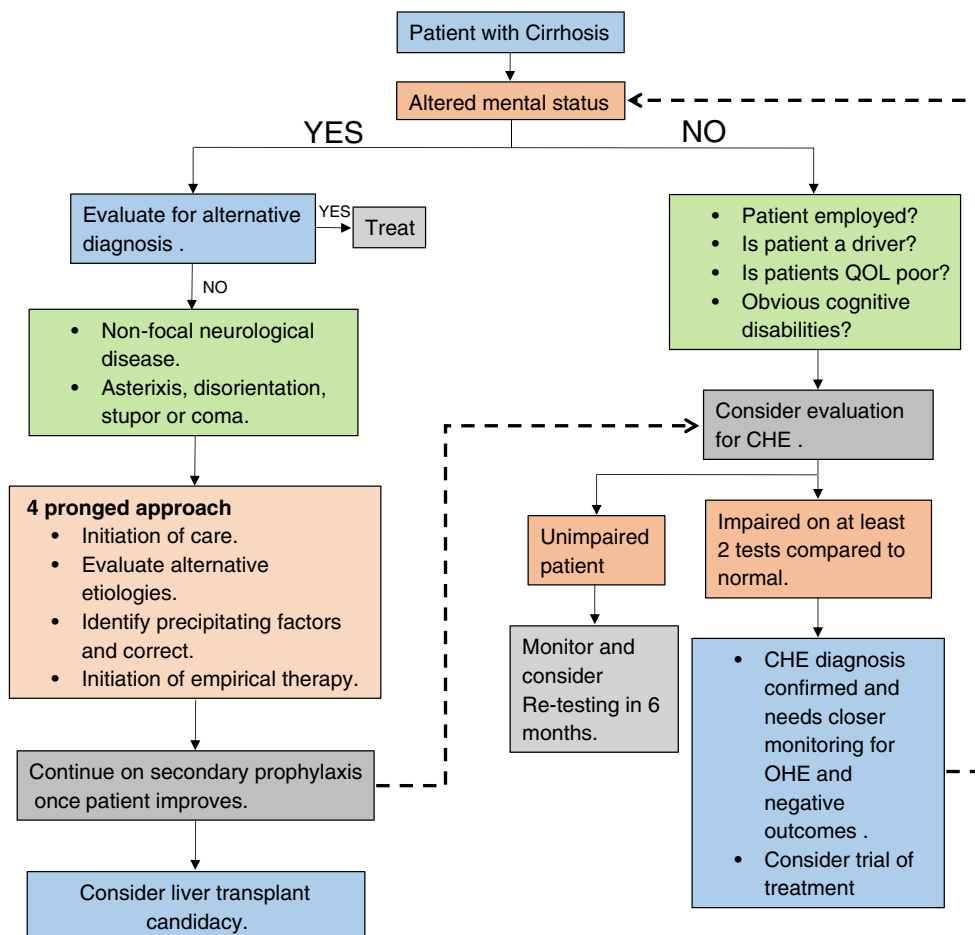
are directly affected by the method of obtaining the sample and if the sample was placed on ice. Additionally, there are multiple other non-liver-related causes of hyperammonemia such as rare congenital urea cycle disorders, to more commonly heavy exercise, GI bleeding, shock, renal disease, total parenteral nutrition, and drugs (valproic acid, salicylates, narcotics, diuretics). An increased ammonia level does not add to changes in mental functioning for the diagnosis of HE; however, in a confused cirrhotic patient, a normal ammonia should lead to reconsideration of the HE diagnosis.

Grading

West Haven Criteria (Conn Score) The WHC is the most commonly practiced grading system which was envisaged as a semi-quantitative system. Therefore, it has subjective portions which can impair its reliability in lower grades of HE. In order to improve inter-observer variability, covert HE, which combines minimal and grade I (the most subjective stage), has been defined, while overt HE has been defined as patients with disorientation and asterixis who require additional or modification of current therapy. Therefore, the staging of grade II–IV is more reliable, although the Glasgow Coma Scale could be used to define the advanced stages further. Over the years, the need for a more objective scoring system has led to the development of alternatives.

Hepatic Encephalopathy Scoring Algorithm (HESA) This scoring algorithm developed by Hassenein et al. refines the WHS into four grades through the incorporation of neuropsychological testing and clinical indicators. It is significantly more detailed, objective, has lower inter-observer variability, and hence is an effective tool for HE diagnosis in the research setting [17]. It was validated by the same group in a large clinical trial across multiple sites and proves to be a reliable diagnostic tool for grade I/II HE for the diagnosis of initial and recurrent HE. Though it is a simple, consistent test with good sensitivity, it is a long test to administer and hence is limited in use to clinical trials and not day-to-day clinical practice.

Modified-Orientation Log (MO-log) This MO-log was developed from the traumatic brain injury literature to refine the overt HE severity [18]. It focuses on a standardized orientation questionnaire, keeping in mind that disorientation to time and person are early cognitive defects in HE, therefore exploring the level of disorientation [19•]. The strengths of the MO-log test lie in its reproducibility, sensitivity to cognitive impairment, predictive ability for HE patients that are at risk for in hospital mortality and at risk for decompensation, and most importantly clinical applicability. The disadvantage is the reliance on orientation as the sole definition of altered mental status.

Clinical Hepatic Encephalopathy Staging Scale (CHESS) The CHESS was developed by Ortiz et al. to standardize observations, incorporating the WHC and GCS, being more definitive [20•]. It is relatively simpler to administer and is useful to monitor HE severity on a scale where 0 (minimal score) signifies normalcy and 9 (maximal score) signifies coma. It has been validated by two large RCTs to be effective in earlier stages of HE [21•, 22].

Full Outline of UnResponsiveness (FOUR) Score Assessment of the level of consciousness in HE does not have a standardized method. The FOUR score was developed and has been endorsed to assess the level of consciousness in comatose patients in general [23]. The FOUR score incorporates four components—visual and motor reflexes, eliminates verbal response, but incorporates assessment of brainstem reflex and breathing patterns. Mouri et al. in a prospective trial compared the Glasgow Coma Scale (GCS) to the FOUR score and validated this score showing that it is not only effective to diagnose HE but also predicts HE (WHC grade 2–4) and has the ability to discriminate between the grades of OHE. The study also showed that the score effectively predicts mortality for scores <16 [24].

Mini-Mental Status Examination (MMSE) The MMSE was initially developed in 1975 as a test to assess the neurocognitive status to diagnose dementia [25]. It has since then been studied extensively in outpatients with HE to ensure that they are able to understand cognitive tests and to exclude dementia. It is not a test for inpatients with OHE [26].

Glasgow Coma Scale (GCS) The GCS is a scale that is utilized for all comatose patients and can be adapted for assessing mental status in advanced grades of HE. It is an objective scoring system that has not been studied extensively in HE per se but can still be used in grade III and IV HE. It has no diagnostic value for grade II HE and below [27•].

Treatment

A four-pronged approach should be taken to manage OHE [2••].

1. *Initiation* of care for patients with altered consciousness. 2. *Evaluation* for alternative etiologies of altered mental status and treating them. 3. *Identification* of precipitating factors and their correction, as a majority of patients can be managed with just correction of the precipitating factor [28]. 4. *Initiation* of empirical HE therapy. Treatment strategies (Table 1) discussed will be for an initial episode of OHE and for recurrent OHE. Management of post-TIPS HE and HE related to portosystemic shunts are beyond the scope of this article.

Table 1 Pharmacotherapy options for HE

Drug	Mechanism	Advantages and disadvantages
Lactulose	Converts NH_3 to NH_4+ preventing systemic absorption	No systemic side effects but requires frequent dosing and causes flatulence. Dehydration from overuse may precipitate HE
Rifaximin	Broad-spectrum anti-bacterial that disrupts RNA synthesis	Minimal side effects profile
BCAAs (isoleucine, leucine, valine)	Promote NH_3 detoxification in skeletal muscle, prevent false neurotransmitter generation, reduce muscle catabolism	Minimal side effects profile. Ease of oral administration. More data required
LOLA	Stimulates the urea cycle and glutamine synthesis, reducing NH_3 levels	Minimal side effects profile but has to be administered IV. Poor evidence for oral formulations
Probiotics	Possibly acts by improving intestinal microbiota	No systemic side effects. No change in post-discharge outcomes
Albumin	Improves volume and organ perfusion	Minimal side effects profile. Insufficient evidence but may improve post-discharge outcomes
Miscellaneous antibiotics (neomycin, metronidazole)	Anti-bacterial and reduces pathogenic intestinal flora	Not safe and not recommended for long-term use due to extensive side effects profile

1. Non-absorbable disaccharides:

    The most widely used drug of this class is lactulose. It has been studied extensively and works primarily by reducing the production and absorption of ammonia in the gut. Lactulose is the backbone of therapy for HE and is used in the management of initial and recurrent HE for secondary prophylaxis [11•]. General consensus for dosing of lactulose is 15–30 ml two to three times a day with a goal of having two to three soft or loose bowels a day. One needs to be cautious in directions of use as overuse can result in dehydration and can rarely precipitate HE itself [29].

2. Antibiotics:

    (a) Rifaximin: Rifaximin is a broad-spectrum gut-specific antimicrobial agent. It Is FDA approved for the prevention of recurrent HE in conjunction with lactulose. It has very limited gut absorption and achieves a great concentration in the gastrointestinal tract. It works by inhibiting bacterial protein synthesis without grossly affecting the composition of the normal gut flora [30]. It has also been studied (along with lactulose) versus lactulose [31] and versus placebo [32••] for the management of recurrent HE and has shown to be effective, but has not been validated independently. It additionally has been shown to improve HRQOL in OHE [33].

    (b) Aminoglycosides: The drugs in this class that have been studied, i.e., neomycin and ribostamycin, are FDA approved for OHE treatment, but have multiple systemic side effects (nephrotoxicity, ototoxicity) and hence are not recommended.

    (c) Miscellaneous antibiotics: The other non-FDA-approved antibiotics that have been studied in OHE are metronidazole, vancomycin, and paromomycin. Metronidazole was studied against neomycin [34], vancomycin was studied against lactulose [35], and paromomycin was studied against rifaximin [36, 37], but side effects, cost, potential for resistant bacteria, and limited data make these options less favorable.

3. Other non-FDA-approved treatment strategies:

    Many novel approaches to management of HE have been investigated. Many of them have been proven to have some effect on control of symptoms, but lack sufficient evidence. These drugs could be tried in the appropriate setting, along with ongoing current standards of treatment. Glycerol phenyl butyrate (GPB) [21•], branched chain amino acids (BCAA) [38, 39], L-ornithine L-aspartate (LOLA) [40], and even albumin [22] have been studied with minimal side effects. Liver assist devices have not demonstrated any mortality benefit in chronic liver disease.

4. Liver transplant: This should always be considered in a patient with HE given that this is the only lasting cure for cirrhosis.

CHE—Diagnosis and Testing

CHE is the equally relevant, more prevalent but unfortunately lesser diagnosed form of HE. It faces many diagnostic challenges owing to the difficulty in diagnosing it using simple clinical examination, and hence often goes unrecognized [41]. It, however, has a significant impact on the health-related quality of life (HRQOL), development rate of overt HE, and

on the hospitalization and survival in cirrhotic patients [42, 43]. Therefore, efforts must be made to diagnose this entity to the fullest extent [44]. Clinicians are gradually getting more aware to this entity, but testing modalities are not yet standardized and are limited by availability, cost, and local population's normative data [45] and as such are not really suitable for regular outpatient clinics. Alternative strategies are to use high-sensitivity tests in clinics that can then be used to guide further diagnosis at a later stage in patients with cirrhosis.

The diagnostic testing would be most productive when focused on patients who would suffer the most if diagnosed with CHE. This includes patients with cognitive complaints, those with poor HRQOL, those who are current drivers, and those who are currently employed. Screening strategies could be the use of four questions of the Sickness Impact Profile [46] or the use of the Stroop EncephalApp.

Broadly, tests for CHE are divided into psychometric and neurophysiological tests. Psychometric tests are divided into simple paper-and-pencil tests and computerized tests (Table 2). The majority of tests are easy to administer after training appropriate staff, but are lengthy for day-to-day clinical practice. Per the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) 2 tests, the Psychometric Hepatic Encephalopathy Score (PHES) and the Repeatable Battery for the Assessment of Neurophysiological status are the preferable paper-and-pencil tests [45]. Computerized tests, clinically, are slightly more advantageous over paper-

and-pencil tests owning to standardization and lesser use of motor functions. Since the changes to cognition and QOL are fine, no clinically valid grading system has been developed yet. For the purpose of practicality, we shall discuss the tests based on the need for specialized equipment and specialists.

Diagnosis

Biochemical Tests

There is no role for serum markers for the diagnosis of CHE, as patients are often normal on general examination.

Test That Do Not Require Specialized Equipment and Trained Personnel

Inhibitory Control Test (ICT) The ICT is a computerized test originally developed to detect deficits in attention and response inhibition in schizophrenia, traumatic brain injury, and attention deficit disorder in children. It has been applied successfully to diagnose CHE and predict OHE in CLD patients, with a sensitivity and specificity of 90 % [47]. It essentially is a computerized test that shows a sequence of letters on a computer screen every 500 ms without any intervals. The subject is then instructed to respond to predetermined alternating patterns of the letters X and Y (targets) and non-alternating presentations of the letters X and Y (lures), and the response

Table 2 Assessment tools for OHE and CHE

Tests for OHE	Special equipment	Trained personnel	Advantages	Disadvantages	Time required
WHC	No	No	Quick bedside test	High inter-observer variability	<5 min
HESA	No	Yes	Accurate with low inter-observer variability	Time consuming for clinical practice and requires expertise	~10–20 min
MO-log test	No	No	Quick bedside accurate test	Requires patient cooperation and restricted in unconscious patients	~10 min
CHESS	No	No	Accurate and detailed with good sensitivity	Can be time consuming for clinical practice	~20 min
FOUR score	No	Yes	Short test with excellent sensitivity	Needs expertise for neurological assessment	~10 min
PHES	No	Yes	Good validity	Not suitable in the USA due to lack of normative data	~15–20 min
RBANS	No	Yes	Applicable in the USA	Incorporates domains not affected in CHE	~30–35 min
ICT	Yes	No	Sensitive and easily available	Requires highly functional patient and lacks repeatability	~15–20 min
SCAN test	Yes	No	Sensitive in detecting neuropsychological abnormalities	Not available in the USA	~20 min
CFF test	Yes	No	Short sensitive bedside test	Equipment	~10–15 min
EncephalApp_ Stroop	No	No	Short and easy to administer	Cannot be applied in color blind	~5 min
EEG	Yes	Yes	Can be administered in advanced HE	Need neurological support and can be confounded easily	Long duration
Evoked potentials	Yes	Yes	Has sensitivity in general	Insufficient evidence, needs cooperation from patient, confounded easily	~30–60 min

times and responses are monitored and scored. This test has good external validity and is easy to administer, but requires a fully functional patient. The ICT has been improved by Amodio et al. to detect MHE based on target accuracy and lures weighted by target accuracy, and appeared to be more sensitive for MHE detection than the original test studies by Bajaj et al. [48]. A positive test correlates with traffic accidents related to MHE [49]. It is readily available for download at the website www.hecme.tv.

Cognitive Drug Research (CDR) The CDR test is a computerized neuropsychometric test that is not available in the USA. It is a computerized test that was originally developed to assess the cognitive functions such as choice reaction time and word and picture recognition in demented patients. It was adapted to CLD patients and assessed five major areas—power and continuity of attention, speed and quality of working memory, and quality of episodic memory. It has been assessed in HE patients [50] and has proven to be a simple test, not requiring any special expertise, but takes up to 20 min requiring functional patients. It does not have norms for the USA.

Scan Test The Scan test is also a computerized test that measures reaction time to visual stimuli, reaction time to choice, and scan reaction time based on the Sternberg paradigm. It is not available in the USA, but has been validated in Europe as a good psychometric test that prognosticates cirrhosis [51]. It has also been endorsed as a test that is clinically useful in CHE diagnosis [52].

EncephalApp Stroop Test The EncephalApp Stroop test is another neuropsychometric test of psychomotor speed and cognitive flexibility, with good sensitivity in the diagnosis of CHE [53].

EncephalApp_Stroop is a reliable and valid test that can be downloaded and administered on any Apple smartphone, in any clinic, with an excellent sensitivity for the detection of the cognitive changes of CHE [54••]. It is limited to use in patients who are not color blind.

Tests That Require Specialized Equipment and/or Trained Personnel

Psychometric Hepatic Encephalopathy Score (PHES/PSE) The PHES, developed by Weissenborn and colleagues at the Hanover Medical School in Germany [55••], is the most recommended test by various consensus groups [2••, 6]. It essentially is a battery of five paper-and-pencil tests, namely (1) Number connection test A (NCT A), (2) Number connection test B (NCT B), (3) Line tracing test, (4) Serial dotting test, and (5) Digital symbol test. These subtests effectively evaluate cognitive motor abilities and visuo-motor coordination, functions that are affected early in HE. To be

positive for CHE, either the score must be significant or two out of four of the individual tests need to be abnormal [6]. The PSE, unfortunately, has limited use outside Germany, Spain, Mexico, and Italy due to the absence of comparative data from the normal population. The test has a good sensitivity (96 %) and great specificity (100 %), but lacks test-retest reliability and is prone to multiple biases during testing [56••]. In an ideal setting, the test should be completed within 20–25 min.

Critical Flicker Frequency (CFF) Test The CFF test is a neurophysiological test where visual signals and cognitive functions are evaluated. The CFF itself is the frequency at which steady fused light begins to flicker. A CFF below 39 Hz is diagnostic for CHE [57]. It also has application in the assessment of recovery of cirrhotic patients post-sedation for endoscopy [58]. The CFF test had excellent diagnostic value and predictive value for grade II and I HE [57], but requires specialized equipment, binocular vision, absence of red-green color blindness, and cooperation. Barring this, it is a simple-to-administer, reliable tool for CHE diagnosis.

Recently, based on the principle that eye movements are affected in HE, Cunniffe et al. showed that saccadic eye movements are altered in CHE and can prove as an accurate, simple diagnostic tool with 75 % sensitivity and specificity [59].

Electroencephalogram The EEG is a simple test that does not require patient involvement. It is a neurophysiological test that studies the cortical cerebral activity, and in the advanced stages of OHE, a triphasic wave is classically seen [60]. EEG classifies HE into five grades of severity as well and requires the expertise of a neurologist to read the tracings. This can lead to inter-observer variability, and hence to eliminate this computerized spectral analysis of the readings is preferred [61, 62]. Spectral analysis of EEG can predict CHE by detecting cerebral alterations when no clinical symptomatology is seen [63]. The limitations of using EEG in routine practice are the requirement of specialized equipment and the presence of underlying confounding metabolic disturbances.

Evoked Potentials Evoked potentials (auditory, visual, and somatosensory) are specialized tests with limited value for OHE diagnosis as they require more patient involvement as opposed to a simple EEG. The principle is that on appropriate stimuli, the brain will show a corresponding EEG response. A delayed response would suggest brain impairment. It has been studied in CHE but have not gained favor due to various drawbacks [64].

Treatment of CHE

The AASLD and other organizations do not recommend routine treatment of CHE [2••]. The current recommendation is evaluation of individual cases and then offering the current treatment standards for OHE. However, rifaximin has been

studied in CHE and has been shown to improve cognitive performance and HRQOL in patients screening positive for CHE [65]. It has also been shown to improve driving simulator performance in CHE patients [66]. Apart from its known mechanism of action on OHE, it has been shown to reduce endotoxemia and regulate the metabiome in CHE patients [67].

Conclusions

The diagnosis and management of HE is an evolving field. Due to the complexity of pathophysiology of this disease process, there is not one single test that can be nominated as a true gold standard. Riggio et al. recently proposed a possible model for prediction of OHE [68]. This model only highlighted that there is not a single test that could predict the clinical course of HE. This is reflective of the spectrum of neurocognitive impairment in cirrhosis (SONIC) and the challenges researchers face. There is also a need to develop alternative cost-effective therapies to lactulose and rifaximin. Over the last decade, the focus has shifted on MHE/CHE as it presents an opportunity to intervene earlier. Given the subtle nature of CHE, the majority of tests require specialized equipment and expertise, posing a challenge in routine clinics to accurately and timely diagnose CHE. Despite extensive research here, there are no guidelines for management of CHE. Given the risks of CHE, it is our advice that patients should be screened for CHE and, if needed, appropriate referrals be given to higher centers that have the right tools for diagnosis. In time as our understanding deepens, we can conclude that the future of HE definitely looks promising.

Compliance with Ethics Guidelines

Conflict of Interest Chathur Acharya declares no conflict of interest.
Jasmohan S. Bajaj has been a consultant for Salix, Merz, Norgine, and Grifols, unrelated to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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