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Useful Tests for Hepatic Encephalopathy in Clinical Practice

Eiman Nabi, MD¹ and Jasmohan S Bajaj, MD, MS²

¹Department of Internal Medicine, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia

²Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, Virginia

Abstract

Hepatic encephalopathy (HE) is a serious complication of liver disease and portosystemic shunting that represents a continuum of neuropsychiatric changes and altered consciousness. It is classified as overt hepatic encephalopathy (OHE) when clinically apparent or as covert hepatic encephalopathy (CHE) in its mildest form. Progression of CHE to OHE and its impact of quality of life make its early diagnosis imperative. Several diagnostic techniques ranging from simple clinical scales to sophisticated computerized tests exist yet diagnosis remains a challenge due to the time, cost and personnel involved. Psychometric tests appear promising due to their high sensitivity and low cost but results are variable depending on age and education. The pros and cons of current diagnostic methods for overt and covert HE are reviewed along with strategy to CHE testing.

Keywords

Covert hepatic encephalopathy; minimal hepatic encephalopathy; overt hepatic encephalopathy; ISHEN; cognitive testing; neurophysiological tests; paper-pencil tests; computerized tests; inhibitory control test; critical flicker frequency; psychometric hepatic encephalopathy score (PHES); stroop App; RBANS

INTRODUCTION

Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction and portal-systemic shunting diagnosed after exclusion of other known brain diseases¹. It affects 30% to 45% of patients with cirrhosis, and its presence and degree of progression signify poor prognosis and high mortality². The Working Party at the 11th World Congress of Gastroenterology, Vienna, under the Organization Mondiale de Gastroentérologie proposed a multi-axial definition of HE that defined both the type of hepatic abnormality and the duration and characteristics of neurological manifestations in chronic liver disease. Type A HE is due to acute liver failure,

Corresponding Author: Jasmohan S Bajaj, MD, MS, Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201, Broad Rock Boulevard, Richmond, Virginia 23249, Telephone: (804)675 5802, Fax: (804)657 5816, jsbajaj@vcu.edu.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Bajaj serves as a consultant for Otsuka. Dr. Bajaj received grants from Grifols, Otsuka, and Salix. In addition, Dr. Bajaj received honoraria from Abbott, Otsuka, Grifols, and Merz.

Human and Animal Rights and Informed Consent

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type B is attributable to portosystemic shunt or bypass, and type C is due to cirrhosis. Type C HE can be further subclassified into episodic, persistent, and minimal¹.

Based on clinical and neuropsychometric testing, HE can be categorized as overt or covert. HE that is clinically apparent is termed as overt hepatic encephalopathy (OHE). HE that is mild without an obvious clinical profile and diagnosed only by specialized cognitive testing is termed as covert hepatic encephalopathy (CHE), previously known as minimal or subclinical hepatic encephalopathy.

Over the past decade, CHE has received growing interest due to its prognostic importance for the development of OHE³. It has a characteristic cognitive profile that cannot be diagnosed clinically^{1,4–6}. CHE is known to be associated with deficits in driving skills^{7–9}, reduction in quality of life^{10,11}, impairment of working capability^{3,12} and, most importantly, predicting the subsequent onset of overt HE^{13–16}. CHE is associated with poor prognosis and is an independent predictor of survival¹⁷. In recognition of the dangerous consequences of CHE, the name of the condition has recently been changed from minimal to covert, a position endorsed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism¹⁸.

SEARCH CRITERIA

A PubMed search was conducted using MeSH term “Hepatic Encephalopathy/diagnosis” between dates 1/1/2009 and 31/12/2013 yielding 309 articles total. Articles were reviewed based on their relevance to the topic. The Hepatic Encephalopathy Update: Reports from Recent Conferences 2013 International Liver Conference was also reviewed.

TESTS FOR GRADING THE SEVERITY OF OVERT HEPATIC ENCEPHALOPATHY

CLINICAL DIAGNOSIS

OHE is diagnosed clinically based on two types of symptoms: impaired mental status, as defined by the West Haven Criteria (WHC), and impaired neuromotor function¹⁹. The current standard for grading HE is based on clinical diagnosis, hence a thorough history and physical exam are imperative. OHE can be further subdivided into episodic or persistent and precipitated or spontaneously occurring¹⁹.

Overt HE remains a diagnosis of exclusion and other causes of altered mentation in cirrhotic patients should be investigated before considering this particular diagnosis.

Ammonia levels—Since ammonia has been regarded as the key precipitating factor, plasma ammonia levels are used widely in patients with cirrhosis and altered mental status to diagnose HE^{20,21}. It represents a common conception that increased ammonia levels in a cirrhotic patient can confirm, or rule out, HE. However, the degree of correlation between ammonia levels and the grading of HE continues to be controversial.

Gundling et al evaluated in a prospective study in an emergency department setting whether elevated blood ammonia levels coincide with HE which was additionally established by the West Haven criteria and the critical flicker frequency, respectively and found that ammonia blood levels do not reliably detect HE. Its use as sole indicator for HE in the Emergency Department may result in frequent misinterpretations²².

Grading of OHE

1. WHC: The well-known West Haven criteria (Conn score) is based upon impairment in consciousness, intellectual function, and behavior¹. It classifies HE into five grades of severity. Grade 0 represents patients without detectable changes in personality or behavior, grade I includes patients with trivial lack of awareness, shortened attention span, and altered sleep and mood, and grades II–IV represent overt HE and coma. To avoid missing the lower grades of HE, the presence of HE should be evaluated by using the mini mental status exam (MMSE) that examines memory and attention in a systematic manner.

The WHC is recommended by the Working Party on Hepatic Encephalopathy for assessment of OHE in clinical trials¹. In a recent study by Bass et al²³ evaluating the efficacy of rifaximin in preventing relapse of HE in patients with overt HE, the investigators used the WHC to grade the stages of HE but failed to mention that the grading was reached by implementing the Hepatic Encephalopathy Scoring Algorithm (HESA)²⁴.

2. HESA: The Hepatic Encephalopathy Scoring Algorithm (HESA), originally devised for use in a multicenter study by Hassanein et al to assess the utility of extracorporeal albumin dialysis in the treatment of patients with severe HE (grade III/IV), may be particularly useful for assessing patients with low grades of HE, as minimal variability was detected between the scores given at the different study sites²⁵. The HESA combined clinical indicators with those derived from simple neuropsychological tests, the latter more often used in milder grades of HE (grade I/II). The performance of each indicator was compared across grades and sites²⁶. HESA is simple, time efficient and sensitive to subtle brain changes like the WHC but offers a more objective approach, which should yield greater reliability across the spectrum of HE. However the length of HESA makes it difficult to apply in clinical practice.

3. CHES: Clinical Hepatic Encephalopathy Staging Scale (CHES)²⁷ was designed to monitor the severity of HE on a scale from 0 (low) to 9 (high) and with aim to reduce interobserver variability. These questions have been used in two recent randomized clinical trials (Simon-Talero et al and Rockey et al)^{28,29}.

4. MO-Log: The Modified-orientation log is an 8-question adaptation of the orientation developed by Novack *et al*³⁰ in traumatic brain injury and extends it to hepatic encephalopathy. Its questions are heavily weighted towards disorientation to time, which is the earliest form of disorientation in OHE. The subjects are asked a particular question and responses to logical cues and multiple choice questions are studied in case the orientation question is not answered correctly; the highest score is 24 and lowest is 0. In their study Salam et al concluded that the Mo-log is a valid tool for assessing severity and is better than West-Haven criteria in predicting outcomes in hospitalized hepatic encephalopathy patients and the change in MO-log over the first 24 hours of hospitalization was especially important in predicting outcomes³¹.

5. GCS: For deeper grades of coma or in which patients are not verbally responsive, there are no specific HE questionnaires but the validated Glasgow Coma Scale (GCS) can be utilized. GCS adds to the assessment of severe HE by providing a wider separation for cases where grades III and IV are present. The study by Hassanein et al indicates weak performance of the GCS in lower grades of HE²⁶.

Summary of overt HE grading—Therefore the current grading of overt HE requires further study beyond the West-Haven criteria and its modifications. Simple questionnaires such as CHES and MO-log can divide the patients' mental status into 9 and 24 levels

respectively. Glasgow Coma scale can be used for patients who are not responsive to questionnaires.

DIAGNOSTIC TESTING FOR COVERT HEPATIC ENCEPHALOPATHY

Standardization of screening tools for diagnosis of covert HE remains a vital issue. The Hepatic Encephalopathy Consensus Group at the World Congress of Gastroenterology in 1998 endorsed the psychometric hepatic encephalopathy score (PHES) as the gold standard for diagnosing CHE¹. Over the past decade, several drawbacks of this testing system have been identified such as test administration and scoring in the outpatient setting. Although the PHES is popular in Europe, it has failed to gain widespread acceptance in the United States, mainly because of copyright issues and the lack of availability of testing material⁹.

CHE does not have a clinically apparent profile hence clinical diagnostic testing cannot be used. The ideal test for CHE diagnosis would be a quick, cheap, reliable, readily available, easy to administer test that accurately predict outcomes. The consequences of CHE on daily living even though patients are asymptomatic³² has led to the need for screening tests and early detection. Neuropsychological and neurophysiological methods have been the most trusted and widely used tests to diagnose CHE^{1,4,5}. These tests should be easy to use, quantifiable and assess the cognitive domain: attention deficit and slow information processing, which are the most prominent disturbances in covert HE³³. A number of computerized psychometric testing systems are being validated for the diagnosis of CHE, but they are not yet at a stage at which they can be implemented or endorsed globally.

NEUROPSYCHOMETRIC TESTS

Neuropsychological or neuropsychometric tests include both 'paper and pencil' tests and computerized tests that can be used to identify impairments in visuo-spatial functioning, attention, processing speed and response inhibition³⁴. These tests are cheap, easy to administer and do not require experienced personnel or expensive equipment. However, their dependence on a patient's age and education, total testing time and applicability restricted to lower grades of HE confers a disadvantage to diagnosis of HE. Present international consensus recommends use of the PHES or RBANS for diagnosing and monitoring CHE depending on availability of local normative data³⁵.

PAPER-AND-PENCIL TESTS

1. PHES—The Psychometric Hepatic Encephalopathy Score (PHES) is the current 'gold standard' pencil-and-paper test battery for the psychometric evaluation of patients with HE, standardized and validated by Weissenborn and colleagues³⁴. This battery measures psychomotor speed and precision, visual perception, visuo-spatial orientation, visual construction, concentration, attention and memory, is simple to perform and can be completed in less than 20 minutes³⁶. The PHES initially comprised of seven tests but the desire for a shorter battery and the poor sensitivity of some of the tests led to the introduction of a revised battery called the Portosystemic Encephalopathy (PSE) Syndrome Test, which includes the line tracing test (LTT), serial dotting test (SDT), digit symbol test (DST) and number connection test A and B (NCT A and B). The sensitivity and specificity of the PHES compared with the standard method of determining HE grade were 96% and 100%, respectively³⁶. Standard normative data of the PHES have been developed in German, Spanish and Italian. Thus, the PHES is predominantly used for detecting CHE in Europe²⁴. Performing this battery can be time consuming and prone to bias from disturbance, mood and interaction with the tester³⁷. This is not available directly in the US and there are no nationwide norms for this. However, it can be obtained through ISHEN.

2. RBANS—The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a 20–25 minutes paper-and-pencil battery used to diagnose neurocognitive disorders such as dementia, traumatic brain injury, stroke, multiple sclerosis and bipolar disorder. It evaluates global cognitive functioning based on language, visual perception, attention, immediate memory, and delayed memory. Although a few studies have now confirmed its usefulness in characterizing cognitive impairment in liver transplant candidates^{38,39} and the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommended its use in patients for CHE³⁵, there are limited data to support its use since two of its domains, delayed memory and language, are not usually impaired in CHE. A modified version of the RBANS that takes about 20–25 minutes to administer has been designed to focus specifically on the cognitive changes that occur in patients with OHE³⁵ and has proven to be effective in screening patients for CHE³⁹. The RBANS is available for a fee in the US through psychological corporation inc.

COMPUTERIZED TESTS

Paper and pencil tests rely heavily on the motor function of the patient and involve multiple cognitive functions for their successful completion. However, computerized testing affords greater control over task stimuli and standardization of presentation, allowing specific cognitive processes to be assessed⁴⁰.

1. ICT—The Inhibitory Control Test (ICT) is a computerized test of attention and response inhibition. It consists of a continuous stream of letters presented on a computer screen every 500 msec with targets (alternating X and Y) and lures (non-target X and Y). The percentage of targets and lures responded to, as well as reaction time, are recorded. A study by Bajaj et al showed that lure responses greater than five out of forty attempts could detect CHE with high sensitivity. Lower lure response, higher target response, and shorter reaction times indicate a good performance⁴¹. However, another study reported that lures alone were not sensitive in detecting MHE; target accuracy and lures weighted by target accuracy showed better discriminating values between healthy controls and patients with MHE⁴². Studies evaluating driving showed that ICT performance was significantly associated with driving simulator performance and traffic accidents^{41,43}. ICT is a sensitive, inexpensive, and easily administered test with good external validity and test-retest reliability, which makes it a good candidate as a diagnostic tool in CHE⁴⁴. Like other neuropsychological measures, the ICT is influenced by prior exposure⁴². This is available for free download at www.hecme.tv.

2. CDR—The Cognitive Drug Research (CDR) battery assesses five cognitive areas including attention power, attention continuity, speed of memory and quality of episodic and working memory via a set of increasingly complex tasks based on yes/no responses that are inputted via a decision box by the patient after the initial learning period. The CDR has shown good correlation with the gold standard PHES test, is well validated across population norms and disease states including many forms of dementia and psychiatric conditions, and has recently been validated in patients with HE⁴⁰. It does not have US-based norms but is available for a fee from the UK.

3. Scan Test—Montagnese et al from Italy assessed the usefulness of the Scan package, a three-level-difficulty computerised reaction time test, to diagnose varying degrees of hepatic encephalopathy⁴⁵. The first level is a simple reaction time (sRT) where the subject is asked to respond to a series of visual stimuli (an asterisk on the computer screen) by pressing the spacebar on the keyboard. Level two is the choice reaction time (cRT) where the subject is presented with either the number 1 or the number 3 on the computer screen and asked to press 1 or 3 on the keyboard, accordingly. Level three is the scan reaction time (ScanRT), which is a digit recognition task based on the Sternberg paradigm and has previously been

shown to be a useful test in patients with cirrhosis^{17,46}. The subject is presented with 36 consecutive pairs of numbers, and asked to press 1 on the keyboard if there are digits in common or press 3 if there are not. For all three levels, the number of correct responses, expressed as a percentage of the total number of stimuli (accuracy), and the accuracy-adjusted, average RT (ms) are calculated. Limitations to this study included that while the Scan test software provides an overall Z score, which is corrected for age/educational attainment, the presented weighed RTs were not normalised, and should be considered valid for populations of patients with cirrhosis similar to that used in this study⁴⁵. Amodio and colleagues found that, among various types of psychometric tests such as the Trail-making Tests and Symbol Digit Modality Tests, the scan test was the most closely related to central brain atrophy⁴⁷. About 50% of cirrhotic patients performed poorly on the scan test, making it valuable in detecting the neuropsychological impairment caused by cirrhosis. Furthermore, patients who had history of OHE performed significantly worse than those who never had a bout of OHE²⁴. This however, is not available in the US.

4. STROOP App test—The Stroop smartphone application (EncephalApp_Stroop) was used by Bajaj et al as a valid, reliable tool to screen for CHE⁴⁸. The Stroop task is a test of psychomotor speed and cognitive flexibility that evaluates the functioning of the anterior attention system and has been found to be sensitive for the detection of cognitive impairment in CHE⁴⁹. The EncephalApp_Stroop (available on iTunes for free download) is easy to administer, simple to score and interpret. This new app has cut-offs that are age-specific but need to be validated in other populations. The details of its download, interpretation and administration can be viewed as webcasts at www.chronicliverdisease.org.

NEUROPHYSIOLOGICAL TESTS

1. CFF—Critical flicker frequency (CFF) can detect a range of neuropsychological abnormalities from visual signal processing to cognitive functions making it a valuable tool in various fields including hepatology, neurology, psychiatry, and ophthalmology^{15,50,51}. Patients are shown light pulses at an initial frequency of 60 Hz gradually reduced by 0.1 Hz decrements per second. Patients are asked to identify the time at which the apparently steady fused light begins to flicker. A critical flicker frequency of below 39 Hz diagnoses CHE with high sensitivity and specificity and test results correlate positively with those of paper-and-pencil neuropsychometric test⁵². Most published studies agree that the sensitivity and specificity of CFF diagnosing CHE is 80% and 65% respectively⁵³. The CFF has the advantage of not being dependent on language, verbal fluency, numeracy or numerics, and therefore studies into its use have been performed in the United States, Europe and Asia³⁷. It is a simple, easy-to-use, and reliable tool that is independent of education, gender, age, and literacy.

In recent studies by Sharma et al, the CFF has been evaluated as an objective measure for grading CHE as well as assessing recovery of patients with cirrhosis from sedation after endoscopy^{53,54}. Other studies assessed the use of CFF as a marker for objective HE evaluation in patients undergoing transjugular intrahepatic portosystemic shunt^{52,55}. Romero-Gomez et al in their study found that CFF together with Child-Pugh class can predict the development of HE grade II and I in follow-up¹⁵. However, further validation and standardization studies are needed to determine its use and applicability in differentiating between HE grades 0 and I. It is not useful in grade III or IV HE either because patients' attention and cooperation are required. Thus CFF has not been established as a diagnostic tool in OHE. A meta-analysis by Torlot et al³⁷ has shown that CFF is a diagnostically accurate test, which could be used as an adjunct to conventional psychometric

test batteries, such as PHES, but could only become a replacement screening test if further studies show an improvement in sensitivity.

2. EEG—Similar to clinical grading, the electroencephalogram (EEG) classifies HE in five grades of severity from normal to coma. In published studies, the diagnostic sensitivity for HE ranges between 43% and 100%³⁴. In mild HE, the increase in confusion is associated with the initial EEG tracings that reveal posterior dominant alpha rhythm slowing, which is typically followed by a gradual appearance of theta and high-amplitude irregular delta waves as the HE progresses into coma. This neurophysiological method is associated with both inter- and intra-observer variability leading some to suggest a lack of objectivity⁵⁶. An alternative objective approach is spectral analysis of the EEG, which is a computerized analysis of the frequency distribution in the EEG. Spectral analysis of the EEG is a simple technique, is more reliable than visual EEG reading, and has prognostic value for the development of HE and mortality in cirrhotic patients^{57,58}. Digital analysis of the EEG analyses EEG in various regions of the brain making more sensitive than conventional or spectral EEG in detecting early HE. 85% of patients with no clinical symptoms of HE show abnormalities on digital analysis proving its high sensitivity for functional cerebral alterations⁵⁹.

3. Evoked Potentials—Visual, auditory and somatosensory-evoked potentials (EPs) have been investigated in patients with HE but their use is limited in patients with OHE due to patient cooperation. Both auditory and visual P300 have been shown to have diagnostic potential in mild HE but are nonspecific to HE and not recommended because of inconsistent results⁶⁰. The P300 is an event-related potential that is elicited by low-probability target items interspersed among high-probability nonstimuli. In response to the oddball stimuli, the brain shows an EEG recognition response at approximately 300 to 600 milliseconds. A delay response greater than 300 milliseconds indicates brain impairment²⁴. Auditory P300 potentials have been used independently and may have value in the diagnosis of CHE. However, the absence of clear cutoffs and guidelines for the sensitivity and specificity that define CHE limit their clinical usefulness. Some researchers suggest that expensive equipment, low sensitivity, and the lack of accompanying behavioral information are drawbacks of these methods^{61,62}.

Summary for covert HE testing in clinical practice

A summary of relative advantages, disadvantages and availability of certain tests are listed in table 1. A suggested checklist and order of testing that could be used for covert HE in US-based clinic is also displayed in table 2 and figure 1 respectively.

Conclusions

A survey among members of the American Association for the Study of Liver Diseases (AASLD) showed that 72% tested less than half their patients for CHE, despite 84% acknowledging that CHE is a significant problem. Furthermore, 85% said that if clinical staff could perform a quick, accurate test, this would increase the likelihood that people would test for CHE⁶³. There is no single ideal test that accurately covers the spectrum of HE, from minimal changes to deep coma²⁶. EEG, which can be done across the spectrum of HE, has not been shown to have a high degree of precision for metabolic encephalopathies⁶⁴. The rest of the tests either work at the beginning or the end of the spectrum of neuro-cognitive impairment in cirrhosis (SONIC)⁶⁵. Tests for covert HE are slowly but steadily making their way into the mainstream with the focus being on end-user ease and cost-effective methods of implementation of these strategies to maximize local

resources. Continued research into this very important field is continuing and further validation studies will be available soon.

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1. Identify patients at risk and counsel them that these tests could be needed for evaluation of their overall daily functioning
2. Train clinic nurses/research personnel/medical assistants/mid-level professionals to administer a high-sensitivity test that can determine who does not need formal testing while the patient is waiting to be seen by you in clinic in a separate quiet area
3. Consider using these results that would be given to you by the medical assistants when the patient is seen by you in clinic
4. Interpret these results to determine who needs formal testing at a separate clinic visit with personnel that have expertise in testing e.g. psychologists or psychiatrists
5. Evaluate the interpretation of the qualified personnel and offer treatment trials if requested by the patient; if patients are unimpaired can consider re-testing in 6 months or sooner if the natural history of the patient changes.

Figure 1.
Suggested Practical Covert HE treatment strategy in order

Table 1

Summary of Tests That Could be Used in Clinical Practice

	Advantages	Disadvantages	Logistics in the US	Time required
Paper Pencil				
PHES	Validated in several non-US populations	Norms not available in the US	Need psychologists to order	15–20 minutes
Combination of NCT-A, NCT-B, DST and BDT	Recommended for populations without PHES norms	Block design test can take longer in more impaired patients	Need psychologists to order	25–30 minutes
RBANS	Has US-based norms	Not performed well since two domains are not affected in covert HE	Need psychologists to order and interpret	30–35 minutes
Computerized				
Inhibitory control test	Does not require psychologists Validated in a few centers	Highly functional patients required	Free download at www.hecme.tv	15–20 minutes
SCAN test	Does not require psychologists	Not validated in the USA	Not available	20 minutes
EncephalApp_ Stroop	Can be given on a mobile platform as an app	Only validated in two centers Cannot be done in color-blind subjects	Available for free download at the iTunes app store	5 minutes
Neurophysiological				
EEG	Easy to perform across all levels of HE severity	Local norms for each hospital available	Need neurological support	Can take hours including interpretation
Evoked potentials	Sensitive for diagnosis	Local norms for each hospital available	Need neurological support	30–60 minutes
Critical Flicker Frequency	Can be given bedside or mobile	Expensive equipment	Available from several companies	10–15 minutes

Table 2

Suggested Checklist Pertaining to Covert HE testing (the answer to most questions should be yes before proceeding to testing)

	Yes	No
Pre-testing Checklist		
Patients who are at risk for accidents or job-related mistakes, have cognitive complaints or poor quality of life		
No current overt HE (alert, oriented, MMSE >25)		
Not on psycho-active drugs (chronic anti-depressants are acceptable)		
No uncontrolled neuro-psychiatric disorders		
Patient is able to comprehend cognitive test procedures		
Adequate vision (corrected with spectacles), hearing and motor strength to perform tasks		
Counseled patient and relatives regarding potential results		
Testing Techniques and Environment		
Quiet environment with relaxed patients		
Using techniques with locally available normative values		
Trained examiner using tests with scripts or protocols		
Post-Testing Questions		
Counseled patient and relatives regarding results and performance		
Offered treatment trial if requested		