

# Hepatic Encephalopathy: A Review of Diagnostic Methods

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## Objectives:

After reading and studying this newsletter, the participant should be able to:

- Describe the classification, prevalence, and etiology of hepatic encephalopathy
- Identify the different categories of diagnostic methods for hepatic encephalopathy
- Assess the relative strengths and weaknesses of the various diagnostic methods for hepatic encephalopathy

Hepatic encephalopathy (HE), a common and potentially devastating complication of both acute liver failure (ALF) and of chronic liver disease,<sup>1</sup> encompasses a broad range of neuropsychiatric deficits from clinically undetectable abnormalities apparent only on psychometric evaluation, to confusion, coma, and death. HE is a defining feature of ALF and complicates 40%-80% of cases of cirrhosis.<sup>2-4</sup> There are several types of HE classified by international expert consensus.<sup>1</sup> Type A HE is due to ALF, type B is attributable to portosystemic shunt or bypass, and type C is due to cirrhosis.<sup>1</sup> Type C HE can be further subclassified into episodic, persistent, and minimal.<sup>1</sup> Over the past decade, minimal hepatic encephalopathy (MHE), originally considered a research diagnosis without clinical consequence, has received growing interest due to its prognostic importance for the development of overt HE (OHE)<sup>4</sup> and subsequent acute-on-chronic liver failure. Additionally, the clinically undetectable neuropsychiatric abnormalities associated with MHE have been shown to reduce driving skills in computerized, simulated driving tests and to lead to a higher number of automobile accidents.<sup>5-7</sup> Patients with MHE, predominantly in lower socioeconomic groups where hand-eye coordination and fine motor skills are required on a daily basis, also have difficulty maintaining employment due to their locomotive and cognitive defects.<sup>4</sup>

It has been difficult to precisely identify the prevalence of HE, as it is a function of the diagnostic methods used and the population studied. MHE has been found in up to 50% of cirrhotic patients<sup>8</sup> and in up to 50% to 70% of cirrhotic patients if psychometric defects are included in the diagnostic definition of HE.<sup>9</sup> By resulting in frequent hospitalizations, episodes of OHE pose a formidable burden on the healthcare system in general.<sup>10</sup> Furthermore, mortality is extremely high in OHE with cerebral edema<sup>11</sup> with a 1-year mortality rate of 54% for patients with severe HE in intensive care units.<sup>12</sup>

The etiology of HE is considered to be multifactorial and elevated levels of ammonia in the blood are thought to play an important and central role. Several other toxins have been implicated in the etiology of HE including false neurotransmitters (octopamine, phenylethanolamine), gamma-amino butyric acid, short chain fatty acids, mercaptanes, neurosteroids, and manganese.<sup>13</sup> In all patients with HE, including those with MHE, some degree of cerebral edema occurs and astrocyte swelling is thought to play a key role. Although the precise molecular mechanisms that cause these changes have yet to be elucidated, it is clear that the burden of disease for cirrhosis is increasing, especially with regard to the

rise in the number of patients with hepatitis C or nonalcoholic steatohepatitis. Therefore, recognition of the complications of cirrhosis, including HE, is imperative.<sup>10,14,15</sup> Additionally, the burden of disease attributable to HE is most likely grossly underestimated<sup>16</sup> as up to 80% of patients with cirrhosis are thought to have some form of HE<sup>17</sup> and this figure is likely to increase with time.<sup>14</sup> In fact, the burden of HE is likely to attain epidemic proportions with increased awareness and improved diagnostic methods.

This newsletter will review several different diagnostic methods for HE and the respective advantages and disadvantages.

## The Importance of Differential Diagnosis

Because several conditions have similar symptoms to HE and the diagnosis of HE is a diagnosis by exclusion, ruling out other causes of encephalopathy is essential. The conditions that share common symptomology with HE include metabolic encephalopathies such as vitamin B1 deficiency, hypoglycemia and hypothyroidism, toxic encephalopathies including delirium tremens, Wernicke-Korsakoff syndrome, drug or alcohol intoxication, and intracranial lesions such as intracerebral hemorrhage, subdural hematoma, and cerebral edema and/or intracranial hypertension.<sup>18,19</sup> Patients with cirrhosis have coagulopathies and an increased risk of falls, making exclusion of subdural hematoma vital for patients who display evidence of changes in mental status.<sup>20</sup> Additionally, other neurological syndromes such as hepatocerebral degeneration and hepatic myelopathy are also associated with liver insufficiency. These syndromes are not only difficult to diagnose and differentiate from HE, but also do not respond to any treatment or to the same treatments used for HE treatment.<sup>20</sup>

## Biochemical Diagnostic Methods

When considering biochemical methods for diagnosing HE, it is important to be mindful of the fact that there is no specific biochemical diagnostic test for HE. However, the toxins that play a role in the pathogenesis of HE can be determined and elevated levels illustrate a diminished hepatic clearance. This does not necessarily mean that a patient suffers from HE, as there is no cut-off point of a toxin level above which the diagnosis of HE can be established. Determination of levels of ammonia, due to its central role in the pathogenesis of HE, is the most utilized biochemical test. Initially, levels of ammonia can be measured to support diagnosis and treatment in patients with a history of underlying liver cirrhosis. Measuring partial pressures of ammonia does not appear to confer any additional advantage over measuring venous samples of ammonia.<sup>21</sup> Two of the reasons that measuring ammonia levels is insufficient for diagnosis of HE stem from the findings

that ammonia levels can be normal in approximately 10% of patients with significant encephalopathy<sup>22</sup> and that ammonia levels can be elevated in up to 69% of patients without signs and symptoms of encephalopathy.<sup>21</sup> Therefore, the clinical utility of ammonia levels in the diagnosis of HE is uncertain given the substantial overlap of ammonia levels in both patients with and without encephalopathy. Additionally, elevated ammonia levels may be attributable to a variety of other causes such as inappropriate blood draws or processing, drug-related causes such as sodium valproate, physiological factors such as high-protein meals and strenuous exercise. While it is clear that elevated ammonia levels correlate positively with the severity of HE,<sup>21</sup> assessment of repeated ammonia levels is not recommended as a replacement for clinical evaluation, as the relationship between ammonia levels and risk of cerebral edema in cirrhosis has yet to be elucidated.<sup>23</sup> Furthermore, the necessity of collecting a blood sample from a stasis-free vein without using a tourniquet and taking care not to cause turbulence or hemolysis can make such tests challenging to perform in the clinic. In addition, samples must be immediately transported on ice to the laboratory to be analyzed within 20 minutes. Advantages and disadvantages of using serum levels of ammonia as a diagnostic tool for HE are listed in Table 1.<sup>19</sup> (see Page 6)

An additional blood marker, cyclic guanosine monophosphate (cGMP), has been recently investigated in patients with MHE based on findings that showed patients diagnosed with MHE had increased cGMP levels.<sup>24</sup> The use of cGMP level monitoring in interventional trials is likely to be more common, although it is not yet part of clinical practice, due to the well-described changes in intracellular and serum cGMP and activation of soluble guanylate cyclase by nitric oxide (NO) in lymphocytes, coupled with a number of pharmacological interventions aimed at the main pathway for cGMP control, the glutamate-NO-cGMP pathway.<sup>25,26</sup> Other blood markers, including interleukin (IL)-6 and IL-18, may also be of interest, as higher levels of IL-6 and IL-18 have been noted in patients with cirrhosis and MHE compared with patients with cirrhosis and no MHE.<sup>27</sup> This finding may take on greater significance if replicated in a larger cohort.

## Clinical Diagnostic Methods

Of all the available diagnostic tools and methods for HE, the clinical diagnosis is considered the “gold standard” and should therefore be performed thoroughly with an adequate history taking and physical examination.<sup>20</sup> HE can be classified in five grades of severity, ranging from normal mental status (grade 0), subtle mental alterations (grade 1) to deep coma (grade 4). Unfortunately, making a correct clinical diagnosis can be difficult due to the subtle and rather subjective criteria used in

the grading of HE. In fact, some cirrhotic patients with subtle attention deficits are not diagnosed with lower grades of HE in clinical practice and therefore suffer the consequences of HE in their daily functioning. To avoid missing the lower grades of HE, the presence of HE should be evaluated by examining memory and attention systematically. For example, short-term memory can be evaluated by asking patients to repeat a 6-digit number, intermediate level memory can be evaluated by asking patients to repeat a simple sentence or three words after 10 minutes, and long-term memory can be evaluated by asking patients about current topics that affect everyone, such as the name of presidents, recent wars, or sporting events. To evaluate attention, patients can be asked to perform simple calculations such as the “serial 7s” test in which patients are asked to subtract 7 from 100, to subtract 7 again from the number obtained, and to continue until 7 has subtracted 5 times. Patients with HE usually forget what they were asked to do when they reach 93 or 86. Despite attempts to perform a systematic examination, not all patients with lower grades of HE will be diagnosed and other diagnostic tools may therefore be required.<sup>20</sup>

Several scales have been devised for the diagnosis of HE. The West Haven criteria, developed in 1977,<sup>28</sup> have been used in a number of studies of HE to semiquantitatively grade patients’ mental states via subjective assessments of behavior, intellectual function, alteration of consciousness, and neuromuscular function. Although the original version comprised four grades ranging from 1, including symptoms such as a trivial lack of awareness, to 4, an unresponsive patient in a coma, substantial variability was detected between observers in their assessments of low grades of HE. In response, a modification that introduced objective scales for the assessment of the individual components of the criteria was proposed in 2004.<sup>29,30</sup> Additional studies are required to determine whether the modified version should be implemented for general use in patients with suspected HE. Other scales designed to reduce interobserver variability such as the Clinical Hepatic Encephalopathy Staging Scale have been proposed,<sup>31</sup> but also require further validation. In addition, the Hepatic Encephalopathy Scoring Algorithm, originally devised for use in a multicenter study that assessed the utility of extracorporeal albumin dialysis in the treatment of patients with HE, 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 sites.<sup>32</sup> For patients with moderate to severe HE, the Glasgow Coma Scale can also be used,<sup>33</sup> although it has not been specifically used and studied in HE and is also used in other types of coma as well. The relative advantages and disadvantages of selected diagnostic scales for HE are listed in Table 1.<sup>19</sup>

## Neuropsychological/Neuropsychometric Diagnostic Methods

Neuropsychological or neuropsychometric tests, which include both ‘paper and pencil’ tests and computerized tests, can be used to identify impairments in a variety of domains including visuo-spatial functioning, attention, processing speed and response inhibition and are mainly used to detect MHE. These tests confer several advantages, as they are easily applicable, not costly, and do not require experienced personnel or expensive equipment. However, certain disadvantages have been associated with such tests including a dependence on a patient’s age and education, and applicability restricted to lower grades of HE, as they require patients’ cooperation and attention.<sup>9</sup> Despite the aforementioned advantages of psychometric testing, these tests are not widely used in clinical practice, perhaps due to the time required to administer them, which most likely surpasses the short time that physicians usually have to examine outpatients.

Because HE is characterized by psychomotor slowing, the Number Connection Test (NCT) has been frequently used as a diagnostic test for HE, as it evaluates cognitive motor abilities (Figure 1).<sup>34</sup> Unfortunately, when patient age is taken into account, the NCT only yields abnormal results in approximately 56% of patients with grade 1 HE.<sup>35</sup> Therefore, a combination of several psychometric tests that evaluate the various neuropsychological aspects of HE is recommended. Specific batteries for the assessment of neuropsychological disturbances associated with MHE include the Portosystemic-Encephalopathy Syndrome Test,<sup>36</sup> the Psychometric-Hepatic-Encephalopathy-Score (PHES),<sup>35</sup> and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).<sup>37</sup> The current ‘gold standard’ pencil-and-paper test battery for the psychometric evaluation of patients with HE is the PHES, originally developed in Germany via collaboration between neurologists and hepatologists and validated from a cohort of nonalcoholic patients.<sup>35</sup> The PHES, which consists of five psychometric tests that measure psychomotor speed and precision, visual perception, visuo-spatial orientation, visual construction, concentration, attention and memory, is simple to perform, can be completed in less than 20 minutes, and has a sensitivity of 96% and a specificity of 100% in the diagnosis of HE.<sup>35</sup> The RBANS paper-and-pencil test, often used to diagnose neurocognitive disorders such as dementia, traumatic brain injury, stroke, multiple sclerosis and bipolar disorder, is another battery that tests five domains including immediate memory, delayed memory, attention, visuo-spatial ability, and language. Although norms are available for the US, the RBANS has not been formally validated for the diagnosis of HE. 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 OHE<sup>38</sup> and has proven to be effective in screening patients for MHE.<sup>39,40</sup> Present international consensus recommends use of the PHES or RBANS for diagnosing and monitoring MHE depending on availability of local normative data.<sup>38</sup>

## Number Connection Test 1.

Patients Name	
Date	
Completion time (seconds)	
Testers Initials	
PT. Chart No.	
Patients Signature	

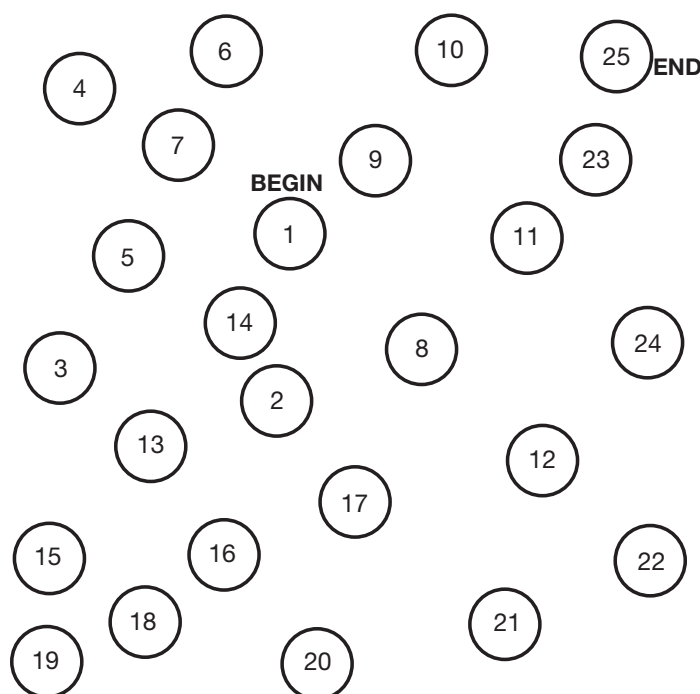


Figure 1: Number connection test: the NCT measures cognitive motor abilities. Subjects have to connect the numbers printed on paper consecutively from 1 to 25, as quickly as possible. Errors are not counted, but patients are instructed to return to the preceding correct number and then carry on. The test score is the time the patient needs to perform the test, including the time needed to correct all errors. A low score represents a good performance. Quero Guillén JC, Herreras Gutiérrez JM. Diagnostic methods in hepatic encephalopathy. Clin Chim Acta 2006;365:1-8.<sup>20</sup>

More recently, computerized psychometric tests have also become available. The inhibitory control test assesses two different cognitive domains that are affected in patients with MHE, response inhibition and attention, using 'targets' and 'lures'.<sup>141,42</sup> Patients are shown a series of different alphabetic sequences that appear on the computer screen one after another, and are expected to respond to patterns of stimuli referred to as targets and not to respond to patterns of stimuli referred to as lures. Lure responses greater than five out of 40 attempts can detect MHE with high sensitivity<sup>41,42</sup> and this test

has been validated against conventional standard psychometric tests. Another computerized psychometric test, the Cognitive Drug Research (CDR) battery, was devised specifically for neuropsychiatric profiling of patients with cirrhosis and MHE.<sup>43</sup> It 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 battery consists of seven tests that comprise over 50 parallel forms of each task. 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 HE.<sup>43</sup> The relative advantages and disadvantages of selected neuropsychological/neuropsychometric tests for HE are listed in Table 1.<sup>19</sup>

## Neurophysiological Diagnostic Methods

Several neurophysiological tests can be used as part of the HE diagnostic process. The critical flicker frequency (CFF) test involves showing patients light pulses at an initial frequency of 60 Hz and gradually reducing the frequency by 0.1 Hz decrements once per second. Patients are asked to identify the time at which the apparently steady fused light begins to flicker. This test takes advantage of the fact that like cerebral glial cells, retinal glial cells in patients with HE also swell, resulting in a condition referred to as hepatic retinopathy. Therefore, the CFF can be used to assess the efficiency of both the visual apparatus and the functional efficiency of the cerebral cortex. It is interesting to note that this test is only slightly dependent on age and is not influenced by sex, occupation, or level of education. The CFF test was validated for the assessment of patients with HE in 2002<sup>44</sup> and for the assessment of patients with HE who were undergoing transjugular intrahepatic portosystemic shunt placement in 2009.<sup>45</sup> The CFF test can be administered in about 10 minutes, is relatively simple and not costly. Most importantly, a critical flicker frequency of below 39 Hz diagnoses MHE with high sensitivity and specificity and test results correlate positively with those of paper-and-pencil neuropsychometric tests.<sup>44,45</sup> Although this tool has been widely used to assess HE in therapeutic trials, it is not useful in grade 3 or 4 HE because patients' attention and cooperation are required.

Similar to clinical grading, the electroencephalogram (EEG) classifies HE in 5 grades of severity from normal to coma. In published studies, the diagnostic sensitivity for HE ranges between 43% and 100%.<sup>29</sup> In lower grades of HE, a slowing of alpha rhythms (8–13.5 cycles/s) is observed, followed by a gradual slowing of the frequency and the appearance of theta



(3.5–8 Hz) and delta (0.5–3.5 Hz) waves as HE progresses into coma. This neurophysiological method is associated with both inter- and intra-observer variability; however, spectral analysis of the EEG, which is a computerized analysis of the frequency distribution in the EEG, is a more objective tool. Unfortunately, the HE grading criteria for spectral analysis are not generally applicable and depend on the type of EEG apparatus, filters, and software used.<sup>46</sup> 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.<sup>46,47</sup> Digital analysis of the EEG, which is more sensitive than conventional or spectral EEG in detecting early HE, allows for the EEG to be analyzed in various regions of the brain. This technique has high sensitivity for functional cerebral alterations such that 85% of patients with no clinical symptoms of HE show abnormalities on digital analysis.<sup>48</sup>

Additionally, visually, auditory-, and somatosensory-evoked potentials (EPs) have been investigated in patients with HE in an attempt to identify specific neurophysiological response deficits in HE. Auditory<sup>3</sup> and visual P300 latencies have been shown to be abnormal in up to 80% of patients with HE and this high sensitivity may be attributable to the fact that the response to event-related EPs is not only dependent on the physical characteristics of the stimulus but also on its significance for the patient. For example, in P300 potentials where the patients' response to two different stimuli is evaluated, subtle alterations in cognitive processes such as evaluation and discrimination of stimuli can be reflected.<sup>49</sup> Unfortunately, the correlation between EPs and psychometric testing is poor.<sup>50</sup> However, auditory P300 potentials have been used independently and may have value in the diagnosis of MHE. Similarly, somatosensory-evoked potentials are abnormal in patients with HE, but at present these tests do not represent a more efficient method of characterization to psychometric testing.<sup>51</sup> Like the CFF test, event-related EPs require patient cooperation and selective attention and are therefore unsuitable for patients with severe HE. The relative advantages and disadvantages of selected neurophysiological tests for HE are listed in Table 1.<sup>19</sup>

## Neuroimaging and Neurometabolism Diagnostic Methods

Additionally, many MRI techniques such as T1-weighted imaging, magnetic resonance spectroscopy, magnetic transfer ratio, and T2-weighted fluid attenuation inversion recovery sequence and diffusion weighted imaging can identify low-grade cerebral edema (Table 2). **(see Page 7)** In fact, 70% of cirrhotic patients have hyperintensity of the globus pallidus on T1-weighted MRI,<sup>53-55</sup> most likely attributable to the local deposition of manganese due to portosystemic shunting

and a diminished biliary clearance.<sup>56</sup> It should be noted that the hyperintensity of the globus pallidus is not specific for HE, as it has also been observed in patients with portal vein thrombosis without HE,<sup>57</sup> and that a relationship exists between hyperintensity, the grade of hepatic insufficiency, and portosystemic flow, but not with the grade of HE. A computerized axial tomography scan of the cerebral cortices can be useful in excluding organic causes of coma and conditions that could either mimic or exacerbate HE, such as subdural hematomas, tumors, or cerebrovascular events. In vivo magnetic resonance spectroscopy (MRS), which assesses neuronal metabolism, may represent a noninvasive method of diagnosis. Not only have <sup>1</sup>H spectroscopy data been correlated with psychometric performance,<sup>58-60</sup> but also suggest an increased glutamine/glutamate signal and a reduction in choline signals, likely attributable to a compensatory response to hyperammonemia, which are modifiable by liver transplantation.<sup>61</sup> Unfortunately, the length of time required to make in vivo MRS measurements remains longer than 30 minutes per patient and requires sufficient expertise to acquire and analyze spectra, which may preclude using this technique as part of standard clinical practice. Positron emission tomography has not traditionally played a role in the diagnosis of HE, although it has potential to do so, as the isotopes that emit positrons like <sup>18</sup>F, <sup>11</sup>C and <sup>15</sup>O can be used for studying cerebral processes and metabolism in HE.<sup>62</sup> The relative advantages and disadvantages of selected neuroimaging tests for HE are listed in Table 1.<sup>19</sup>

## Summary

The importance of correctly diagnosing HE cannot be understated, as it affects both a patient's quality of life and prognosis. The diagnosis of MHE is particularly difficult due to the subjective nature of the symptoms and the fact that subtle memory or attention deficits in cirrhotics are not always caused by HE. Differential diagnosis, although difficult, is critical and additional adequate diagnostic tests may be required. A determination of blood ammonia levels, preferably from arterial blood, is one of the first diagnostic tests that should be performed in a patient suspected of having HE. Because elevated arterial ammonia levels do not always result in HE, a diagnosis should be confirmed using electrophysiological methods. Both EEG and EPs, always abnormal in clinical HE, and the choice of tests depend on local possibilities and expertise. Psychometric tests are highly attractive as diagnostic screening tools for HE because they are relatively inexpensive and sensitive but are only effective for the detection of lower grades of HE and results may be influenced by age and education level. The application of newer neuroimaging and neurometabolism diagnostic techniques are limited, in part due to scant availability.

# Hepatic Encephalopathy: A Review of Diagnostic Methods

Advantages and disadvantages of diagnostic tests for hepatic encephalopathy		
Diagnostic test	Advantages	Disadvantages
Serum levels of ammonia	Positively correlated with the severity of HE	Does not change approach to diagnose and manage HE Can be challenging to take appropriate blood samples in the clinic
<i>Clinical scales for OHE</i>		
West Haven criteria	Well-established classification criteria (in use for ~30 years) Used in multiple studies of OHE	Interobserver variation influences test results (especially for low grades of HE)
HE Scoring Algorithm	Minimal variability in results between different test sites Characterizes low grades of HE	Time consuming (which may be a limiting factor in the outpatient setting)
<i>Neuropsychometric tests ('paper and pencil' tests) for MHE</i>		
Psychometric HE score	Specifically designed to diagnose subtle cognitive changes in patients with MHE Endorsed as the 'gold standard' by the Working Party at 1998 World Congress of Gastroenterology, Vienna, Austria	Poor test of memory Difficult to interpret and score Excessive reliance on measuring fine motor skills Unpopular in USA (lack of US-specific normative data and availability)
Repeatable Battery for the Assessment of Neurological Status	Tests can be completed rapidly (within 25 min)	Difficult to interpret and score Excessive reliance on measuring fine motor skills
<i>Computerized psychometric tests for MHE</i>		
Inhibitory control test	Detects MHE with high sensitivity validated against existing psychometric tests	Studies using this test have mostly been conducted in a single institution located in either Wisconsin or Virginia, USA
Cognitive Drug Research System	Correlates well with neuropsychometric tests	Time consuming, which could be a limiting factor Trial run needed before formal testing
<i>Neurophysiologic tests</i>		
Critical flicker frequency	High sensitivity and specificity Correlates well the neuropsychometric tests Widely used in clinical trials	Lack of widespread availability in the USA to permit use in ambulatory patients
Electroencephalography	HE associated with slow frequency of electrical activity	Variable sensitivity for the diagnosis of HE (43-100%)
<i>Brain imaging</i>		
MRI	Multiple techniques available Identifies several brain abnormalities associated with HE (e.g. levels of glutamate)	Can be expensive (especially the newer techniques that show low grades of cerebral edema)
Computed Axial Tomography (CT)	Useful for excluding other causes of encephalopathy Identifies conditions that worsen HE (subdural hematoma or a cerebrovascular event)	Poor detection of low grades of cerebral edema in most patients with HE Risk associated with radiation exposure.
Abbreviations: CDR, Cognitive Drug Research computerized assessment; HE, hepatic encephalopathy; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy.		

Table 1. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. *Nat Rev Gastroenterol Hepatol* 2010;7:515-525.<sup>19</sup>

Brain imaging modalities for diagnosis of hepatic encephalopathy		
MRi Technique	Imaging Abnormality	Clinical Correlate
T1-weighted imaging	Bilateral, symmetrical, high-intensity signal in the basal ganglia (globus palidus and substantia nigra)	Attributed to preferential deposition of manganese in the basal ganglia. Found in patients with cirrhosis who have substantial portosystemic shunts No quantitative relation to severity of HE Reverses after liver transplantation
Proton spectroscopy ( <sup>1</sup> H MRS)	Increase in glutamate and glutamine signals Decrease in myoinositol and choline signals	Homeostatic compensatory metabolic changes occur in the astrocytes of patients with chronic liver failure that prevent massive cerebral edema Changes seen on MRS imaging usually correlate with the severity of HE Changes resolve after liver transplantation
Magnetic transfer ratio	Mild, diffuse reduction in magnetic transfer ratio in the white matter	Reflects mild cerebral edema Reverses after liver transplantation
T2-weighted FLAIR sequence and diffusion weighted imaging	Diffuse increase in white matter signal intensity in the cerebral hemispheres and the corticospinal tract	Observed changes because of cerebral edema Could explain neurologic abnormalities in patients with cirrhosis Reverses after liver transplantation
Abbreviations: FLAIR, fluid attenuation inversion recovery; HE, hepatic encephalopathy; MRS, magnetic resonance spectroscopy.		

Table 2. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. *Nat Rev Gastroenterol Hepatol* 2010;7:515-525.<sup>19</sup>

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## Posttest

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 10-13) and fax to 973-939-8533.

Required with 70% passing

Must get 4 out of 5 correct to pass

### 1. Type A HE is due to:

- a. Cirrhosis
- b. Astrocyte swelling
- c. ALF
- d. Portosystemic shunt or bypass

### 2. Two of the reasons that measuring ammonia levels is insufficient for diagnosis of HE are:

- a. Ammonia levels can be normal in approximately 25% of patients with significant encephalopathy and can be elevated in up to 39% of patients without signs and symptoms of encephalopathy
- b. Ammonia levels can be normal in approximately 20% of patients with significant encephalopathy and can be elevated in up to 49% of patients without signs and symptoms of encephalopathy
- c. Ammonia levels can be normal in approximately 15% of patients with significant encephalopathy and can be elevated in up to 59% of patients without signs and symptoms of encephalopathy
- d. Ammonia levels can be normal in approximately 10% of patients with significant encephalopathy and can be elevated in up to 69% of patients without signs and symptoms of encephalopathy

### 3. When performing the “serial 7s” test in which patients are asked to subtract 7 from 100, to subtract 7 again from the number obtained, and to continue until 7 has been subtracted 5 times, patients with HE usually forget what they were asked to do when they reach:

- a. 93 or 86
- b. 96 or 79
- c. 79 or 72
- d. 72 or 65

### 4. The PHES, originally developed in Germany via collaboration between neurologists and hepatologists, was first validated from a cohort of which type of patients?

- a. Alcoholic
- b. Nonalcoholic
- c. Drug-addicted
- d. Non-drug-addicted

### 5. The CFF test involves showing patients:

- a. Light pulses at an initial frequency of 40 Hz and gradually reducing the frequency by 0.2 Hz decrements once per second
- b. Light pulses at an initial frequency of 60 Hz and gradually reducing the frequency by 0.1 Hz decrements once per second
- c. Light pulses at an initial frequency of 40 Hz and gradually reducing the frequency by 0.1 Hz decrements twice per second
- d. Light pulses at an initial frequency of 60 Hz and gradually reducing the frequency by 0.2 Hz decrements twice per second

## Evaluation

Annenberg Center for Health Sciences at Eisenhower respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

### How well did this activity meet the following learning objectives?

	<i>This learning objective did (or will) increase/ improve my:</i>	<i>High Impact</i>	<i>Moderate Impact</i>	<i>No Impact</i>	<i>Not Applicable</i>
• Describe the classification, prevalence, and etiology of hepatic encephalopathy	<b>Knowledge</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Competence</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Performance</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Patient Outcomes</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Identify the different categories of diagnostic methods for hepatic encephalopathy	<b>Knowledge</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Competence</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Performance</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Patient Outcomes</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• Assess the relative strengths and weaknesses of the various diagnostic methods for hepatic encephalopathy	<b>Knowledge</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Competence</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Performance</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<b>Patient Outcomes</b> .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### Impact of the Activity

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity (*select all that apply*):

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> Patient care or patient-centered care   | <input type="checkbox"/> Interdisciplinary teams | <input type="checkbox"/> System-based practice |
| <input type="checkbox"/> Practice-based learning and improvement | <input type="checkbox"/> Professionalism         | <input type="checkbox"/> Utilize informatics   |
| <input type="checkbox"/> Interpersonal and communication skills  | <input type="checkbox"/> Quality improvement     | <input type="checkbox"/> None of the above     |
| <input type="checkbox"/> Employ evidence-based practice          | <input type="checkbox"/> Medical knowledge       |  |

- The content of this activity matched my current (or potential) scope of practice.

- ☐ No \_\_\_\_\_
- ☐ Yes, please explain \_\_\_\_\_

- Was this activity scientifically sound and free of commercial bias\* or influence?

- ☐ Yes \_\_\_\_\_
- ☐ No, please explain \_\_\_\_\_

\* Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.

## Evaluation

### Impact of the Activity

	Strongly Agree	Agree	Disagree	Strongly Disagree	Not Applicable
• The educational activity has enhanced my professional effectiveness in treating patients .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• The educational activity will result in a change in my practice behavior .....	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
• How will you change your practice as a result of participating in this activity ( <i>select all that apply</i> )?					
<input type="checkbox"/> Create/revise protocols, policies, and/or procedures	<input type="checkbox"/> I will not make any changes to my practice				
<input type="checkbox"/> Change the management and/or treatment of my patients	<input type="checkbox"/> Other, please specify: _____				
<input type="checkbox"/> This activity validated my current practice	_____				
• What new information did you learn during this activity? _____					
_____					
_____					
• Please indicate any barriers you perceive in implementing these changes.					
<input type="checkbox"/> Lack of experience	<input type="checkbox"/> Reimbursement/insurance issues				
<input type="checkbox"/> Lack of resources (equipment)	<input type="checkbox"/> Patient compliance issues				
<input type="checkbox"/> Lack of time to assess/counsel patients	<input type="checkbox"/> No barriers				
<input type="checkbox"/> Lack of consensus of professional guidelines	<input type="checkbox"/> Cost				
<input type="checkbox"/> Lack of opportunity (patients)	<input type="checkbox"/> Other _____				
<input type="checkbox"/> Lack of administrative support	_____				
• If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients' outcomes? _____					
_____					
_____					
• Comments to help improve this activity? _____					
_____					
_____					
• Recommendations for future CME/CPE topics. _____					
_____					
_____					

To assist with future planning,  
please attest to time spent on activity:

I spent \_\_\_\_ hours on this program



*Please do not use abbreviations. We need current and **complete** information to assure delivery of participation acknowledgement.*

☐ MD/DO    ☐ PharmD/RPh    ☐ NP/PA    ☐ RN    ☐ Other \_\_\_\_\_

Last Name:

[illegible]

First Name:

[illegible]

Middle Initial:

7

[illegible][illegible]

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[illegible][illegible]

Date Completed: \_\_\_\_\_

☐ I participated in the entire activity and claim 1.0 AMA PRA Category 1 Credit(s)<sup>TM</sup>.

☐ I participated in only part of the activity and claim credits

☐ I do not wish to claim credits