Conflicts of interest
Brian Bressler serves on the advisory board, as a consultant, and received grant support from Abbvie and Janssen delivered CME lectures for Abbvie and Janssen. Corey A. Siegel serves on the advisory board, as a consultant, and received grant support from Abbvie, Janssen, and UCB, and delivered CME lectures for Abbvie, Janssen and Merck. He is supported by Grant number 1R01HS021747-01 from the Agency for Healthcare Research and Quality.

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Deciphering the Spectrum of Low-Grade Hepatic Encephalopathy in Clinical Practice

See "Value of critical flicker frequency and psychometric hepatic encephalopathy score in diagnosis of low-grade hepatic encephalopathy," by Kircheis G, Hilger N, Häussinger D, on page 961.

In the current issue of Gastroenterology, Kircheis et al[1] explored the usefulness of critical flicker frequency (CFF) and psychometric hepatic encephalopathy score (PHES) in the diagnosis and management of patients with low-grade hepatic encephalopathy (HE). Although comparisons with computer-based psychometric tests have previously yielded conflicting results, this study (which included >500 patients with cirrhosis) supports the usefulness of CFF in identifying various stages within the spectrum of HE. The spectrum of HE encompasses patients with no alterations, patients with mild neuropsychological derangement without criteria for minimal HE (MHE), patients with MHE, patients with low-grade HE, and patients with overt HE (Figure 1). West Haven criteria and Glasgow coma scale have been used widely in determining overt HE staging. However, patients with low-grade HE could be overlooked if they have not been systematically investigated with tools carrying higher sensitivity.

Neuropsychological impairment in patients with cirrhosis with or without mild neuropsychiatric disorders has been explored using psychometric tests which can range from paper and pencil–based psychometric tests (same as the PHES) to computerized psychometric tests such as the Vienna test system, inhibition control test and cognitive drugs research and also neurophysiological methods such as electroencephalography, evoked potentials, and CFF (Figure 1). By exploring cognition, behavior, biologic regulation, and emotion, we could define different neuropsychological stages strongly related to, but without complete overlap with, MHE. This MHE, in the middle of the spectrum of low-grade HE, requires a normal mental status but impaired performance on psychometric tests and/or neurophysiological tools.[2] These methods are complementary. They explore different pathways and mechanisms of disease, and identify patients at risk of suffering overt HE with diminished motor vehicle driving fitness, increased risk of falls, and impaired quality of life. The results of these diagnostic methods indicate a continuum and, as such, establishing a specific threshold that defines neuropsychological impairment (or MHE) has been controversial. A score beyond the normal distribution range while not reaching the cutoff for the diagnosis of MHE could be related, more or less, to neuropsychological alteration in patients with cirrhosis (ie, a PHES scoring of -3 is not normal, but does not reach MHE diagnosis). Thus, the debate is still ongoing as to how to interpret the altered psychometric test values, in the absence of MHE. The prevalence of this entity varies depending on the type of test, and the threshold used to define MHE. As reported by Kircheis et al,[1] using values just 1 standard deviation away from the mean to diagnose MHE (using computerized psychometric tests), the prevalence of covert HE increased by two thirds. Using stricter criteria(<-4 in PHES or <39 Hz in CFF), the prevalence was around one third of those with cirrhosis. A balance between sensitivity of analysis and clinical impact needs to be addressed. Indeed, CFF of <38 Hz was observed to be better than CFF of <39 HZ in the prediction of short-term overt HE,[3] but the latter cutoff seems to better define MHE.[4] To date, several methods (including PHES, CFF, and computerized tests) have been well-established as being able to diagnose MHE, but any change in these tools leads us into a vicious circle. Any new diagnostic method requires comparison between individuals with cirrhosis versus a healthy control group, and a demonstration of an impact on the risk of developing overt HE, or even on survival. Indeed, "modified" PHES, despite its attractive performance, has yet to demonstrate that MHE (defined as modified PHES of ≤1) is related to increased risk of overt HE or survival. Clearly, further prospective studies are warranted rather than comparative analyses with reference methods.

Despite PHES having been validated as a useful test for MHE diagnosis, some doubts have emerged. The PHES battery includes the Number Connection Test A and B, digit symbol test, serial dotting, and line drawing test. PHES seems to be influenced not only by age and education level but also by cultural issues. For example, in serial dotting (consisting of drawing a dot in the center of 100 circles) some people being tested do it as rapidly as possible, whereas others prefer carrying out the task in a slower, more accurate manner. However, this latter variable is not included in the evaluation of this test. Although the value of PHES has been questioned because of these drawbacks, in a recent study in Korea the PHES (corrected for German, Spanish, and Italian algorithms) achieved promising results.[5]

CFF has been gaining credence in the diagnosis of MHE and to delineate the spectrum of HE, as reported in a recent meta-analysis.[4] Post-transjugular intrahepatic portosystemic

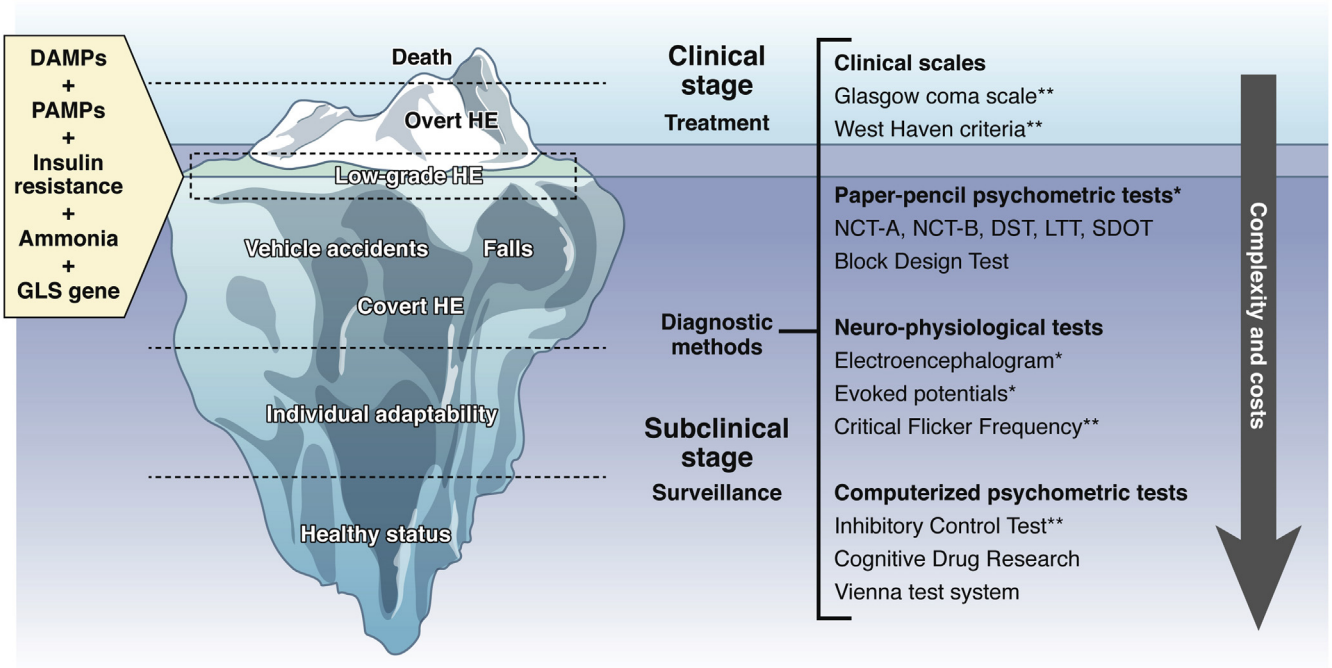

Figure 1. The spectrum of Hepatic Encephalopathy. DAMPs, damage-associated molecular patterns; GLS, glutaminase; PAMPs, pathogen-associated molecular patterns.

shunt overt HE could be predicted accurately with CFF, but not with PHES.[6] CFF has been widely used over the past 45 years to investigate the effects of psychoactive drugs, and it has been shown to correlate with brain damage associated with several neurologic disorders, such as multiple sclerosis and Alzheimer's disease. CFF measures the ability of the central nervous system to detect flickering light, which is directly influenced by cortical activity.[6] In patients with cirrhosis, alterations in the CFF do not indicate altered motor function but, rather, an altered state of the patient's attention capacity. CFF has no contraindications and could be implemented in patients with cirrhosis who understand the procedure and who have no visual, uncorrected defects. CFF has been reported to be significantly lower in patients with migraine compared with healthy control individuals. Hence, this aspect needs to be taken into account in cirrhotic patients with migraine.[7]

Computer-based psychometric tests include (a) cognitive drug research score consisting of a battery of 5 psychometric subsets that assess different areas such as attention span and continuity, speed of memory, quality of episodic recall, and working memory. Cognitive drug research score has been correlated with PHES and ammonia levels, the latter returning to within the reference range following liver transplantation.[8] (b) Inhibitory control test (ICT) is a computerized variant of the continuous performance test that evaluates sustained attention, and the ability to inhibit responses to potentially relevant stimuli during a stress-induced working memory evaluation. The ICT has been validated in a US population, the results indicating 88% sensitivity for the diagnosis of MHE and for overt HE.[9] Further, it was correlated with motor vehicle driving impairment and with traffic accidents. However, both these computerized tests showed some drawbacks. Apart from being time consuming to conduct and not widely available, Cognitive drug research scoring requires a prior practice session and no prior computer experience on the part of the test subject. In case of ICT, there are doubts regarding the usefulness of the number of noninhibited responses in the diagnosis of MHE (unless adjusted for target accuracy) because the numbers of ICT lures (ie, a measure of the inhibition ability) have been shown to depend on target accuracy, which reflects attention ability.[10] (c) The Vienna Test System (available at: http://www.schuhfried.com/index.php) in which several tests (selected from within the neuropsychology clinical specialization) have been found to be useful in a large number of clinical conditions.

HE emerges as the final result of the combination of several factors promoting the activation of the inflammasome plus hyperammonemia, depending on genetic predisposition. The impact of these factors on brain dysfunction supports the concept of a dynamic shift between stages. Indeed, after resolution of an overt HE bout, some minor alterations could persist, and patients could return to any of the stages of the HE spectrum.[11] Both inflammation from bacterial translocation as the main source for pathogen-associated molecular patterns and damage-associated molecular patterns from nuclear or mitochondrial DNA, promote insulin resistance.[12] Hyperammonemia derives from glutamine metabolism and glutaminase activity in the small intestine and kidneys. Our group has identified a microsatellite in the promoter region of the glutaminase gene that correlates with the longest form microsatellite and higher glutaminase activity, thus raising the risk for overt HE from 20% to around 40%.[13] Awareness of this entity needs to be improved. For example, in 2 surveys carried out in Spain and