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CLINICAL—LIVER

Value of Critical Flicker Frequency and Psychometric Hepatic Encephalopathy Score in Diagnosis of Low-Grade Hepatic Encephalopathy

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BACKGROUND & AIMS: Critical flicker frequency (CFF) and psychometric hepatic encephalopathy score (PHES) analyses are widely used to diagnose hepatic encephalopathy (HE), but little is known about their value in the diagnosis of low-grade HE. **METHODS:** The diagnostic values of CFF and PHES were compared using a computerized test battery and West Haven criteria as reference. We performed CFF analysis on 559 patients with cirrhosis and 261 without (controls). Of these 820 patients, 448 were evaluated using a modified PHES system and 148 were also evaluated using the conventional PHES system. **RESULTS:** CFF distinguished between patients with overt HE and without minimal or overt HE in the entire study population with 98% sensitivity and 94% specificity and in the subgroup of patients who were evaluated by conventional PHES with 97% sensitivity and 100% specificity. Conventional PHES identified patients with overt HE with 73% sensitivity and 89% specificity. CFF distinguished between patients with and without minimal HE with only 37% sensitivity but 94% specificity (entire study population). In the subgroup of patients evaluated by conventional PHES, CFF distinguished between patients with and without minimal HE with 22% sensitivity and 100% specificity; these values were similar to those for conventional PHES (30% sensitivity and 89% specificity). The modified PHES distinguished between patients with and without minimal HE with 49% sensitivity and 74% specificity. The diagnostic agreement values between CFF and conventional or modified PHES in patients with minimal HE were only 54% or 47%, respectively. **CONCLUSIONS:** In an analysis of patients with cirrhosis and controls, CFF distinguished between patients with overt HE and without minimal or overt HE. PHES testing produced a statistically significant difference among groups, but there was considerable overlap between controls and patients with overt HE. PHES, CFF, and a combination of PHES and CFF could not reliably distinguish patients with minimal HE from controls or those with overt HE.

Keywords: Advanced Liver Disease; MHE; Neuropsychology; Cognitive Function.

The Working Party of the 11th World Congress of Gastroenterology in Vienna proposed a large study to redefine neuropsychiatric abnormalities in liver disease, which would allow the diagnosis of minimal hepatic encephalopathy (MHE) on firm statistical grounds.[1] Since then, several new parameters in the diagnosis of MHE have been proposed,[2–4] but the diversity in defining MHE still exists and hampers many studies in the field. The only generally accepted statement is that the term "MHE" refers to a significant proportion of cirrhotic patients who appear normal on clinical examination but exhibit various quantifiable neuropsychological deficits.[1,5] Thus, the term describes a poorly defined syndrome at the border between normality and overt hepatic encephalopathy (HE), which by definition cannot be picked up by the West Haven criteria[1,6,7] and is defined by the diagnostic test used.

Two tests are widely used to diagnose MHE: the critical flicker frequency (CFF) and the psychometric hepatic encephalopathy score (PHES) test battery and its variants.[2,8–11] CFF is a reproducible parameter with only little bias by training effects, educational level, and daytime variability.[3,10,11] The paper-and-pencil tests used in PHES testing have drawbacks inherent to psychometric testing in general (ie, the influence of age, education, occupation, and sociocultural background),[8] which limit their reliability.[12] The aim of the present study was to compare CFF and PHES with respect to their value for diagnosing no HE (HE0), MHE, and overt HE. The data show that CFF is superior to PHES testing in separating HE0 from overt HE; however, both approaches are unable to diagnose MHE with the required accuracy. This may explain frequent contradictory study results in the past, the well-known uncertainties in medical treatment of HE, and the variable prevalence of MHE among cirrhotic populations (ranging from 20% to 80%).[5,13]

Abbreviations used in this paper: **AUC, area under the receiver-operating characteristic curve; CFF, critical flicker frequency; COG, Cognitrone Test; DST, Digit Symbol Test; HE, hepatic encephalopathy; HE0, no hepatic encephalopathy; HE1, hepatic encephalopathy grade 1; HE2, hepatic encephalopathy grade 2; LTT, Line Tracing Test; MHE, minimal hepatic encephalopathy; NCT-A, Number Connection Test A; NCT-B, Number Connection Test B; PHES, Psychometric Hepatic Encephalopathy Score; ROC, receiver-operating characteristic; SDOT, Serial Dotting; TIPS, transjugular intrahepatic portosystemic shunt; VPT, Visual Pursuit Test; VRT, Vienna Reaction Test.**

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Patients and Methods

Study Cohort and Design

A total of 820 patients with either no liver disorder (n = 261, control group) or alcoholic or nonalcoholic cirrhosis (n = 559) who were admitted to our hospital from December 2002 to March 2011 as inpatients or outpatients were studied (for characteristics, see Table 1). Cirrhosis was diagnosed on a clinical basis involving laboratory tests, ultrasonography, and transient elastography. Causes of nonalcoholic cirrhosis were chronic hepatitis B or C virus infection, α_1-antitrypsin deficiency, autoimmune hepatitis, primary biliary cirrhosis, and hemochromatosis. Cirrhotic patients who gave informed consent to participate in the study and met the inclusion criteria underwent a neuropsychological test battery. Exclusion criteria included the presence of severe HE (mental state grade 3 or 4); acute gastrointestinal hemorrhage or spontaneous bacterial peritonitis during the past 7 days; significant nonhepatic diseases such as decompensated heart, respiratory, or renal failure; decompensated or poorly controlled diabetes mellitus; overt or anamnestic neurological diseases (except HE) such as Alzheimer disease, Parkinson disease, and nonhepatic metabolic encephalopathies; uncooperativeness; obvious alcohol abuse before the investigation; ophthalmologic disorders; and anamnestic red/green visual blindness. Patients undergoing treatment with psychoactive drugs, such as antidepressants or sedatives, were also excluded; other concomitant medications were allowed and not discontinued. A total of 261 patients without evidence for acute or chronic liver disease who otherwise fulfilled the inclusion criteria served as controls (Table 1). All patients underwent psychometric testing and determination of CFF.

Assessment of Severity of HE

A total of 559 patients with cirrhosis (for biochemical findings, see Table 1) underwent computerized psychometric testing and evaluation of their mental state for assessment of the severity of HE. In addition, 4 (modified PHES test) or 5 (conventional PHES test) paper-and-pencil tests were performed (Tables 2 and 3), but grading of the severity of HE was exclusively based on the results of the computerized psychometric testing and mental state. Patients without evidence for overt HE based on mental state (West Haven criteria) were classified as having HE0 when none or only 1 of the computerized psychometric test results was abnormal and classified as having MHE when 2 or more of the computerized psychometric test results were abnormal. The definition of an abnormal computerized test result was based on the −1 SD threshold. Patients were classified as having HE grade 1 (HE1) or HE grade 2 (HE2) based on their mental state. Grading of the mental state was performed according to the West Haven criteria.[6] Grading of HE was performed by the same investigators (G.K. and D.H.), who were blinded to the CFF results.

Psychometric Testing

A battery of 5 computer-based neuropsychological tests with 22 evaluable neurophysiological parameters directed to cognition (attention, concentration, visuopraxis, psychomotor speed), emotion, behavior, and biological regulation was chosen from the Vienna Test System (Dr Schuhfried Inc, Mödling, Austria) and used as previously described.[3] Test results were considered abnormal when they were outside 1 SD from the mean of a large age-matched control population, using data

Table 1. Patient Characteristics of the Study Population (559 Cirrhotic Patients and 261 Controls; N = 820)

		Nonovert HE		Overt HE	
Patient population	Controls	HE0	MHE	HE1	HE2
n	261	106	200	165	88
Sex, n (female/male)	98/163	34/72	70/130	59/106	30/58
Age (*y*)	48.1 ± 15.5	51.5 ± 12.6[a]	55.2 ± 12.0[b,c]	60.6 ± 9.4[b,c]	63.5 ± 9.1[b]
Sodium (*mmol/L*)	139.9 ± 2.7	139.0 ± 3.9[a,d]	137.9 ± 4.4[d,e,f]	135.9 ± 5.0[e,f]	133.8 ± 6.7[e]
Alanine aminotransferase (*U/L*)	21.4 ± 16.4	45.3 ± 35.2[b,g]	51.3 ± 50.8[b,g]	60.8 ± 55.8[a]	57.8 ± 98.6
Quick (%)	101.0 ± 14.4	82.8 ± 19.8[e,g]	80.2 ± 20.3[e,f,g]	74.1 ± 19.6[e,f]	69.8 ± 19.5[e]
Albumin (*g/dL*)	4.56 ± 0.34	3.97 ± 0.52[e,h]	3.72 ± 0.68[e,f,h]	3.33 ± 0.74[e,f]	3.06 ± 0.70[e]
Bilirubin (*mg/dL*)	0.69 ± 0.46	1.54 ± 1.62[e,h]	1.64 ± 1.44[c,e,h]	2.47 ± 3.19[c,e]	3.02 ± 3.89[e]
Creatinine (*mg/dL*)	0.91 ± 0.21	0.87 ± 0.21	0.97 ± 0.47[c]	1.25 ± 1.22[c,e]	1.39 ± 0.92[e]
CFF	42.4 ± 2.5	41.7 ± 2.1[b,g]	39.9 ± 2.3[e,f,g]	36.0 ± 1.6[e,f]	31.6 ± 2.4[e]

NOTE. All values are expressed as mean ± SD unless otherwise noted. In cirrhotic patients, CFF and laboratory results worsened with increasing severity of HE. In total, 54.8% of the patients with cirrhosis had no clinical signs of HE (nonovert HE). A total of 106 patients (19.0%) had HE0, whereas 200 cirrhotic patients did not have clinical signs of HE but had pathological values (MHE, 35.8%) on at least in 2 computerized tests. A total of 253 patients had overt HE; 165 patients (29.5%) had HE1 and 88 patients (15.7%) had HE2 according to the West Haven criteria. A total of 261 subjects without evidence for liver disease served as sex-matched controls. Quick = Prothrombin time.

[a] $P < .05$ vs control.
[b] $P < .01$ vs control.
[c] $P < .01$, MHE vs HE1.
[d] $P < .05$, MHE vs HE0.
[e] $P < .001$ vs control.
[f] $P < .001$, MHE vs HE1.
[g] $P < .01$, MHE vs HE0.
[h] $P < .001$, MHE vs HE0.