CLINICAL TRIALS STUDY

Covert hepatic encephalopathy: Agreement and predictive validity of different indices

Sara Montagnese, Esmeralda Balistreri, Sami Schiff, Michele De Rui, Paolo Angeli, Giacomo Zanus, Umberto Cillo, Giancarlo Bombonato, Massimo Bolognesi, David Sacerdoti, Angelo Gatta, Carlo Merkel, Piero Amodio

Sara Montagnese, Esmeralda Balistreri, Sami Schiff, Michele De Rui, Paolo Angeli, Giancarlo Bombonato, Massimo Bolognesi, David Sacerdoti, Angelo Gatta, Carlo Merkel, Piero Amodio, Department of Medicine, University of Padova, 35128 Padova, Italy
Giacomo Zanus, Umberto Cillo, Department of Surgical, Oncological, and Gastroenterological Sciences, University of Padova, 35128 Padova, Italy
Author contributions: Montagnese S contributed to the study concept and design; acquisition, analysis and interpretation of data; drafting of the manuscript; Balistreri E contributed to the acquisition, analysis and interpretation of data; drafting of the manuscript; Schiff S contributed to the acquisition, analysis and interpretation of data; technical and material support; De Rui M contributed to the acquisition, analysis and interpretation of data; drafting of the manuscript; Angeli P, Zanus G, Cillo U, Bombonato G contributed to the acquisition of data; patient recruitment, technical and material support; Bolognesi M and Sacerdoti D contributed to the acquisition of data; technical and material support; Gatta A contributed to the study supervision; technical and material support; Merkel C contributed to the study concept and design; analysis and interpretation of data; Amodio P contributed to the study concept and design; analysis and interpretation of data; study supervision.
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Correspondence to: Sara Montagnese, MD, Department of Medicine, University of Padova, Via Giustiniani 2, 35128 Padova, Italy. sara.montagnese@unipd.it
Telephone: +39-49-8218675 Fax: +39-49-8754179
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Abstract

AIM: To investigate the agreement and prognostic value of different measures of covert hepatic encephalopathy (CHE).

METHODS: One-hundred-and-thirty-two cirrhotic outpatients underwent electroencephalography (EEG), paper-and-pencil psychometry (PHES) and critical flicker frequency, scored on the original/modified (CFFo/CFFm) thresholds. Eighty-four patients underwent Doppler-ultrasound to diagnose/exclude portal-systemic shunt. Seventy-nine were followed-up for 11 ± 7 mo in relation to the occurrence of hepatic encephalopathy (HE)-related hospitalisations.

RESULTS: On the day of study, 36% had grade I HE, 42% abnormal EEG, 33% abnormal PHES and 31/21% abnormal CFFo/CFFm. Significant associations were observed between combinations of test abnormalities; however, agreement was poor (Cohen's κ < 0.4). The prevalence of EEG, PHES and CFFo/CFFm abnormalities was significantly higher in patients with grade I overt HE. The prevalence of EEG and CFFm abnormalities was higher in patients with shunt. The prevalence of EEG abnormalities was significantly higher in patients with a history of HE. During follow-up, 10 patients died, 10 were transplanted and 29 had HE-related hospitalisations. Grade I HE (P = 0.004), abnormal EEG (P = 0.008) and abnormal PHES (P = 0.04) at baseline all predicted the subsequent occurrence of HE; CFF did not.

CONCLUSION: CHE diagnosis probably requires a combination of clinical, neurophysiological and neuropsychological indices.

Core tip: Covert hepatic encephalopathy is a hetero-

geneous entity, which should probably be sought for by a combination of clinical, neurophysiological and neuropsychological indices. Grade I hepatic encephalopathy (HE), as diagnosed by an experienced clinician, holds prognostic relevance and is associated with a higher degree of hepatic failure. Thus, while its use as an outcome for clinical trials is not recommended, the abolition of Grade I HE seems premature.

INTRODUCTION

The diagnosis of hepatic encephalopathy (HE) is problematic. Clinical scales have been criticized because of limited specificity and considerable inter-operator variability, especially in relation to mild HE[1]. Similarly, there is no real agreement as to which psychometric, neurophysiological, and/or psychophysical tests should be utilized[2].

Recently, the term covert hepatic encephalopathy (CHE) has been proposed. CHE encompasses both minimal HE (*i.e.*, abnormalities detected on neuropsychological, neurophysiological and/or psychophysical testing) and grade I overt HE, based on the West Haven classification[3]. The idea behind the proposal is that the clinical diagnosis of grade II overt HE is less controversial than that of grade I. Thus, grouping any alteration which is milder than grade II may help contain disagreement between centres and facilitate comparisons in multicentre clinical trials. However, CHE has been agreed upon but not formally defined or assessed. In addition, while its potential advantages are clear in relation to the top end of the HE severity spectrum ($\geq$ HE grade II), there is more uncertainty as to which test/test combination should be utilized to distinguish unimpaired patients from patients with CHE (bottom end of the HE severity spectrum).

The aim of the present study was to investigate the agreement and prognostic validity of clinical, psychometric, neurophysiological and psychophysical indices of CHE, also in relation to ammonia levels, portal-systemic shunt, HE history and the development of HE-related hospitalisations over time.

MATERIALS AND METHODS

The patient population comprised 132 consecutive outpatients with cirrhosis (94 men; age: 58 ± 11 years) from 1 June 2009 to 1 November 2011. The diagnosis of cirrhosis and its etiology were determined by use of clini-

cal, laboratory, radiological, and, where needed, histological variables. The functional severity of the liver disease was assessed using the Child-Pugh grading system[4] and model for end-stage liver disease (MELD)[5]. Patients were excluded if they were < 20 years or > 80 years of age, could not comply with the study procedures, had misused alcohol in the preceding 6 mo, had a history of significant head injury, cardiovascular/cerebrovascular disease or significant neurological/psychiatric co-morbidity, were taking psychoactive drugs, had symptoms or signs of infection or had overt HE $\geq$ grade II according to the West Haven criteria.

Neuropsychiatric assessment

Neuropsychiatric assessment was conducted in one morning session after breakfast. All patients underwent clinical assessment, EEG recording, PHES and CFF, in the aforementioned order.

Clinical assessment: Each patient's mental status was assessed by an experienced physician (MS or AmP). The assessment included a detailed and comprehensive medical history, full neurological examination; exclusion of concomitant neurological disorders or other metabolic encephalopathies; and a clinical grading of the neuropsychiatric abnormalities according to the West Haven criteria[6]. Patients were finally qualified as having/not having grade I overt HE and were excluded from the study if they had overt HE $\geq$ grade II.

Neurophysiology: EEGs were recorded for 10 minutes, eyes-closed, in a condition of relaxed wakefulness, using a 21-electrode EEG cap. Electrodes were placed according to the International 10-20 system; the ground electrode was Fpz; the reference electrode was Oz; impedance was kept below 5 kΩ. Each channel had its own analogue-to-digital converter; the resolution was 0.19 μV/bit (Brainquick 3200, Micromed, Italy equipment). One continuous 80-100 s period of artifact-free EEG tracing was selected for subsequent spectral analysis by Fast Fourier Transform. The following spectral parameters were calculated on the P3-P4 derivation: the mean dominant frequency (MDF), which is an estimate of the background frequency of the EEG, and the relative power of the spectral bands delta (1-3.5 Hz), theta (4-8 Hz), alpha (8.5-13 Hz) and beta (13.5-25.5 Hz). EEGs were classified as normal/abnormal based on the spectral criteria proposed by Van der Rijt *et al*[7] and subsequently modified by Amodio *et al*[8].

Psychometry: Psychometric performance was assessed, under standardized conditions, using number connection tests A and B, the digit symbol subtest of the Wechsler adult intelligence scale, and line tracing and serial dotting tests[9]. Individual psychometric test results were scored in relation to age- and education-adjusted Italian norms[10]. Psychometric performance was classified as impaired if the sum of the integer scores of each test computed from age- and education-adjusted Z values

(integer score = -3 for $Z \leqslant$ -3, -2 for -3 < $Z \leqslant$ -2, -1 for -2 < $Z \leqslant$ -1, 0 for -1 < Z < 1, 1 for $Z \geqslant$ 1), known as psychometric hepatic encephalopathy score (PHES), was $\leqslant$ -4[9,10]. The mean psychometric Z score (MPZS) was also calculated, as suggested by Amodio *et al*[10].

Psychophysiology: Critical flicker frequency (CFF) is the highest frequency in cycles per second at which the flicker of a flickering light source can be detected; at frequencies above the cutoff the light source appears to be continuous. CFF was measured with a Hepatonorm analyzer and two alternative thresholds for abnormality were utilised: the original one (o) proposed by Kircheis *et al*[11] (abnormal < 39; CFFo) and the modified one (m) proposed by Romero-Gómes *et al*[12] (abnormal < 38; CFFm).

Plasma ammonia
Fasting venous ammonia was measured in the emergency laboratory immediately after blood had been drawn in an iced tube.

Portal-systemic shunts
Doppler ultrasound evaluations were obtained in 84/132 patients (64%) by three equally experienced operators (BG, BM, SD), using one ultrasound machine (ATL 5000, Philips) with a 5 MHz convex probe provided by a colour- and pulsed-Doppler device. Patients were qualified as having portal-systemic shunts if convoluted, anechoic channels were detected, and venous flow confirmed by colour-Doppler[13].

HE history and HE development
Information about previous episodes of overt HE (clinical records plus patients'/relatives' reports) was obtained in 120 patients, of which 76 (63%) had a positive history. Finally, 79/132 patients (60%) patients were followed prospectively for 11 ± 7 mo, in relation to the occurrence of death/transplantation and HE-related hospitalisations.

One patient (male 50, Child-Pugh score B7, MELD 11) was studied prior to, and on three occasions after placement of a transjugular intrahepatic portal-systemic shunt (TIPS); one patient (male 70, A6, MELD 9) was studied immediately and 18 wk after TIPS placement; two patients (male 63, B9, MELD 14 and male 69, B7, MELD 9) were studied during and after the resolution of an episode of grade Ⅱ overt HE.

Ethics
The protocol was approved by the Hospital of Padua Ethics Committee. All participating subjects provided written, informed consent. The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and European Good Clinical Practice guidelines.

Statistical analysis
Differences between groups were examined using Mann-Whitney *U* or Student *t*-test, as appropriate. Differences between multiple groups were examined using ANOVA (*post-hoc*: Tukey test) or Kruskal-Wallis ANOVA, as appropriate. Categorized indices were compared by Pearson's χ^2. Agreement between categorized indices was assessed by Cohen's kappa coefficient (poor: $0 < \kappa < 0.4$; fair: $0.4 < \kappa < 0.6$; good: $0.6 < \kappa < 0.8$; excellent: $0.8 < \kappa < 1$). The predictive validity of different variables on the occurrence of HE-related hospitalizations was assessed using the Kaplan-Meier cumulative survival method; patients hospitalized because of HE were qualified as complete cases.

RESULTS
The etiology of cirrhosis was viral (hepatitis C or B) in 54 (41%) patients, alcohol in 49 (37%), mixed (viral plus alcohol) in 19 (14%), cryptogenic in three (2%), autoimmune and Wilson's disease in two each (1.5%), and nonalcoholic steatohepatitis, primary biliary cirrhosis and haemochromatosis in one each (1%). Functionally, 44 patients (33%) were qualified as Child-Pugh class A, 62 (47%) B, and 26 (20%) C. The average MELD score was 13 ± 5.

On the day of study, 47 (36%) patients had grade Ⅰ HE, 56 (42%) had abnormal EEG, 44 (33%) abnormal PHES and 41/28 (31/21%) abnormal CFFo/CFFm. Significant associations were observed between combinations of test abnormalities; however, agreement was poor (Tables 1 and 2). Similarly, significant correlations were observed between neurophysiological and neuropsychological/psychophysical indices analysed as continuous variables (MDF *vs* MPZS: *r* = 0.51, *P* < 0.0001; MDF *vs* CFF: *r* = 0.20, *P* < 0.05; MPZS *vs* CFF: not significant).

Of the 47 patients with grade Ⅰ HE, 34 (72%) had abnormal EEG, 30 (64%) abnormal PHES and 20/14 (43/30%) abnormal CFFo/CFFm. Such prevalence was significantly higher compared to that of patients with no grade Ⅰ HE for all three types of indices (EEG: 72% *vs* 26%, *P* < 0.0001; PHES: 64% *vs* 16%, *P* < 0.0001; CFFo/CFFm 43% *vs* 25%, *P* = 0.03, 30% *vs* 16%, *P* = 0.07). Similarly, when quantitative neuropsychiatric indices were analysed as continuous variables, patients with grade Ⅰ HE had slower EEG and worse PHES and CFF performances than their counterparts with no grade Ⅰ HE (Table 3).

Trend/significant differences in ammonia levels were observed in patients with/without grade Ⅰ HE (91 ± 62 μmol/L *vs* 67 ± 52 μmol/L, *P* = 0.07) and patients with abnormal/normal EEG (101 ± 60 μmol/L *vs* 52 ± 42 μmol/L, *P* < 0.001). In contrast, ammonia levels were comparable in patients with/without PHES (86 ± 64 μmol/L *vs* 70 ± 52 μmol/L, *P* > 0.05) or CFFo/CFFm abnormalities (81 ± 62 μmol/L *vs* 74 ± 55 μmol/L, *P* > 0.05, 94 ± 67 μmol/L *vs* 71 ± 53 μmol/L, *P* > 0.05).

Of the 85 patients with no grade Ⅰ HE, 22 (26%) had abnormal EEG, 14 (16%) abnormal PHES and 21/14 (25/16%) abnormal CFFo/CFFm. Depending on the CFF threshold utilised 47/51 (55/60%) patients had no test abnormalities (unimpaired). No significant associations were observed between combinations of

Table 1 Number of subjects with varying combinations of electroencephalographic and psychometric/psychophysic abnormalities

	PHES		CFFo		CFFm	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
EEG normal	58	18	57	19	64	12
EEG abnormal	30	26	34	22	40	16
Association	$\chi^2 = 7.5$, $P = 0.006$		$\chi^2 = 3.0$, $P = 0.08$		$\chi^2 = 3.1$, $P = 0.08$	
Cohen κ	0.23		0.15		0.14	

EEG: Electroencephalography; PHES: Psychometric hepatic encephalopathy score; CFFo/m: Critical flicker frequency original/modified.

Table 2 Number of subjects with varying combinations of psychometric and psychophysic abnormalities

	CFFo		CFFm	
	Normal	Abnormal	Normal	Abnormal
PHES normal	69	19	75	13
PHES abnormal	22	22	29	15
Association	$\chi^2 = 11.0$, $P = 0.001$		$\chi^2 = 6.5$, $P = 0.01$	
Cohen κ	0.3		0.21	

PHES: Psychometric hepatic encephalopathy score; CFFo/m: Critical flicker frequency original/modified.

test abnormalities (abnormal EEG *vs* abnormal PHES or CFFo/CFFm; abnormal PHES *vs* abnormal CFFo/CFFm). However, significant correlations were observed between neurophysiological and neuropsychological indices analysed as continuous variables (MDF *vs* MPZS: *r* = 0.30, *P* < 0.01; MDF and MPZS *vs* CFF: not significant).

Of the 84 patients who underwent Doppler ultrasound, 60 (71%) were qualified as having portal-systemic shunts. Trends were observed for a higher prevalence of EEG (50% *vs* 29%, *P* = 0.08) and CFFm abnormalities (25% *vs* 4%, *P* = 0.03) in patients with portal-systemic shunt; in contrast, the prevalence of PHES and CFFo abnormalities was comparable in the two groups. When quantitative neuropsychiatric indices were analysed as continuous variables, patients with portal-systemic shunt had slower EEG (delta power: 11% ± 12% *vs* 5% ± 3%, *P* = 0.02), while PHES and CFFo/CFFm performances were comparable in the two groups (Table 3).

Of the 120 patients in whom HE history was obtained, 76 (63%) had a positive history. The prevalence of EEG abnormalities was significantly higher in patients with a positive history (51% *vs* 27%, *P* = 0.01) while those of PHES and CFFo/CFFm abnormalities were comparable in the two groups. When quantitative neuropsychiatric indices were taken as continuous variables, patients with a history of HE had slower EEG (*P* < 0.01 for most spectral indices, Table 2) and worse PHES scores (-2.9% ± 3.9% *vs* -1.5% ± 3.5%, *P* = 0.05) than their counterparts with negative history, while CFF was comparable in the two groups (Table 3).

During follow-up, 10 patients died, 10 were transplanted and 29 had HE-related hospitalisation. The presence of grade I HE (*P* = 0.004), abnormal EEG (*P* = 0.008) and abnormal PHES (*P* = 0.04) at baseline all predicted the subsequent occurrence of HE; CFFo/CFFm
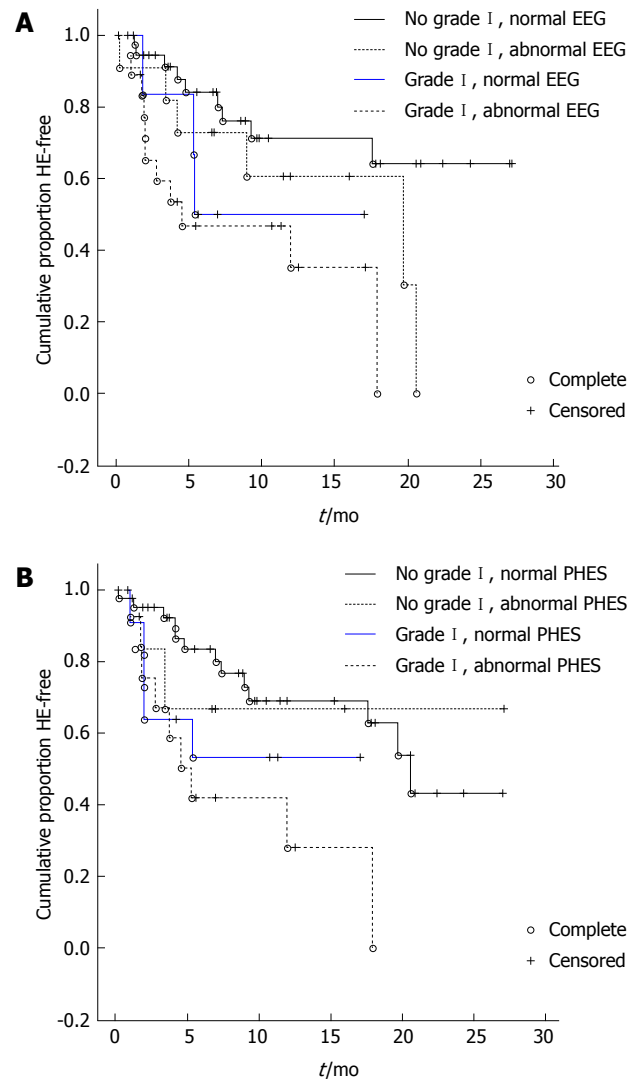

Figure 1 Cumulative hepatic encephalopathy-free survival. Cumulative hepatic encephalopathy (HE)-free survival over the follow-up period in relation to the combination of electroencephalographic (EEG) and clinical abnormalities (panel A, χ^2 = 8.2, *P* = 0.041) and the combination of psychometric hepatic encephalopathy score (PHES) and clinical abnormalities (panel B, χ^2 = 7.8, *P* = 0.050) at baseline.

did not. The presence of grade I HE had independent, additional prognostic value compared to tests alone as patients with grade I HE (with or without EEG/PHES abnormalities) had worse prognosis than those with EEG/PHES abnormalities who appeared clinically normal (Figure 1). In addition, only patients with a com-
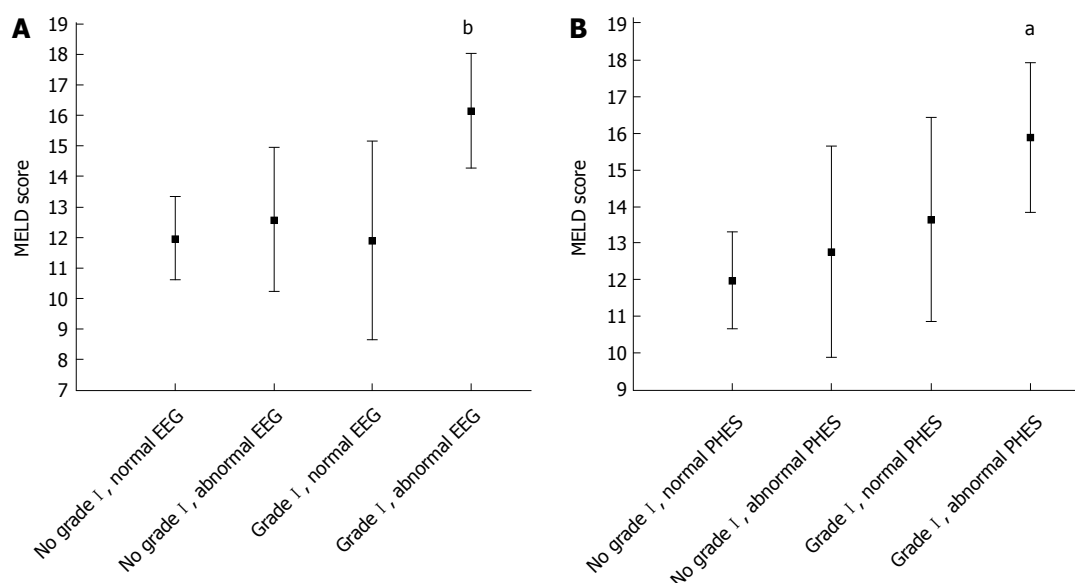
Figure 2 Model for end-stage liver disease scores in patients. Model for end-stage liver disease scores (MELD) in patients grouped based on the combination of electroencephalographic (EEG) and clinical abnormalities (panel A) and the combination of psychometric hepatic encephalopathy score (PHES) and clinical abnormalities (panel B). [a]$P < 0.05$, [b]$P < 0.01$ *vs post-hoc* comparisons.

Table 3 Electroencephalographic, psychometric and psychophysic indices in relation to the presence of grade I hepatic encephalopathy, portal-systemic shunt and a history of hepatic encephalopathy

	EEG					Psychometry		CFF
	MDF (Hz)	δ	θ	α	β	PHES	MPZS	
No grade I HE (n = 85)	10.3 ± 1.8	7% ± 6%	26% ± 17%	45% ± 17%	21% ± 13%	-0.9 ± 2.9	-0.2 ± 0.9	41.9 ± 5.4
Grade I HE (n = 47)	8.2 ± 1.9[b]	15% ± 16%[b]	43% ± 17%[b]	29% ± 18%[b]	12% ± 8%[b]	-5.3 ± 4.0[b]	-1.5 ± 1.1[b]	39.9 ± 5.3[a]
No portal-systemic shunt (n = 24)	10.1 ± 1.8	5% ± 3%	29% ± 23%	44% ± 18%	21% ± 13%	-1.3 ± 2.8	-0.3 ± 0.8	42.8 ± 5.1
Portal-systemic shunt (n = 60)	9.3 ± 2.2	11% ± 12%[d]	35% ± 19%	36% ± 19%	18% ± 13%	-2.6 ± 3.8	-0.7 ± 1.1	41.2 ± 5.7
No HE history (n = 44)	10.2 ± 1.7	6% ± 7%	25% ± 17%	48% ± 18%	21% ± 12%	-1.5 ± 3.6	-0.3 ± 1.1	41.9 ± 5.9
HE history (n = 76)	9.1 ± 2.1[f]	12% ± 12%[f]	37% ± 19%[f]	35% ± 19%[f]	17% ± 12%	-2.9 ± 4.0	-0.8 ± 1.1[e]	40.6 ± 5.3

[a]$P < 0.05$, [b]$P < 0.01$ *vs* no grade I hepatic encephalopathy (HE); [d]$P < 0.01$ *vs* no portal-systemic shunt; [e]$P < 0.05$, [f]$P < 0.01$ *vs* no HE history. EEG: Electroencephalography; CFF: Critical flicker frequency; MDF: Mean dominant frequency; PHES: Psychometric hepatic encephalopathy score; MPZS: Mean psychometric Z score.

bination of EEG/PHES abnormality and grade I HE had significantly higher MELD scores than unimpaired patients (Figure 2).

In the four patients studied on repeat occasions, both the EEG and the PHES reflected changes in clinical conditions and modified treatment regimes, at least to some degree, while the CFF did not (Table 4).

DISCUSSION

The results of this study indicate that CHE is a heterogeneous syndrome.

The presence of grade I HE, diagnosed by an experienced hepatologist based on the original West Haven criteria[6], was associated with previous and subsequent HE episodes, with higher ammonia levels and with more profound alterations in psychometric, neurophysiological and psychophysical indices. In addition, patients with grade I HE and EEG/PHES abnormalities had higher MELD scores than unimpaired patients, while those with EEG/PHES abnormalities alone did not. This suggests that even mild neuropsychiatric alterations should be sought for on clinical examination, despite difficulties in their formal definition and in comparing them over time and/or across centres[1]. The fact that patients with grade I HE had higher MELD scores and were at higher risk of HE development makes it unlikely that their being qualified as grade I HE, even in the absence of PHES and/or EEG abnormalities, was a result of clinical misclassification.

Table 4 Electroencephalographic, psychometric and psychophysic indices in four patients who were studied in different conditions over time

Patient	Condition	Time	EEG					Psychometry		CFF
			MDF (Hz)	δ	θ	α	β	PHES	MPZS	(Hz)
1 male 55, B7, MELD 11	Baseline	0	10.8	8%	19%	49%	24%	5	1.6	41
1	Post-TIPS, overt grade I	+ 11 mo	9.6	3%	34%	49%	14%	5	1.6	49
1	Post-TIPS, treated	+ 19 mo	10.5	3%	15%	64%	18%	2	0.9	46
1	Post-TIPS, treated	+ 23 mo	11.5	4%	11%	59%	27%	4	1.2	46
2 male 70, A6, MELD 9	Post-TIPS, overt grade I	0	7.9	7%	64%	20%	9%	0	-0.2	46
2	Post-TIPS, treated	+ 18 wk	10.7	10%	18%	44%	28%	-1	-0.1	39
3 male 63, B9, MELD 14	Overt grade II	0	4.8	42%	50%	6%	2%	-6	-1.8	42
3	Treated	+ 11 wk	8.2	4%	67%	21%	7%	-1	-0.5	57
4 male 69, B7, MELD 9	Overt grade II	0	5.4	45%	38%	10%	7%	-9	-2.4	37
4	Treated	+ 6 wk	10.8	4%	21%	51%	24%	-3	-0.7	39

HE: Hepatic encephalopathy; EEG: Electroencephalography; CFF: Critical flicker frequency; MDF: Mean dominant frequency; PHES: Psychometric hepatic encephalopathy score; MPZS: Mean psychometric Z score; TIPS: Transjugular intrahepatic portosystemic shunt.

The agreement between abnormalities in psychometric, neurophysiological and psychophysical indices was poor. In patients without grade I HE, abnormalities in these indices were not even associated with one another. These observations are probably related to a number of factors. Firstly, psychometric, neurophysiological and psychophysical tools measure different aspects of brain functioning, which do not necessarily change simultaneously, or even in parallel, especially in patients with mild/no clinical signs of HE[14]. It has already been highlighted that psychometric, neurophysiological and psychophysical tests can all be expected to be normal in very well compensated cirrhotics, and abnormal in those with severe, overt HE[2]. However, in intermediate states, their behavior is probably more erratic, and more sensitive to confounding factors[15]. Secondly, thresholds for abnormality of these indices for patients with cirrhosis have been derived in different ways, often on relatively small populations, and may need improving. For example, the original spectral EEG thresholds were derived by comparison of patients graded on the West Haven criteria[7]. In contrast, PHES thresholds were defined as deviations from normal reference values, adjusted for age and education, and then assessed in patients with cirrhosis with no/varying degree of clinical abnormality[9]. The hypothesis that threshold adjustment may be needed is supported by the fact that while limited associations were observed between test abnormalities, there were significant correlations between continuous psychometric, neurophysiological and psychophysical indices. Thirdly and finally, changes in psychometric, neurophysiological and psychophysical indices may reflect different pathogenic mechanisms. For example, EEG slowing has been shown to reflect high ammonia and indole levels, while abnormalities in PHES performance seem more closely associated with raised inflammatory markers[16].

Based on the above considerations, and the observation that grade I HE, the EEG and the PHES all predicted subsequent HE-related hospitalizations, their association may represent a reasonable screening system for CHE. Similarly, the EEG and the PHES could be utilized to monitor patients over time, as they were also shown to reflect, albeit on a small number of representative cases, changes in clinical conditions and therapeutic regimes. In addition, their association would ensure that both hyperammonaemia and inflammation, which are considered major pathogenic mechanisms in relation to HE development, are "covered"[17].

The fact that CFF, based either on the original or the modified threshold, had less obvious relationships with clinical status, a history and the subsequent development of HE is only partially in contrast with previously published data. In the original paper by Kircheis *et al*[11], considerable overlap was observed between CFFo performances of patients qualified as having no, subclinical and grade I HE; these classes would now all be part of CHE. At odds with our results, in the study by Romero-Gómez *et al*[12], correlations were observed between CFF and PHES performance in patients with minimal HE, and CFF at baseline predicted the development of HE over time. However, in the same study the agreement between PHES and CFFm abnormalities was poor, as in our study. This was also the case in a study by Dhiman *et al*[18], who also suggested that CFF, contrary to previous observations, might be strongly influenced by age. This was recently confirmed by Goldbecker *et al*[19] who, in line with our results, also showed limited sensitivity of CFF in confirming the diagnosis of overt HE.

In conclusion, our results suggest that CHE is a heterogeneous entity, which should probably be screened for by a combination of clinical, neurophysiological and neuropsychological indices. The presence of clinically detectable signs of HE, albeit mild, holds prognostic relevance. Thus the definition of a more reproducible, less operator-dependent diagnostic system for grade I HE seems worthy of further research efforts.

COMMENTS

Background
The diagnosis of hepatic encephalopathy relies on clinical, neurophysiological, psychometric and psychophysical indices. However, their respective relevance, agreement and predictive validity are unknown.

Research frontiers
The nomenclature/grading of hepatic encephalopathy have been recently modified.

Innovations and breakthroughs
The current study contributes to a better definition of covert hepatic encephalopathy.

Applications
To current study provides the first set of data on the usefulness of different neuropsychiatric tools for the diagnosis of covert hepatic encephalopathy.

Terminology
Covert hepatic encephalopathy is a newly introduced class of disease severity, which encompasses the minimal and mild overt forms of the disease.

Peer review
In this article, authors analyse the agreement between clinical assessment, psychometric (PHES), neuropsycological (EEG) and psycophysical test (original and modified critical flicker frequency) in cirrhotic patients with covert hepatic encephalopathy (minimal and grade I overt hepatic encephalopathy). The authors conclude that covert hepatic encephalopathy is a heterogeneous entity, which should probably be evaluated by a combination of clinical, neurophysiological and neuropsychological tests. The study also evaluates the prognostic capacity of these tools, finding that the presence of grade I hepatic encephalopathy, abnormal EEG or abnormal PHES predict the development of a new episode of hepatic encephalopathy.

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