Covert Hepatic Encephalopathy: Does the Mini-Mental State Examination Help?

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Background/objectives: **The Mini-Mental State Examination (MMSE) has been utilized for the diagnosis of hepatic encephalopathy (HE). However, its threshold of abnormality has not been formally tested in patients with cirrhosis and its diagnostic/prognostic validity remains unknown. The aim of this study was to assess it in a large group of well-characterized outpatients with cirrhosis and no overt HE.** ***Methods:*** **One-hundred-and-ninety-one patients underwent clinical assessment, MMSE, electroencephalography (EEG) and paper-and-pencil psychometry (PHES); 117 were followed up for 8 ± 5 months in relation to the occurrence of HE-related hospitalizations.** ***Results:*** **On the day of study, 81 patients (42%) had abnormal EEG and 67 (35%) abnormal PHES; 103 (60%) had a history of HE. Average MMSE was 26.6 ± 3.5; 22 (19%) patients had abnormal MMSE based on the standard threshold of 24. Patients with abnormal EEG/PHES/history of HE had worse MMSE performance than their counterparts with normal tests/negative history (25.7 ± 4.2 vs. 27.3 ± 2.7; $P < 0.01$; 25.5 ± 3.2 vs. 27.9 ± 1.8, $P < 0.0001$; 26.3 ± 3.7 vs. 27.4 ± 2.6, $P < 0.05$, respectively). Based on the above results, MMSE thresholds of 26 and 27 were tested against abnormalities in clinical/EEG/PHES indices and significant associations were observed. An MMSE threshold of 26 was also a predictor of HE-related hospitalization (Cox–Mantel: $P = 0.001$); patients with MMSE <26 were significantly older than those with MMSE ≥26 but comparable in terms of liver dysfunction and ammonia levels. When MMSE items were considered separately, those which correlated most significantly with standard HE indices where spatial orientation and writing.** ***Conclusion:*** **In conclusion, an MMSE <26 identifies older patients with cirrhosis who are more prone to manifest HE signs.** **(J Clin Exp Hepatol 2014;4:89–93)**

The Mini-Mental State Examination (MMSE) is a short, practical instrument which can be used in routine clinical practice to assess global cognitive functioning. The MMSE was originally devised to diagnose dementia[1] and the threshold which is normally utilized for this purpose is 24.[2] However, an MMSE of >24 does not imply the absence of cognitive impairment [i.e.: pre-dementia or mild cognitive impairment is diagnosed by the combination of MMSE >24, and the presence of specific memory deficits[3]]. For its ease of administration, the MMSE has subsequently been 'borrowed' to screen for cognitive impairment in patients with various diseases, such as stroke,[4] diabetes[5,6] and even metabolic syndrome[7] or cancer.[8] As the test was originally conceived for a geriatric population,[1,9–11] reference norms and age-adjustment tools tend to be available only for older ages.[9]

A proportion of patients with cirrhosis exhibit disturbances in orientation, attention, constructional praxia, psychomotor speed and executive function, which are collectively termed hepatic encephalopathy (HE).[12–15] The MMSE covers such cognitive domains,[1] at least to some extent, and has been utilized also in this patient population.[16,17] Its use has been welcome as the milder forms of clinically overt HE pose a considerable diagnostic problem, and the criteria currently in use—the so-called West Haven criteria[18]—have been criticized and deemed to be far too operator-dependent.[19]

The aim of this study was to formally assess the usefulness of MMSE in a large group of well-characterized cirrhotic patients without overt HE.

PATIENTS AND METHODS

The patient population comprised 191 patients with cirrhosis (137 men; mean ± SD age: 58 ± 11 years). The functional severity of liver disease was assessed using the Child-Pugh grading system[20] and the Model for End-stage Liver Disease (MELD).[21] Patients were excluded if they had ≥grade II HE according to the West Haven criteria, a history of head injury, cardio/cerebro-vascular

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Abbreviations: EEG: electroencephalography; HE: hepatic encephalopathy; MELD: model for end-stage liver disease; MMSE: mini-mental state examination; PHES: psychometric hepatic encephalopathy score
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disease or neurological/psychiatric comorbidity. Patients who were on psychoactive drugs or unable to comply with the study procedures were also excluded.

Neuropsychiatric Assessment

All patients underwent clinical assessment, MMSE, PHES and EEG recording in the aforementioned order.

Clinical Assessment

The clinical assessment included a full neurological examination and a clinical grading of the neuropsychiatric abnormalities. Each patient's mental status was assessed by an experienced physician. The assessment included detailed and comprehensive medical history, full neurological examination, exclusion of concomitant neurological disorders or other metabolic encephalopathies, clinical grading of the neuropsychiatric abnormalities according to the West Haven criteria.

Neuropsychological Assessment

This was performed by an experienced neuropsychologist (MC, MT and SS) in the morning, after breakfast, in a quiet well-lit room, in standardized conditions.

Mini-Mental State Examination (MMSE): The test includes 11 items, divided into two sections. The first section requires verbal responses to questions assessing orientation, memory and attention (orientation to place/time, repetition, calculation, recall); the second section tests the ability to name objects (denomination), follow verbal and written commands (complex verbal/written comprehension), write a sentence spontaneously, copy a drawing and praxia (writing, copying a complex geometrical drawing). Each item is attributed a different set of points, ranging from 1 to 5. The total score ranges from 0 to 30, and scores below 24 are considered abnormal.[1,2]

Psychometric Hepatic Encephalopathy Score (PHES): Psychometric performance was assessed, under standardized conditions, using the paper-and-pencil PHES battery.[13] Assessment included the Trail Making Tests A and B, the Digit Symbol Test (Wechsler Adult Intelligence Scale), the Line Tracing Test and the Serial Dotting Test. 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 $Z \leq -3$, -2 for $-3 < Z \leq -2$, -1 for $-2 < Z \leq -1$, 0 for $-1 < Z < 1$, 1 for $Z \geq 1$), known as Psychometric Hepatic Encephalopathy Score (PHES), was ≤ -4.[22]

Electroencephalography (EEG) Recordings

EEGs were recorded with a 21-electrode EEG cap, eyes-closed, in a condition of relaxed wakefulness. Electrodes were placed according to the International 10–20 system; the ground and reference electrode were Fpz and Oz, respectively; impedance was kept below 5 KΩ. Each channel had its own analog-to-digital converter; the resolution was 0.19 μV/bit (Brainquick 3200, Micromed, Italy equipment). One continuous 80–100 s period of artifact-free tracing was selected for subsequent spectral analysis by Fast Fourier Transform. EEGs were classified as normal/abnormal based on the spectral criteria proposed by Van der Rijt et al[23] and subsequently modified by Amodio et al.[24]

Plasma Ammonia

In 115 (60%) patients, fasting venous ammonia was measured in the emergency laboratory immediately after blood had been drawn in an iced tube.

HE History and Development

Information were obtained on previous episodes of overt HE (clinical records plus patients/'relatives' reports), and 117 (61%) patients were followed up prospectively for 8 ± 5 months in relation to the occurrence of HE-related hospitalizations.

Ethics

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

Statistical Analysis

The distributions of the variables were tested for normality using the Shapiro–Wilk's W test. Differences between groups were examined by the Student *t* or Mann–Whitney *U* tests, as appropriate. Relationships between prevalence of abnormalities in different tests were assessed by the Pearson χ^2. HE-free survival analysis was performed with the Kaplan–Meier cumulative survival method (post-hoc test: Cox–Mantel); patients who were hospitalized because of HE during the follow-up period were qualified as complete cases.

RESULTS

The etiology of cirrhosis was viral (hepatitis C or B) in 78 (41%) patients, alcohol in 67 (35%), mixed (viral plus alcohol) in 29 (15%), cryptogenic in 6 (3%), metabolic in 4 (2%), autoimmune and Wilson's disease in two each (1%), primary biliary cirrhosis, cystic fibrosis and hemochromatosis in one each (0.5%). Functionally, 67 patients (35%) were qualified as Child-Pugh class A, 86 (45%) B, and 38 (20%) C. The average MELD score was 13 ± 5.

One-hundred-and-three patients (54%) of the 170 whose detailed history was available had previous episodes of HE. On the day of study, 81 (42%) patients had abnormal EEG and 67 (35%) abnormal PHES. Average, fasting ammonia levels were 72 ± 52 μmol/L.

Average MMSE was 26.6 ± 3.5 and 22 (19%) patients had abnormal MMSE based on the standard threshold of 24. Patients with abnormal EEG/PHES/history of HE had worse MMSE performances than their counterparts with normal EEG/PHES and a negative history (25.7 ± 4.2 *vs.* 27.3 ± 2.7; $P < 0.01$; 25.5 ± 3.2 *vs.* 27.9 ± 1.8, $P < 0.0001$; 26.3 ± 3.7 *vs.* 27.4 ± 2.6, $P < 0.05$, respectively).

Based on the above results, MMSE thresholds of 26 and 27 were tested against abnormalities in EEG and PHES, and significant associations were observed (MMSE-26 *vs.* EEG/PHES/HE history: $\chi^2 = 7$, $P < 0.01$; $\chi^2 = 23$, $P < 0.00001$; $\chi^2 = 7$, $P < 0.01$, respectively; MMSE-27 *vs.* overt EEG/PHES/HE history: $\chi^2 = 13$, $P < 0.001$; $\chi^2 = 28$, $P < 0.00001$; NS, respectively). An MMSE threshold of 26 was also a significant predictor of HE-related hospitalization over the follow-up period (Cox–Mantel: $P = 0.001$), as were the EEG (Cox–Mantel: $P = 0.01$) and the PHES (Cox–Mantel: $P = 0.004$); the MMSE threshold of 27 was not.

Age, MELD scores and ammonia levels by significant predictors of HE-related hospitalizations are presented in Table 1.

When the MMSE domains where considered separately, those with the strongest associations with EEG/PHES abnormalities and a history of HE were orientation to space and writing (Table 2).

DISCUSSION

The MMSE correlated with other, more specific neuropsychiatric indices of HE and predicted, to a degree, the development of HE-related hospitalizations. However, patients with abnormal MMSE were older than their counterparts with normal MMSE, and comparable in terms of ammonia levels and hepatic insufficiency. These findings suggest that lower MMSE identifies a group of elderly patients with cirrhosis, who are probably more susceptible to hyperammonaemia and HE precipitants.[25,26]

Cognitive performance is known to be generally sensitive to age, particularly for such domains as attention and memory.[27] An older age is also associated with an increase in cortical atrophy. It has been demonstrated that both an older age[28] and the presence of brain atrophy[29] increase the likelihood of developing HE in patients with surgical shunts/alcohol-related cirrhosis, respectively.[28,29]

The results of the present study are only partially at odds with those recently published by Koziarska et al (2013),[17] who suggested that MMSE is not useful for diagnosing minimal HE, and does not correlate with EEG spectral parameters. The differences between the two studies may relate to differences in: i) HE classification (unimpaired vs. minimal HE vs. overt HE in Koziarska et al[17]; covert hepatic encephalopathy in the present study); ii) degree of hepatic failure (the prevalence of Child B/C patients is higher in the present study); iii) methods for HE classification (the present study also included standard psychometry as opposed to EEG only).[30]

The cognitive system can be modeled as the modular combination of eight main domains: perception, attention, memory, language, recognition, praxia, mathematical ability and executive function. The MMSE covers each of these domains, and provides a basic assessment of an individual's cognitive functioning. As in the study by Koziarska et al,[17] the sub-areas of the MMSE which were more strongly associated with 'harder' indices of HE (EEG, PHES and a positive HE history) were orientation to space and writing, which were originally identified by Sherlock and collaborators[31] as being affected by HE. Along the same lines, Davidson and Summerskill[32] highlighted significant changes in writing and drawing ability after surgery for porto-caval shunt.

Since the pioneering observations of Sherlock and coworkers,[31] the neuropsychological profile of patients with HE has been defined in considerably more detail.[13,33] Most published studies indicate that HE is characterized by a basic reduction in brain activation, in attention and the ability to disengage attention from an object of interest to a second object of interest and/or a distracting stimulus.[34] This supports the clinical observation that patients with cirrhosis are prone to distraction,[35] and often unable to cope with conflicting tasks.[36] In addition, the documented inefficiency in their inhibitory mechanisms[37] results in intrusions (i.e. the ongoing cognitive process is disturbed by related or unrelated thoughts, verbal and perceptive material that should normally be inhibited), leading to a sort of 'overload' and generally

Table 1 Age, Degree of Hepatic Failure and Venous Ammonia Levels in Patients Classified by Predictors of HE Development.

	MMSE		EEG		PHES	
	≥26	<26	Normal	Abnormal	Normal	Abnormal
Age (yrs)	56 ± 11	63 ± 10***	56 ± 10	61 ± 10****	55 ± 11	61 ± 11**
MELD score	13 ± 5	13 ± 5	12 ± 4	15 ± 6***	12 ± 4	15 ± 6**
Ammonia (μmol/L)	75 ± 52	66 ± 52	54 ± 38	95 ± 57****	63 ± 47	85 ± 56*

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

MMSE: Mini-Mental State Examination; EEG: Electroencephalogram; PHES: Psychometric Hepatic Encephalopathy Score; MELD: Model for End-stage Liver Disease.

Table 2 Average MMSE Items in Patients with Cirrhosis with and Without PHES Abnormalities, EEG Abnormalities, HE History.

MMSE items (score range)	PHES		EEG		HE history[a]	
	Normal (*n* = 124)	Abnormal (*n* = 67)	Normal (*n* = 110)	Abnormal (*n* = 81)	Negative (*n* = 67)	Positive (*n* = 103)
Orientation to time (0–5)	4.7 ± 0.5	4.5 ± 0.8**	4.6 ± 0.7	4.5 ± 0.9	4.7 ± 0.6	4.5 ± 0.9
Orientation to place (0–5)	4.8 ± 0.5	4.4 ± 0.6****	4.8 ± 0.5	4.4 ± 0.8****	4.8 ± 0.5	4.5 ± 0.7*
Repetition (0–3)	3.0 ± 0.0	2.9 ± 0.2*	2.9 ± 0.1	2.9 ± 0.2	3.0 ± 0.0	2.9 ± 0.1
Attention and calculation (0–5)	4.9 ± 0.3	4.3 ± 1.3****	4.8 ± 0.8	4.4 ± 1.3**	4.8 ± 0.8	4.5 ± 1.1
Recall (0–3)	1.9 ± 0.9	1.6 ± 1.1*	1.9 ± 1.0	1.6 ± 1.0	1.9 ± 1.0	1.8 ± 1.0
Denomination (0–2)	2.0 ± 0.1	1.9 ± 0.2	1.9 ± 0.2	2.0 ± 0.0	1.9 ± 0.3	2.0 ± 0.0
Sentence repetition (0–1)	0.8 ± 0.5	0.6 ± 0.5**	0.7 ± 0.4	0.7 ± 0.5	0.8 ± 0.4	0.7 ± 0.5
Written comprehension (0–1)	0.9 ± 0.1	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	0.9 ± 0.2	0.9 ± 0.1
Complex verbal comprehension (0–3)	2.7 ± 0.5	2.6 ± 0.6*	2.7 ± 0.5	2.6 ± 0.6	2.7 ± 0.5	2.6 ± 0.6
Writing (0–1)	0.9 ± 0.2	0.8 ± 0.4***	0.9 ± 0.2	0.8 ± 0.4**	0.9 ± 0.2	0.9 ± 0.3*
Drawing copying (0–1)	0.9 ± 0.2	0.7 ± 0.4****	0.9 ± 0.3	0.8 ± 0.4	0.9 ± 0.3	0.8 ± 0.4

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.
MMSE: Mini-Mental State Examination; PHES: Psychometric Hepatic Encephalopathy Score; EEG: Electroencephalogram; HE: Hepatic Encephalopathy.
[a]Data available in 170 patients.

poor performance.[36,37] Motor abnormalities, which may impinge on writing, have also been documented. Even in the absence of clinically detectable rigidity[38] or flapping tremor, these patients often exhibit bradykinesia, difficulties in movement initiation[39] and in smooth pursuit eye movements.[16] In contrast, both short- and long-term memory are generally preserved.[12,40,41] Thus, while we agree with Koziarka and co-workers[17] that the MMSE is not an adequate tool for HE screening, some of its items detect cognitive abnormalities which are typical of HE, such as spatial disorientation and difficulties in writing. Therefore, it reasonable to imagine that clinical scales aimed at HE screening should include questions on such items.

Finally, an MMSE threshold of 26 was found to predict the development of HE-related hospitalizations, most likely by identifying a group of older patients. The fact that such threshold is higher than 24 is an expected finding, as the patient population consisted of cirrhotic patients with no obvious neuropsychiatric dysfunction and an average age below 60.

In conclusion, while the MMSE can pick up on neuropsychiatric abnormalities which are part of the HE spectrum, it is not adequate for HE diagnosis. An MMSE below 26 identifies patients with cirrhosis who are prone to manifest HE not because of their liver failure but because of their older age.

CONFLICTS OF INTEREST

All authors have none to declare.

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