Subclinical Hepatic Encephalopathy: The Role of Neuropsychological and Electrophysiological Tools in Diagnosis.

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ABSTRACT

Background: Subclinical hepatic encephalopathy (SHE) indicates cognitive deficits in the absence of overt encephalopathy. It is frequently found in patients with cirrhosis. SHE prevalence depends on the diagnostic procedures used in its detection but there isn't yet a standardized method for its diagnosis. **Subjects and methods:** 40 cirrhotic patients *{20* patients with overt hepatic encephalopathy (HE) and 20 patients with no encephalopathic manifestations (NE)} and 25 healthy controls were studied in this work for the prevalence of neuropsychologic and neuropsychological abnormalities. A battery of psychometric tests (Digit Span test (DS), Similarities, Digit Symbol Test (DST), Block Design (BD) and Mini Mental State Examination (MMSE) and a neurophysionogic test as Electroencephalography (EEG) were used in this work. **Results**: There was a significant difference between patients groups (NE and HE) and normal controls and in the DS test (PO.02). Also a significant difference has been found between the two patients groups (NE and HE) in the DS test (20% and 30% respectively), DST (25% and 40% respectively) and MMSE (15% and 25% respectively) tests (P<0.02, <0.001 and <0.001 respectively). EEG showed abnormalities in 8 NE patients (40%) classified as mild and in 16 HE patients (80%) classified as moderate (60%) and mild (20%). **Conclusion:** this work shows that the neuropsychological tests are of importance in the diagnosis of SHE, as they are simple, easy to perform, and suitable to be applied to outpatient hepatic clinics.

Key words: Subclinical hepatic encephalopathy, Neuropsychological test, Electrophysiological tests.

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INTRODUCTION

Clinical manifestations of hepatic encephalopathy include decreased intellectual function, personality changes, an altered level of consciousness, and neuromuscular dysfunction[1]. In addition to clinically manifest liver encephalopathy a subclinical form has been described, which requires specific neuropsychological and neurophysiological examination to detect its presence[2].

Clinical relevance of Subclinical Hepatic Encephalopathy (SHE) is attributed to two reasons: First, it could be a preceding stage of clinical manifest hepatic

encephalopathy[3]. However, this possibility is weak as only one follow-up study[4] supports this view. Second, the psychomotor deficits found in SHE could impose potential risk on patients' daily functioning, e.g., driving a car or erroneous performing at work[5].

The aim of this work is to determine the prevalence of neuropsychological and neurophysiological defects in stable cirrhotic patients attending an outpatient clinic using 5 neuropsychometric tests (2 verbal abilities tests: Digit Span (DS) and Similarities tests, 2 performance abilities tests: Digit Symbol Test (DST) and Block Design (BD) test and Mini Mental State Examination (MMSE) and a neurophysiological test (EEG).

SUBJECTS AND METHODS

Forty outpatients, suffering from liver cirrhosis, were included in this study: 20 patients (18 males and 2 females with age range 41-68 years) with hepatic encephalopathy (HE) and 20 patients (16 males and 4 females with age range 32-65 years) without clinical encephalopathy (NE). The control subjects were 25, age and sex matched normal subjects (20 males, 5 females) ranging in age from 40 to 67 years. The inclusion criteria of the healthy controls were absence of neuropsychiatric or medical diseases and not receiving medications that influence cognitive functions All patients were subjected to thorough clinical evaluation with special emphasis on neuropsychiatric examination.

Liver cirrhosis was diagnosed by liver biopsy in 20 patients, but was not performed in the remaining 20 patients due to complication with coagulopathy and/or ascites .The diagnosis of cirrhosis was accomplished by doing liver function tests, including serum billirubin, serum protein, serum albumin, globulins, alanine transaminases (ALT), aspartate transaminases (AST), serum alkaline phosphatase, prothrombin time and concentration.

Abdominal ultrasonography was done using an apparatus Hitachi HUB 515 with a convex linear probe

Upper GIT endoscopy was done using an Olympus XQ40 fiberscope, with special emphasis on the grade of varices.

The Child- Pugh score was used to assess the severity of liver disease. Three biochemical variables (serum albumin, billirubin, and prothrombin time) and two clinical characteristics (presence or absence of ascites and encephalopathy) determine the Child-Pugh score, each variable is given I to 3 points, leading to score ranging from 5 (excellent liver function) to 15 points (poor liver function).

Neuropsychological Assessment:

1) The Wechsler Adult Intelligence Scale[6] ***(WAIS)***: 4 subsets of the scale were used;
a) For the verbal abilities:

The Digit Span (DS) Text: The ability of reciting increasingly numbers of digit mentioned to the subject forward and backward. It is a measure of immediate memory and concentration. Test consists of seven pairs of random number sequences that the examiner reads aloud at the rate of one per second.

The Similarity Test: The ability of telling in what way pairs of items are similar. It is a test of verbal concept formation and help to assess the general mental ability. The word pairs range in difficulty from the simplest to the most difficult. The test begins with the first item for all subjects and is discontinued after four failures

b) For the performance abilities.
The Digit Symbol Text (DST): The ability of pairing arbitrarily assigned symbols with numbers. It is a measure of motor speed and accuracy. The subject is given a list of digits from I to 9 associated with symbols and is asked to fill in blanks with symbols that correspond to each number. The test score is the total number of correct sequential matching of symbols to numbers in 90 second interval. After explanation of the test an abbreviated demonstration was administered to ensure that the subject understood the test correctly.

The Block Design (BD) Test: It is used for assessing the spatial component in perception. It is a construction test in which the subject is presented with red and white blocks, four or nine, depending on the item. Each block has two white and two red sides and two half- red half- white sides with the colors divided along the diagonal .The task is to use the blocks to construct replicas of two block constructions made by the examiner and seven designs printed in smaller scale.

2) The Mini Mental State Examination (MMSE) (7)**.** It is probably the most widely used brief screening test for detection of cognitive impairment. It assesses orientation, attention immediate and short-term recall, language and the ability to follow simple verbal and written commands. When interpreting the results of DS. Similarity, BD, DST, and MMSE tests a score equal to or less than 9.5, 9, 8.5, 8 and 24 respectively were considered abnormal.

Neurophysiologjcal Assessment:

The neurophysiological test performed in this study is the conventional electroencephalogram using bipolar and referential montages. EEG abnormalities were graded into borderline, mild, moderate and marked[8].

Statistical analysis:

Comparisons were evaluated by using the Student's I test (2-tailed probability). A chi square test was used to study the frequency distribution of the results. The significance of correlation was estimated by the Spearman's correlation coefficient. Significance was considered with $p<0 \cdot 05$.

RESULTS

None of the stable cirrhotic patients (non-enchephalopatic, NE) included in this study had clinical signs of encephalopathy. The etiology of cirrhosis in our patients was post chronic viral hepatitis with or without schistosomal periportal fibrosis as proved by liver biopsy (20 patients) and/or biochemical and serologic tests and abdominal ultrasound. None of our patients gave history of alcohol intake.
Table (1) shows the clinical and biochemical data of the study population at the entry of the study. All patients had spleenomegaly and most of them had a variable degree of ascites. All patients with

HE were Child C, where NE patients were Child B (50%) and Child C (50%).

Concerning psychometric tests, there was significant difference between normal controls (NC) and patients groups (NE and HE) and between the 2 patients groups in DS, DST and MMSE tests (P<0.02, 0.001 and 0.001 respectively), while in similarities and BD tests, there was no significant differences (Table 2)

Table 1: Clinical and Biochemical Data of the Study Population.

		NC (N=25)	NE (N=20)	HE (N=20)
Age	Years	50.1+9	48.5+9.06	51.7+7.5
Sex	M/F	20/5	16/4	18/2
Liver	Average Shrunken		12 (60%) 8 (140%)	10 (50%) 10(50%)
Spleen	Splenomegaly		20(100%)	20(100%)
Ascites	Ascites No Mild Moderate Marked		4 (20%) 6 (30%) 8 (40%) 2 (1 0%)	6 (30%) 4 (20%) 8 (40%) 2 (1 0%)
Child-Pugl grade	A B C		0 10 10	0 0 20
Median Pugli score			10	1 1
Blood chemistry	Bilirubin (mg/dl) ALT (U/L) AS'I (U/L) Albumin (g/dl) rothrombin T.	0.9 ± 0. 1 10.2 ±2.2 11.4 ±1.2 4.6 ±1.2 I 1.4±0.4	1 99 ± 0.55 22.4±9.68 26.2 ± 12.7 2.35±0.34 18.2±2.6	2.06±0 36 23.8±1 1.5 34.54±10 2.46±0.55 22.1±3.5
Esophageal varices	Grade I Grade II Grade III Grade VI		0 10 (50%) 6 (30%) 4 (20%)	0 0 9(45%) 11 (55%)

Note: Age and biochemical data are given as means ± SD. Normal ranges: ALT and AST<12 U/L, albumin <1.1 mg/dl

Table 2: Psychiatric and Electrophysiological Characteristics of the Study Population.

Psychometrie Tests		NC (N=25)	Nl- (N=20)	HE (N=20)
Verbal test:	DS Similarities	•9.96 + 1.17 @ 10.59+2.36	9.15 + 1.2-4 @9.85 +2.1	9 +1.68 @ 10.1+2.1
Performance tests	DST BD MMSE	◊● 9.2 +.147 @ 8.67 + 1.83 ♠ 24.78 + 1.87	7.25 + 1.13 @8.1 + 1.76 23.2 + 0.87	6.36 + 1.7 @7.77 + 1.6 22.2+ 1.8

The EEG showed abnormalities in 8 patients (40%) with stable cirrhosis (NE), the abnormalities were classified as mild. While EEG abnormalities in patients with HE were detected in 16 patients (80%), the abnormalities were classified as moderate in 12 patients (60%) and as mild in the remaining 4 patients (20%). No significant correlation was found between the severity of liver disease, as determined by Child-Pugh, and the EEG grades (Table 3).

Table 3: EEC Findings in Studied Patients.

EEG Grades	NE (20)		HE (20)	
Child's	**B**	**C**	**B**	**C**
Normal	6 (30%)	6 (30%)	0	4 (20%)
Mild	4 (20%)	4 (20%)	0	4 (20%)
Moderate	0	0	0	12 (60%)

In the statistical analysis, the chi square test for the two samples confirms the fact that the two groups of patients had differing results in all the tests, with the HE patients presenting the greater alterations from the normal. In the two groups of patients (NE and HE), concerning the neuropsychological tests, although the percentage of altered values of DST were higher than other psychometric tests,-there was no significant difference between these tests with regard to the contribution to the total chi square probability in the two groups of patients (table 4).

No significant difference between non-encephalopathic cirrhotic patients with SHE (NE-2) or without SHE (NE-1) concerning clinical and biochemical characteristics (only S. bilirubin gave a significant difference $P<0.01$) (table 5).

Table 4: Frequency of Abnormal Test Results in Patients Studied.

Psychometric Tests		NE (N=20)	HE (N=20)
Verbal tests:	**DS**	4 (20%)	6(30%)
	Similarities	3(15%)	7(35%)
Performance tests	**DST**	5 (25%)	8(40%}
	BD	2(10%)	6(30%)
	MMSE	3(15%)	5(25%)
Neurophysiol-ogic Tests	**ECG, EEG**	8 (40%)	16(80%)

Table 5: Clinical biochemical & data of stable cirrhotic patients with & without SHE.

		NE-1 (N=8)	HE-2 (SHE) (N=12)
Sex	**M/F**	6/2	10/2
Liver size	**Average**	4 (50%)	4 (33.3%)
	Shrunken	4 (50%)	8 (66.7%)
Ascites		6 (75%)	12 (100)
Child-Pugh grade	**B/C**	4/4	6/6
Liver functions	**S.bil**	1.625 $\pm$	2.23 $\pm$
	ALT	0.373	0.534
	AST	22.75 $\pm$	22.167 $\pm$
	S.albumin	12.68	7.71

DISCUSSION

Hepatic encephalopathy (HE) is a metabolic clinical syndrome affecting the brain which may occur during chronic and acute liver diseases. It is of special clinical importance to detect latent or sub-clinical forms of HE (SHE), when patients show no clinical signs, but show changes of complex cerebral functions as well as sub-cortical psychomotor deficits on psychometric tests. The most common neuro-cognitive deficits in SHE are attentional and motor abnormalities, as well as sleep disturbances, which may be a part of the SHE spectrum.

Because patients experience significant limitations in everyday life[9] and the presence of such deficits has prognostic value concerning their life expectancy, detection of SHE is of high clinical importance[10].

Karin et al. studied attention, memory and cognitive function in hepatic encephalopathy and found that the deficits in attention and arousal play a major role in clinical presentation of hepatic encephalopathy11.

Essentially, the diagnosis of hepatic encephalopathy is clinical, but in the past few years neurophysiological and neuropsychological investigations have added an objective evaluation approach of central nervous system abnormalities in patients with severe liver diseases.

In reviewing methods for diagnosing hepatic encephalopathy in patients with cirrhosis, there was a number of individual techniques which access different aspects of cerebral function that can be used singly or in combination including mental state assessment, psychometric testing, electroencephalography, sensory and cognitive evoked potentials, and neuroimaging[12].

Here we studied 40 cirrhotic patients (20 with HE and 20 without HE) and 25 healthy controls for the prevalence of neuropsychologic and neurophysiologic abnormalities using some psychometric tests (DS, similarities, DST. BD of Wechsler test and MMSE) and a neurophysiologic test (EEG). EEG showed abnormalities in 8 NE patients (40%) and in 16 HE patients (80%). Abnormalities in EEG were reported as mild in NE patients (4 patients with Child's B and 4 patients with Child's C) while in HE patients mild abnormalities were reported in 20% and moderate in 60% (all were Child's C). Although the percentage of moderate EEG abnormalities was higher in Child's C patients, no significant correlation was found between EEG abnormalities and Child's grade. Controversy exists in the literature concerning the reliability' of using EEG in detecting SHE. Neurophysiological abnormalities were correlated to the degree of severity of hepatic encephalopathy using EEG spectral (13-14). They detected EEG-abnormalities in 8 cirrhotic patients (61.5%) with HE and in one patient (9.1%) without HE and reported that the routine EEG is of no help in detecting latent hepatic encephalopathy. By using automated EEG analysis showed that EEG abnormalities in 17% of cirrhotic patients without HE[4].

Concerning psychometric tests our data revealed significant difference between normal controls (NC) and patients groups (NE and HE) and between the two patients groups (NE and HE) with each other in DS, DST and MMSE tests ($P<0.02$, 0.001 and 0.001 respectively), while in similarities and BD tests, no significant differences were found. The presence of abnormalities varied with the technique used, being highest with the performance test DST (25% in NE and 36.4% in HE patients) and the verbal test DS (20% in NE and 27.3% in HE patients). These findings suggest the usefulness of using the psychometric tests in detecting SHE.

The higher percentage of DST in detecting SHE and HE compared to other tests was in agreement with that impairment in

performance was more marked than in verbal skills in their cirrhotic patients[15]. Among the neuropsychometric tests, done in our study, the DST has been shown to be the most reliable in detecting SHE. According to literature, SHE is present in 30% to 84% of cirrhotic patients according to the tests used.

The prevalence of SHE will also vary depending on the population tested. Our population consisted mainly of patients with advanced liver disease (Child-Pugh grade B and C), which could explain the high prevalence of SHE found in this study. Quero et al. found a significant increase in prevalence of SHE from 14% in Child-Pugh grade A to 45% in Child-Pugh grade B or C[4]. Also the altered psychometric tests were related to the severity of liver disease, independently of its etiology[16].

Psychometric tests acquired their importance in diagnosis of SHE by being easy to perform and their ability to demonstrate a reasonable sensitivity. Our data showed that patients with SHE had no specific clinical or biochemical results that could differentiate them from cirrhotic patients without SHE. Thus a simple, easy to perform test not influenced by the patient's education is needed to diagnose SHE. So we may advice the use of the Digit Symbol Test (DST), in hepatic outpatient clinics as a quick reference for the psychomotor or performance abilities of the patients, in addition to the Mini Mental Stale Examination either in its full version or in its short one (10 questions) to assess the possible cognitive impairment.

In a study of subclinical hepatic encephalopathy in Chinese patients with stabilized hepatic cirrhosis using Number Connection Test part A and Digit Symbol Test, found that the psychometric tests are simple and reliable indicators for screening SHE[17]. While in comparing psychometric test to Inhibitory Control Test in diagnosing minimal hepatic encephalopathy found that the time taken and costs of the test is smaller than using the standard psychometric tests[18].

The clinical importance of SHE diagnosis is that anti encephalopathy treatment could be considered in certain individuals as they may be effective in prevention of SHE progression to overt hepatic encephalopathy19. The effect of SHE on patient's daily functioning studied impling impaired daily functioning and warrants attempts at treatment[9]. The neuropsychologic tests retained their importance, as they are simple, and easy to perform, in diagnosis of SHE, suitable to be applied to outpatient hepatic clinics.

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