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Diagnosis of Minimal Hepatic Encephalopathy of Cirrhotic Patients Using a Combination of Neuropsychiatric and Neurophysiological Tests

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ABSTRACT

Background: Minimal Hepatic Encephalopathy (MHE) is characterized by mild cognitive impairment, attention deficits, psychomotor slowing and impaired vasomotor and bimanual coordination. These non-evident symptoms can be revealed with neuro psycho metric and neuro physiological testing. **Aim:** to validate a comprehensive set of neuropsychiatric test battery in addition to the neuro physiological tests in detecting MHE. **Patients and Methods:** Thirty patients with liver cirrhosis and no clinical evidence of HE were selected for this study. Patients underwent laboratory screening, Neuropsychiatric and Neuro physiological tests. **Results:** Impairment of at least one psychometric test was documented in 50% of patients, with 50% abnormal NCTA, 46.7% abnormal DST and 40% abnormal LTT. VEP records showed prolonged P100 in 46.7% of patients with 40% prolongation of P100 in the right eye and 46.7% in the left eye. EEG recording was abnormal in 43.3% patients and the recorded abnormalities included; slow theta waves in 33% of patients, slow delta waves 10%, and 56% had normal EEG. **Conclusion:** The incidence of MHE can vary according to the strategy of diagnosis and while strict dependence on neuropsychiatric tests can diagnose MHE in 50% of patients, adopting a more strict policy that incorporate neuro physiological tests can limit the diagnosis 40% of patients. There is moderate concordance between neuropsychiatric and neurophysiologic tests.

Keywords: Cirrhosis of liver, Psychometric tests, electroencephalogram, visual evoked potential, Minimal hepatic encephalopathy.

INTRODUCTION

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or Porto systemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma [(1)].Along with its cognitive impairment, liver cirrhosis results in utilization of more health care resources in adults than any other manifestation of liver diseases [(2)]. Traditionally HE was graded into four stages of severity, ranging from abnormal behavior to coma. In addition, a subclinical stage has been described, in which patients of cirrhosis show a number of quantifiable neuropsychological defects, yet has a normal mental and neurological status on global clinical examination [(3)].This subclinical stage started to

come into light when several studies showed that many liver cirrhosis patients without clinical signs of encephalopathy (normal conventional neurological and mental assessment) performed significantly worse in psychometric tests as compared to healthy controls[(4)].They were initially labeled as suffering from 'latent' or 'subclinical' HE for which the recent term 'minimal hepatic encephalopathy' (MHE) is used[(5)].MHE is more difficult to diagnose and more often to require the use of specialized testing to do[(6)]so, the diagnostic methodologies were a combination of neuropsychometric (NP) and neurophysiologic testing strategies[(4)]. MHE is manifested by impairment in specialized testing and is considered by most of the clinicians to predict the development of OHE [(6)].Patients with evidence of MHE poses a potential danger to themselves or to the community in the operation of heavy equipment and motor vehicles [(7)]. Moreover, MHE can have a far-reaching impact on the quality of life and the ability to function in daily life [(8)].

AIM OF THE WORK

In this study we aimed to the validity of a comprehensive set of neuropsychiatric test battery [NCT, DST and LTT] in addition to the neurophysiologic tests; EEG and VEP in detecting MHE.

PATIENTS AND METHODS

This is a prospective cohort study that was conducted at the internal medicine department of El-Hussein university Hospital in Cairo, Egypt, thirty patients with liver cirrhosis and no clinical evidence of HE were selected for this study. Patients underwent laboratory screening, EEG scans, visual evoked potential and neuropsychiatric tests (Number connection test A, Digit symbol test and Line tracing task).

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Inclusion criteria:

- Patients with liver cirrhosis confirmed by an abdominal US and or laboratory investigations.
- Basic literacy education "able to read and write".

Exclusion Criteria:

- Patients with overt hepatic encephalopathy.
- Illiterate patients.
- Patients on psychoactive drugs.
- Patients with alcoholism.
- Patients with cerebro vascular accident affecting motor function.
- Patients with neurodegenerative disorders as Parkinsonism or dementia.
- Patients with other end organ failure i.e., renal, cardiac or respiratory.
- Patients with hypo natremia or hypoglycemia.

Methods

1. History talking, clinical examination including detailed neurological examination.

2. Blood ammonia [9]

Venous blood (4 ml) was collected from cirrhotic patients following an overnight fast to measure the level of blood ammonia and full biochemical tests (full liver profile, CBC, INR, serum urea and creatine).

3. Psychometric tests [1]

We selected 3 tests to be utilized after Arabic translation [10]. MHE was diagnosed when only one test was abnormal [11].

- **Number connection test:**

Number connection test A (**fig. 1)** is one of the components of the psychometric hepatic encephalopathy score that was validated as a single test for MHE. An Arabic version of the test was designed for use with the patients [12] the test measures cognitive processing speed involving psychomotor responding in which patient should draw a line from number (1) to number (2) and from (2) to number (3) till reaching number (25), without elevating the pencil from the paper. The time was recorded in seconds. If the patient made an error, the examiner told him to correct it, but the timing was not stopped. The average score was29 s, while the deficient score was > 78 s and the rule of thumb was that most completed it in 90 s. The rule of thumb is a broadly accurate guide or principle, based on practice rather than theory [12].

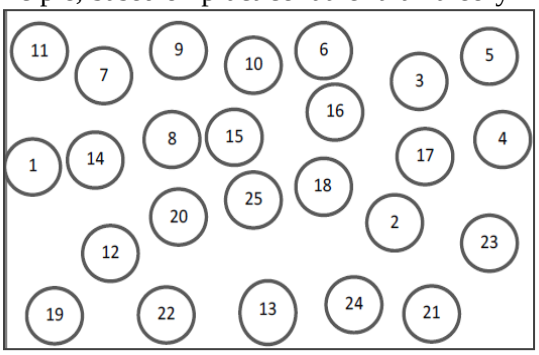

Figure (1): Number connection test A.

- **Digit symbol test:**

Digit symbol test **(fig2)** is a part of the Wechsler intelligent scale tests that had been validated in the diagnosis of MHE[13].An Arabic version of the test was revised by Melaka [10].for use with the patients. The test measures cognitive processing speed involving psychomotor responding. A coding key was presented consisting of nine abstract symbols, each paired with a number. The patient was required to scan the key and write down the symbol corresponding to each number as rapidly as possible. Ninety seconds were given to the patient and when the time was finished, the number of symbols performed by the patient was counted. The score was recorded in points. If the patient made any errors, timing continued towards their 90 s, and the patient might lose time. A healthy individual should be able to complete the test in 90 s or less. A fall of 1 to 1.5 SD below the mean is considered suggestive of cerebral dysfunction [14].

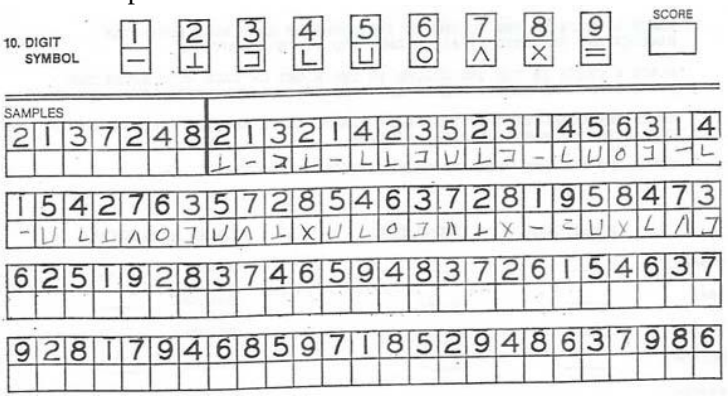

Figure (2): Digit symbol test

Line tracing task:

Line tracing test **(fig. 3)** measures fine motor skill impairments and visuo-spatial impairments. The patients have to follow the route of the labyrinth without crossing or even touching the borderlines. For the assessment of the test result the whole route is divided into small section and each touching or crossing the border in a section is counted. The number of mistakes and the time needed to go through the labyrinth; both are represented in the scoring system [(15)].

4. Electroencephalogram

EEG was 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. One continuous 80-100 s period of artifact-free EEG tracing was selected for subsequent spectral analysis by Fast Fourier Transform. 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, was calculated [(16)].

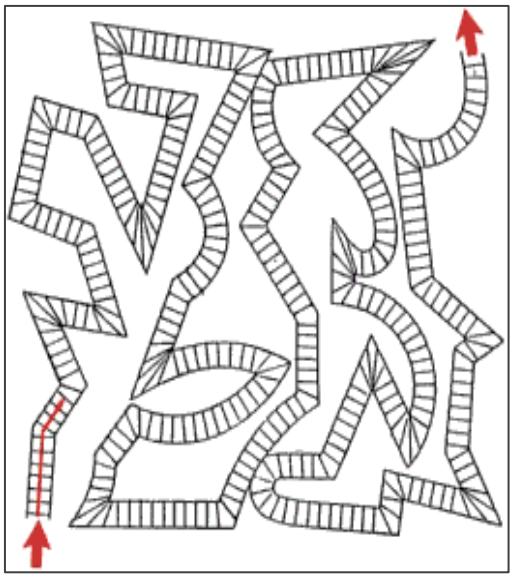

Fig (3): Line trcing test

5. Visual Evoked Potential

VEP testing, visual-evoked potentials paradigms were used. The VEP parameters which we evaluated were amplitudes and latencies of P100 wave after pattern stimulation (P-VEP). The latency of the P100 wave of PVEPS which proved to be of value in detecting mild HE was recorded.[(17)].

Statistical analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp)[(18)]. Qualitative data were described using numbers and percent. The Kolmogorv-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. The Significance of the obtained results was judged at the 5% level. The used tests were Chi-square test, Monte Carlo correction, Student t-test, Mann Whitney test, Sensitivity, Specificity, Positive Predictive value (PPV),Negative Predictive value (NPV), Accuracy and Kappa (κ).

Table (1): Demographic and clinical features of the studied group (n= 30)

	No.	%
Age		
<50	9	30.0
≥50	21	70.0
Mean ± SD.	54.10 ± 9.40	
Gender		
Male	21	70.0
Female	9	30.0
Education		
≤6	23	76.7
>6	7	23.3
Mean ± SD.	5.40 ± 2.74	
Causes of liver disease		
HBV*	1	3.3
HCV**	28	93.3
Shiest osmosis	1	3.3
Previous hepatic encephalopathy	14	46.7
Child classification		
A	10	33.3
B	12	40.0
C	8	26.7

*HBV: hepatitis B virus, **HCV: hepatitis C virus put in results

Table (2): Prevalence of minimal hepatic encephalopathy according to used tests (n= 30)

		No.	%
PTB	**NCTA**		
	Normal	15	50.0
	Abnormal	15	50.0
	Min. – max.	18.0 – 172.0	
	Median	47.50	
	DST		
	Normal	16	53.3
	Abnormal	14	46.7
	Min. – max.	4.0 – 25.0	
	Median	21.50	
	LTT $_{\text{Errors + time}}$		
	Normal	18	60.0
	Abnormal	12	40.0
	Min. – max.	22.0 – 115.0	
	Median	37.50	
	PTB		
	Normal	15	50.0
	Abnormal	15	50.0
VEP	**Right**		
	Normal	18	60.0
	Abnormal	12	40.0
	Min. – Max.	90.30 – 135.0	
	Median	106.65	
	Left		
	Normal	16	53.3
	Abnormal	14	46.7
	Min. – Max.	89.10 – 142.20	
	Median	109.25	
	VEP		
	Normal	16	53.3
	Abnormal	14	46.7
EEG	Slow theta wave	10	33.3
	Slow delta wave	3	10.0
	Normal EEG	17	56.7

(PHE) psychometric hepatic encephalopathy score
(NCTA) number connection test A (VEP) visual evoked potential (DST) digit symbol test (LTT) line tracing test (EEG) electroencephalogram

Table (3): Relation between education and PHES

	Education				□□	FEp
	≤6 (n= 23)		>6 (n= 7)			
	No.	%	No.	%		
NCTA						
Normal	12	52.2	3	42.9	□□□□□	1.000
Abnormal	11	47.8	4	57.1		
DST						
Normal	12	52.2	4	57.1	0.053	1.000
Abnormal	11	47.8	3	42.9		
LTTE errors + time						
Normal	15	65.2	3	42.9	1.118	0.392
Abnormal	8	34.8	4	57.1		
PTB						
Normal	12	52.2	3	42.9	0.186	1.000
Abnormal	11	47.8	4	57.1		

χ2: **Chi square test** for comparing between the two groups
FEP: p value for Fisher Exact for **Chi square test** for comparing between the two groups
(NCTA) number connection test A (DST) digit symbol test (LTT) line tracing test (PTB) psychometric test battery

Ethics and patient consent

The study was approved by the Ethics Board of Al-Azhar University. Oral consents was taken from all patients before collecting any information or starting any procedure.

RESULTS

Thirty patients with liver cirrhosis were included in the study of them 21 were males and 9 were females. Their mean age was 54.10 ±9.40. The cause of liver disease was HCV infection in 28 patients, HBV one patients and shistosomiasis in one patient. Fourteen patients reported a past history of hepatic encephalopathy dating at least one month ago. Severity of liver disease as reflected by Child's classification was documented as; 10 patients as Child–Turcotte–Pugh (CTP) A, 12 patients to be CTPB and 8 patients CTPC (table1).

Psychometric test battery (PTB) results:

The results showed that psychometric test battery were impaired in 50% of patients, with 50% abnormal NCTA, 46.7% abnormal DST and 40% abnormal LTT (table 2). An important observation of the current study that education level did not impact the result of any psychometric test **[p > 0.05]** (table 3). Poor scoring of psychometric tests was associated with impairment of hepatic function as reflected by CTP classification, S.Ammonia, platelet, S.Albumin, S.Bilirubin and INR **[P < 0.05]** for each variable (table 4).

VEP test results:

VEP records showed prolonged P100 in 46.7% of patients with 40% prolongation of P100 in the right eye and 46.7% in the left eye (table 2).It showed no relation to the liver function status and to either EEG or psychometric tests **[P> 0.05]** (table 5). Also there is no relation between cases which have abnormal VEP in both eyes and liver function tests (Table 6). In regards agreement with the other tests, it had a reasonable agreement with PTB with sensitivity of 66.67% and specificity of 73.33% (table 8) and moderate agreement with EEG with a sensitivity of 76.92 and specificity of 76.47% (table 9).

Table (4): Factors associated with prevalence of minimal hepatic encephalopathy using PTB (n= 30)

	PTB				P
	Normal (n= 15)		Abnormal (n= 15)		
	No.	%	No.	%	
Gender					
Male	9	60.0	12	80.0	0.427
Female	6	40.0	3	20.0	
Age (years)					
Mean ± SD.	54.93 ± 10.32		53.27 ± 8.67		0.636
Causes of cirrhosis					
B	0	0.0	1	6.7	0.477
C	15	100.0	13	86.7	
SH	0	0.0	1	6.7	
Previous hepatic encephalopathy					
HE	5	33.3	9	60.0	0.143
No	10	66.7	6	40.0	
Child classification					
A	8	53.3	2	13.3	0.018*
B	6	40.0	6	40.0	
C	1	6.7	7	46.7	
s.ammonia(25-80µg/d)					
Mean ± SD.	71.33 ± 13.17		89.73 ± 22.39		0.012*
WBCs (4 – 11×10^3)					
Mean ± SD.	6.39 ± 1.89		7.53 ± 2.95		0.350
Platelet (150 – 450×10^3)					
Mean ± SD.	179.13 ± 61.51		108.93 ± 59.16		0.005*
s.albumin (3.5 – 5gm/d)					
Mean ± SD.	3.33 ± 0.52		2.77 ± 0.45		0.004*
s.bilirubin (0 – 1gm/d)					
Mean ± SD.	1.33 ± 0.49		1.95 ± 0.64		0.009*
INR (0.8 –1.2)					
Mean ± SD.	1.18 ± 0.31		1.55 ± 0.42		0.010*

χ^2:**Chi square test** for comparing between the two groups
t, p: t and p values for **Student t-test** for comparing between the two groups
U, p: U and p values for **Mann Whitney test** for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

Table (5): Factors associated with prevalence of minimal hepatic encephalopathy using VEP (n= 30)

	VEP				P
	Normal (n= 14)		Abnormal (n= 16)		
	No.	%	No.	%	
Gender					
Male	10	62.5	11	78.6	0.440
Female	6	37.5	3	21.4	
Age (years)					
Mean ± SD.	53.13 ± 9.28		55.21 ± 9.77		0.553
Causes of cirrhosis					
B	1	6.3	0	0.0	
C	15	93.8	13	92.9	0.730
SH	0	0.0	1	7.1	
Previous hepatic encephalopathy					
HE	8	50.0	6	42.9	0.696
No	8	50.0	8	57.1	
Child classification					
A	7	43.8	3	21.4	
B	4	25.0	8	57.1	0.273
C	5	31.3	3	21.4	
s.ammonia(25-80µg/d)					
Mean ± SD.	75.28 ± 16.64		86.54 ± 23.01		0.133
WBCs (4 – 11×10^3)					
Mean ± SD.	6.77 ± 2.44		7.18 ± 2.64		0.618
Platelet (150 – 450×10^3)					
Mean ± SD.	157.50 ± 77.41		128.64 ± 57.39		0.406
s.albumin (3.5 – 5gm/d)					
Mean ± SD.	3.17 ± 0.64		2.91 ± 0.43		0.195
s.bilirubin (0 – 1gm/d)					
Mean ± SD.	1.63 ± 0.68		1.66 ± 0.62		0.851
INR (0.8 –1.2)					
Mean ± SD.	1.36 ± 0.45		1.37 ± 0.37		0.954

χ^2:**Chi square test** for comparing between the two groups
t, p: t and p values for **Student t-test** for comparing between the two groups
U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Table (6): Factors associated with prevalence of minimal hepatic encephalopathy using VEP in patintes which have prolonged p100 in both eyes (n= 28)

	VEP				P
	Normal (n= 16)		Abnormal VEP in both eyes (n= 12)		
	No.	%	No.	%	
Gender					
Male	10	62.5	9	75.0	$^{FE}p=0.687$
Female	6	37.5	3	25.0	
Age (years)					
Mean ± SD.	53.12 ± 9.27		57 ± 9.4		0.287
Causes of cirrhosis					
B	1	6.3	0	0.0	$^{MC}p=$ 0.680
C	15	93.8	11	91.7	
SH	0	0.0	1	8.3	
Previous hepatic encephalopathy					
HE	8	50.0	5	41.7	0.662
No	8	50.0	7	58.3	
Child classification					
A	7	43.8	3	25.0	$^{MC}p=$ 0.509
B	4	25.0	6	50.0	
C	5	31.3	3	25.0	
s.ammonia(25-80µg/d)					
Mean ± SD.	75.28 ± 16.64		88.75 ± 23.99		0.112
WBCs (4 – 11×10^3)					
Mean ± SD.	6.77 ± 2.44		7.4 ± 2.76		0.516
Platelet (150 – 450×10^3)					
Mean ± SD.	157.5 ± 77.41		127.84 ± 60.85		0.457
s.albumin (3.5 – 5gm/d)					
Mean ± SD.	3.1 ± 0.64		2.9 ± 0.46		0.260
s.bilirubin (0 – 1gm/d)					
Mean ± SD.	1.62 ± 0.68		1.7 ± 0.65		0.761
INR (0.8 –1.2)					
Mean ± SD.	1.38 ± 0.43		1.4 – 0.38		0.780

χ^2: **Chi square test** for comparing between the two groups t, p: t and p values for **Student t-test** for comparing between the two groups U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Table (7): Factors associated with prevalence of minimal hepatic encephalopathy using EEG (n= 30)

	EEG				P
	Normal (n= 17)		Abnormal (n= 13)		
	No.	%	No.	%	
Gender					
Male	11	64.7	10	76.9	0.691
Female	6	35.3	3	23.1	
Age (years)					
Mean ± SD.	52.18 ± 9.20		56.62 ± 9.42		0.206
Causes of cirrhosis					
B	1	5.9	0	0.0	
C	16	94.1	12	92.3	0.694
SH	0	0.0	1	7.7	
Previous hepatic encephalopathy					
HE	8	47.1	6	46.2	0.961
No	9	52.9	7	53.8	
Child classification					
A	6	35.3	4	30.8	
B	8	47.1	4	30.8	0.523
C	3	17.6	5	38.5	
s.ammonia(25-80µg/d)					
Mean ± SD.	75.91 ± 16.89		86.58 ± 23.42		0.158
WBCs (4 – 11×10^3)					
Mean ± SD.	6.38 ± 2.24		2.72 ± 2.71		0.143
Platelet (150 – 450×10^3)					
Mean ± SD.	156.12 ± 67.76		128.23 ± 70.56		0.250
s.albumin (3.5 – 5gm/d)					
Mean ± SD.	3.14 ± 0.55		2.92 ± 0.57		0.297
s.bilirubin (0 – 1gm/d)					
Mean ± SD.	1.56 ± 0.63		1.75 ± 0.67		0.474
INR (0.8 –1.2)					
Mean ± SD.	1.26 ± 0.36		1.50 ± 0.45		0.120

χ^2: **Chi square test** for comparing between the two groups
t, p: t and p values for **Student t-test** for comparing between the two groups
U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Table (8): Agreement (sensitivity, specificity and accuracy) for EEG and VEP according to PTB

	PTB				Sensitivity	Specificity	PPV	NPV	Accuracy
	Normal (n= 15)		Abnormal (n= 15)						
	No.	%	No.	%					
EEG									
Normal	12	80.0	5	33.3	66.67	80.0	76.92	70.59	73.33
Abnormal	3	20.0	10	66.7					
κ(p)	0.467*(0.010*) **Moderate agreement**								
VEP									
Normal	11	73.3	5	33.3	66.67	73.33	71.43	68.75	70.0
Abnormal	4	26.7	10	66.7					
κ(p)	0.400*(0.028*) **Fair agreement**								

κ: kappa test
*: Statistically significant at $p \leq 0.05$

Value of K	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Table (9):Agreement (sensitivity, specificity and accuracy) for VEP according to EEG

	EEG				Sensitivity	Specificity	PPV	NPV	Accuracy
	Normal (n= 17)		Abnormal (n= 13)						
	No.	%	No.	%					
VEP									
Normal	13	76.5	3	23.1	76.92	76.47	71.43	81.25	76.67
Abnormal	4	23.5	10	76.9					
κ(p)	0.529(0.004*) **Moderate agreement**								

κ: kappa test
*: Statistically significant at $p \leq 0.05$

Value of K	Strength of agreement
< 0.20	Poor
0.21 - 0.40	Fair
0.41 - 0.60	Moderate
0.61 - 0.80	Good
0.81 - 1.00	Very good

Table (10): Patients which have abnormal more than one test and it's percentage

	Abnormal EEG		Abnormal VEP		Abnormal PTB	
	No.	%	No.	%	No.	%
Abnormal EEG(13)	-	-	10	76.9	10	76.9
AbnormalVEP (14)	10	71.4	-	-	10	71.4
Abnormal PTB (15)	10	66.6	10	66.6	-	-
Abnormal 3 tests	**8(26.7)**					

EEG test results:

EEG recording was abnormal in 43.3% patients and the recorded abnormalities included; slow theta waves in 33% of patients, slow delta waves 10%, while, 56% had normal EEG (table 2) Similar to VEP, abnormal EEG

tracing was not associated with any of the variables related to liver function (table 7). EEG exhibited a moderate agreement with PTB and it displayed a sensitivity of 66.67% and a Specificity of 80% in detecting PTB (table 8).

Relation between different tests:

Ten patients (33.3%) had both poor psychometric tests and abnormal EEG, while 10(33.3%) patients had abnormal VEP and psychometric. Finally, 8 patients reported abnormality in all 3 test categories (table 10)

DISCUSSION

This study aimed to test the validity of a comprehensive set of psychometric test battery [NCT A, DST and LTT], EEG and VEP in detecting MHE. The present study shows that the impairment in cognitive performance of patients with cirrhosis can be measured using psychometric test battery, electroencephalogram (EEG) and visual evoked potential (VEP). The current study showed that the used psychometric test battery were impaired in 50% of patients, with 50% abnormal NCTA, 46.7% abnormal DST and 40% abnormal LTT (table 2). Classically, the diagnosis of MHE was based on neuropsychiatric test abnormalities and a variety of tests had been utilized for this purpose. As in **Amodio *et al.*** who had studies 82 outpatients with liver cirrhosis in stable condition where The PHES was found to be altered in 28% of patients.[20] another study utilizing a different battery of neuropsychologist test "DST and NCT" in thirty patients reported the incidence of MHE to be 56.6% and 60% in individuals with chronic liver disease respectively. Indeed the authors of that study used different diagnostic criteria, considering the diagnosis of MHE if only one test was positive [21].In another study implementing the PHES criteria, abnormal psychometric test performance had been reported in80% of cirrhotic patients. And the neuropsychiatric symptoms were significantly affected in 40% of their cohorts (but was not sufficient to diagnose OHE according to the PHES criteria) so zero% of patients fulfilled the MHE diagnosis criteria ,However, that study was conducted in Egypt and the authors did not mention the standardization process they have utilized which again questions the unanimous use of PHES as a gold standard test for MHE diagnosis. [22].

Another research group reported that MHE was diagnosed in 26 patients (49.1%) and the individual tests NCT-A and DST were able to diagnose MHE with a sensitivity of 76.9%and a specificity of 96.3 %[23]. A conclusion can be drawn from the last study that not all individual tests within the PHES score have the same power.

An important observation of the current study that education level did not impact the result of the any psychometric test **[p > 0.05]** (table 3). Contrary to this study results all individual tests of PTB were influenced in cirrhotic patients by age and educational status but this observation was absent in normal persons [23].This discrepancy can be explained by the fact that76.7% of our cohorts received more than6 years of education (table1).Our results display that poor scoring of psychometric tests was associated with impairment of hepatic function as reflected by S.Ammonia, platelet count, S.Albumin, S.Bilirubin and INR **[P < 0.05]** (table4)for each variable. Furthermore, higher CTP classification yielded more frequent poor scoring as 13.3% of Childs' A, 40.0% of Child's B and 46.7% of Child's C had at least one abnormal psychometric test (table 4). A myriad of studies linked poor performance of psychometric tests with the progression of liver cirrhosis marked by CTP scoring[20,21,22,23].

The pathogenesis of HE is multifactorial, and ammonia is considered an important risk factor[24]. In the current study patients with abnormal PTB showed higher s.ammonia [P= 0.012] (table4), abnormal VEP had no significant with s.ammonia [P= 0.133] (table5) and abnormal EEG had no significant with s.ammonia [P= 0.158] (table7) this result is compatible with **Nwabuaku et al** in which a record form was used to evaluate the clinical and laboratory features of 65 consecutive patients with CLD,. and 65 controls with two neuropsychometric tests: NCT-A and NCT-B were administered to all subjects. Showing the mean venous ammonia was significantly higher in patients with CLD than in controls (p value –0.001) However, amongst the patients with CLD, there was no significant difference in the mean venous ammonia levels among those with MHE (mean ammonia level - 72.35μg/dl) than in those without MHE (mean ammonia level - 52.00μg/dl), with a p value of

0.057. There was a significant rise in the ammonia levels with worsening severity of liver disease using the Child-Pugh's classification, (p value – 0.001). [25] and in ***Li et al***. who measured Venous ammonia concentration in 26 cirrhotic patients and was found to be similar between the MHE and non-MHE groups (t= 1.086, P = 0.288). [23] Also in ***Gad et al.*** designed their study to screen for MHE in drivers with liver cirrhosis the diagnosis of MHE was made when one or both symbol digit test (SDT) and number connection test (NCT) appeared abnormal after overnight fasting, venous blood samples were taken for hematologic tests and routine liver function tests by conventional methods a significantly elevated. S.Ammonia level (p-value <0.001) and a bad self-reported driving history ($p < 0.05$) in the MHE-positive group when Compared with the MHE-negative group. [26]

VEP records showed prolonged P100 in 46.7% of patients with 40% prolongation of P100 in the right eye and 46.7% in the left eye (table2). However, It showed no relation to the liver function (table 5) [**P>0.05]**. In addition, there is no relation between cases which have bilateral abnormal VEP and liver function tests (table 6). In regards agreement with the other tests, it had a reasonable agreement with PTB with sensitivity of 66.67% and specificity of 73.33% (table 8) and moderate agreement with EEG with a sensitivity of 76.92 and specificity of 76.47%. (Table 9**).**

In one study, the flash visual evoked potential showed a series of changes which correlated with the clinical grade and the delta activity of the electroencephalogram in chronic liver disease, and with the delta activity of the electroencephalogram but not with the clinical grade in acute hepatic damage [27] However, no similar observation was documented in our study.

Rayan *et al.*had studied 48 healthy volunteers and 70 patients of them 30 had overt hepatic encephalopathy with P100 prolongation (108.1±7.7), 13 had MHE with P100 prolongation (110.1±7) and 27 had unimpaired with P100 prolongation (106.5±5.5)[28]**.**

Zamir et al. reported that prolonged VEP was observed in 71% of cirrhotic patients furthermore, VEP heralded the development of overt encephalopathy as five out of 10 patients with pathologic VEP developed hepatic encephalopathy during a follow-up of one year, compared to one out of 4 patients with normal VEP recording. And in analogy to our data, No correlation was found between VEP P100 delay and either psychometric score nor blood ammonia level[29]**.**

In another study, less than half of patients diagnosed with minimal hepatic encephalopathy "based on psychometric tests" exhibited significant prolongation of VEP. However, all cirrhotic patients in that study had significant longer VEP latencies when compared to normal control[30]**.**These results together with current study results, point out that psychometric tests are generally more sensitive in detecting subtle neurological deterioration. Alternatively, VEP was prolonged in cirrhotic patients and showed correlation psychometric hepatic encephalopathy score[30] **.**

Among the findings, EEG recording was abnormal in 43.3% patients and the recorded abnormalities included; slow theta waves in 33% of patients, slow delta waves 10%, and56% had normal EEG (table2). Similar to VEP, abnormal EEG tracing was not associated with any of the variables related to liver function (table7) and it exhibited a moderate agreement with PTB (table8) displaying a sensitivity of 66.67% and a specificity of 80% in detecting PTB. The EEG is without doubt a valid, objective and reliable means for diagnosing brain dysfunction. A major advantage is the independency from age, education and cultural effects, which is in contrast to neuropsychological tests

Evidence of the utility of EEG as a test for MHE dates even before the coining of the term subclinical hepatic encephalopathy as **Parsons-Smith** and co-workers[30]**.**observed EEG alterations in 43% of their patients despite of a normal clinical status.

Also,our results are in the same direction with Nwabuaku et al who reported that abnormal EEG findings were detected in 34.4% of stable cirrhotic patients.[25] Additionally, Alemam, et al reported that EEG records showed that 64.7% of thepatients had no slow waves, 23.5% showed theta waves, 9.8% showed delta waves, while no patients showed triphasic waves and there was a very significant correlation between psychometric test battery and Child's score ($P < 0.05$), while

it was not present between Child score and slow waves in EEG records[22].

Amodio and co-workers observed pathological slowing of the EEG in 31 of 100 cirrhotic patients without clinical signs of HE. [20] In contrast, EEG alterations were found with visual as well as computerized analysis in only 17% of patients without clinical signs of HE and in only 35% of the patients with grade I HE[30].

CONCLUSION

The incidence of MHE can vary according to the strategy of diagnosis and while strict dependence on neuropsychiatric tests can diagnose MHE in 50% of patients,

RECOMMENDATION

We should incorporate neurophysiological tests like EEG and VEP in diagnosis of MHE which can increase the objectivity of the diagnostic process of MHE. However, more studies are needed to define the Egyptian normative data for neuropsychiatric test.

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