The Diagnosis and Prevalence of Subclinical Hepatic Encephalopathy in Apparently Healthy Children and Adolescents with Cirrhosis

M. El Ayouty[1], A. El Sharabasy[2], M. Ezz El Regal[3], A.Megahed[4]
Departments of Pediatric Neurology[1], Audiology[2], Pediatric Hepatology & Gastroentrology[3], Neurology[4], Mansoura University

ABSTRACT

Subclinical or minimal hepatic encephalopathy (SHE or mHE), in contrast to hepatic encephalopathy is not associated with overt neuropsychiatric symptoms but rather with subtle changes detected by special psychomotor and or neurophysiologic tests. The purpose of this study was to elucidate the validity of the neuropsychological and neurophysiological methods to diagnose SHE in children and adolescents with liver cirrhosis. Furthermore, to detect its prevalence in a specific period. A prospective controlled study was applied on 23 patients (10 males and 13 females with mean age 10.24±3.87 years) with different etiologies of liver cirrhosis, through the period from August 2002 to August 2003. Fifteen healthy children and adolescents with matched age, sex and education standard, were included as a control group. All patients and controls were subjected to: thorough clinical evaluation, laboratory tests of liver functions, neuropsychological assessment using the Egyption version of Wechsler intelligence tests, visual and mapping analysis of electroencephalographic records and event related potential (P300) testing. ***Results revealed:*** *Patients and controls were age and sex matched and showed no significant difference in periods of education. Serum bilirubin and prothrombin time were significantly affected in patients compared with controls. Verbal, performance and full scale IQ were all significantly affected in patients compared with controls; a cut off point of abnormal test performance was seated at scaled score 2 SD below the mean of the controls. Patients have significant slowing in EEG background activity compared to controls (P=0.001); a cut off point for diagnosis of slow activity was seated at 6.8 C/S. Prevalence of SHE among cirrhotic patients was 47.8% by applying two abnormal neuropsychologic tests and 65.2% by applying two abnormal psychologic tests together with significant slowing of EEG background activity. Prevalence of SHE among patients with Child-Pugh class B/C cirrhosis was significantly higher than that recorded in patients with class A cirrhosis (P<0.05). Event related potentials (P300) mean wave latency and mean wave amplitude showed no significant differences between patients and controls, however, cirrhotic patients with SHE had significant prolongation of mean P300 wave latency than patients without SHE (P=0.031). Clinical follow up (5±1.64months) revealed that two out of fifteen mHE diagnosed patients died after 3 and 5 months from initial testing and the two were Child-Pugh class C and overt encephalopathy was precipitated by sepsis.* ***Conclusion:*** *Minimal hepatic encephalopathy is quite prevalent in our patients (65.2%) and the diagnosis can be ascertained by special neuropsychological and/or neurophysiological tests. Minimal hepatic encephalopathy is thought to predict the development of overt hepatic encephalopathy, thus it is clinically relevant.* **(Int. J. Ch. Neuropsychiatry, 2004, 1(1): 83-96)**

INTRODUCTION

The syndrome of hepatic encephlopathy (HE) is characterized by disturbance of mental state and neuromuscular function. In clinical practice, HE is classified into four grades, with progressive deterioration of mental state with each grade[1]. On the other hand, subclinical hepatic encephalopathy (SHE) is not associated with overt neuropsychiatric symptoms but rather with subtle changes detected by special psychomotor tests and is typically reversible with therapy[2]. The prevalence of SHE in adult cirrhotic patients varies from 30% to 84% according to many studies using appropriate methods[3,4,5,6]. It is also estimated to vary from 14% in patients with Child-Pugh A cirrhosis to 45% in patients with child Pugh B/C Cirrhosis[7,5].

Diagnosis of SHE was defined as the presence of at least one abnormal psychometric test and/or abnormal slowing of electroencephalogram (EEG)[5]. Many investigators have proposed to use a combination of two or three psychometric tests as a diagnostic screen for SHE[8,9.]

As neuropsychological performance is known to be influenced by age, education and repetitive testing, several investigators have used neurophysiologic tools such as; evoked potentials[7,4] or quantitative EEG analysis[10] for diagnosis of SHE. However, controversy exists in literatures whether neurophysiologic methods are as sensitive as psychometric tests or not.[11,12].

Recently, the endogenous P300 event related potentials (P3ERP) have been studied and shown to be highly sensitive and reliable in the detection of cognitive disturbances in the early stages of encephalopathy[13,14] .

Our aim was to elucidate the validity of the neurophysiologic and neuropsychological methods to diagnosis SHE in children and adolescents with liver cirrhosis, as to our knowledge, no previous studies were conducted on that age group.

SUBJECTS AND METHODS

Study design:

A controlled prospective study was conducted from August 2002 to August 2003, at Mansoura University Children Hospital (MUCH), Faculty of Medicine, Mansoura University, Egypt. Two groups were included:

I. The patient group:

Twenty-three children with established liver cirrhosis of different etiologies and Child-Pugh classes, without any overt neurological signs or symptoms at time of testing. were selected from the inpatients & outpatients of hepatogastroentrology unit, MUCH. Their mean age was 10.54 ± 3.87years and mean duration of illness was 4.4 ± 2.3 years. Diagnosis of liver cirrhosis was suspected by clinical, laboratory, imaging features of chronic liver diseases and confirmed by liver biopsy in all cases.

Inclusion criteria:

1) Cirrhosis proved by liver biopsy.
2) Age 4 – 16 years

Exclusion criteria:

- Clinically overt hepatic encephalopathy.
- Inability to perform neuropsychological or neurophysiological tests.
- History of recent (less than 6 weeks) use of benzodiazepines, antiepileptics, or psychotropic drugs[15].

- Severe medical problem such as severe heart disease, pulmonary disease and neurological disease.

II) The control group:

Fifteen healthy children with matched age, sex and education standard, were included and subjected to neuropsychological, neurophysiological & laboratory tests. They were selected from the general pediatric outpatient clinic (MUCH) while consulting for minor illnesses and instructed for a date of testing after convalescence.

Methods:

All subjects included in the study group were subjected to the followings:

1. ***Clinical assessment:*** A thorough history taking including educational level, duration of illness from earliest symptom, neurological symptoms (with special concern of insomnia, disturbed sleep rhythm, drowsiness, confusion, impaired memory, bizarre behavior, irritability & tremors), symptoms of hepatic dysfunction, past history of hepatic encephalopathy and history of drug intake especially benzodiazepines, antiepileptics and psychotropic drugs.

   Full clinical examination including general examination with special attention to manifestations of liver cell failure.

2. ***Laboratory assessment:*** Liver function tests were done at MUCH laboratories (using the commercially available kits). Investigations for etiological diagnosis e.g. viral hepatitis markers, autoimmune markers and enzymes assay for metabolic liver diseases were applied.

   The Child-Pugh score was used to assess the severity of liver cirrhosis. Three biochemical variables (serum albumin, bilirubin and prothrombin time) in addition to two clinical characteristics (ascites and hepatic encephalopathy) determine the Child-Pugh score. Each variable is given one to three Points, leading to scores ranging from 5 (excellent liver function) to 15 points (poor liver function). Table (1) illustrates the Child-Pugh classification. We had two groups of patients: Child – Pugh class A cirrhosis (n=16) and class B/C cirrhosis (n=7).

Table 1. Child-Pugh Classification of Cirrhosis[16].

Feature	1 point	2 points	3 points
Encephalopathy (stage)	0 (absent)	1-2 (mild)	3-4 (sever)
Ascites	Absent	Mild	Marked
Bilirubin (mg/dL)	<2.0	2.0-3.0	>3.0
Albumin (gm/dL)	>3.5	2.8-3.5	<2.8
Prothrombin time (sec.)	<4.0	4.0-6.0	>6.0

Each feature is assigned 1, 2, or 3 points.
Class A: 5-6 points, Class B: 7-9 points, Class C: 10-15 points.

3. ***Imaging techniques:*** Conventional and Colored Doppler abdominal ultra-sonography for assessment of portal and hepatic veins to determine portal vein diameter; direction of portal blood flow; and congestion index were performed by staff members of MUCH radiology section.

4. ***Liver biopsy:*** Liver biopsy was done for all patients included in the study and liver cirrhosis was diagnosed according to the modified Knodell score.

5. ***Neuropsychological tests:*** All subjects of both the study group and control group were tested using Egyptian version of Wechsler Intelligence Tests[17,18], which are well established and practiced by well trained psychologists, tests were performed at Psychiatry Department, Mansoura University Hospital (MUH), Faculty of Medicine, Mansoura University. These tests were quoted from the original version of Wechsler Intelligence Tests.

Calculation of results was done in the following sequence:

First step: The raw score for each individual subtest was transformed to **Scaled Score** (age and sex matched) using standardized tables.

Second step: The scaled scores of performance subtests and verbal subtests were summated to obtain the **performance & verbal scaled score**.

Third step: The performance & verbal scaled score were summated to obtain the **full-scale scaled score**.

Fourth step: The full-scale, performance & verbal scaled scores were transformed to full-scale, performance & verbal IQ respectively.

Results obtained (scaled scores for each subtest & full-scale, performance & verbal IQ_s) were compared in both cirrhotic children and control groups. Abnormal performance of any given result was considered if less than 2 SD from the mean performance of the control group[9,19].

6. ***Neurophysiological tests:***

A. Electroencephalogram (EEG):

Electroencephalogram was recorded to every subject in the study at Pediatric neurology unit, (MUCH). Electrodes were attached to the scalp according to the international 10-20 system of electrode placement. We used five electrodes applied at positions; T3, T4, O1, O2 and CZ (with filter at 0.3 and 50, and a gain of 70 µV/mm).

CADWELL apparatus was used in the study. All records were evaluated using standard visual analysis. Records were considered abnormal if background frequency showed slowing when compared with background frequency of normal children of the same age[14]. Some artifact-free recordings, for comparison, were selected and fed into a computer specialized software program, *[Persyst EEG Suite; EEG Review, Reveal program for Spike & Seizure Detection, Voltage/Frequency Mapping (Prism) & analysis and Magic Maker for Hyper-trending and Remote Monitoring].*

B. Event related potential (P300) testing:

The event related potential (P300) recordings were performed at Mansoura University Audiology unit. The (P300) responses were elicited by the standard auditory "oddball paradigm" [20]. Evoked potentials **Bio-logic Navigator** two channels system, was used for P300 recording.

1) The oddball paradigm:

To elicit P300 waves, two tones were presented in a random series at a rate of 0.5/sec. A frequent tone (1000 Hz) was presented in 80% of test time, and a target tone (2000 Hz) was presented randomly in 20% of testing time. The two stimuli had a rise/fall time of 50 msec. and a plateau duration of 200 m.sec. The stimuli were presented at intensity of 80 dB and earphones telephonic 49 were used in the test.

One hundred stimuli were recorded in each run. Children were instructed to count the total number of target tones (the 2000 Hz tone). Younger Children who were unable to count were instructed to give a hand signal to the examiner whenever they hear the target tone. The accepted percent of correct identification of the number of the target stimuli was judged to be 90% or more. If lesser percentage were obtained, retest after training was done.

2) Subject preparation and electrode montage:

The responses were obtained from Cz electrode (vertex) with referential linked electrodes at A1 and A2 (Bimastoid)[14]. Electrodes sites were cleaned with alcohol.

3) Response analysis and measurement:

- Waveform identification: The (P300) was identified as the positive peak or series of peaks in the vicinity of 300 m sec. Which was presented in the waveform evoked by the infrequent (target) tone[21].
- P300 latency: If a single peak was present after 250 m sec in the anticipated target window, it was identified as the P300. The latency in this condition was taken at the middle of that peak. If two peaks were present the latency was measured by taking the average values calculated from values obtained at each peak. If multiple peaks or broad response were present, latency was obtained from intersection of the extrapolated lines from the ascending and descending slopes (intersect procedure) [21].
- P300 amplitude: The measures were taken: trough to maximum peak of the ascending, and trough to maximum peak of the descending limb of the P300 waveform, and taking the average of these two measurements as the response amplitude [22].

7. Clinical follow up of cases for the development of overt hepatic encephalopathy: All cases included in the study were clinically followed up & regularly reassessed for at least 4 months, to monitor the development of overt hepatic encephalopathy at intervals of 2-4 weeks duration.

8. ***Statistical analysis of obtained results:*** Data was analyzed using SPSS software program version 10, for windows, (www.spssscience.com). Quantitative variables were found to be parametric so, mean and standard deviation (SD) were the parameters of central tendency and dispersion. Student t-test was used for analysis of difference between two groups and Chi square test for association between categorical variables. P is significant at a value <0.05.

RESULTS

Patients and controls were age and sex matched and showed no significant difference in periods of education (P>0.1). Serum bilirubin and prothrombin time were significantly affected in cirrhotic patient compared to controls (P<0.001), however values of serum albumin showed no significant difference (P=0.73) (table 2).

Neuropsychological tests showed that, only five tests, i.e. (information, digit span, block design, coding and object assembly tests) were significantly affected in cirrhotic patients compared to controls. A cut off point of abnormal test performance was seated at scaled score 2 SD below the mean of the controls. Four tests: sentences test, animal house test, mazes & geometric design test were applied to children below 6 years old (n=3 in both controls and cirrhotic groups), where mean values for each test scaled score in controls versus patients were (9.5± 1.3, Vs 9.2±1.1) for sentences test, (9±1 Vs 9±1) for animal house ; (9.7± 0.6 Vs 8.5 ±1) for mazes test and (10±1 vs 9.3±1.1) for geometric design test, respectively. (Table 3a). Verbal, performance and full scale IQ were all significantly affected in cirrhotic patients compared to controls (Table 3b).

Patients tend to have significant slowing in background activity in EEG recording as compared to controls. (P=0.001); a cut off point for diagnosis of slow background was seated at 6.8 c/s. (Table 4 and figure 1).

Prevalence of SHE among cirrhotic children was 47.8% by applying two abnormal neuropsychological test results of the five selected ones. The prevalence raised to 65.2% by applying two abnormal neuropsychological tests together with significant slowing of EEG background activity. Moreover, the prevalence of SHE among patients with Child-Pugh class B/C cirrhosis was significantly higher than that recorded in patients with class A cirrhosis (P<0.05)(by applying different diagnostic criteria).

Event related potentials (P300) mean wave latency and mean wave amplitude showed no significant differences between controls and patients (p=0.23, 0.91, respectively) (Tables 5 and figure 2). On the other hand, patients with SHE (diagnosed by applying at least two abnormal neuropsychological tests and slow EEG background) showed significant prolongation of mean P300 wave latency, compared with patients without SHE (mean values = 342.3±8.2 vs 328.9±19.6 respectively, P=0.031).

Clinical follow up of cirrhotic children at 2-4 weeks interval (mean duration 5 ±1.64 months) revealed that, two (13.3%) children out of the 15 m HE diagnosed children developed signs of overt HE after 3 and 5 months from the time of initial testing. Both cases were Child-Pugh class C, and overt encephalopathy was precipitated by sepsis. No case with mHE free children developed overt HE during the same period of follow up.

Table 2. Comparison of demographic and serum biochemical values of control group & cirrhotic children.

Parameter	Controls (n=15)	Cirrhotics (n=23)	P value
Age in years [mean ± SD & range]	9.9 ± 4.0 (4.2 - 17.0)	10.5 ± 3.9 (4.3 - 17.0)	0.602
Male/Female* **Number** **%**	6 / 9 40% / 60%	10 / 13 43.5% / 56.5%	0.83
Education duration **in years [mean ± SD & range]**	3.9 ± 3.8 (0 – 11.0)	4.4 ± 3.4 (0 – 10.0)	0.67
S. Albumin **gm/dl [mean ± SD& range]**	4.7 ± 0.7 (3.6 - 5.2)	4.0 ± 0.9 (2.2 – 5.0)	0.73
S. Bilirubin **mg/dl [mean ± SD & range]**	0.6 ± 0.2 (0.3 – 0.9)	1.8 ± 1.50 (0.4 - 5.3)	<0.001
Prothrombin time prolongation in sec. **[mean±SD & range]**	1.3 ± 0.2 (1.0 – 2.0)	3.6± 2.7 (2.0 - 10.4)	<0.001

[student *t*-test & chi square test with Yat′s correction*].

Table 3a. Individual neuropsychological tests results: Comparison between controls & cirrhotic children.

Parameter		Controls (n =15)	Cirrhotics (n =23)	P value
Verbal subtests	Information **[mean ± SD]**	10.8 ± 1.0 (n=15)	9.3 ± 1.8 (n=23)	=0.005
	Vocabulary **[mean ± SD]**	9.2 ± 2.9 (n=15)	8.8 ± 1.4 (n=23)	0. 6
	Arithmetics **[mean ± SD]**	9.5 ± 2.8 (n=15)	9.0 ± 2.5 (n=23)	0.59
	Similarity **[mean ± SD]**	10.6 ± 1.9 (n=15)	9.4± 2.1 (n=23)	0.081
	Comprehension **[mean ± SD]**	9.7 ± 1.7 (n=15)	9.5 ± 2.0 (n=23)	0.82
	Digit span **[mean ± SD]**	9.1 ± 1.2 (n=12)	6.2 ± 2.0 (n=20)	< 0.001
Performance subtests subteststsubteste	Picture completion **[mean ± SD]**	9.3 ± 1.0 (n=15)	8.8± 3.1 (n=23)	0.56
	Block design **[mean ± SD]**	9.1 ± 1.1 (n=15)	7.6 ± 2.6 (n=23)	0.002
	Picture arrangement **[mean ± SD]**	9.5 ± 0.8 (n=12)	8.6 ± 3.7 (n=20)	0.38
	Coding (DST & symbol search) **[mean ± SD]**	9.8 ± 1.5 (n=12)	6.7 ± 2.8 (n=20)	<0.001
	Object assembly **[mean ± SD]**	9.1 ± 1.1 (n=12)	7.4 ± 2.0 (n=20)	< 0.001

[student *t*-test].

Table 3b. Verbal, Performance & Full scale IQ mean values: Comparison between controls & cirrhotic children.

Parameter	Controls (n=15)	Cirrhotics (n=23)	P value
Verbal IQ. **[mean ± SD]**	108.7 ± 5.6	98.6 ± 10.3	=0.001
Performance IQ.**[mean ± SD]**	95.5 ± 2.7	82.2 ± 13.6	< 0.001
Full scale IQ. **[mean ± SD]**	102.6 ± 3.7	90.8 ± 10.9	< 0.001

[student *t*-test].

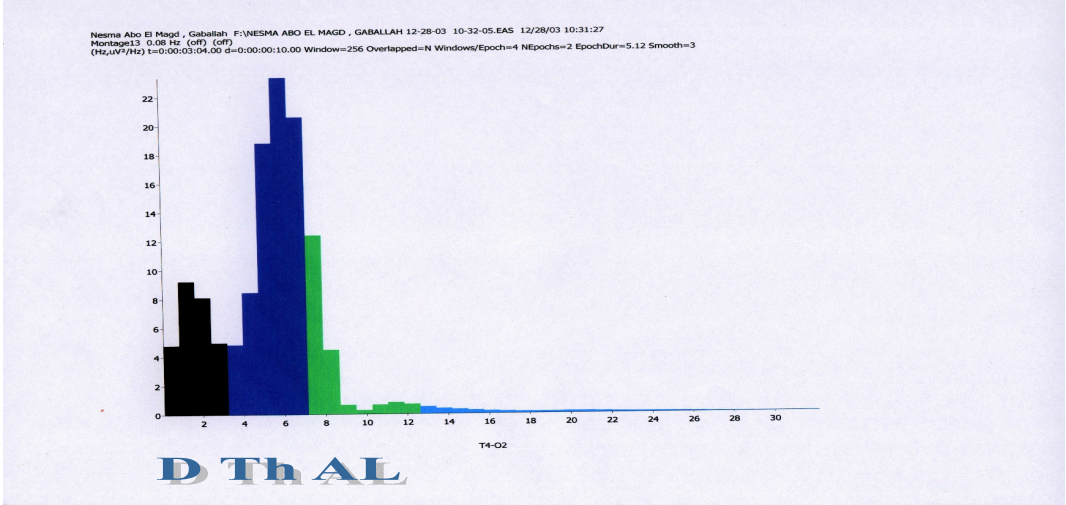
Table 4. Electroencephalogram (EEG) background mean frequency: Comparison between controls (n=15) and cirrhotic children (n=23).

	Controls (n=15)	Cirrhotics (n=23)	Cut off point	P value
EEG background mean frequency (cycle / sec.) **[mean ± SD]**	10 ± 1.6	7.2 ± 3.1	6.8	0.001

[student *t*-test].

Table 5. Event related potential (P300) mean wave latency and mean wave amplitude in controls and patients.

	Controls (n=15)	Cirrhotics (n=23)	P value
(P300) mean wave latency m. sec. **[mean ± SD & range]**	333.6 ± 17.6 (294 – 352)	339.7 ± 10.5 (308 – 351)	0.23
(P300) mean wave amplitude in µV **[mean ± SD & range]**	13.8 ± 4.1 (6.2 – 19.3)	14.0 ± 6.7 (3.3 – 29)	0.91



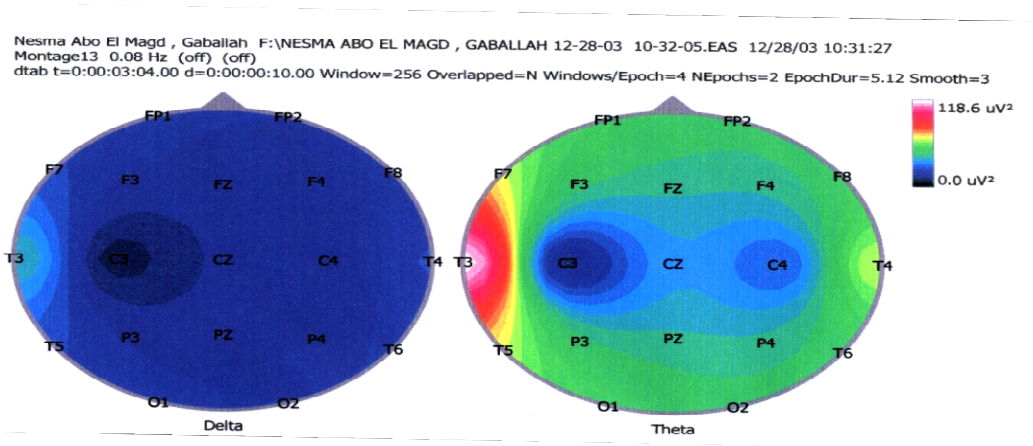


Fig. (1): Prism, frequency and Topography in adolescent female patient, 13 years old, demonstrating EEG background frequency of delta,(D) theta (Th) and alpha (AL). T_4-O_2 channel.

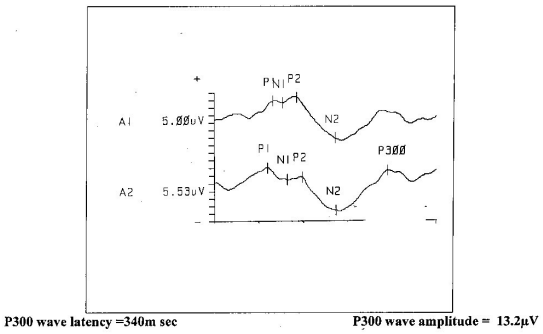


Fig. (2a): P300 wave record (case No. 6).

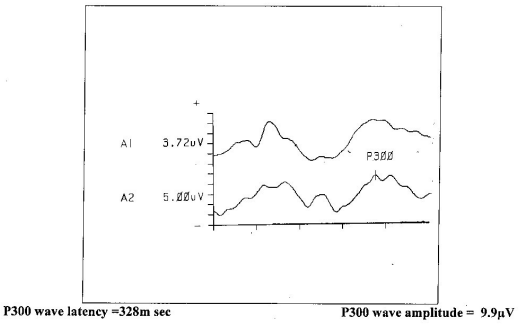


Fig. (2b): P300 wave record (control No.9).

DISCUSSION

Clinically, patients with SHE (mHE), appear to be free of neuropsychiatric abnormalities, meanwhile they exhibit specific, reversible, quantifiable, neuropsychologic and/or electroencephalographic abnormalities[1,19]. Subclinical hepatic encephalopathy was defined as the presence of at least one abnormal psychometric test and/or abnormal slowing of the EEG[5].

Unfortunately, the diagnostic approach to the assessment of mHE is not uniform. Various combinations of psychometric tests with or without neurophysiologic measures like EEG and evoked potentials have been studied for their use in the diagnosis of mHE in adult cirrhotic patients[5,14]. Most investigators have studied the neuropsychological characterization of SHE in adult cirrhotic patients by using the trail making test type A (NCT) and the digit symbol test (DST). The effect of SHE on daily functioning was tested by using the Sickness Impact Profile (SIP) which is a questionnaire containing a number of statements on daily functions that could be specifically abnormal in SHE. Unfortunately, those tests were not applicable for children, thus and after communication with Dr. Quero, Dr. Groeneweg & Dr. Bahatia, August 2002, who are experts in this field, we decided to use the Egyptian version of Wechsler intelligence tests, the visual EEG and the auditory P3ERP in our proposed study.

Concerning the neuropsychological tests, our study revealed an overall abnormalities in our patients, where both verbal scales and performance scales were significantly affected in cirrhotic patients compared with healthy controls ($P = 0.001$ & $P < 0.001$ respectively), with consecutive affection of the full scale IQ ($P < 0.001$)

Out of the used neuropsychological tests, five tests were found to be of significant value: Information test, was found to be abnormal in 9 patients (39.1%) with significantly lower mean scaled score in patients compared to controls ($P = 0.005$); digit span test was abnormal in 11 (55%) of tested patients, with significantly lower mean scaled score in patients compared to controls ($P<0.001$). Also coding test (DST & symbol

search test), object assembly test and block design test were abnormal in 45%, 35%, 39.1% of tested patients respectively, with significantly lower mean scaled scores in patients compared to controls ($P < 0.001$, $P < 0.001$ & $P = 0.002$ respectively). In studies done on adult patients with liver cirrhosis without overt signs of hepatic encephalopathy, Groeneweg et al. [15] found that only 3% of patients have abnormal DST, while Yu Qiang et al.[19] and Das et al.[9] found abnormal DST performance in 9.1% and 31.5% respectively. Object assembly test and block design test were additionally studied by Das et al. [9] and found to be abnormal in 31.5% and 41.8% respectively.

From previously mentioned we can decide a validation of these tests in both children and adults with suspected mHE. Moreover, many investigators have proposed to use a combination of two to three psychometric tests as a diagnostic screen for mHE [9,23,8]. Accordingly; we have 11 patients (47.8%) with at least 2 abnormal neuropsychological tests performance and met with the diagnostic criteria of mHE.

The electrophysiological (EP) tests viz. EEG and evoked potentials have been used to add objectivity to the diagnosis of SHE[24,4]. However, inconclusive data are available on the relative sensitivity of the EP methods in comparison to psychometric tests in detection of SHE [13,25,26]. The use of more sophisticated measures like the P300 latency, the most sensitive neurophysiologic parameter for the diagnosis of HE, remains limited because of the requirements for special equipment and the need to elaborate normal data in each lab.[7,27,28,14]

In the present study visual analysis of EEG records was done using five electrodes applied at positions T_3, T_4, O_1, O_2 and Cz; few cases were subjected to automated EEG analysis for comparison. Significant slowing of EEG background was noticed in cirrhotic children compared with controls [mean frequencies 7.2±3.1 & 10±1.6 respectively]. Cut off point for diagnosis of mHE was seated at EEG background wave frequency 2 SD below the mean of controls, (6.8 cycle/sec).

The EEG provides information on metabolic encephalopathy because it reflects neuronal electrogenesis which, in turn, is quite sensitive both to the influence of nutritive and energy-providing metabolic systems, and to the influence of electrolyte homeostasis and the clearance of toxic substances[29]. However, information regarding the relationship between EEG and liver function in cirrhosis is scanty. Quero et al.[5] showed a trend towards a higher degree of EEG alteration in Child-Pugh class B/C patients than in class A patients, and a relationship between the prevalence of EEG alteration and ammonia plasma levels. Such relationship clearly stands out in our study, where EEG abnormalities were significantly correlated with Child-Pugh class B/C patients than class A patients ($P = 0.006$).

Quero et al.[5] had defined SHE as the presence of at least abnormal psychometric test and/or abnormal slowing of the EEG, Saxena et al.[14] adopted this definition. They respectively demonstrated abnormal EEG slowing in 17% & 21% of adult cirrhotic patients without signs of overt HE. While Quero et al.[5] used automated EEG analysis; Saxena et al.[14] preformed visual analysis of EEG records, and EEG background frequency (<8c/sec) was considered abnormal by the later. Amodio et al.[30] demonstrated EEG alterations in 38% of adult cirrhotic patients by using automated EEG analysis, the variables considered for EEG evaluation were the mean dominant

frequency (MDF), and the relative power of the theta and delta bands. Van der Rijt et al.[10] conducted a study for objective measurement of hepatic encephalopathy by means of automated EEG analysis, the same EEG variables were considered.

From the previously mentioned; our results show relatively higher prevalence of mHE. This difference may be viewed in two bases: First; the difference in the age sample population, as development of background EEG activity varies with age. It is in the range of 6-7 Hz frequency by 9 –18 months and remains fairly stable until 2 years of age when it will vary between 7 and 8 Hz by the age of 3 years, the dominant waking rhythm of childhood is within the alpha range in 82% of children and the mean frequency is 9 Hz by 7 years of age and 10 Hz by 15 years of age[31]. Secondly; the difference in the method of analysis where automated spectral analysis supplies more definite accuracy than the visual analysis.

I n the present study, the results of event related potential P300 revealed no significant difference in P300 mean wave latency nor in amplitude between cirrhotic children and controls. Saxena et al.[32] demonstrated this finding related to the accuracy of P300 in diagnosis of SHE in younger adult cirrhotic patients, they observed no significant prolongation of P300 wave latency in younger cirrhotics less than 40 years and age matched controls.

In spite of the absence of significant P300 wave latency prolongation in cirrhotic children as compared with controls, we found that P300 wave latency of cirrhotic children with SHE, (342.3 ± 8.2 m sec.), was significantly prolonged as compared with cirrhotic children without SHE, (328.9 ± 19.6 m.sec., P = 0.031). As we could not establish a cut off point of normality as regard P300 wave latency, P300 was not included in the proposed diagnostic tools for mHE. Again it is seemingly wise to reestablish normal age matched P300 values, for more fair judgment and better standardization of the test. .

As previously discussed, no single test has received the widespread acceptance as a "gold stander" for the diagnosis of mHE. We have proposed and tried to validate a considerably reliable test battery for mHE diagnosis in children, meanwhile a large scale multicenter national study is assumed to be done, if the problem of mHE in children patient with cirrhosis is looked for. According to our diagnostic tools, mHE was defined as abnormal performance of at least two tests out of the five included psychometric tests namely (information, digit span, black design, coding and object assembly) and/or abnormal EEG record with slow EEG discharge less than (6.8cycle /sec). Accordingly, 15 out of 23 cirrhotic children (65.2 %) were diagnosed to have mHE, 9 (60%) of them had abnormal both neurophysiological & neuropsychological results, 4 (26.7%) had abnormal EEG alone, while only 2 (13.3%) had abnormal neuropsychological results alone, The sensitivity of EEG was (86.7%), compared with (73.3%) of the appropriate neuropsychological methods, that is to say; the neurophysiological methods not only add more objectivity to mHE diagnosis, but also add more sensitivity. Regarding the Child-Pugh classification the prevalence of mHE is estimated to vary from 14% in patients with Child-Pugh A cirrhosis to 45% in patients with Child-Pugh B/C cirrhosis[7,5]. We demonstrated significant difference as regards the prevalence of mHE among cirrhotic children where it was 50% in Child-Pugh A patients and 100% in Child-Pugh B/C patients, (P = 0.026).

Conclusion

Minimal hepatic encephalopathy is quite prevalent in our patients (65.2%) and the diagnosis can be ascertained by special neuropsychological and/or neurophysiological tests. Minimal hepatic encephalopathy is thought to predict the development of overt hepatic encephalopathy, thus it is clinically relevant.

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