Diagnostic Parameters of Minimal Hepatic Encephalopathy: Clinical, Electrophysiological, and Neuroimaging Study

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ABSTRACT

Background: Cirrhotic patients with minimal hepatic encephalopathy (MHE) have subtle cognitive deficits that can be detected by neuropsychometric tests, P300 event related potential. EEG, and increased signal on T1-weighted brain Magnetic Resonance Imaging. Objectives: The present study was designed to assess the magnitude of cognitive dysfunction, a marker of minimal hepatic encephalopathy (MHE); to evaluate diagnostic usefulness of neuropsychological cognitive tests, EEG, P300 ERP latency, and MRI brain signs; and to investigate the clinical outcome of patients with MHE in terms of progression to overt encephalopathy. Patients and Methods: A total of 43 well-compensated cirrhotic patients without signs of encephalopathy were studied by neuropsychological cognitive test battery, P300 ERP latency, EEG, conventional MRI brain. The patients were followed-up for 2 yrs. to monitor subsequent episodes of overt encephalopathy. Child-Pugh classification was done throughout the study to assess severity of liver cirrhosis. Forty-six healthy subjects, age, sex, and education matched, served as a control group. Results: Minimal HE was diagnosed in 21(48.8%), out of 43 cirrhotic patients. Inverted sleep rhythm was reported in 85.7% of cirrhotic with MHE. Delayed P3ERP latency were seen in 38.1% of cirrhotic patients with MHE, while Number Connection Test (NCT-A & B) time were prolonged in 71.4% of the patients. EEG abnormality was detected in 47.6%, while MRI signs were reported in 80.9% of cirrhotic with MHE. Out of 43 patients, 18(41.8%) developed overt encephalopathy, 66.7% of the patients with MHE progressed to overt encephalopathy within a mean duration of 9 months, while only 13.6% of the non-MHE patients did so. Of the patients who developed overt encephalopathy, 83.3% had abnormal EEG, 77.8% had abnormal NCT, while 59.3% had P3ERP latency prolongations. Conclusion: The results of the present study suggest that inverted sleep rhythm, abnormal NCT, slow EEG activity, and delayed P300 latency are valid tools for the screening of MHE in cirrhotic patients as there is a greater likelihood of overt encephalopathy development in patients with an abnormality detected by these tests than in patients without such abnormality. EEG is useful for follow-up screening and prediction of the development of overt hepatic encephalopathy. (Egypt J. Neurol. Psychiat. Neurosurg., 2007, 44(2): 577-596)

INTRODUCTION

Minimal hepatic encephalopathy is the term that has replaced the old terms of latent or sub-clinical hepatic encephalopathy. It was felt that these older terms did not reflect the important effects of this syndrome on patients’ lives.¹ It has been recognized for some time that with appropriate neuropsychological tests, patients who were felt clinically to be free from hepatic encephalopathy do in fact demonstrate signs of cognitive impairment.²,³ Only quite recently, however, were these more subtle deficits shown to affect patients’ lives,² and the current consensus is that they should be treated.⁴ The term minimal hepatic encephalopathy refers to the subtle
changes in cognitive function, electrophysiological parameters, cerebral neurochemical/ neurotransmitter homeostasis, cerebral blood flow, metabolism, and fluid homeostasis that can be observed in patients with cirrhosis who have no clinical evidence of hepatic encephalopathy. Depending on the tests used and the population studied, minimal hepatic encephalopathy seems to affect between about 20% and 84% of patients with liver disease.6-11

The term hepatic encephalopathy refers to the syndrome of neuropsychiatric disturbances that may arise as a complication of acute, subacute, or chronic hepatocellular failure.12 The syndrome is associated with increased portal-systemic shunting of gut derived constituents of portal venous blood, due to their impaired extraction by the failing liver and, in most instances, their passage through intrahepatic and/or extrahepatic portal-systemic venous collateral channels.13 The term portal-systemic encephalopathy is often used interchangeably with hepatic encephalopathy, but portal-systemic encephalopathy can be defined to include encephalopathy associated with increased portal-systemic shunting in the absence of unequivocal evidence of hepatocellular insufficiency.14

The complex neuropsychiatric syndrome of hepatic encephalopathy that complicates chronic liver disease becomes clinically manifest in its early stages in the form of slight personality changes, discrete psychomotor dysfunction, and alteration of sleep rhythm.15 In 2002, a working committee task force on HE standardized the definition and classified HE into 3 types, as follows: Type A: HE associated with acute liver failure, Type B: HE associated with portal-systemic bypass with no intrinsic hepatocellular disease, Type C: HE associated with cirrhosis and portal hypertension or portal-systemic shunts. In cases of chronic liver disease, type C encephalopathy can be episodic or persistent.16

The most frequent neurological disturbance in liver cirrhosis is not evident on clinical examination: mild cognitive abnormalities only recognizable with psychometric or neurophysiologic tests (minimal or subclinical encephalopathy).17 (Table i)

Table i. Clinical characteristics of various forms of hepatic encephalopathy.17

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic or recurrent</th>
<th>Chronic</th>
<th>Subclinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asterixis</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Precipitating factor</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reversibility</td>
<td>±</td>
<td>+</td>
<td>-</td>
<td>±</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Short, lethal</td>
<td>Short, transient</td>
<td>Continuous</td>
<td>Insidious</td>
</tr>
</tbody>
</table>

+, associated; -, not associated; ±, may or may not be associated.

The pathogenesis of minimal hepatic encephalopathy is not understood. It would seem likely, however, that the same mechanisms affecting neurotransmission in overt hepatic encephalopathy also underlie minimal hepatic encephalopathy.18-20,21,23 Alterations in the pattern of cerebral blood flow have been demonstrated in patients with minimal hepatic encephalopathy, and it would seem likely that this also plays a role in its pathogenesis.22

Psychometric evaluations are of value for establishing the diagnosis and perhaps for monitoring response to therapy in subclinical PSE. The number-connection test and the Trail-Making Test are pragmatic approaches and are used widely at the bedside. More formal testing may not be feasible with many patients, in part due to the length of time taken to administer the tests, and also because of uncooperativeness. However, the results of psychometric testing in subclinical PSE may be of prognostic value independent of the Child-Pugh score of disease severity.24-26,27 The issue of a reliable diagnosis of SHE is steadily gaining importance since SHE has
been shown to affect the quality of life of patients.28-30 Till date the diagnosis of SHE has been based on a variety of neuropsychological and electrophysiological tests. The neuropsychological tests are known to be influenced by age,31-33 education, sociocultural background, and repetitive testing.34 It is now generally agreed that neuropsychological tests offer the best option for diagnosing minimal hepatic encephalopathy, but there is considerable debate about which tests should be used and how the results should be interpreted.1 Generally, any battery of neuropsychological tests should assess a broad range of cognitive functions,36 and in the case of liver dysfunction, should probably include tests of psychomotor speed, visuopraxis, attention and concentration.1,35 It has been suggested that tests of language and memory need not be included in assessing minimal hepatic encephalopathy.35

EEG studies of patients in PSE grades 1-3 may demonstrate high voltage and low-frequency triphasic waves of 1-3 Hz. These also may be seen in uremia but are characteristic of HE. With progression to coma, the EEG typically shows delta-wave activity, representing a generalized slowing of the cortex, a nonspecific pattern seen in toxic and metabolic encephalopathies. The EEG is most helpful in excluding the presence of other causes for encephalopathies, such as status epilepticus and akinetic seizures, or the demonstration of postictal slowing with or without focal spike and wave activity that suggests prior seizures. EEG monitoring frequently is useful in assisting with the diagnosis of HE, especially subclinical HE. Computer-assisted or spectral EEG analysis may demonstrate characteristic abnormalities, but the incremental benefit over conventional EEG is unclear.37-40

Exogenous evoked potentials viz. visual, brain stem auditory, and somatosensory evoked potentials lack the sensitivity required for the detection of SHE.41-46 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.47-49 Till date, the neuropsychiatric test batteries and exogenous evoked potentials have been primarily used in detection of SHE.49,50 No data are available regarding the utility of widely recommended P3ERP latency in measurement of latent stage of encephalopathy.

 Neuroimaging techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET) have been used in the assessment of minimal hepatic encephalopathy, but at the moment they are more useful in research and in further establishing the pathophysiology of the condition.51,52 Similarly, the morphological brain abnormalities identified in this population, including mild brain edema, hyperintensity of the globus pallidus and other subcortical nuclei observed in cerebral MR studies, and the central and cortical atrophy observed in neural imaging studies, are unlikely to have diagnostic utility. It is becoming widely recognized that patients with chronic liver disease and portal-systemic shunts exhibit typical abnormalities on cerebral magnetic resonance imaging (MRI).53-56 These consist of an abnormally high signal on T1-weighted imaging in the basal ganglia, particularly the globus pallidus. This high signal is now believed to be due to manganese deposition.57 and post-mortem studies have shown levels up to seven times normal in the globus pallidus.58-58 How these patients should be treated is uncertain. Studies have shown an improvement in cognitive functioning with dietary protein restriction or lactulose treatment. Benzodiazepines should not be used for patients with sleep difficulties.59

Aim of the work:

The present study was designed to assess the magnitude of cognitive dysfunction, a marker of minimal hepatic encephalopathy (MHE); to evaluate diagnostic usefulness of neuropsychological cognitive tests, EEG, P300 ERP latency, and MRI brain signs; and to investigate the clinical outcome of patients with MHE in terms of progression to overt encephalopathy.
SUBJECTS AND METHODS

A total of 43 ambulant patients (72.1 % male, 27.9 % female; age range 23-68 yrs) with well compensated liver cirrhosis, were selected for this cross-sectional and prospective longitudinal study, from hepatology outpatient clinic, to be referred to Neuropsychiatry Department, Tanta University Hospital, during the period between December, 2004 and December, 2006. The control group consisted of 46 healthy subjects that were age, sex, and schooling matched to patient group. Informed consent were given by all participants.

The diagnosis of cirrhosis was made on the basis of suggestive clinical features, deranged liver function tests, and evidence of portal hypertension on ultrasonography and endoscopy. If the coagulogram permitted (prothrombin time < 3 sec prolonged over control value), a liver biopsy was performed to confirm the diagnosis. Eight of the patients had a previous history of esophageal variceal bleeding.

All patients were screened and evaluated by detailed history taking including sleep questionnaire, full neurological examination, mental state examination, meticulous systemic examination, laboratory investigations, PSE psychometric testing, electroencephalographic (EEG) analysis, P300 ERP, CT scan and MRI brain. All tests were performed more than six weeks after the last episode of variceal bleeding. The majority of participants (66.5%) had completed elementary school, 22.9% had completed middle and high school education and 10.6% were university graduates.

The patients were joined to present study according to the following inclusion criteria: age range of 20-80 yrs, normal neurological examination including MMSE,GCS, auditory and visual system, normal mental state examination, normal liver biochemical tests (bilirubin < 35 micromole / L, albumin > 35 g / L, INR < 1.7), and no evidence of ascites. Only patients of grade 0 (no detectable abnormalities) by criteria of West Haven were included in the study22. Tremor, dysarthria, ataxia or gross memory disturbances were not present in any patient.

Exclusion criteria were clinical hepatic encephalopathy(overt HE), past history of hepatic encephalopathy, neurological or psychiatric disorder, alcohol intake, use of benzodiazepines, anti-epileptics or other psychotropic drugs, visual deficit, hearing deficit presence of diabetes, congestive heart failure, pulmonary disease, renal failure, cerebrovascular events and inability to perform psychometric tests due to illiteracy.

Minimal hepatic encephalopathy (MHE) was defined by the presence of at least one abnormal psychometric test, abnormal slowing of the EEG, and/or delayed P300 latency160. The patients were subdivided into 2 groups: cirrhotic patients without MHE (COE), and cirrhotic patients with MHE (CWE). They were evaluated by Child-Pugh scale to assess severity of liver cirrhosis (Table ii)15, NCT-A, NCT-B, DST, BDT, DS-F, DS-B, EEG, P300 ERP, CT, liver function test, venous ammonia and MRI brain, as a baseline evaluation at the start of study, and as follow-up within study period of 2 yrs. to evaluate the natural course of MHE. Serial neuropsychological cognitive test battery were done at regular period of 6-8 weeks. The study end-point was the development of overt hepatic encephalopathy (grade I-IV).

Table ii. Child-Pugh Score.15

<table>
<thead>
<tr>
<th>Clinical or biochemical measurement</th>
<th>Points scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy grade</td>
<td>1</td>
</tr>
<tr>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>35</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>&gt;35</td>
</tr>
<tr>
<td>PT (secs. prolonged)*</td>
<td>1-4</td>
</tr>
<tr>
<td>[INR]</td>
<td>&lt;1-7</td>
</tr>
</tbody>
</table>

*Score prothrombin time or INR; Child-Pugh A Score < 6; Child-Pugh B Score 7-9; Child-Pugh C Score >10.
I. Neuropsychological Cognitive Test Battery:

Neuropsychological testing can range from an extensive battery to a single test office-based screening approach. The Number Connection Test, parts A and B; the Digit Symbol Test; and the Block Design Test have been the tests most frequently employed. Normal cut-off values were set at the mean±2SD from the normal control arm, with a low value indicating abnormal DST, BDT, DS-F, and DS-B and a higher score indicating a poor performance in NCT-A and NCT-B test. Results were evaluated according to age and education. Comparisons were made between groups by unpaired t-test and p<0.05 was regarded as a significant level.

1. Number Connection Test (NCT-A): This test measures visuo-spatial orientation and psychomotor speed. Each patient has to connect 25 consecutively numbered circles from 1 to 25 on a sheet of paper. After a short explanation, each are asked to start and score is recorded as time in seconds required to complete the test. This test is simple to explain to patients, to perform and score, inexpensive, readily available and reliable.

2. Number Connection Test-B: It is the test of psychomotor speed, visuo-spatial orientation, and attention shift. The circles include the numbers from 1 to 13 and the letters from A-L. The subjects are asked to connect numbers and letters in alternating manner, that means go from 1-A-2-B-3-C and so on. Test result is the time needed including error correction time.

3. Wechsler Adult Intelligence Scale (WAIS) – Verbal and Performance Subtest.

The full, verbal and performance IQs may be influenced by a variety of factors including the individual’s cognitive capacity, ability to concert to the tasks presented, neurological status and previous exposure to various educational and social experiences. The ability to solve problems quickly under time pressure may also influence scores, particularly on the performance subtests. The performance IQ usually is based on all five of the WAIS performance subtests. It reflects the efficiency and integrity of the individual’s perceptual organization, including non-verbal reasoning skills, the ability to employ visual images in thinking and the ability to process visual material. WAIS-performance subtests consist of picture completion, picture arrangement, block design, object assembly, and digit symbol.

Block Design: The subtest uses a set of nine cards containing designs in red and white and a set of identical one-inch blocks sides are painted red, white, and finally red and white. The subject is shown one design at a time, which he has to reproduce by choosing and assembling the proper blocks. It reflects the individual’s ability to analyze abstract figures visually and construct them.

Digit Symbol: This version of the familiar code substitution test, which has often been included in non-language intelligence scale. The key contains nine symbols paired with the nine digits. With this key before him, the subject has 1 minute to fill in as many symbols as he can under the numbers on the answer sheet. It reflects the individual’s visual motor speed, visual memory coordination and ability to learn non-verbal material.

Digit Span: It is well known as apart of WAIS-Verbal subtest. Orally presented lists of three to nine are to be orally reproduced. In the second part, the subject has to reproduce lists of two to eight digits backwards. Test result is the number of digits repeated in the right order. It reflects the individual’s attention span, ability to concentrate, and working memory.

Norms and Scoring: Luis Kamil Milika has translated the WAIS into Arabic and adequate norms exist for this modification. The WAIS standardization sample was chosen with special care to ensure its representatives. Normal cut-off values of tests were set at the mean±2SD from the normal control arm, with a low value
indicating a poor performance in DST, DS-F, DS-B, and BD test.

II. Neurophysiological Measures

a) EEG:
Digital EEG (DEEG) was acquired for all participants using XLTEK 32 channel apparatus (XLTEK, NwDb Version 3.3.0 Build 171, Ontario, Canada, L6H5S1). Electrodes were placed using the standard positions of the 10-20 system. The recording procedure was standardized. Provocation by hyperventilation for 3 minutes and photic stimulation using 5-30 Hz light flash were used. Each participant had undergone DEEG recording for a minimum of one hour. After recording, the DEEG was reviewed using anteroposterior and transverse bipolar and referential montages.

b) P300 ERP
Acquisition of event related potentials: Auditory ERPs were elicited using an “oddball” paradigm. Tone stimuli (100ms duration, 10 ms rise and fall time) at 70 dB were presented monaurally through headphones at a rate of 1.1/s. Eighty five percent of the tones were 1000 Hz (background tones) and the remaining fifteen percent were 750 Hz (target tones). The sequence of tones was randomly intermixed with the constraint that no two-target tones were presented in succession. The stimulus-evoked responses were recorded from the midline site (Cz) of the international 10-20 system. Linked earlobes served as reference. Ground electrode was placed at the forehead. All electrode impedance was maintained at 5 KW or less throughout the recording. All subjects were seated in a reclining comfortable chair. Auditory thresholds were determined before. This was followed by the demonstration of the two tones to be presented. Subjects were instructed to mentally counting the deviant stimuli they heard (i.e. those that deviate from a sequence of standard stimuli). P300 event related potential measurement: P300 responses were elicited by the standard ‘auditory odd ball paradigm using a Medelac Sapphire Premier system. The first major positive peak between 250-500 msec for the rare tone was identified as the P300 response and was marked. Latency was measured from the point of stimulus to the peak of P300 waveform in msec. A P3ERP latency was considered abnormal if it was above +2 standard deviations (SD) of the mean latency measured in age matched controls (n=46). The controls were individuals who had no evidence of present or past liver disease, no psychiatric or neurological disorders, and no history of alcohol intake within last two months.

III. Neuroimaging Study:
All MRI were performed on a 1.5T Magnetom VISION system (Siemens Inc, Iselin, NJ, USA) equipped with a standard quadrature head coil. The MRI protocol consisted of sagittal T1 weighted scout view images, transverse and coronal scans. T1 and T2 weighed spin-echo pulse sequences were applied. Imaging parameters were TR520, TE21 for axial, TR520, TE20 for coronal and TR340, TE17 for sagittal images. The measurement parameters were TR/TE1/TE2 2500/20/80 ms, field of view (FOV) 192 × 256 mm², matrix size 154 × 256, in plane resolution 1.25 × 1.00 mm², and 3 mm slice thickness covering the whole brain from the vertex to the most inferior part of the cerebellum. MRI abnormalities were classified as grade one if bilateral globus pallidi with mild to moderate hyperintensity relative to white matter was seen. Grade II abnormality was noted if there was marked hyperintense globus pallidi together with mildly increased intensities in the surrounding structures such as the putamine, internal capsules and cerebral peduncles. In order to exclude possible parenchymal calcifications, which can be mistakenly evaluated as hyperintensity in MRI imaging, we also studied cranial computerized tomography (CT) scan brain in all patients.
Statistical Analysis

The statistical analysis was done using Chi-square test, Fisher exact test, student t-test, ANOVA test and Spearman correlation coefficient, followed by Tukey as post-hoc test and logistic regression. For data processing and statistical analysis the SPSS, version 10 software package was applied. Significance was defined as P<0.05.

RESULTS

A total of 43 patients with liver cirrhosis (31 males and 12 females) were studied. The mean age of patients was 49.3±11.8 years and the mean years of formal school education was 13.7±4.1 years. Seventy-nine % of patients were in an advanced stage of liver disease i.e. Child's grades B and C. None of the patients showed evidence of overt hepatic encephalopathy at least within last one month. The patients were subdivided into 2 groups: cirrhotic patients without MHE (COE), and cirrhotic patients with MHE (CWE) according to presence of minimal encephalopathy. We compared healthy controls, cirrhotic patients without MHE (COE), and cirrhotic patients with MHE (CWE) as regard to demographic and clinical characteristics. Table (1) showed no significant differences (P>0.05) between patients and controls regarding age, sex, and schooling (education). Out of 43 patients with liver cirrhosis, 21(48.8%) had minimal hepatic encephalopathy. The most striking sleep disturbance was inverted sleep rhythm with excessive day time sleeping that occurred in 85.7% of patients who had MHE (CWE) with highly significant difference (P<0.01) compared to those patients who had not MHE (COE). Furthermore, non-encephalopathic cirrhotic patients exhibited significant difference (P<0.05) regarding inverted sleep rhythm in comparison with healthy control. On follow-up of patients,3 out of 22 COE patients (13.6%), compared to 14 out of 21 CWE patients (66.7%), developed overt encephalopathy within average duration of 9 months with significant difference between the two groups, reflecting that minimal encephalopathy might be a risk factor for developing overt encephalopathy. The rate of progression to overt encephalopathy was 41.9 % of all cirrhotic patients.

Neuropsychological cognitive test battery is a reliable, simple, inexpensive method of evaluation of early stage of hepatic encephalopathy (MHE). Table (2) and Fig. (3) summarize frequency of abnormalities in different measures used in our study to detect minimal HE and overt HE during follow-up. Nearly, 81% of patients with MHE, had abnormal 2 or more neuropsychometric tests, with high figures related to abnormality in NCT-B (38.1%), NCT-A (33.3%),and block design (28.6%). Age and education dependent normal values of this NCT were investigated in 46 healthy people. The mean values of this control population were then noted. In this study, 16 out of 21 patients (76.2 %) among patients with mHE , 17 out of 18 (94.4%) among patients with overt HE, with subclinical neuropsychiatric abnormalities were detected by NCT-A and NCT-B. The influence of the variables on the results of DST and NCT is shown in Table 6. No significant difference was found in alcohol drinking habits, and the etiology of cirrhosis (P>0.05), but the difference was related to Child-Pugh’s grade (P<0.01). Consequently, Child-Pugh’s grade was a risk factor of mHE (P<0.01).

There were no significant differences regarding the grade of MRI abnormalities and the presence of subclinical neuropsychological deficits in this study. The patients without CT and MRI abnormalities also is useful for all kinds of hepatic encephalopathy. However it generally requires transportation of the patient, expensive and sometimes sophisticated equipment and skilled staff. had normal NCT scores and EEG findings. Out of 43 patients, 20 (46.5%) had characteristic symmetric hyperintensities in the globus pallidi on T1-weighted images. The bilateral globus pallidi were homogenously hyperintense compared with the adjacent internal capsule. Eight of the 43 (18.6%) patients had grade I abnormalities and 12 (27.9%) had grade II abnormalities (Figs. 1 and 2). The patients with grade II changes had evidence of signal intensity alterations within the putamen.
There was a significant difference between COE and CWE patients regarding MRI abnormality grading. Moreover, both encephalopathic (CWE) and non-encephalopathic (COE) patients exhibited significant difference in comparison with controls. T2-weighted images were unremarkable, with no signal intensity alterations. Four patients with grade 2 intensity changes also had signs of cerebral and cerebellar atrophy. This finding was also present on cranial CT scan in these patients. Cranial CT revealed no other abnormalities in any of the patients.

As shown in Table (3) and Fig(4), the mean P3ERP latencies of the cirrhotics (373.5±31.3 msec) were found to be significantly prolonged (p<0.01) when compared with those of age matched controls (346.7±25.6 msec). No significant difference was observed in the P3ERP latencies of patients with or without alcoholic etiology of cirrhosis (368±33 msec and 361±32 msec respectively). However, both the groups had significantly longer latencies than the controls (p<0.01). P300 latency was significantly delayed (p<0.01) in cirrhotic patients with mHE, compared to patients without mHE. It was observed that the latencies grew longer with increase in severity of the disease, with statistically significant difference (p<0.05). Latencies of patients with low severity i.e. Child's grade A (362.3±28.7 msec) were significantly different from those of controls (p<0.05). In patients with Child's B and C grade of liver disease, the latencies were highly significantly longer than those of controls (p<0.01). Using the cutoff of 385 msec, 9 (20.9%) of all cirrhotics were found to have P3ERP latency prolongations i.e. suffered from mHE. Occurrence of delays in latency beyond the cutoff was higher in alcoholics (30.3%) than in non alcoholics (16.2%) but the difference was not statistically significant. Similarly, a higher proportion of patients in advanced stage of liver disease had prolongation in latencies (p<0.01) compared to less severe cases. We compared the demographic variables such as age, education, alcoholism and biochemical variables (serum albumin, child's scores calculated from bilirubin, albumin, ascites, encephalopathy and prothrombin time) in patients with or without mHE i.e. with or without P3ERP latency prolongations respectively. Cirrhotics with mHE had significantly lower (p<0.01) albumin (2.4±0.3% vs. 3.5±3.9g%) and higher child's scores (8.9±1.3 vs. 7.1±1.3) when compared with patients without MHE. No significant difference was observed in other variables in MHE and non-MHE cirrhotics.

Table (4) demonstrated that EEG recordings detected 11 out of 43 patients (25.6%) with subclinical neurophysiologic abnormalities. There was intermittent slow wave activity of short duration, with predominantly alpha frequency basic activity. These eleven patients had grade two MRI findings and eight of them also had an abnormal NCT result. However, the difference was not significant in patients with grade I or grade II MRI abnormalities regarding subclinical EEG deficits. The most interesting EEG finding was high percentage (83.3%) of abnormality with progression to overt HE, denoting that EEG is beneficial diagnostic tool during follow-up of patients without clinical signs of encephalopathy as shown in Table (1). Delayed P300 latency was detected in 8 out of 21 patients with mHE (38.1%), 12 out of 18 patients with overt HE (66.7%).

Table (5) summarizes some demographic and laboratory characteristics of the patients with grade I and grade II MRI abnormalities. As seen from the table, the liver synthesis functions (albumin levels and prothrombin times) of the patients with grade 2 abnormalities deteriorated more than that of those with grade I abnormalities. However, plasma levels of ammonia were not significantly different between the groups of patients. Grade II abnormalities were detected in patients with higher Child scores with a more significant difference than in patients with grade I MRI abnormalities (p<0.05). The prevalence of MHE increased from 40.2% and 58.2% in Child-Pugh’s grade A and B groups to 76.9% in Child-Pugh’s grade C group (P<0.001) as shown in table (6). In Cox-regression, mHE, esophageal varices, longer NCT time and higher Child-Pugh’s score were the independent variables related to development of overt hepatic encephalopathy in follow-up.
Table 1. Demographic and Clinical Data among Study Groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group N = 46</th>
<th>Cirrhotic without mHE (COE) N = 22</th>
<th>Cirrhotic with mHE (CWE) N = 21</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD) yrs</td>
<td>48.2±11.4</td>
<td>49.2±12.3</td>
<td>49.9±13.6</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>32/14</td>
<td>16/6</td>
<td>15/6</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Education (mean ± SD) yrs</td>
<td>14.3± 4.6</td>
<td>14.2±4.1</td>
<td>14.8±4.5</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Inverted Sleep Rhythm (No,%)</td>
<td>1 (2.2%)</td>
<td>6 (27.3%)</td>
<td>18 (85.7%)</td>
<td>P1 &lt; 0.05* P2 &lt; 0.01*</td>
</tr>
<tr>
<td>Severity of Liver Cirrhosis Child-Pugh Grading (No,%)</td>
<td>NA</td>
<td>6 (4.5%)</td>
<td>5 (4.8%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>10 (4.5%)</td>
<td>9 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>6 (9.1%)</td>
<td>7 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt HE</td>
<td>NA</td>
<td>2 (9.1%)</td>
<td>9 (42.8%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>Grade I</td>
<td></td>
<td>1 (4.5%)</td>
<td>3 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td></td>
<td>0</td>
<td>2 (95%)</td>
<td></td>
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<tr>
<td>Grade III</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
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<tr>
<td>Grade IV</td>
<td></td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N=Number, NA = Not applicable, HE=Hepatic Encephalopathy, mHE=Minimal Hepatic Encephalopathy, COE=Cirrhotic without Minimal Encephalopathy, CWE=Cirrhotic with Minimal Encephalopathy, P1=Control vs. COE, P2=COE vs. CWE., *= Significant

Table 2. Frequency (number & %) of abnormalities in neuropsychometric tests, EEG, P300 Latency, and MRI among Study Groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control N=46</th>
<th>Cirrhotic without mHE (COE) N=22</th>
<th>Cirrhotic with mHE (CWE) N=21</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT-A</td>
<td>0</td>
<td>0</td>
<td>7 (33.3%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>NCT-B</td>
<td>0</td>
<td>1(4.5%)</td>
<td>9 (38.1%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>DST</td>
<td>0</td>
<td>0</td>
<td>5 (23.8%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>BDT</td>
<td>0</td>
<td>0</td>
<td>6 (28.6%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>DS-F</td>
<td>0</td>
<td>0</td>
<td>4 (19.1%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>DS-B</td>
<td>0</td>
<td>0</td>
<td>5 (23.8%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>Total N of &gt; 2 abnormal NPT</td>
<td>0</td>
<td>0</td>
<td>17 (80.9%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>EEG</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>10 (47.6%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>P300 Latency</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>8 (38.1%)</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>MRI T1w Image High Signal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>7 (33.3%)</td>
<td>P &lt; 0.05*</td>
</tr>
<tr>
<td>Grade II</td>
<td>0</td>
<td>2 (9.1%)</td>
<td>10 (47.6%)</td>
<td></td>
</tr>
</tbody>
</table>


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Fig. (1): Axial T1 weighted spin-echo image shows grade 1 signal hyperintensity in globus pallidus (Right).

Fig. (2): Coronal T1 weighted spin-echo image shows grade 2 signal hyperintensity in globus pallidus, Putamen and cerebral peduncle (Left).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group N = 46</th>
<th>Cirrhotic without mHE (COH) N = 22</th>
<th>Cirrhotic with mHE (CWH) N = 21</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT-A (TMT-A)</td>
<td>41.45±17.36</td>
<td>83.67±32.79</td>
<td>130.94±50.84</td>
<td>P1&lt; 0.05*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.01*</td>
</tr>
<tr>
<td>NCT-B (TMT-B)</td>
<td>64.73±23.68</td>
<td>158.63±51.12</td>
<td>205.65±59.52</td>
<td>P1&lt; 0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.01*</td>
</tr>
<tr>
<td>DST</td>
<td>11.13±2.94</td>
<td>9.16±2.64</td>
<td>7.26±3.34</td>
<td>P1&lt; 0.05*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.05*</td>
</tr>
<tr>
<td>BDT</td>
<td>12.3±3.98</td>
<td>11.35±3.91</td>
<td>9.73±2.43</td>
<td>P1&lt; 0.05*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.01*</td>
</tr>
<tr>
<td>DS-F</td>
<td>7.35±1.25</td>
<td>5.1±0.87</td>
<td>4.61±1.11</td>
<td>P1&lt; 0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.01*</td>
</tr>
<tr>
<td>DS-B</td>
<td>5.15±1.12</td>
<td>3.35±0.67</td>
<td>2.35±156</td>
<td>P1&lt; 0.01*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P2&lt; 0.01*</td>
</tr>
</tbody>
</table>

NCT-A=Number Connection Test- part A, TMT-A=Trail Making Test-Part A,NCT-B=Number Connection Test-Part B,TMT-B= Trail Making Test-Part A, DST=Digit Symbol Test, BDT=Block Design Test, P1=Control vs. COE, P2=COE vs. CWE., *= Significant

Table 3. Neuropsychometric Cognitive Scales among Study Groups.

586
Table 4. EEG, P300 latency, and MRI findings among study groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Group N = 46</th>
<th>Cirrhotic without mHE (COE) N = 22</th>
<th>Cirrhotic with mHE (CWE) N = 21</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal EEG paroxysmal slow wave</td>
<td>0</td>
<td>2 (4.5%)</td>
<td>9 (9.5%)</td>
<td>P1 &lt; 0.05*</td>
</tr>
<tr>
<td>P300 Latency (mean±SD) msec</td>
<td>346.7±25.6</td>
<td>363.7±33.2</td>
<td>398.6±43.8</td>
<td>P1 &gt; 0.05, P2 &lt; 0.01*</td>
</tr>
<tr>
<td>Delayed P300 L (N, %)</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>8 (38.1%)</td>
<td>P &lt; 0.05*</td>
</tr>
<tr>
<td>MRI T1W Image High Signal</td>
<td>0</td>
<td>3 (13.6%)</td>
<td>17 (80.95%)</td>
<td>P &lt; 0.01*</td>
</tr>
</tbody>
</table>

P1=Control vs. COE, P2= COE vs. CWE., *= Significant

Table 5. Demographic, clinical, and laboratory data of patients with grade (1) and grade (2) MRI abnormalities.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MRI Grade 1 N = 10</th>
<th>MRI Grade 2 N = 19</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD ) yrs</td>
<td>46.4±12.5</td>
<td>47.1±12.6</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/3</td>
<td>13/6</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Child –Pugh Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5 (50.0%)</td>
<td>7 (36.8%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>B</td>
<td>3 (30.0%)</td>
<td>4 (21.1%)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>2 (20%)</td>
<td>3 (42.1%)</td>
<td></td>
</tr>
<tr>
<td>Variceal Bleeding</td>
<td>5</td>
<td>10</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>57.5±32.5</td>
<td>58.2±31.7</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.9±0.54</td>
<td>3.11±0.65</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>4.7±198</td>
<td>5.01±3.12</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Prothrombin time (Sec)</td>
<td>14.8±098</td>
<td>19.7±3.64</td>
<td>P &lt; 0.01*</td>
</tr>
<tr>
<td>Venous Ammonia (U/L )</td>
<td>1.5±0.8</td>
<td>1.2±0.7</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>

Table 6. Multivariate logistic analysis for etiology and severity of liver cirrhosis in patient group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>NCT-A</th>
<th>DST</th>
<th>mHE(%)</th>
<th>P2</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.430</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>12</td>
<td>72.3±41.1</td>
<td>8.0±2.6</td>
<td>54.2 %</td>
<td>P1 0.0541</td>
<td>0.0153</td>
</tr>
<tr>
<td>Non-Alcoholic</td>
<td>31</td>
<td>68.7±40.3</td>
<td>8.5±2.8</td>
<td>51.6 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>A</td>
<td>11</td>
<td>57.6±35.8</td>
<td>8.89±2.9</td>
<td>40.2 %</td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>B</td>
<td>19</td>
<td>74.7±41.6</td>
<td>7.6±2.3</td>
<td>58.3 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>13</td>
<td>85.3±49.7</td>
<td>6.3±2.1</td>
<td>76.9 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

N=Number, P1= P value within groups; P 2 = P value among groups in logistic analysis.
**Fig. (3):** Frequency of abnormalities in neuropsychometric tests, EEG, P300 L, and MRI among patients with overt encephalopathy.

**Fig. (4):** Cirrhotic patients with mHE (boldface line) exhibited significantly delayed P300 latency in comparison with Cirrhotic patients without mHE (thin line).
In patients with minimal HE there are no detectable neurological findings, but there may be subtle cognitive changes that are brought up by neuropsychologic and neurophysiologic testing. Minimal hepatic encephalopathy is diagnosed in patients that demonstrate deficits in attention and visuo-motor co-ordination but otherwise show no evident or only transient symptoms of cerebral dysfunction. The prevalence of minimal HE in cirrhotic patients is variable, but is expected to be high as shown by many studies. Patients who develop minimal HE tend to be older, have more severe liver disease, and more often have esophageal and fundal varices. Many studies have shown that these patients have impaired quality of life, and disturbed sleep and daily life activities. One major concern is car driving as one study showed that at least 44% of patients with well compensated cirrhosis and features of minimal HE are not actually fit to drive. Patients with minimal HE may improve, remain the same or, more often, deteriorate and go on to develop overt recurrent HE. There is currently no single method which can precisely and reproducibly quantify the severity of hepatic encephalopathy. The most common technique is the assessment of mental state, which by itself has multiple aspects such as state of consciousness, orientation, personality and behavior, intellectual function etc. Each of these aspects is difficult to assess and quantify individually. Electrophysiologic assessment

The present study detected a prevalent sleep disturbance in the form of inverted sleep rhythm with excessive day time sleep among cirrhotic patients without mHE (27.3%). This figure was raised to reach 85.7% of cirrhotic patients with mHE, with significant difference between the two groups, reflecting that sleep history is of importance in diagnosis of minimal hepatic encephalopathy (mHE). Our findings go in harmony with the result of Velissaris et al., who found sleep disturbances in 92.3% of their cirrhotic patients with mHE versus 7.7% of healthy control. The occurrence of inverted sleep rhythm in cirrhotic patients with and without mHE may be due to disrupted hypothalamic suprachiasmatic biological clock and disturbed circadian rhythm resulting from cerebral neurotoxins overload and loss of cerebral biochemical homeostasis on account of compromised detoxifying power of cirrhotic liver. Patients with MHE appeared to have no clinical symptoms. However, they might be at risk when they performed complex motor activities as operating a heavy machinery or driving an automobile. They might have abnormal behaviors such as altered sleeping pattern and impaired cognitive function. Patients with MHE were vulnerable to overt HE. However, medical treatment and dietary management in these patients could improve the psychometric tests.

Our results revealed significant abnormality of neuropsychological cognitive tests among patients with MHE, with the following figures: abnormal NCT-B in 38.1%, NCT-A in 33.3%, and the two tests together were abnormal in 71.4% of patients with MHE, denoting that the main domain of early cognitive disturbance is cognitive-motor speed & accuracy (psychomotor speed), visuospatial orientation, and attention shift. The present results are in accordance with a lot of studies. In addition digit symbol test was abnormal in 23.8% of patients with MHE, reflecting impaired visual motor speed, visual memory coordination and ability to learn non-verbal material. This finding is in agreement with Yu-Yuan Li, et al., who found abnormal NCT-A and DST tests in 29.1% of patients, 13.0% were abnormal only in DST and 8.8% only in NCT-A. Taken together, SHE was diagnosed in 208 (50.9%) cirrhotic patients of Yu-Yuan study by this test battery. In the same context, block design test was abnormal in 28.6% pointing at impaired visual perception, visual construction, motor and attentional skills. Interestingly, Weissenborn et al., reported that patients with a pathological PSE-Test result differed significantly from controls in all attention tests applied, while the patients with normal PSE-Test results achieved attention test results similar to that of the controls.
Thus, they concluded that the neuropsychological features of minimal hepatic encephalopathy point to a disorder of executive functioning, particularly selective attention and psychomotor speed, but other abnormalities may be observed. In agreement with previous results, digit span backward and forward were abnormal in 23.8% and 19.1% respectively, reflecting impaired attention, concentration, and working memory in our patients.

Our EEG results point at intermittent slow wave activity of theta range (6-7cps) in 47.6% of cirrhotic patients with MHE with significant difference compared to healthy control. It is worthy noted that decreasing EEG frequency during follow-up of patients may predict the development of overt HE, with 83.3% of patients had abnormal EEG. These findings go in parallel with Weissborn et al., who reported that clinical improvement in patients with HE is often preceded by an increase in EEG frequency, while on other hand, impending HE episode may be foreseen when the EEG frequency of a patient decreases. Moreover, EEG abnormality reported in our study was significantly correlated to overt encephalopathy \( \rho =0.83, p<0.05 \) (Spearman rank correlation coefficient). On contrary, Quero et al. stated that the sensitivity of the EEG for the diagnosis of MHE is limited compared to psychometric tests.

Recently, the P3ERP latency has been used in the assessment of cognitive dysfunction of early encephalopathy associated with chronic liver disease. Delays have been observed in the P3ERP latency in clinically encephalopathic patients suggesting a definite deterioration of their stimulus evaluating abilities. Presence of latency prolongations in clinically non encephalopathic cirrhotics would, therefore, signify presence of MHE. In fact P3ERP latency has been found to be a better marker of SHE when compared with other evoked potentials as well as the psychometric tests.  

We detected delayed P300 latency in 38.1% of the cirrhotics in this study. Saxena et al. found delayed auditory P300 latency in 48.8% of their cirrhotic patients. In another study, involving patients with cirrhosis as well as non cirrhotic liver disease, P300 latencies have been reported to be similar in nonecephalopathic patients as well as the controls, thereby suggesting that P3ERP latencies were not sensitive in detection of SHE. Gallai et al, using the same method showed delays in latency in 6 out of 11 cirrhotics (54.6%) with Grade 0 encephalopathy (MHE). Kuiger et al., used the visual mode P3ERP and reported abnormality in latency in 78% of the 37 cirrhotics investigated; the higher percentage reported being attributed possibly to the visual stimulus used. Our data is therefore in agreement with most other studies and indicates that P3ERP can be a useful technique in the evaluation of hepatic encephalopathy.

Serum albumin was low, INR, and Child's score were higher in patients with MHE as compared to those without MHE. Other parameters of liver function however showed no significant difference. In fact, studies, have shown that the degree of cognitive dysfunction detected by P3ERP in patients with cirrhosis appears related to the reduction in hepatic metabolic capacity. Our study documented the prevalence of MHE using a highly validated electrophysiological test, which has been recommended for measuring this disorder which is difficult to diagnose but is very important for future prognosis. At present the use of BAEPs is limited to being a prognostic marker and in follow up of comatose patients. In fact, in chronic alcoholics with or without overt liver disease, ethanol induced demyelination is thought to be the underlying cause of abnormal BAEPs. Therefore, BAEPs have not been recommended in detection of SHE.

Our study demonstrated characteristic brain MRI findings of portosystemic encephalopathy in cirrhotic patients with and without minimal encephalopathy. This finding has been reported in 50% to 75% of cirrhotics in different studies. We detected MRI abnormalities in 46.5% in patients with and without minimal encephalopathy, and 94.4% in patients with overt encephalopathy. In
the present study, the grade of MRI abnormalities seemed to be affected primarily by liver synthetic functions measured by albumin level, prothrombin time, and INR and Child scores. This confirms that our MRI findings reflect changes in association with liver failure. This relationship is also supported by some authors who showed a significant correlation between severity of liver disease and signal intensity in the globus pallidus. A correlation between the period of liver cirrhosis and the MRI changes has also been suggested, but as in our patients, the time of onset of cirrhosis is obscure in most affected patients. The presence of portosystemic shunting, as demonstrated in our patients, could be an important factor in the development of MRI signal changes in cirrhosis. Bright basal ganglia in T1-weighted magnetic resonance images have also been found in patients with portal vein thrombosis without liver cirrhosis. Thus, some authors have supported the idea that bright basal ganglia primarily represent shunt-induced alterations. However, it may be possible that hepatic dysfunction and portosystemic collaterals may both allow some toxic substances with special affinity to basal ganglia to pass the blood brain barrier and change paramagnetic properties of local brain areas. The most commonly accused substance in this respect is manganese (Mn). Mn deposition within the globus pallidus was demonstrated at MR imaging after parenteral administration of manganese chloride to monkeys. Paramagnetic properties of Mn results in astrogliotic reaction and this causes signal intensity increases in T1-weighted MRI images. Mn causes local depletion of brain dopamine due to autooxidation and significant changes in other neurotransmitters. Other than Mn, copper, another paramagnetic trace element, is suggested to contribute to the changes in signal intensity on MRI images in patients undergoing long term total parenteral nutrition. Some authors suspect copper to be another possible paramagnetic substance, which may play a role in hyperintense basal ganglia as copper concentrations in globus pallidus and putamen of patients with cirrhosis have also been reported to be high (50% more than normal). In the present study, plasma levels of ammonia, another toxic agent in cirrhotic patients, widely fluctuated, with no differences in respect to grades of MRI abnormalities. At present, the literature is conflicting regarding the role of ammonia and intensity changes in the brain of cirrhotics. We could not show a relationship between plasma ammonium and the degree of MRI abnormalities in our patients.

Minimal (subclinical) hepatic encephalopathy is not a temporary phenomenon without morphologic abnormalities in the brain. Investigators have detected objective organic cerebral changes in patients with SHE. This is especially confirmed after demonstration of the biochemical nature of changes in the brain with proton spectroscopic analysis of patients with subclinical hepatic encephalopathy. Authors have concluded that if hyperintense globus pallidi are detected in neurologically asymptomatic patients with cirrhosis, the patient should be considered as having MHE because they show good correlation with previous attacks of hepatic encephalopathy with MRI abnormalities. However, no differences were found in the grade of MRI abnormalities in our patients regarding the presence or absence of neuropsychologic and neurophysiologic deficits detected by NCT, EEG and P3 ERP measurements.

Conclusion:
Early diagnosis and treatment of MHE seem extremely important in Egypt, because of the big population and high prevalence of liver diseases in this country. A high prevalence of MHE in cirrhotic patients should lead us to pay attention to these important findings frequently encountered in our medical practice. The results of the present study suggest that inverted sleep rhythm, abnormal NCT, slow EEG activity, delayed P300 latency, T1 MRI high signal are valid tools for the screening of MHE in cirrhotic patients as there is a greater likelihood of overt encephalopathy development in patients with an abnormality detected by these tests than in patients without such abnormality. Psychometric tests are simple and reliable indicators for screening...
SHE among Egyptian cirrhotic patients. By using a NCT and DST battery, MHE could be found in 66.7% of cirrhotic patients without overt clinical encephalopathy. The prevalence of MHE is significantly correlated with the severity of liver functions. EEG is useful for follow-up screening and prediction of the development of overt hepatic encephalopathy.

**Recommendations:**

The present study recommends the following: (1) Sleep history, particularly inverted sleep rhythm, simple neuropsychological cognitive tests particularly NCT-A, NCT-B, DST, BDT have to be used as a routine work-up in every patient with liver cirrhosis; (2) Delayed P300 latency, EEG slow frequency and MRI signs are reliable measures to confirm the diagnosis of minimal encephalopathy in certain patients with liver cirrhosis; (3) EEG is a useful measure for follow-up of already diagnosed patients with minimal encephalopathy to predict the development of overt encephalopathy; (4) Special care has to be paid for cirrhotic patients particularly drivers, and operators of hazardous machines by regular neuropsychometric follow-up and working under certain precautions or a recommendation to avoid driving an automobile or operating machinery; (5) Cross-sectional and follow-up study by MRI Spectroscopy in patients with and without minimal hepatic encephalopathy.

**Acknowledgement**

We are greatly indebted to Dr. Abdulaziz Yassine, Prof. of Family and Community Medicine, Faculty of Medicine, Tanta University for his unlimited help in statistical study.

**REFERENCES**


الدلالات التشخيصية لاعتلال المخ الغير ظاهر إكلينيكيا الناجح عن التليف الكبدي

دراسة إكلينيكية وإيكولوجية وأبعاد الرنين المغناطيسي على المخ

الملخص العربي

دلالات التشخيصية لاعتلال المخ الغير ظاهر إكلينيكيا الناجح عن التليف الكبدي

دراسة إكلينيكية وإيكولوجية وأبعاد الرنين المغناطيسي على المخ

مرجع البحث: يشمل عدد من عوامل ظاهر الأكليينيكية لاعتلال المخ الكبدي في مراحله الأولى إلا أنه يوجد

أهداف البحث: تقييم مدى ذكاء الاختبارات والقياسات الذكاء العقلي وتطبيقات المخ الكهربائي والجهد العقلي الممار

وأثناء الرنين المغناطيسي لتخليص مشخصات اعتلال المخ الغير ظاهر إكلينيكيا الناجح عن التليف الكبدي مع متابعة المرضى

لحين حدوث الاعتلال المخ الظاهر والغيبوبة الكندية بدفعها المختلفة لدى هؤلاء المرضى.

الموضوع والطرق البحث: تكونت عينة البحث من 43 مريض بالتفريق الكبدي و46 شخص سليم كمبيه ضابطة وتم

قياس الوظائف الذكاء العقلي بعض القياسات مثل اختبار توصيل الأرقام والحوش وأختبار نزول الأرقام واختبار عدد

الأرقام وأختبار تشكيل المكعبات بالاضافة لتطبيقات المخ الكهربائي والجهد العقلي الممار أثناء الرنين المغناطيسي على المخ

مع وظائف الكبد الكمالية ونسبة الأمونيا وتم تقسيم المرضى إلى اثنين من حسب وجود الاعتلال المخ الكبدي غير ظاهر

إكلينيكيا من عدمه مع متابعة هؤلاء المرضى لمدة ستين.

النتائج: أظهرت النتائج وجود اضطرابات في النوم مع النعاس والتقلص للنوم أثناء النوم في حوالي 86٪ من المرضى

من ما قد تكشف خطورة على المريض أثناء قيادة السيارة والعمل أثناء النوم وأوضحت القياسات الذكاء العقلي وجودة خلل في

التركيز والانطباع والذاكرة الصررد وضعف الوظائف الذكاء مع تأخر الاستجابة ورد الفعل بصورة ذا دلالة إحصائية وكان

48٪ من مرضى اعتلال المخ غير ظاهر إكلينيكيا لديهم نشاط كهربائي في تخطيط المخ ونسبة 38٪ من مرضى اعتلال

المخ الغير ظاهر إكلينيكيا لديهم طول الموجه ب 300 من الجهد العقلي الممار فضلا على أن تخطيط المخ الكهربائي قد

تبيّن بعد الاعتلال المخ الكبدي الظاهر والغيبوبة الكندية وأوضحت أضداد الرنين المغناطيسي للمخ بعض الاعترافات في

العقد الإخباري لإخبار نسبة 81٪ من مرضى اعتلال المخ غير ظاهر إكلينيكيا التي لها علاقة بحركة الإنسان مما قد يفسر

البطط في دائرة القدرة على التلف الكبدي ودليه أثبتت بعض الاختبارات في الاختبارات الذكاء العقلي بصورة روبية عند مرضى التليف الكبدي وضربة الأذن في

الاختبارات ذات الذكاء العقلي لمرضى التليف الكبدي وخطورة قيادة السيارات وتشنج الموسيقى وذلك بالقياس الفروي لهذه

المريضي كما أنه يمكن الاعتماد على تخطيط المخ الكهربائي والجهد العقلي الممار وادعى الرنين المغناطيسي للمخ في

تأثير تشخيص اعتلال المخ غير ظاهر إكلينيكيا الناجح عن التليف الكبدي مع متابعة هؤلاء المرضى بتطبيقات المخ الكهربائي

تلقائيا لدوى الاعتلال المخ الظاهر والغيبوبة الكندية وذلك بالعلاج المبكر.