STUDY OF ELECTROENCEPHALOGRAPHY CHANGES AND NEUROPSYCHIATRIC TESTS IN MINIMAL HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS OF LIVER

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ABSTRACT

Hepatic Encephalopathy (HE) is the complex and potentially reversible neuropsychiatric syndrome which is characterized by symptoms like somnolence, confusion, asterixis, extrapyramidal rigidity, convulsions and coma. It is difficult to diagnose Minimal Hepatic Encephalopathy (MHE) among the patients with liver disease because these patients will be clinically normal. Neurophysiological tests such as various psychometric tests mainly Psychometric Hepatic Encephalopathy Score (PHES) is used in identifying this entity.

METHODS: We conducted a crosssectional study to analyse the prevalence of MHE and to assess the utility of neurophysiological tests, uses of PHES in diagnosis and to study EEG changes among the patients with MHE, involving 70 cases diagnosed with liver cirrhosis and 70 controls.

RESULTS: The average age of patients in our study population was 49.43±10.2 years with male predominance. We found prevalence of MHE was 38% with male predominance. Severity of HE increased with increase in Child-Pugh grade but there was no statistically significant association. Time taken to complete NCT, DCT and line drawing tests were significantly higher among MHE patients compared to the normal individuals. Also, 12 (30.76%) of the population with MHE had slow wave pattern of EEG, followed by theta waves among 7 (17.94%). 3 (7.7%) and one patient had delta wave pattern and triphasic wave pattern respectively.

CONCLUSION: The prevalence of MHE was 38% in our study with male predominance. Alcohol abuse was the most common cause of cirrhosis. Severity of HE increased with increase in Child-Pugh grade. Time taken to complete NCT, DCT and line drawing tests were significantly higher among MHE patients compared to the normal individuals. 12 patients (30.76%) in the study population with MHE had slow wave pattern of EEG followed by theta waves among 7 (17.94%) patients. 3 (7.7%) and one patient had delta wave pattern and triphasic wave pattern respectively.

Key Words: Chronic liver disease, Minimal hepatic encephalopathy, EEG changes, PHES**.**

INTRODUCTION

Hepatic encephalopathy (HE) is a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain diseases. In cirrhosis of liver, three major syndromes are recognized 1. **Episodic (precipitant-induced) encephalopathy**, commonly seen in the hospital setting, following superimposed event is a key factor. 2. **Persistent (chronic) encephalopathy,** seen with extensive portal–systemic shunts and after portocaval shunt surgery or placement of transjugular intrahepatic portosystemic shunt (TIPS). 3**. Minimal (subclinical) Hepatic Encephalopathy (MHE)** reflects alterations in cognitive function in patients who clinically exhibit a normal mental state[1]. Minimal hepatic encephalopathy (MHE), the mildest form of HE, is characterized by subtle motor and cognitive deficits, and impairs health-related quality of life (HRQOL).[2] Cirrhotic patients with MHE have a normal neurological and mental status by the standard of clinical examination, but have quantifiable neuropsychological defects[3]. These subtle neurocognitive abnormalities primarily affect attention, speed of information processing, and motor abilities and coordination that are not recognizable on standard neurological examination. These neurocognitive abnormalities are independent of sleep dysfunction or problems with overall intelligence[4-8]

There are less studies done in diagnosis of minimal hepatic encephalopathy (MHE), due to lack of clinical features and routine assessment with serum ammonia levels will be practically difficult in all centres. Patients with minimal hepatic encephalopathy (MHE) will have clinically unrecognsed cognitive abnormalities, which are only detectable on psychometric or neurophysiological testing, in the absence of features of overt hepatic encephalopathy (OHE)[9,10]. Neuropsychological testing is an established methodology for quantifying cognitive impairment due to various forms of encephalopathy, including low-grade or minimal hepatic encephalopathy. Psychometric tests are considered the gold standard for the diagnosis of MHE. These psychometric tests specifically assess the cognitive domains.[11] The Psychometric Hepatic Encephalopathy Score (PHES) is composed of five tests, including the number connection test-A (NCT-A), number connection test-B (NCT-B), serial dotting test(SDT), line tracing test (LTT) and digit symbol test (DST). PHES can be used to assess a number of parameters, like motor speed, motor accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction and memory. These parameters are commonly impaired in MHE[11]. **Neuropsychological tests directly measure cognitive functions that are directly relevant to activities of daily living**. Quantitative neurophysiologic tools include Simple electroencephalography (EEG), evoked potentials (auditory, visual, Somatosensory) and P300 (type of auditory evoked potential)[12]. The major finding on EEG is a general decrease in wave frequency. The prevalence of MHE in patients with cirrhosis of liver varies between 30% and 84%.[2]

Hence, screening of all patients with cirrhosis for MHE using psychometric tests (PHES), and of those patients diagnosed to have MHE can be treated early and prevent the further progression of the clinical condition.[6] Overall absence of overt features of encephalopathy makes MHE underdiagnosed.

This study was conducted to assess the prevalence of MHE using bedside psychometric tests in patients with chronic liver disease and to compare the sensitivity of the electroencephalography (EEG) versus psychometric tests in its early diagnosis.

This study was carried out among the patients admitted in medical wards with clinical and ultrasound evidence of chronic liver disease.

AIMS AND OBJECTIVE(S) OF THE STUDY
- To study the prevalence of minimal hepatic encephalopathy (MHE) in patients with chronic liver disease.
- Diagnosis of MHE in patients with chronic liver disease using neuropsychological tests and their relation with severity liver disease using child's grade.
- Electro Encephalography changes and Neuropsychiatric tests in diagnosis of MHE .

MATERIALS AND METHODS
We conducted a one year cross sectional study by recruiting the patients who were attending the either the out-patient department or the in-patient department, diagnosed with chronic liver failure at Raja Rajeswari Medical College and Hospital, Bangalore.

INCLUSION CRITERIA:
1. Both male and female gender
2. Patients aged between 30-80 years.
3. Patients with chronic liver disease diagnosed by history, clinical examination, laboratory findings, ultrasonography or liver biopsy.
4. For control group healthy individuals with no history of any psychiatric illness were recruited.
5. The patients who are ready to give the written informed consent and willing to participate in the study were recruited.

EXCLUSION CRITERIA:
1. Patient having clinical features of overt hepatic encephalopathy.
2. Presence of other psychiatric and neurological diseases causing cognitive dysfunction.
3. Individuals on psychotropic drugs
4. Head injury.
5. Patients on hepato-toxic drugs.
6. Patients with primary neoplasm and secondaries in liver diagnosed by ultrasonography.
7. Suspected case of metabolic encephalopathy.

SAMPLING METHOD: Simple purposive sampling. 140 patients (70 cases and 70 controls) attending the department of general medicine, Raja Rajeswari medical college between 1st January 2021 to 30th January 2022.

STUDY DESIGN:
Study was conducted after obtaining the ethical committee clearance. It was a cross sectional study. The study was conducted on 70 patients after taking written consent from every patient. Also, 70 healthy volunteers willing to participate in the study were recruited.

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All patients who met with inclusion criteria were subjected for face-to-face interview to obtain the detailed medical history, past history, alcohol consumption, high risk behaviour, demographic details and detailed physical examination was carried out.

Routine investigations such as vitals and blood investigations had been suggested.

Also, the following investigations were done among both cases and control group.

All the obtained parameters were tabulated and compared between both groups.

The following investigations done:

Liver function tests (LFT), PT, INR, RFT, RBS, Serum ammonia levels.

Also, all these recruited study population were subjected for USG abdomen.

Patients were assessed for following neuropsychiatric tests on bedside for analysis;

1. **Standardized mini mental status examination (SMMSE):**
    25 to 30: Normal impairment
    21 to 24: Mild/ Early impairment
   10 to 20: Moderate impairment
    0 to 9: Severe impairment

2) PHES Score:

a) Number connection test A (NCT-A): This is to asses of visuo-spatial orientation and psychomotor speed. The study participants were shown a sheet of paper with 25 numbered circles which are randomly spread over the paper. The task is to connect the circles from 1-25 as quick as possible. Test result is the time needed by the subject including error correction time.

b) **Number connection test B (NCT -B):** In this test, many circles were drawn and were numbered from 1-13 and the letters from A-L. The subjects were asked to connect numbers and letters in alternating manner, like 1-A-2-B-3-C and so on.

Test result is the time needed including error correction time. Besides visuo-spatial orientation and psychomotor speed this test is appropriate to study the ability to shift attention.
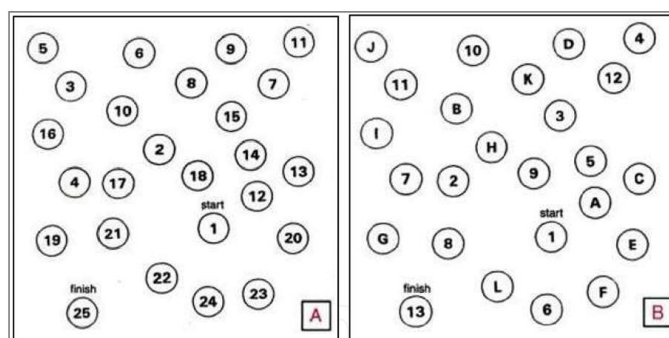

c) Digit symbol test (DST): Different simple symbols were selected. Each symbol was designated with a number, empty blocks with only numbers mentioned were given and patients were ask to fill with reference symbol. Time taken to complete the task was noted.

d) Serial dotting test: This is the most-simple test of pure motor speed. The patients were asked to put a dot in each of the 100 circles given on the sheet, after they have prepared by dotting the 20 circles at the top of the sheet first.
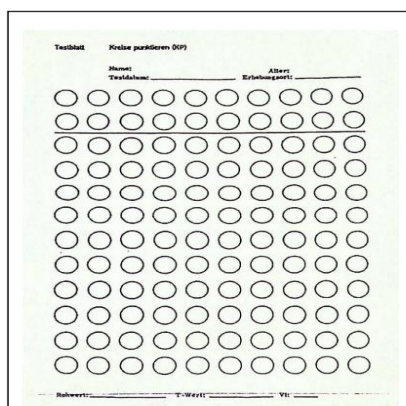
e). Line tracing test: This is the test of motor speed and accuracy. The patients have to follow the route of this labyrinth without crossing or even touching the borderlines.
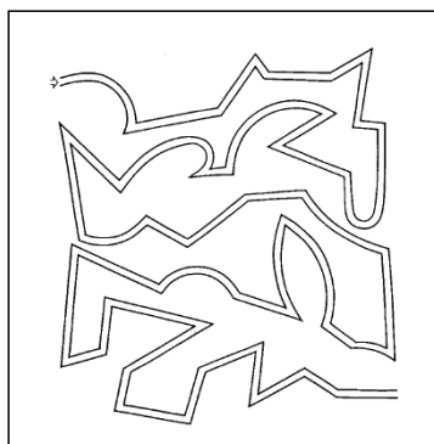
Severity of disease was graded based on Child-Pugh score.
- Encephalopathy: None = 1 point, Grade 1 and 2 = 2 points, Grade 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, moderate = 3 points
- Bilirubin: under 2 mg/ml = 1 point, 2 to 3 mg/ml = 2 points, over 3 mg/ml = 3 points
- Albumin: greater than 3.5mg/ml = 1 point, 2.8 to 3.5mg/ml = 2 points, less than 2.8mg/ml = 3 points
- Prothrombin Time* (sec prolonged): less than 4 sec = 1 point, 4 to 6 sec = 2 points, over 6 sec = 3 points

*Frequently INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7 to 2.2 = 2 points, INR above 2.2 = 3 points

The severity of cirrhosis:
- Child-Pugh A: 5 to 6 points
- Child-Pugh B: 7 to 9 points
- Child-Pugh C: 10 to 15 points

All the obtained parameters were tabulated in Microsoft excel. Clinical and psychometric analysis done was compared between these two groups in order to assess the difference in PHES to be considered as MHE. Then all the recruited patients were subjected for EEG. The findings were noted and tabulated in Microsoft Excel.

STATISTICAL METHODS:

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

The one-way analysis of variance (ANOVA) is employed to determine whether there are any statistically significant differences between the means of three or more independent (unrelated) groups.

RESULTS

The study was conducted at Raja Rajeswari Medical College and Hospital, on 70 patients after taking written consent from every patient. 70 healthy volunteers were recruited as controls in the study. The following results were observed.

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Average age of the recruited cases was 45.24±7.6 years and the controls were 47.38±5.2 years. Majority of the patients in cases were aged between 45 to 54 years about 32.9% (23/70) followed by 35 to 44 years 27.1% (19/70). 18 (25.7%), 8 (11.4%) and 2 (2.9%) were aged between 55- 64, 25 – 34 and 65 – 74 years respectively. There were 43 (61.4%) and 27 (38.6%) of the males and females present among the case group. Whereas 48 (68.6%) and 22 (31.4%) of the males and females participated in the study among control group.

35 (50%) patients had history of chronic alcoholism and 29 (40.8%) were chronic smokers. 9 (12.9%) patients had HbsAg positive. Whereas in the control group, 23 (31.9%) and 12 (17.1%) had history of alcoholism and smoking respectively.

The severity of CLD was classified based on the Child-Pugh grade. According to which we found 31 (44.3%), 25 (37.5%) and 14 (20%) were diagnosed with grade A, B and C grades. We found 9 patients from CPG A and C, 21 from CPG C were diagnosed with MHE (Table 1).

Table 1: Distribution of Child-Pugh grade in cases:

Grade	Number of patients	%	Patients with MHE
Child-Pugh grade A	31	44.3	9
Child-Pugh grade B	25	35.7	21
Child-Pugh grade C	14	20.0	9

In Table 1, We found 31 patients were in Child Grade A out of which 9 had features of MHE, 25 patients with child B grade among them 21 had features of MHE, 14 patients with grade C out of which 9 patients had features of MHE.

Table 2. Explains the distribution of severity of hepatic encephalopathy using west-haven criteria. We observed that, 39 (55.7%) were found to be to be grade 0 followed by 21 (30%) patients with grade 1. 8 patients (11.4%), 2 patients (2.9%) and 1 (1.4%) patient among the study population were belonged to grade 2, 3 and 4 respectively based on the observed signs and symptoms.

Table 2: West-Haven criteria among the cases

West-Haven criteria grading	N	%
0	39	55.7
1	21	30.0
2	8	11.4
3	2	2.9
4	1	1.4

The Standardized mini mental status examination among grade A, B and C was 22.61±12.54, 14.32±8.9 and 7.23±4.1 respectively. We observed that there was significant reduction in the SMMSE score as the severity of CLD increased.

Table 3: Comparison of various neuro psychometric scores (PHES) between cases and controls.
Time taken to complete the task is mentioned in seconds

Type of test	Cases	Controls	P value
NCT A	118±52.4	55±10.3	<0.001
NCT B	124±6.5	71±12.7	<0.001
Serial dot test	52±18.2	62±8.4	<0.001
Digital symbol test	113±29.4	90±5.9	<0.001
Line tracing test	82±5.9	59±3.7	<0.001

The average time taken for NCT A test was 118±52.4 and 55±10.3 seconds in cases and controls with significantly increased among cases (Table 3). The time taken to complete NCT B was 124±6.5 and 71±12.7 seconds respectively with significant difference of p value <0.001. The SDT, DST and LTT in cases was 52±18.2, 113±29.4 and 82±5.9 seconds. Among controls group it was 62±8.4, 90±5.9 and 59±3.7 seconds to complete SDT, DST and LTT respectively with significantly higher time in cases. The results were strikingly confirmed that patients with diagnosis of cirrhosis had abnormal test results compared to controls. It was alarming us bedside psychometric tests had significant application in diagnosis of symptomatic HE or MHE.

The distribution of outcome from the various neuropsychiatric tests based on the severity of CLD (Table 4). Time taken to complete NCT A test was 102±42.5, 128±34.6 and 131±27.9 seconds among Child-Pugh grade A, B and C respectively. 124±37.1, 139±10.2 and 139±12.7 seconds was the time taken to complete NCT B among Child-Pugh severity grade A, B and C groups respectively. The time taken to complete the SDT, DST and LTT in grade A of CLD was 45±2.9, 117±12.8 and 82±4.8 seconds. Whereas in Grade B was 49±8.5, 123±11.4 and 91±7 respectively.

Table 4: Correlation between Child-Pugh severity grade and psychometric analysis tests

Grading	NCT A In sec	NCT B In sec	Serial dot test In sec	Digital symbol test In sec	Line tracing test In sec
A	102±42.5	124±37.1	45±2.9	117±12.8	82±4.8
B	128±34.6	139±10.2	49±8.5	123±11.4	91±7
C	131±27.9	139±12.7	49±9.13	124±8.9	91±8.9
p value	<0.001	<0.001	0.015	<0.001	0.042

We found time taken in SDT, DST and LTT were 49±9.13, 124±8.9 and 91±8.9 seconds respectively. We observed that there was statistically significant association between the severity of CLD and the time taken to complete the tasks (Table 4). We found time taken to complete tasks were prolonged among cases group as progressive increase in severity of the disease.

Out of 38 patients with changes in their EEG, 23 (58.9%) of them had EEG changes among them slow wave pattern was observed among 12 (30.76%) of the population followed by theta waves among 7 (17.94%), delta wave 3 patients (13.4%) and one patient had triphasic wave pattern.

DISCUSSION

Hepatic encephalopathy (HE) is the complex and potentially reversible neuropsychiatric drome which is characterized by symptoms like somnolence, confusion, asterixis, extrapyramidal rigidity, convulsions and coma. This can be divided into two primary components: minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (OHE). MHE in patients with cirrhosis of liver could be defined by the presence of unexplained cognitive abnormalities which are detectable on psychometric or neurophysiological testing. There is lack of Indian clinal data about the EEG and neuropsychiatric tasks in MHE patients. There are also lack of studies evaluating bedside tests in diagnosing MHE. Hence, we had taken the study to analyse the prevalence of MHE using the neuropsychiatric tests. Also, we did analyse the EEG changes among these CLD patients with MHE.

In our study of 70 individuals in each group, comprising of patients with cirrhosis of liver and 70 in control groups. Among the cases group, patients were diagnosed as CLD based on clinical and ultrasound evidence. Both cases and the controls who included in the study, did not have psychiatric illness. In our study, the average age of the patients included in cases group was 45.24±7.6 years and the controls were 47.38±5.2 years. Average age of the patients with MHE was 49.43±10.2 years. Whereas the similar study by Bamidele O et al found that the average age of their study population was 47.1 ±14.6 years.[13] In the present study, there were 35 (50%) the patients presented with history of chronic alcoholism.

In the present study, disease severity of patients was classified based on the Child-Pugh grade. According to which we found 31 (44.3%) 25 (37.5%) and 14 (20%) were diagnosed with grade A, B and C type of CLD. 9 (23.07%) each from CPG A and C, 21 (53.84%) from CPG C in our study had diagnosed with MHE. Bamidele O et Al[13]., observed that 82.1% of the patients with MHE were belonged to Child-Pugh grade B and C. Out of 160 study population in Seo YS et al.,[14]129 (80.6%), 21 (13.1%), and 10 (6.3%) had Child-Pugh grades A, B, and C, respectively, MHE was diagnosed in 41 patients (25.6%), of which 26 (20.2%), 9 (42.9%), and six (60.0%) had Child-Pugh grades A, B, and C, respectively in their study.

We can observe that majority of the patients, 38 (54.28%) were found to be to be grade 0 of WHC followed by 21 (30%) patients with grade 1, 8 (11.4%), 2 (2.9%) and 1 (1.4%) of the study population were belong to grade 1, 2 and 3. This determines that the incidence of MHE in our study was 45.7%. In contrast to our findings, the reported incidence of MHE in by Bamidele O et al was 43.8%. Seo YS et al., in their study prevalence of MHE in their study was 25.6% only. Also, in Badea MA et al., in which the prevalence of MHE was 34.7% [15].

In our study, mini mental status examination among grade A, B and C was 22.61±12.54, 14.32±8.9 and 7.23±4.1 respectively. We can see that there was significant reduction in the SMMSE score as the severity of CLD increased.

In our study, we conducted various bed side psychometric tests (PHES), we observed the average time taken for NCT A test was 118±52.4 and 55±10.3 seconds in cases and controls with significantly increased among cases. The time taken to complete NCT B was 124±6.5 and 71±12.7 seconds respectively with significant difference of p value <0.001. The SDT, DST and LTT in cases was 92±18.2, 113±29.4 and 82±5.9 seconds. Also, the controls took 62±8.4, 90±5.9 and 59±3.7 seconds to complete SDT, DST and LTT respectively with significantly higher time in cases. The results were strikingly confirmed that patients with diagnosis of cirrhosis had abnormal tests results compared to controls. Which showed us bedside psychometric tests had significant application in diagnosis of symptomatic HE or MHE.

Bamidele O et al[13] in their study also observed the similar findings. They had divided the patients based on the time taken for completion of the tasks <93 seconds and >93 seconds. They found that the patients with MHE had taken significantly higher time to complete the given tasks. They also observed that 11/64 individuals spent more than 240 seconds to complete the LTT and also had constructional dyspraxia. In the present study, out of 23 patients with changes in their EEG, slow wave pattern was observed among 12 (52.17%) of the population followed by theta waves among 7(30.4%). 3 (13.07%) and 1 (4.34%) patient had delta wave pattern and triphasic wave pattern respectively. Study by Alemam AI et[16] reported 23.5% showed theta waves and 9.8% showed delta among their patients with HE. We found time taken to complete tasks were prolonged among cases group as progressive increase in severity of the disease.

CONCLUSION
The incidence of MHE was 38% in our study with male predominance. Severity of HE increased with increase in Child-Pugh grade but did not have significant association. In our bedside tests PHES, Time taken to complete NCT, DCT and line drawing tests were significantly higher among MHE patients compared to the normal individuals. Also, there was significantly elevated liver enzymes and ammonia among MHE. Increase in these parameters had positive association with the severity of the HE. Also, 12 patients (30.76%) among the study population with MHE had slow wave pattern of EEG, followed by theta waves among 7 (17.94%). 3 (7.7%) and one patient had delta wave pattern and triphasic wave pattern respectively. Routine bedside tests among patients with cirrhosis of liver helps in early diagnosis and treatment of hepatic encephalopathy. Development of life threatening complications such as hepatic coma cerebral edema, prolonged hospitalization and ICU stay can be avoided among these patients. These bedside tests should keep alert physicians to prevent overt hepatic encephalopathy.

LIMITATIONS OF THE STUDY
Single centre study. Study should be done with bigger sample size.

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