

Slowing of Alpha Waves on EEG, an Early Marker of Minimal Hepatic Encephalopathy

Nikhilkumar Pradipkumar Patel^{1*}, Neelima Deodatta Chafekar² and Pratibha Balasaheb Sonwane³

¹PG Student, Department of Medicine, Dr. Vasantrao Pawar Medical College Hospital and Research Centre, Adgaon - 422003, Nashik, Maharashtra, India; drnikhil1991@gmail.com

²Professor and Head, Department of Medicine, Dr. Vasantrao Pawar Medical College Hospital and Research Centre, Adgaon - 422003, Nashik, Maharashtra, India; neelimachafekar@yahoo.com

³Assistant Professor, Department of Medicine, Dr. Vasantrao Pawar Medical College Hospital and Research Centre, Adgaon - 422003, Nashik, Maharashtra, India; pratibhasonwane@gmail.com

Abstract

Introduction: Minimal Hepatic Encephalopathy (MHE) is the mildest form of spectrum of Hepatic Encephalopathy (HE) which remains undiagnosed due to lack of awareness. MHE has a negative effect on patient's daily functioning due to cognitive impairment. Electro-Encephalo-Gram (EEG) and Mini Mental State Examination (MMSE) are useful in early diagnosis and follow up of MHE. **Aim:** To study evidence of MHE in patients with liver cirrhosis by psychometric tests and also its correlation with EEG changes. **Materials and Methods:** The study was carried out as a prospective case control study of 70 patients diagnosed with Cirrhosis of liver, over a period of two years in accordance with European Association for the Study of the Liver (EASL) and Asociacion Latinoamericana para el Estudio del Hígado (ALEH) criteria with MMSE score >24 and were diagnosed as Minimal Hepatic Encephalopathy if 2 out of 3 psychometric tests were abnormal EEG was performed in them and was compared with 70 healthy controls. **Results:** Study showed male predominance (90%) with mean age of 45.49 ± 11.76 . Alcohol related cirrhosis (70%) was found to be more common than HBV (8.57%) and HCV (2.86%) infection related cirrhosis. Pedal edema, icterus, pallor and ascites were the most common presenting manifestations. Most cirrhotic cases (80%) were under Child Pugh Class-A. On USG of abdomen all cases had Coarse echotexture and nodular surface of liver among them 11 cases had Hepatomegaly, 10 cases had splenomegaly, 42 cases had ascites and 24 cases had increased portal venous diameter of mean size 14.02 ± 0.48 mm. MMSE score of all selected cirrhotic cases was >24. Psychometric Tests i.e. Number Connection Test-A, Number Connection Test-B and Line tracing test were performed in all selected cirrhotic cases and they were not able to perform it within designated time. All cases were subjected to EEG and compared with equal number of comparable healthy controls, which shows change in frequency and amplitude of Alpha wave which was highly significant whereas no significant changes of frequency and amplitude of Beta, Theta and Delta waves between cases and controls. **Conclusion:** There is significant changes in alpha wave frequency and amplitude in patients with minimal hepatic encephalopathy.

Keywords: Cirrhosis, Electro-Encephalo-Gram (EEG), Minimal hepatic encephalopathy, Psychometric Test

1. Introduction

Hepatic encephalopathy is a major complication that develops in some for mandate some stage in a majority of patients with liver cirrhosis. 30 to 45% of cirrhotic patients progress to overt hepatic encephalopathy^{1,2}.

Minimal Hepatic encephalopathy (MHE) is the mildest form of spectrum of Hepatic encephalopathy (HE). But most of the times they remain undiagnosed due to lack of awareness of MHE among the physicians. MHE was recognized as a clinical entity in the 1970's by hepatologists who were working on Hepatic encephalopathy. Different

*Author for correspondence

studies show that MHE can be prevalent from a range of 30% to 84% in cirrhotic patients^{3,4}. Subclinical cognitive alterations in cirrhotic patients could have prognostic value on survival in the first year of follow-up⁵. MHE has a negative effect on patient's daily functioning⁶. The West Haven criteria^{7,8} classify the degree of mental status disturbance in encephalopathy which range from reversal of sleep patterns with mild alteration in cognition to deep coma. Grade 0 of the West Haven criteria corresponds to minimal hepatic encephalopathy.

The progression of MHE into overt HE has increased risk, requiring hospitalization and overall mortality of patients. Accurate assessment of MHE can help to treat them at an earlier stage, thus improving the quality and effectiveness of treatment for them. The overall awareness of MHE among medical practitioners is 75%. Physicians who screen for MHE are only 6.3%⁹. Due to psychomotor impairment, there is impairment of performances that requires attention, judgement, vigilance, co-ordination and quicker flexes actions. Studies showed that working on harmful machines, driving a car and other tasks which require attention and vigilance are affected in MHE patients. MHE patients have higher occurrence of falls, Injuries and accidents while driving, appropriate counseling of the MHE patients should be done. Hence, to avoid this, screening and early diagnosis of all patients with cirrhosis for MHE and treatment of those patients diagnosed to have MHE has been recommended. It presented as a condition in cirrhotic patients who were normal on clinical examination but had alterations either in EEG or simple neuropsychiatric tests. In spite of exhaustive research to have an optimal approach towards MHE patients, there is no gold standard or criteria which had been defined. Various methods have been used to diagnose MHE, these range from visual and automated EEG analysis, visually evoked potentials, single paper-pencil tests like the Number Connection Tests, batteries of paper-pencil tests (e.g. PSE-Syndrome-Test, Repeatable Battery for the Assessment of Neuropsychological Status – RBANS), computer-based tests (like the Inhibitory Control Test-ICT, Continuous Reaction Time Test (CRT) or Stroop Test) or test batteries such as the Cognitive Drug Research test battery, and a psychophysiological measure, the Critical Flicker Frequency (CFF). A combination of these investigations and tests have helped used fine and identify patients with MHE. There are very few studies on correlation of MHE with EEG changes, so we

planned the present study to see evidence of minimal hepatic encephalopathy in patients with liver cirrhosis by psychometric tests and correlation of Minimal Hepatic Encephalopathy with EEG changes.

2. Materials and Methods

The present study was conducted in the Department of Medicine, in Tertiary Care Teaching Hospital from August 2015 to December 2017. 70 patients, including 63 males and 7 females were recruited in our study. Cirrhotic patients diagnosed in accordance with EASL and ALEH criteria¹⁰ admitted because of complications other than hepatic encephalopathy and fitting into the criteria of MHE^{8,11,12} were included in our study. Cirrhotic patients already in overt hepatic encephalopathy and with any other neurologic abnormality affecting cognition and condition causing tremors were excluded. Patients of cirrhosis who have other comorbid factors contributing to encephalopathy were excluded. We evaluated all study participants with MMSE and patients with MMSE>24 performed psychometric tests i.e. NCT-A, NCT-B and LTT. If 2 of these 3 tests are abnormal then they are diagnosed as MHE and then EEG was performed and compared with 70 healthy controls. EEG analysis was done in awake subjects with both eyes open and eyes closed states, at least 3 min in each state using a digital EEG equipment (RMS EEG 24 Brain View Plus, Chandigarh) and the International 10-20 scalp electrode placement system approved by International Federation of Societies for EEG and Clinical Neurophysiology (IFSECN; Jasper 1958) Recorded for at least 30 minutes. All total 24 scalp electrodes were used including the two ear electrodes, the reference electrode (at nasion) and the ground. EEG recorded in three montages, 2 bipolar and one unipolar with 16-18 channels. The filter range was 1-70Hz. After data collection, it was analyzed using Microsoft office excel 2007.

3. Results

The mean age group in the study group was 45.49 +/- 11.76 with minimum age of 25 years and maximum age of 76 years. Of these majority were in 41-50 years group whereas as only 2 cases had age >71 years. Out of 70 cases in study population 63 patients that is 90% were male and 7 cases that is 10% were females. Most common cause

was alcohol related contributing 49 cases out of 70 that is 70% with the mean age of 46.43 ± 11.57 whereas HBV related were 6 cases that is 8.57% with the mean age of 46.67 ± 10.23 and HCV related were 2 cases that is 2.86% with the mean age of 41.00 ± 12.73 and others in which cause was not found were 17 that is 24.29% with the mean age of 43.00 ± 12.72 . Bilateral pedal edema was found in majority in 49 cases that is in 70% followed by icterus and pallor in 44 cases that is 62.86%. Gynaecomastia saw only in 4 patients (i.e. 5.71%), testicular atrophy in 3 patients (i.e. 4.29%) whereas Dupuytren's contracture seen in 1 patient only (i.e. 1.43%) and no one had flapping tremors. Out of 70 cases in study population, 56 cases (i.e. 80%) were in Child-Pugh class A; 12 cases (i.e. 17.14%) were in Child-Pugh class B and 2(2.86%) in Child-Pugh class C.

All cases had coarse echotexture and nodular surface of liver among them 11 cases (i.e. 15.71%) had Hepatomegaly with *meansize* > 17.23cm, 10 cases (i.e. 14.28%) had splenomegaly with *meansize* > 13.75cm, 42 cases (i.e. 60%) had ascites and 24 cases (i.e. 34.28%) had increased portal venous diameter.

Table 1. Mean MMSE score in CPC-A, CPC-B, CPC-C and of all 70 patients

CPC	Mean Score
CPC-A	28.73
CPC-B	28.17
CPC-C	27.00
MMSE score (Mean $\pm$ SD)	28.59 $\pm$ 0.99

All the cases had MMSE score more than 24. Mean score in CPC-A was 28.73 in CPC-B was 28.17 and in CPC-C was 27 and overall mean of 70 patients was 28.59 $\pm$ 0.99 (Table 1).

Table 2. Time (in minutes) required to complete NCT-A, NCT-B

Time (min.)	NCT-A (No. of cases)	NCT-A (%)	NCT-B (No. of cases)	NCT-B (%)
2-3	18	25.71	10	14.28
4-5	36	51.42	29	41.42
5-7	16	22.85	25	35.71
>7	0	0	6	8.57

Maximum time required in NCT-A was 5-7 minutes whereas in NCT-B was >7 minutes. Maximum number

of cases that is 36 (51.42%) took 4-5 minute to complete the NCT-A similarly maximum number of patients that is 29 (41.42%) took 4-5 minute to complete the NCT-B (Table 2).

Table 3. Time required completing NCT-A according to CPC

CPC	Mean $\pm$ SD	Range
CPC-A	4.38 $\pm$ 1.36	2-7
CPC-B	5.08 $\pm$ 1.16	3-7
CPC-C	6.00	6

Table 4. Time required complete NCT-B according to CPC

CPC	Mean $\pm$ SD	Range
CPC-A	5.00 $\pm$ 1.55	2-8
CPC-B	5.92 $\pm$ 1.08	4-8
CPC-C	8.00	8

Cases in CPC-A completed the NCT-A in 4.38 ± 1.36 min (*mean value*) and NCT-B in 5.00 ± 1.55 mins (*mean value*). Whereas cases in CPC-C completed the NCT-A in 6 min (*mean value*) and NCT-B in 8 mins (*mean value*). Thus, the *mean time* for NCT-A and NCT-B is in increasing trend with CPC (Table 3&4).

Table 5. Number of errors made while performing Line Tracing Test

No. of errors	No. of cases	No. of cases (%)
0	5	7.14
1	6	8.57
2	6	8.57
3	15	21.42
4	20	28.57
5	11	15.71
6	7	10

Maximum numbers of errors in Line Tracing Test were 6 made by only 7 cases (i.e. 10%). Maximum number of cases that is 20 (i.e. 28.57%) have made 4 errors. 6 cases (i.e. 8.57%) have made only 1 error and 7 cases (i.e. 10%) have made 6 errors which is maximum. There are 5 cases that have made no error while performing LTT (Table 5). So, there were 65 cases that were not able to perform all 3 Psychometric tests whereas 5 cases were not able to perform 2 out of 3 psychometric tests.

Table 6. Mean number of errors in Line Tracing Test according to CPC

CPC	Mean $\pm$ SD	Range
CPC-A	3.18 $\pm$ 1.70	0-6
CPC-B	4.17 $\pm$ 0.83	3-6
CPC-C	6.00	6

Patients with CPC-A have made minimum errors with mean 3.18 and patients with CPC-C have made maximum errors with mean 6. Thus, the *number of errors* in Line tracing test is in increasing trend with CPC (Table 6). We have compared two groups that is study group & control group which are comparable to each other with age and sex and then evaluated for the presence EEG changes.

Mean frequency of Alpha wave in cases was 10.60 $\pm$ 1.59 in comparison with controls in which mean frequency was 11.61 $\pm$ 1.03 with p value <0.001 that is change in frequency of Alpha wave in cases is highly significant. Mean amplitude of Alpha wave in cases is 35.43 $\pm$ 19.18 in comparison with controls in which mean amplitude is 48.24 $\pm$ 7.26 with p value <0.001 that is change in amplitude of Alpha wave in cases is highly significant. There were no significant changes of frequency and amplitude of Beta, Theta and Delta waves between cases and controls (Table 7).

4. Discussion

In our study, there was significant Male preponderance i.e. 90% which correlates with available literature^{13,14}. Male preponderance found in the present study may be due to preferential drinking habit in males compared to females in this part of the country¹⁵. Mean age of cirrhotic patients

in present study was 45.49 $\pm$ 11.76 years^{13,14}. There were fewer patients older than 60 years in this study, who could show the effect of age on MHE prevalence. In the present study alcohol, related cirrhosis was found to be more common than HBV & HCV infection related cirrhosis^{16,17}. The current prevalence of alcohol abuse in India is 21.4% as per National Survey 2004¹⁸. Pedal edema (70%), Icterus (62.86%), ascites (60%) & anemia (62.86%) being most common presenting manifestations. Other physical signs of hepatic cell failure like spider angiomas, white nails, testicular atrophy, etc which were expected to be present in such cases of cirrhosis were observed infrequently and mere absence of those signs did not exclude cases of cirrhosis¹⁹. In present study we found parotid enlargement 48.57% cases, whereas¹⁹ found it to be present only in 1.2% which were due to alcohol related cirrhosis cases were more in present study. In present study, we found that 80% patients were of CPC-A class and 17.14% were of CPC-B and only 2.86% patients were of CPC-C class. In present study, we had 80% cases of CPC-A which means patients with a good liver function, which is similar to study²⁰ in which they found 71% cases of CPC-A (a good liver function). In our study, most of our patients were CPC grade A which supports the lower grade of CPC correlated with lesser level of encephalopathy. MHE and higher CPC scores were associated with a high health-related quality of life (HRQoL) scores (reflecting poorer quality of life). In present study, we found 12.86% cases with esophageal varices all cases were in CPC-B and CPC-C²¹. In present study MMSE score was 28.59 $\pm$ 0.99²². The prevalence of MHE in cirrhosis depends on the kind and number of tests used and the population tested^{23,20}. In this study, we have used at least 2 abnormal psychometric tests out of 3 for diagnosis of MHE^{7,8,11,24}. Taken two abnormal psychometric test^{6,20} result and/or abnormal

Table 7. Comparison of EEG waves between cases and controls

		Cases (n=70) Mean $\pm$ SD	Control (n=70) Mean $\pm$ SD	p-value
Alpha activity	Frequency (Hz)	10.60 $\pm$ 1.59	11.61 $\pm$ 1.03	0.000
	Amplitude (mV)	35.43 $\pm$ 19.18	48.24 $\pm$ 7.26	0.000
Beta activity	Frequency (Hz)	15.37 $\pm$ 1.46	15.40 $\pm$ 1.41	0.906
	Amplitude (mV)	9.01 $\pm$ 1.01	9.09 $\pm$ 1.03	0.680
Theta activity	Frequency (Hz)	5.77 $\pm$ 1.30	5.83 $\pm$ 1.32	0.797
	Amplitude (mV)	10.24 $\pm$ 0.67	10.03 $\pm$ 0.74	0.075
Delta activity	Frequency (Hz)	3.07 $\pm$ 0.92	3.06 $\pm$ 0.90	0.926
	Amplitude (mV)	53.86 $\pm$ 9.64	53.34 $\pm$ 7.86	0.730

slowing of EEG. Considered one abnormal psychometric test^{13,25} result. Severity of liver disease correlated with the presence of MHE²⁰. Similarly, in our study as severity of liver disease increases indicated by CPC score, time required to perform psychometric test also increases. In our study, we compared frequencies and amplitude of waves in cases and controls. The change in frequency of alpha waves was found to be statistically significant in our study. This shows direct correlation that alpha waves show slowing of frequency in MHE patients. We applied the independent t test to our data for this analysis. These finding is similar to²⁶ which showed low frequency alpha rhythm. Also was showing²⁷ alpha rhythm which was disturbed by random waves at 5-7 per sec. The EEG could be still used for follow up examination and monitoring and estimation of prognosis²⁸. Strength the study is, to our knowledge, we first time observed slowing of alpha waves as early indicator of MHE and correlated EEG with MHE in Indian population at a tertiary care hospital. Limitation of study was wide geographic coverage was not possible due to feasibility. Future study can explore the management and effect of early diagnosis related to MHE in specific work population.

5. Conclusion

For diagnosis of MHE, significant reduction in at least two of batteries of psychometric tests can be used. The slowing of alpha waves in EEG is seen in early MHE which may be used as supportive evidence as well as for monitoring and prognosis of the MHE.

6. References

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