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ORIGINAL ARTICLE

MINIMAL HEPATIC ENCEPHALOPATHY IN ALCOHOLIC CIRRHOSIS

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ABSTRACT: BACKGROUND: Minimal hepatic Encephalopathy (MHE) has severe and important health implications which affects the quality of life as well as the survival of patients with liver disease. Psychometric hepatic encephalopathy score (PHES) has been validated for diagnosis of MHE. **AIM OF THE STUDY:** To detect the prevalence of minimal hepatic encephalopathy (MHE) in alcoholic cirrhosis patients and to compare the patterns of alcohol consumption in patients with MHE to those without MHE (NON-MHE). **SETTINGS AND DESIGN:** The study was conducted in Chettinad Hospital and Research Institute, Kelambakkam, a 1000 bedded academic medical centre in South India. This was a prospective observational study. **MATERIALS AND METHODS:** 25 alcoholic cirrhotic patients without overt hepatic encephalopathy and 20 patients who are alcoholics without any liver disease were given the five tests of PHES (Number connection test A (NCT-A), Figure connection test (FCT), Line Tracing Test (LTT), Circle Dotting Test (CDT) and Digit Symbol Test (DST)) in a quiet well lit room. Individual performance test values more than 1 S.D from the mean were considered abnormal. Based on the nomogram of healthy volunteers, the patients were classified as having MHE when they had impaired performance in ≥2 tests. **RESULTS:** There was no significant difference in the baseline characteristics between the two groups. In liver cirrhosis patients, MHE was diagnosed in 7 patients (28%). In NCT-A 28% (n=7) did abnormally, in FCT 16% (n=4), in LTT, CDT and DST 24% (n=6), 12% (n=3), 24% (n=6) respectively had impaired performance. NCT-A and LTT showed statistically significant difference between the study group. Hence these 2 tests were considered to have high sensitivity for screening of MHE (p-0.003, p-0.004). The proportion of patients with MHE increased as the duration of alcohol consumption increased. 73.3% of those with MHE had more than 10 years of alcohol consumption. **CONCLUSION:** The prevalence of MHE in alcoholic cirrhosis in our population was 28% which is close to that reported from other populations. Age and education had major influence on the overall test performance and it needs to be taken into consideration while interpretation of test results. The greater the duration of alcohol intake there was an increase in the occurrence of Minimal hepatic encephalopathy. Those even with harmful drinking pattern for longer duration are prone to develop DCLD and complications of hepatic encephalopathy.

KEYWORDS: MHE, PHES, Minimal Hepatic Encephalopathy, Psychometric Hepatic Encephalopathy Score, Alcoholic cirrhosis, Cognitive impairment.

INTRODUCTION: Alcohol is one of the leading causes of morbidity and mortality. Globally, two billion people worldwide consume alcohol and one-third (Nearly 76.3 million) is likely to have one or more alcohol use disorders[1] Alcoholic liver disease affects 1 million population worldwide.[2] It encompasses a spectrum of disorders ranging from mild deterioration in liver function as in fatty liver to hepatitis and cirrhosis both compensated and decompensated stages. Chronic liver disease and its complications have a great impact on the quality of life and also cause a significant economic burden on the family and the community.

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Hepatic encephalopathy constitutes one of the most important complications and a marker of survival among patients with cirrhosis. Minimal hepatic encephalopathy (MHE) although a part of the spectrum of hepatic encephalopathy (HE) does not manifest clinically and does not show any obvious signs. The prevalence of MHE has been estimated to be between 20% and 74% in the previous studies.[3] According to the West- Haven criteria MHE belongs to the stage O where there is no clinical sings of overt encephalopathy HE but exhibit cognitive dysfunction and trivial lack of awareness.[4] Cognitive dysfunction includes attention deficit, working memory problems and decreased speed of processing. They also exhibited impairment in quality of life like social interaction, alertness, sleep, recreation and emotional behavior[5] as assessed by the questionnaire for quality of life.

MHE adversely affects driving abilities with impaired navigation skills and response inhibition resulting in increased road traffic accidents.[6] So the prompt recognition of these subtle changes becomes extremely important for drivers, pilots and other professionals who are involved in the safety of other people. Psychometric hepatic encephalopathy scoring (PHES) includes a battery of tests recommended by the working group on hepatic encephalopathy for the diagnosis of MHE. It is also associated with the risk of overt hepatic encephalopathy and death, if untreated. The present study was undertaken to identify the prevalence of MHE among the cirrhosis patients in our population and to identify the factors associated with MHE.

PATIENT SELECTION: All sequentially encountered alcoholic male patients between 20 and 50 years without overt hepatic encephalopathy were screened for MHE. We recruited a total of 45 cases which included 20 patients who are alcoholics with AUDIT score (Alcohol Use Disorders Identification Test) ≥ 8 without any evidence of liver disease and 25 patients of alcoholic cirrhosis confirmed by clinical, laboratory and sonographic evidence. Those who can identify numbers, those who have not abstained from alcohol but not under the influence of alcohol at the time of examination are included.

Those in the same age group (20-50 yrs), of same economic and social background, who have not consumed alcohol, will form the control group.

Exclusion Criteria: Patients with visual disturbances and those who cannot identify numbers, patients under the influence of alcohol and those in withdrawal state at the time of examination, those with symptoms and signs of encephalopathy or previous history of hepatic encephalopathy, those with coexisting Viral hepatitis, Renal impairment significant enough to affect his mental status (creatinine>1.5), electrolyte abnormalities, concomitant neurological or other psychiatric disorders and use of drugs acting on CNS. All patients gave written informed consent. Study protocols were approved by the ethics committees in accordance with the Principles of Declaration of Helsinki.

METHODOLOGY: Physical examination, laboratory testing, and medical history documentation.

We documented careful medical history which included the Basic demographic data - the age of the patient, educational status, occupation, duration of alcohol consumption. These patients were then assessed for the mental status by Mini Mental State Examination (MMSE) questionnaire (Table 1). Maximum score is 30; 20-25 – possible impairment; <20-definitive impairment. Anybody who scores more than 25 were considered to have a normal mental status i.e., no overt encephalopathy and those patients were subjected for further evaluation.

The severity of alcohol consumption was also assessed using AUDIT questionnaire (Alcohol Use and Disorders Identification Disorder Test) Table 2 and were graded into harmful, Hazardous and alcohol Dependence.

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MINI MENTAL STATE EXAMINATION SCORE (MMSE)	Points
Orientation	
Name: season/date/day/month/year	5 (1 for each name)
Name: hospital/floor/town/state/country	5 (1 for each name)
Registration	
Identify three objects by name and ask patient to repeat	3 (1 for each object)
Attention and calculation	
Serial 7s; subtract from 100 (e.g., 93–86–79–72–65)	5 (1 for each subtraction)
Recall	
Recall the three objects presented earlier	3 (1 for each object)
Language	
Name pencil and watch	2 (1 for each object)
Follow a 3-step command (e.g., "Take this paper, fold it in half, and place it on the table")	3 (1 for each command)
Write "close your eyes" and ask patient to obey written command	2
Ask patient to write a sentence	1
Ask patient to copy a design (e.g., intersecting pentagons)	1
Total	**30**

TABLE 1

A Score of > 25 is considered as normal.

AUDIT QUESTIONNAIRE (Table 2):

1. How often do you have a drink containing alcohol?
□Never □Monthly or less □2□4 times a month □2□3 times a week □4 or more times a week.

2. How many standard drinks containing alcohol do you have on a typical day when drinking?
□1 or 2 □3 or 4 □5 or 6 □7 to 9 □10 or more.

3. How often do you have six or more drinks on one occasion?
□Never □Less than monthly □Monthly □Weekly □Daily or almost daily.

4. During the past year, how often have you found that you were not able to stop drinking once you had started?
□Never □Less than monthly □Monthly □Weekly □Daily or almost daily.

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5. During the past year, how often have you failed to do what was normally expected of you because of drinking?
Never Less than monthly Monthly Weekly Daily or almost daily.

6. During the past year, how often have you needed a drink in the morning to get yourself going after a heavy drinking session?
Never Less than monthly Monthly Weekly Daily or almost daily.

7. During the past year, how often have you had a feeling of guilt or remorse after drinking?
Never Less than monthly Monthly Weekly Daily or almost daily.

8. During the past year, have you been unable to remember what happened the night before because you had been drinking?
Never Less than monthly Monthly Weekly Daily or almost daily.

9. Have you or someone else been injured as a result of your drinking?
No.
Yes, but not in the past year.
Yes, during the past year.

10. Has a relative or friend, doctor or other health worker been concerned about your drinking or suggested you cut down?
No.
Yes, but not in the past year.
Yes, during the past year.

For questions 9 and 10, which only have three responses, the scoring is 0, 2 and 4.

A score of 8 or more is associated with harmful or hazardous drinking, a score of 13 or more in women, and 15 or more in men, is likely to indicate alcohol dependence.

Further physical examinations and laboratory assessments that included biochemical tests (alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, Blood urea Nitrogen, serum creatinine, prothrombin time, serum potassium, serum sodium, virological tests [hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), and diagnostic imaging (ultrasonography) were done to assess the etiology and severity of cirrhosis.

The presence of Minimal Hepatic Encephalopathy was assessed using a pencil-paper battery of tests namely 1. Number connection Test (NCT 2). Figure connection test (FCT) 3. Line Tracing Test (LTT) 4. Circle Dotting Test (CDT) 5. Digit Symbol Test (DST).

1. **NUMBER CONNECTION TEST (NCT A):** In the NCT A (Fig. 1), which measures cognitive motor abilities, patients connect numbers from 1 to 25 printed on paper as quickly as possible. The time taken by the subject to complete the test is recorded in seconds. It assesses psychomotor speed, efficiency of visual scanning, sequencing, attention and concentration.

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2. **FIGURE CONNECTION TEST (FCT):** FCT (Fig. 2) although similar to NCT, the numbers are replaced by figures. Each circle has one to five motifs, thus giving the required 25 figures. In FCT A, all circles with the same motif are connected in the order of increasing numbers of motifs and in sequences specified in the chart. It overcomes linguistic and educational barriers. It assesses Visual perception, visual scanning efficiency, psychomotor speed, attention, concentration and working memory. This modification is as per the example provided by Dr. Radha K. Dhiman, Additional Professor, Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh, India. Department of Hepatology, PGI Chandigarh.

3. **LINE TRACING TEST:** The line drawing test (Fig. 3) tests motor speed and accuracy. The patients have to follow the route of this labyrinth without crossing or even touching the borderlines. The time taken to complete is recorded in seconds. If any patient performs grossly abnormally by crossing the boundaries of the labyrinth, it was taken as abnormal even though if it was performed in less time. The whole route is divided into small sections and each touching or crossing the border was counted and if more than 5 times the test was considered to be abnormal.

4. **CIRCLE DOTTING TEST (CDT):** This is the simplest of the tests and involves serially dotting the 50 circles after the patient initially prepares by dotting in the top 20 circles. It measures the motor speed. (Fig. 4).

5. **DIGIT SYMBOL TEST:** The Digit Symbol test (DST) (Fig. 5) the subject is given nine fixed pairs of numbers and symbols at the top of the test sheet and a series of double-boxes with only the number in the upper part of the box. The task is to draw a symbol pertinent to this number into the lower part of the boxes. Test result is the time taken to complete the two rows. It assesses working memory, associative learning, graphomotor speed, cognitive speed and visual perception.

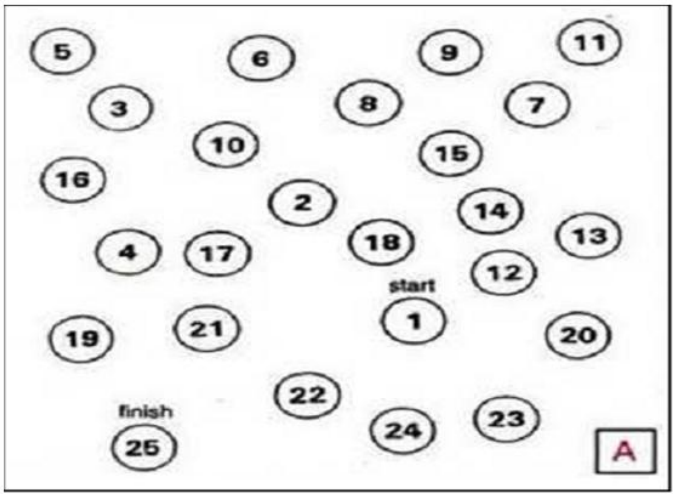

Fig. 1: NUMBER CONNECTION TEST (NCT)

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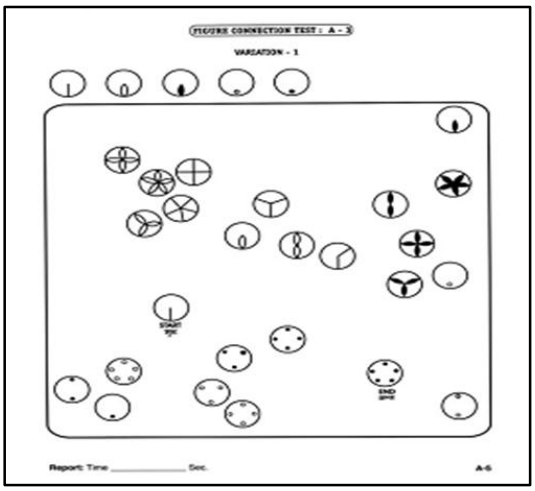

Fig. 2: Figure connection test

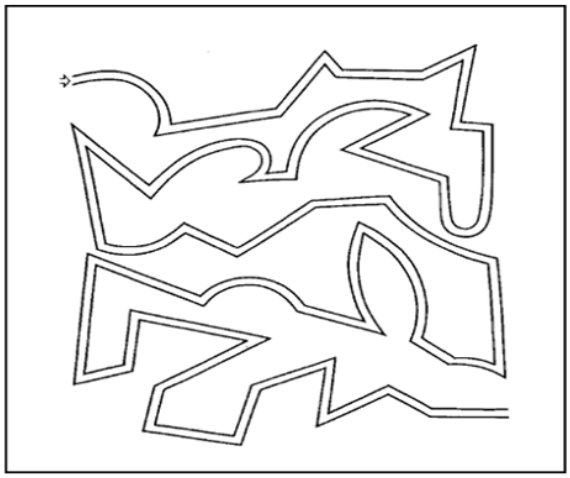

Fig. 3: line tracing test

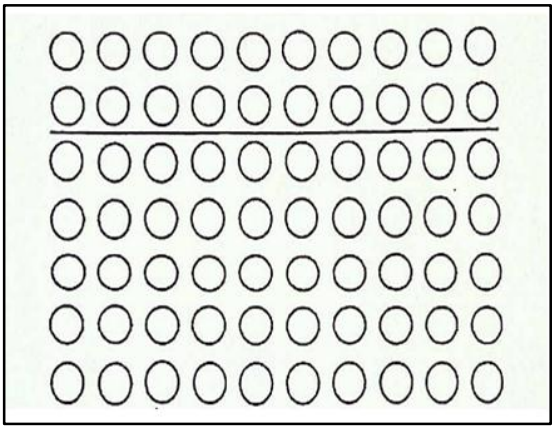

Fig. 4: Circle dotting test

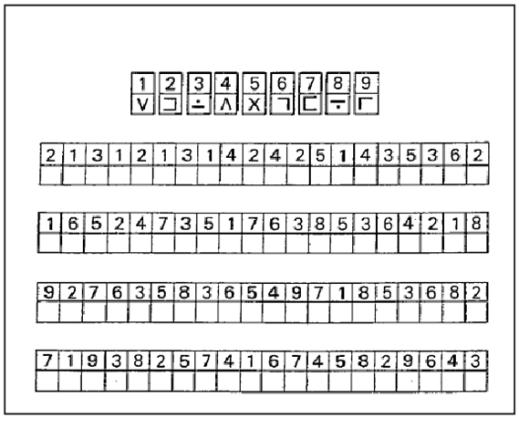

Fig. 5: Digit Symbol Test

Minimal HE (MHE), the mildest form of HE[7,8] is defined as patients with normal mental and neurological examinations and impairment of performance in any of the 2 tests when compared to the control performance (in seconds) required completing each of the test.[9,10] The controls were taken from the same educational and geographical back ground. In our study; those who performed with values beyond 1 S. D from the mean were considered as abnormal which improved the sensitivity. Despite the limitations like lack of representative normative data for the study sample, influence of age, education, socio - cultural back ground, the advantage of low cost, high sensitivity, specificity and simplicity these tests can be used even at the primary health care levels for detection of MHE.

STATISTICAL ANALYSIS: Continuous variables were expressed as mean±SD or median (range), wherever appropriate. Categorical variables were described as the number and proportion of each category. In order to determine relevant risk factors for MHE, characteristics such as age, education, pre-existing ascites, variceal bleeding, occupation, driving, duration and severity of alcohol drinking according to AUDIT questionnaire, were included in the univariate analysis. The $\chi 2$ or Fisher's exact

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test was used for categorical variables, and the Mann-Whitney U test or analysis of variance (ANOVA), was performed as appropriate to determine associations for continuous data. Pearsons scoring was used to assess the effect of age and education on the influence of the test results. All tested variables with P values < 0.05 were considered significant. Software used for analysis was Statistical Package for Social Science (SPSS, version 11.0).

OBSERVATIONS AND RESULTS: Forty five patients (20 alcoholics and 25 alcoholic cirrhotics), recruited over a period of 6 months were analysed for the following data. Demographic Data. 1. Age 2. Educational status. 3. Duration of alcohol abuse. 4. AUDIT score Clinical assessment. 1. Number connection test (NCT). 2. Figure connection test (FCT). 3. Line tracing test (LTT). 4. Circle dotting test (CDT). 5. Digit symbol test (DST).

BASELINE CHARACTERISTICS: Included patients were diagnosed with decompensated liver cirrhosis (DCLD) (n=25) and no liver disease (n=20) with etiology being alcohol. All the other category cirrhosis was excluded. About 17.8% belonged to less than 30 years of age, 35.6% between31-40 and 46.7% were more than 40 years of age. Majority of those in the both the study groups (50.7% and 48.8%) had < 5 years of education.

DURATION AND SEVERITY OF ALCOHOL CONSUMPTION: In the DCLD group, 76% consumed alcohol for more than 10years, 24% between 6-10 years. Among the patients without liver disease 35% consumed more than 10 years with 30% in the 6-10 years and 35% had less than 5 years of alcohol consumption. Assessing the severity of alcohol consumption using the AUDIT score revealed 64% and 75% had harmful drinking patterns in DCLD and no liver disease categories respectively, while majority of the people in the alcohol dependence categories belonged to DCLD group.

Chart 1: Relation between type of Liver Disease and Duration of Alcohol Consumption.

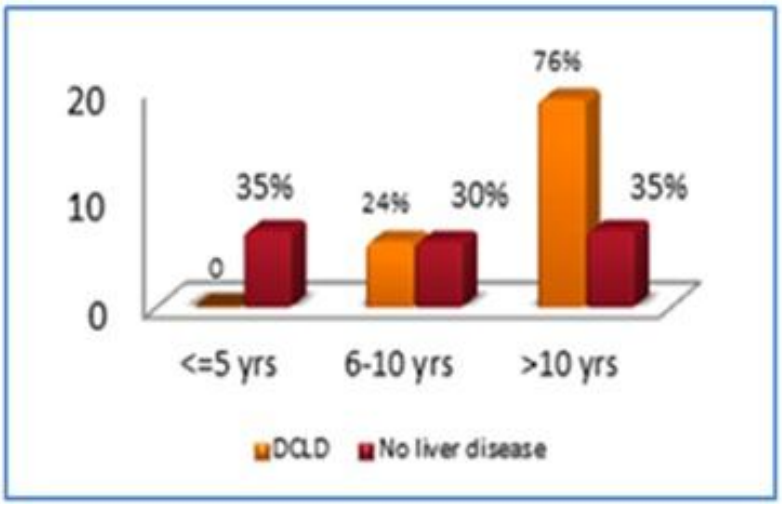

Chart 1

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Chart 2: Audit score VS type of liver disease.

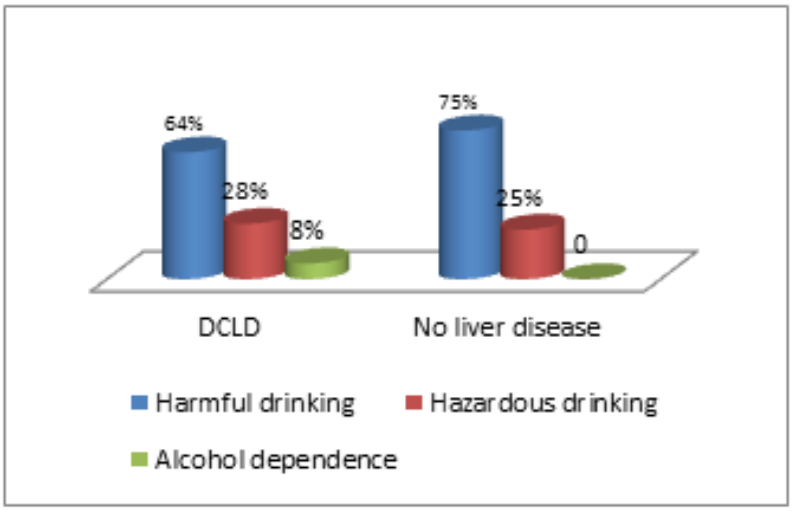

Chart 2

PSYCHOMETRIC HEPATIC ENCEPHALOPATHY SCORE: The median time taken by the two groups of patients (DCLD and No liver disease) in performing the five tests of Psychometric hepatic encephalopathy score has been summarized in the following table (Table 3).

Tests	DCLD(in seconds)	ALCOHOLICS
NCT A	149 ± 52.2	114.5±40.5
FCT	145.16±76.6	113 ± 38.2
LTT	165.3±43.4	127± 44.2
CDT	115.2±45.8	86.3±49
DST	170.96±62.9	157.6±78

TABLE 3: Time taken (in sec) to complete each of the five tests

This table clearly indicates that the median time taken by the patients with DCLD was significantly higher in all the tests while comparing to patients without liver disease.

The number connection test (NCT A) and the Line tracing test (LTT) showed statistically significant difference in the test values (p=0.003) and (p=0.006) respectively between the 2 groups. Although the other tests did not show statistical significance, there was a comparative increase in the time taken to complete the psychometric analysis between the two groups. Comparing to the normative data obtained from the performance of the 25 normal people who never consumed alcohol, patients were classified as having Minimal Hepatic Encephalopathy (MHE) if they had impaired performance in at least two of the tests.

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PREVALENCE OF MINIMAL HEPATIC ENCEPHALOPTHY: According to our study, MHE was prevalent in 28% (n=7) of the people with cirrhosis. Even in patients who did not have any obvious evidence of liver disease 20% of them (n=2) had impaired test scores. (Chart 3).

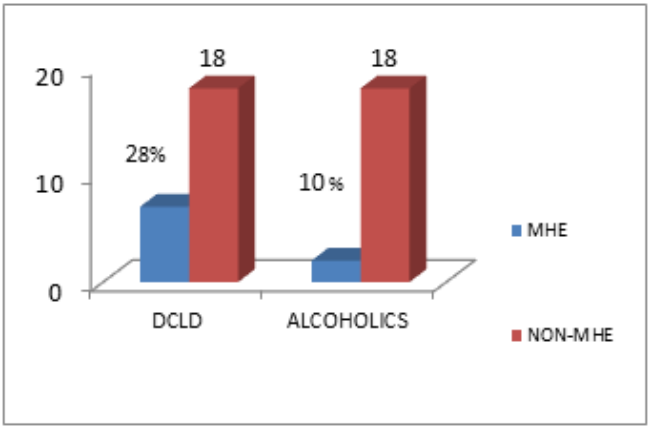

CHART 3: Prevalence of MHE

When we analysed patients with and without MHE, it revealed patients with MHE had higher duration of alcohol consumption and higher AUDIT scores and majority of them had grade 2 or 3 varices. These point needs further large scale studies to confirm whether or not an association really exists between them.

DISCUSSION: Minimal hepatic encephalopathy (MHE) refers to the neurocognitive abnormalities in patients with cirrhosis or portosystemic shunts which are diagnosed after excluding overt encephalopathy. MHE adversely affects the quality of living, driving abilities with impaired navigation skills and response inhibition resulting in increased road traffic accidents.[11] Despite the impact of MHE on daily living, screening for MHE is not routinely done because of lack of simple tools and they remain untreated. PHES remains an easy diagnostic tool which has been validated in Germany, Spain, Italy and other countries. To date, studies on the prevalence of MHE in Indian population especially in south India remains very limited. Due to a higher prevalence of alcoholics and alcoholic liver diseases in our population and since MHE in these populations can have a significant impact on the morbidity and mortality, screening for MHE is of utmost importance.

The prevalence of MHE in our study was 28% in patients with cirrhosis. The prevalence of MHE in other studies varies between 30% and 84% in cirrohosis.[12-14] This wide variation in the prevalence is due to several factors which includes 1) the criteria for diagnosis, 2) the population studied including the age, education 3) the severity of liver dysfunction, 4) alcoholic etiology-duration and severity and 5) presence of porto-systemic shunts.[15] Study of cordoba et al showed that neurocognitive impairment was observed even in patients with normal liver function due to presence of spontaneous porto-systemic shunts.[16]

The norms for the PHES battery were provided by Prof. Karin Weissenborn for DST, CDT, LTT[17] and for NCT – A and FCT data from studies of Amodio et al[18,19] were also used. The PHES system was initially standardized in Germany followed by spain and Italy.[20,21] In India an altered test vision has been standardized by Thumburu K.K., Khurmi R et al.[22] The Indian group substituted NCT-B with figure correction test (FCT) because they have to deal with a number of non-alphabetized

patients.[23] In our study, all of the 5 tests have been used and among the five tests the Number connection test (NCT A) and the Line tracing test (LTT) showed statistically significant difference in the test values (p=0.003) and (p=0.006) respectively between the two study groups.

Majority of the population (88%) consumed hard liquor and 8% consumed locally brewed products and 4% consumed beer or wine. There was quiet an increased number of individuals who had binge drinking. Among the decompensated liver disease patients, 64% of them had harmful drinking and 29.3% had hazardous drinking patterns. This shows that even harmful drinking patterns and not necessarily alcohol dependence need to be considered strictly and advice on cut down of consumption needs to be given for those patients.

Analysis of patients with MHE revealed that the mean age group was 40.86±8.19 years. Age and education had significant impact on the score but to minimize the effect, age and education matched controls were taken. 77.8% had consumed alcohol for more than 10 years, 11.1% between 5-10 years and 11.1% less than 5 years of alcohol consumption. Most of them showed a harmful drinking pattern (73.3%) (p-0.666). So even harmful drinking patterns and increased duration of alcohol consumption were considerable risk factors for the development of minimal hepatic encephalopathy and complications. These people should be advised to cut down the alcohol consumption and avoid further complications.

Physicians earlier obviated the need to screen for and treat MHE in cirrhotic patients without a prior history of OHE.[24] However, after the knowledge on the impact of MHE, great emphasis on OHE (overt hepatic encephalopathy) has recently been shifted towards MHE. Because of psychomotor defects, patients with MHE have been shown to have reduced driving skills, more likely to suffer from falls and develop episodic HE more frequently.[25] Our study found that half of MHE patients had the habit of driving. Due to the potential risks, there is a need to assess the presence of MHE in these patients. Similarly, screening of cirrhotic patients may be valuable in reducing the risk of work related accidents, and while handling machinery.[26] Compared to OHE, there are fewer randomized clinical trials about the treatment of MHE. Some studies show that treatments using lactulose and/or rifaximin can improve the health associated quality of life. The duration of treatment and choice of medication remain unclear.[27] Therefore, high quality large scale studies are needed to substantiate the recommendations for treatment in liver cirrhosis and MHE

CONCLUSION: The prevalence of MHE in our study was 20% (in cirrhosis 28% and in alcoholics 8%). In Psychometric Hepatic Encephalopathy Score (PHES), NCT-A and LTT have high sensitivity for detecting MHE. Hence these two tests can be used for screening purposes. Longer duration of alcohol consumption has been identified as one of the significant risk factors for MHE.

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