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Minimal Hepatic Encephalopathy in Patients with Cirrhosis Using Psychometric Hepatic Encephalopathy Score Tests

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ABSTRACT

Minimal hepatic encephalopathy (MHE) is defined as changes in cognitive ability, electrophysiology, and homeostasis of neurotransmission and blood flow in the cerebrum. It is observed in patients with chronic liver disease and cirrhosis who do not have clinical features of overt hepatic encephalopathy. The International Society for Hepatic Encephalopathy and Nitrogen recommend the Psychometric Hepatic Encephalopathy Score (PHES) to easily detect and treat these patients. **Objectives:** To calculate the frequency of MHE amongst patients with cirrhosis of the liver based on the Psychometric Hepatic Encephalopathy Score. **Methods:** This cross-sectional study was conducted at the Department of Medicine, Al Tibri Medical College, Karachi. A total of 235 patients with cirrhosis of the liver with normal mental status were included. Patients were given 5 printed sheets of paper, one each for the number connection test A and test B, line tracing, serial dotting test and digit symbol test. A score of two or less was labelled as minimal hepatic Encephalopathy. Chi-square test was applied for checking the association, and a p-value≤0.05 was considered significant. **Results:** There were 62.13% male and 37.87% female. The mean age was 45.47 ± 13.28 years. The mean duration of cirrhosis was 5.54 ± 3.7 years. Most of the patients (53.6%) successfully performed four and five PHES tests, while 22.13% patients successfully performed three tests. 15.32% and 8.94% were successfully performed two and one PHES test, respectively. Minimal hepatic encephalopathy was observed in 24.68% cases. **Conclusions:** It was concluded that the PHES is easily detected and can treat minimal hepatic encephalopathy.

INTRODUCTION

Around 33 % of liver cirrhotic patients suffer from its major complication, i.e. hepatic encephalopathy (HE). Since HE causes significant reductions in the quality of life, it tends to impact the socio-economic status of people. In addition, a high rate of mortality is associated with HE [1, 2]. In the management of HE, scientific bodies such as the European Association for the Study of Liver and the American Association for Liver Diseases laid out the management guidelines [3]. HE is classified according to two factors, the clinical setting in which the symptoms take place [4]. Encephalopathy of liver cirrhosis is similar in characteristics to acute hepatic failure, however, with some unique features as well. Three main types of HE symptoms can occur in patients with cirrhosis: episodic encephalopathy (precipitant-induced), which is seldom observed in hospitals, wherein the superimposed event remains the pivotal factor. The second is persistent encephalopathy (chronic) reported in patients undergoing surgery for portocaval shunt, having extended portosystemic shunts or having TIPS (Trans jugular

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Intrahepatic Portosystemic Shunt) in place. The third type is the minimal encephalopathy (subclinical), reflecting altered cognition amongst patients that exhibit normal clinical mental state [5]. The initial or first phase of clinical HE is the minimal HE occurring in a range of 30 to 84 % of cirrhotic patients [6]. Minimal HE patients show defective neuro-cognition in terms of coordination, attention, vigilance, reaction time, fine motor abilities and memory [7]. In the absence of any recognizable symptoms of HE, the mildest of minimal HE form characteristically includes subtle deficits in psychomotor and cognitive [8]. Minimal HE (MHE) patients report higher prevalence of road traffic accidents, higher chances of development of episodic overt HE and poorer quality of life, thus imposing a considerable socio-economic burden on both family and overall healthcare systems [9]. Generally, minimal HE is linked to a poor prognosis and possibly as an independent survival predictor. Mostly alcoholics, elderly populations are more prone to developing minimal HE, who might already have a history of overt HE with hepatic dysfunction coupled with esophageal varices [10]. PHES questionnaire encompasses five exams (pencil and paper) viz: Connection of Numbers Test- A and B (NCT- A/B) and (SDT), Line Drawing Test (LDT) and Serial Dotting Test (SDT) and Digit Symbol Test (DST). Each and every test evaluates separate neurocognitive abilities [11]. Clinicians can conveniently use PHES across various cultures. Nonetheless, PHES test results might or tend to be influenced by educational levels, age and gender [12]. Moreover, a study reported that around 30-50 % hepatic cirrhosis patients demonstrate minimal HE after testing by PHES or critical flicker frequency (CFF), which is a type of neurophysiological technique. This represents the first stage of the spectrum of HE [13, 14]. By using a simple Psychometric Hepatic Encephalopathy Score, it is possible to easily detect and treat these patients. Early detection and treatment not only improve cognition and psychomotor deficits and quality of life.

Till date, there has been no study conducted in Pakistani population regarding prevalence of minimal HE and there is a need to have a data regarding such patients and rationale is to know the magnitude of these patients with minimal hepatic encephalopathy requiring early recognition and treatment which will avoid development of overt HE thus reducing the economic burden. This study aimed to determine the frequency of MHE in patients with cirrhosis of the liver using the PHES.

METHODS

A cross-sectional descriptive study was carried out on outpatients visiting the Department of Medicine, Al Tibri Medical College and Hospital, Karachi, from January to July 2024 (ERC Approval Number- ATMC/IERC/13th (01-2023)/23). The sample size was calculated by using the WHO sample size calculator by assuming an expected prevalence of minimal hepatic encephalopathy of 25%, a confidence level of 95%, and a margin of error (precision) of 5% [6]. A total of 235 patients of either gender aged 18 to 70 years suffering liver cirrhosis and normal mental status were included. After explaining the study's protocol, informed consent was obtained. A non-probability consecutive sampling was used. Patient with overt encephalopathy, altered mental status with Glasgow coma scale of less than 15, abnormal EEG record, had history of TIPS or shunt surgery, had any known neurological disease and with electrolyte imbalance (Blood sugar >250mg/dl or <50 mg/dl, Urea >50mg/dl, Creatinine >2.0 mg/dl, Sodium >150 mEq or <130 mEq, and Potassium >4.5 mEq or <3.0 mEq) were excluded. Minimal HE was defined as failure to perform two (2) of the Five (5) psychomotor hepatic encephalopathy score (PHES) tests (One point was given to each test performed successfully) [12]. The patients were shown a paper having numbered circles totaling 25 at random. The task was connecting circles starting from 1 and ending on 25, with a time limit of 30 seconds. The patients were shown a paper with 26 circles, having 13 numbered circles and 13 circles with alphabets (A to L) at random. It was a matter of associating the numbers and letters alternately, i.e. Interchanging 1-A-2-B-3-C and so on in 1 minute. The patients were advised to follow the pattern of the 5mm broad path as fast as he could without crossing the boundaries. Tracing should be completed in 10 minutes. The patients were requested to fill in the center of circles on a sheet of paper, which had 100 circles. The task was to complete in 1 minute. The Digit symbol was administered wherein the participant was presented with several double-boxes in a sheet of paper with the numbers furnished on the upper area. One way to draw a symbol related to this number in the lower side of the boxes. There were nine fixed pairs of numbers and symbols which were placed at the top of the test sheet to be referred. The exercise would have entailed making accurate ticking in at least 50 boxes within 90 seconds. Cirrhosis was declared Hepatic disorder of any cause more than 6 months with a decompensation phenomenon as regards presence of any three of the following clinical and laboratory elements i.e. Jaundice (yellow discoloration of sclera with bilirubin level >2 mg/dl), PT >2 seconds over control or INR >1.3, Albumin <3gm/dl, Platelets <100000/cmm, and Ascites, Splenomegaly, Hepatic encephalopathy, Presence of varices on Upper GI endoscopy, presence of fibrosis and nodule formation in liver. A consultant neurologist examined all the patients to assess their mental status and GCS. Each of the patients was provided with 5 pieces of printout papers, each one being Number connection test A,

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Number connection test B, Line tracing (trail drawing test), Serial dotting test and Digit symbol test (PHES test). The results were customized in the pre-approved Performa. SPSS version 25.0 was used to compare the data collected. Statistical calculations were done. Chi-square test has been used to test the association of minimal hepatic encephalopathy with gender, age and ASA class. Fisher's exact test was implemented, where the minimum criteria of count did not apply in the method of meeting the standard of applying a chi-square test. A p-value of 0.05 or less was assumed to be significant.

RESULTS

The mean age of study subjects was 45.47 ± 13.28 years (95%CI: 43.77 to 47.18). The age was also evaluated in patients with/without MHE. The results showed that the mean age was 46.62 ± 13.57 years among patients with MHE, and it was 45.09 ± 13.20 years among patients without MHE. The average duration of cirrhosis pain was 5.54 ± 3.7 years. Duration of cirrhosis was 5.46 ± 3.69 years and 5.56 ± 3.71 years, respectively, among patients with or without MHE (Table 1).

Table 1: Descriptive Statistics of Age and Cirrhosis (n=235)

Variables	Overall	With MHE	Without MHE
Age (Years)			
Mean ± SD	45.47 ± 13.28	46.62 ± 13.57	45.09 ± 13.20
95%CI (LB – UB)	43.77 – 47.18	43.05 – 50.19	43.13 – 47.05
Median (IQR)	47.0 (21.0)	48.0 (20.25)	46.0 (21.0)
Range	52.0	51.0	52.0
Minimum	18.0	18.0	18.0
Maximum	70.0	69.0	70.0
Duration of Cirrhosis (Years)			
Mean ± SD	5.54 ± 3.70	5.46 ± 3.69	5.56 ± 3.71
95%CI (LB – UB)	5.06 – 6.02	4.49 – 6.43	5.01 – 6.11
Median (IQR)	5.0 (5.0)	5.0 (6.0)	5.0 (4.5)
Range	19.0	14.0	19.0
Minimum	1.0	1.0	1.0
Maximum	20.0	15.0	20.0

It was also observed that overall, 146 male and 89 females were included. It was observed that the age of 37 patients was ≤30 years, 50 were between 31-40 years, 60 between 41-50 years, 56 between 51-60 years' age group, and the age of 32 patients was 61-70 years. As far as the duration of cirrhosis was concerned, it was evaluated that 151 patients had cirrhosis since <5 years, 58 patients for 5-10 years, and 26 had cirrhosis for 10 years (Table 2).

Table 2: Frequency Distribution of Gender, Age, Duration of Pain, and Confounders (n=235)

Variables		Frequency (%)
Gender	Male	146 (62.13%)
	Female	89 (37.87%)
Age Group (Years)	≤ 30	37 (15.74%)
	31-40	50 (21.28%)
	41-50	60 (25.53%)
	51-60	56 (23.83%)
	61-70	32 (13.62%)
Duration of Cirrhosis (Years)	< 5	151 (62.46%)
	5-10	58 (24.68%)
	> 10	26 (11.06%)

The results showed that 8.94% of patients successfully performed one PHES test, 15.32% successfully performed two PHES tests, 22.13% successfully performed three PHES tests, 31.06% successfully performed four PHES tests, and 22.55% performed five PHES tests (Figure 1).

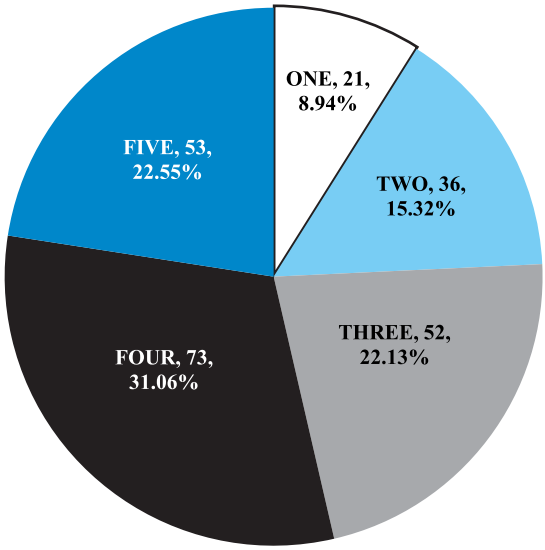

Figure 1: Percentage of Successfully Performed ONE PHES Test (n=235)

The outcome, i.e. Minimal HE using psychometric hepatic encephalopathy score, showed 24.68% patients had MHE with a 95 % CI of 19.60 % to 30.57 % (Figure 2).

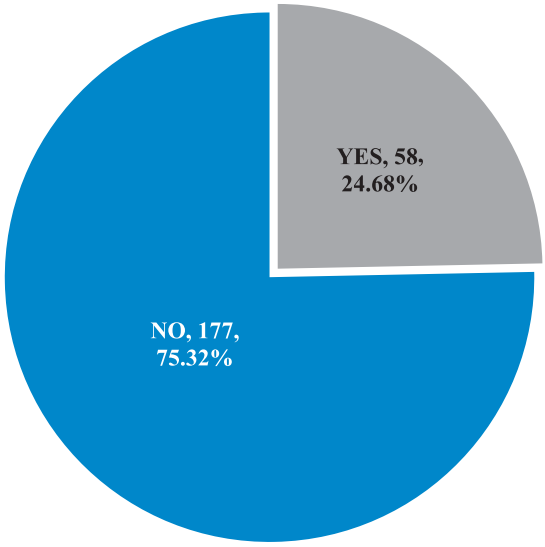

Figure 2: Percentage of MHE (n=235)

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The association of MHE using the PHES was evaluated with gender, age, and duration of cirrhosis. Results demonstrated no significant association of MHE with gender (p=0.52), age (p=0.48), and duration of cirrhosis (p=0.85(Table 3).

Table 3: Association of Minimal Hepatic Encephalopathy with Gender, Age, and Duration of Cirrhosis(n=235)

Variables		Minimal Hepatic Encephalopathy		Total	p-Value	Odds Ratio	95 % CI
		Yes (n=58)	No (n=177)				
Gender (Years)	Male	34 (23.3%)	112 (76.7%)	146	0.526**	0.82	0.45-1.51
	Female	24 (27%)	65 (73%)	89			
Age Group (Years)	≤30	8 (21.6%)	29 (78.4%)	37	0.480**	1.45	0.49-4.30
	31-40	8 (16%)	42 (84%)	50		1.00	-
	41-50	18 (30%)	42 (70%)	60		2.25	0.88-5.74
	51-60	15 (26.8%)	41 (73.2%)	56		1.92	0.74-5.02
	61-70	9 (28.1%)	23 (71.9%)	32		2.05	0.7-6.05
Duration of Cirrhosis	<5	39 (25.8%)	112 (74.2%)	151	0.859**	1.21	0.59-2.47
	5-10	13 (22.4%)	45 (77.6%)	58		1.00	-
	>10	6 (23.1%)	20 (76.9%)	26		1.04	0.35-3.12

**Not Significant at 0.050 level

DISCUSSION

In a study, the prevalence of Minimal HE was varied and was found in around 20 to 84% patients having cirrhosis [15]. Minimal HE is described as defects in cognition in cirrhotic patients and/or shunting of porto-systemic, which is diagnosed post overt HE exclusion and alternate neuropsychological impaired diagnoses are made [16]. Various neuropsychological techniques are utilized for diagnosing deficits in cognition among cirrhotic patients. Such included extended neuropsychological assessments, computerized testing. Extended neuropsychological assessments are done on the basis of referral by experts, which is sometimes difficult to validate [17]. In current study, the mean age was 45.47 ± 13.28 years (95% CI: 43.77 to 47.18). Out of 235 cases, 146 (62.13%) were male and 89 (37.87%) female. The male-to-female ratio was 1.64:1. In present study, most patients (53.6%) successfully performed four and five PHES tests, while 52 (22.13%) patients successfully performed three tests, and 36 (15.32%) and 21 (8.94%) successfully performed two and one PHES test, respectively. Frequency of minimal HE (MHE) was observed in 24.68% (58/235). Maldonado-Garza *et al.* reported in their study that, prevalence of MHE was 55.8% (n=58)[18]. In another study, Li *et al.*, in 409 cirrhotic patients using TMT and SDT, the prevalence of MHE was 29% [19]. By various validation studies, the cutoff of PHES for diagnosis MHE was ≤ -4 points [20-22]. However, validation studies in other countries reported a cutoff of PHES for diagnosis MHE at ≤ -5 points [23]. In another investigation, 48% of patients with cirrhosis were found to be afflicted with MHE. In a study, however, a reduced MHE incidence (25.6%) had been reported [24]. It may be because the liver function of the patients involved in the research was not the same. In another research, age and education impacted all 5 neuropsychological PHES tests. However, they were not discriminated against by gender at any age bracket. PHES did not correlate with age, education and gender in the healthy volunteer group [25]. This study was limited by the use of a single diagnostic tool (PHES), which may not capture all aspects of cognitive impairment, and the lack of consideration of confounding factors such as liver disease severity and educational status. Future studies should incorporate multiple neuropsychological tools and stratify patients by disease severity to improve the accuracy of MHE diagnosis.

CONCLUSIONS

It was concluded that this research brings to the fore the usefulness of the DOTS-psychometric hepatic encephalopathy score (PHES) tests in the identification of minimal hepatic encephalopathy of cirrhotic patients and the importance of screening patients routinely. Disease progression can be stopped by intervention, and early diagnosis can enhance the patient outcome and boost the standard of living.

Authors' Contribution

Conceptualization: HZ
Methodology: HZ, AM, HK
Formal analysis: HZ
Writing and Drafting: AK, WM, HA, MFW
Review and Editing: HZ, AK, WM, HA, MFW

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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