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Aetiology, Clinical Features and Diagnostic Performance of Psychometric Hepatic Encephalopathy Test Scores for Minimal Hepatic Encephalopathy among Cirrhotic Patients in a Teaching Hospital in Ghana

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Abstract

Introduction: Minimal Hepatic Encephalopathy (MHE) is the earliest manifestation of Hepatic Encephalopathy (HE). It affects a significant number of cirrhotics and contributes significantly to morbidity and mortality. It is underdiagnosed because of its subtle presentation. This study determined the aetiology, clinical features, and diagnostic performance of psychometric hepatic encephalopathy test scores for minimal hepatic encephalopathy among cirrhotic patients in a teaching hospital in Ghana.

Methods: This was a cross-sectional study at the Korle Bu Teaching Hospital in Accra, Ghana. Patients with liver cirrhosis were screened for MHE using the Psychometric Hepatic Encephalopathy Test Scores (PHES); The Number Connection Test A & B (NCT-A&B), Line Tracing Test (LTT), Digit Symbol Test (DST) and Serial Dotting Test (SDT). Cut-off points identified in normal populations were used to determine the presence of MHE. Summary statistics, independent sample t-test, chi-square and ROC curves were used in data analysis using STATA 17.

Results: Of the 136 patients with liver cirrhosis recruited 51% had MHE. The mean age (SD) of patients with MHE was 44.8 ± 13.2 years with male predominance (1.6:1). 48.5% of patients had Chronic Hepatitis B. Edema, weight loss, abdominal distension, serum ALT, GGT, albumin levels and higher Child -Pugh scores were associated with MHE. Each of the 5 PHES showed significant difference between patients with MHE and those without. NCT-B and DST had the highest predictive values of MHE with AUC of 97% and 92% respectively, while SDT had the least predictive value with an AUC of 65. The AUC for NCT-A and LCT were 89 and 81 respectively.

Conclusion: Minimal Hepatic Encephalopathy (MHE) is a prevalent condition with frequent complications of liver cirrhosis and is strongly associated with disease severity. Psychometric tests, particularly NCT-B and DST, proved effective for diagnosing MHE. Routine screening for MHE in cirrhotic patients using these tools is recommended to enable early intervention and improve clinical outcomes.

Keywords: Minimal hepatic encephalopathy • Liver cirrhosis • Psychometric hepatic encephalopathy test scores • Korle Bu Teaching Hospital • Diagnostic performance

Introduction

Hepatic Encephalopathy (HE) is a common and significant complication of liver cirrhosis. It is a potentially reversible metabolic disruption of central nervous system function that presents with a wide spectrum of neuropsychiatric abnormalities [1]. Based on the severity, HE can be classified into two groups: the more severe Overt HE (OHE) which manifests either episodically or continuously, with obvious and clinically detectable symptoms; and the less severe covert HE (CHE) [2]. Minimal Hepatic Encephalopathy (MHE) represents the earliest stage in the CHE continuum and is characterized by subtle cognitive and psychomotor deficits without recognizable clinical symptoms and signs of OHE. It is only detectable by Neuro-Psychometric (NP) and neurophysiological tests.

MHE is common with a reported prevalence of up to 84% and many patients with cirrhosis may experience it at some point in the course of their illness, especially as the liver disease progresses. Studies have shown that short-term memory, attention, visual-spatial ability, and fine motor skills are often affected in MHE [3]. Several studies have also reported MHE predicts a higher risk of falls and road traffic accidents, a higher risk of OHE, a poorer quality of life and a worse prognosis [4,5]. Despite these debilitating effects, many patients with MHE and their caregivers are unaware of their challenges because their verbal and communicative skills are often spared.

Additionally, MHE is associated with an increased utilization of healthcare resources because affected persons have a significantly higher risk of developing their first overt HE episode and associated hospitalization [6]. Factors such as severity of liver disease, presence of varices, aetiology (alcohol consumption) and episodes of hyponatremia have been linked to the prevalence of MHE [7-9].

Ideally, every patient with cirrhosis should be tested for MHE at the time of diagnosis and later during follow-up. However, in a 2007 survey by the American Association for the Study of Liver Diseases (AASLD) only 50% of physicians evaluated cirrhotic patients for MHE and as many as 38% had never performed a psychometric evaluation of these patients [10]. Unlike in OHE where patients have obvious neurological deficits, testing for MHE requires a more comprehensive neurological assessment using either psychometric, neurophysiologic or neuroimaging studies.

Psychometric tests are a series of "paper-pencil tests" that assesses psychomotor speed and skill, attention, concentration, visuospatial orientation

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and memory. It lasts approximately 15 minutes and is relatively simple to understand and complete. Neurophysiological examinations such as EEG on the other hand require complex equipment and are less sensitive than psychometric tests. EEG studies cortical activity and analysis of spectral EEG provides quantitative measures of brain dysfunction. Other neurophysiological tests also known as computerized tests such as Critical Flicker Frequency (CFF), Inhibitory Control Test (ICT) and Control Reaction Time (CRT) on the other hand, yield more accurate results than "paper-pencil" tests since they typically rely on repeating many tests. Brain imaging is important to exclude structural causes of brain dysfunction in patients with MHE but has a limited role in MHE diagnosis. Peculiar changes observed on MRI such as reduction in both white and gray matter may be seen in patients with liver cirrhosis and HE, but these are not specific to MHE.

Although the Working Group on Hepatic Encephalopathy and The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) practice recommendations propose PHES as the gold standard for the diagnosis of MHE, none of these tests acting alone is optimal for the diagnosis because they explore different brain functions. Results from at least two of these psychometric tests that are two SD above normal are used as the basis for the current definition of MHE [11].

Because of the shared pathogenesis between MHE and OHE, the management strategies for MHE are like that for OHE. These include Lactulose and Rifaximin use. Several studies have confirmed the positive impact of these on the psychometric tests results and clinical complications [12,13].

Morbidity and mortality from cirrhosis is common in Ghana. However, there is dearth of information on the contribution of MHE to these clinical outcomes. The aim of this study was to determine the prevalence of MHE and its associated factors among cirrhotic patients at the Korle Bu Teaching Hospital (KBTH) in Accra, Ghana, using neuropsychometric tests (PHES).

Materials and Methods

Study design and study site

This was a cross-sectional study which took place from January 15th, 2022, to June 20th, 2022, at the Gastroenterology Clinic of the Department of Medicine, Korle-Bu Teaching Hospital (KBTH), Accra.

Data collection

The study population included all consecutive patients presenting with liver cirrhosis above the age of 18 years, who passed the Mini Mental State Exam (MMSE) to exclude overt hepatic encephalopathy. After thoroughly explaining the study to patients, those who gave their consent were administered the questionnaire. Physical examination and laboratory investigations; liver function test, INR, blood urea, creatinine and electrolytes, full blood count and an abdominal Ultrasound Scan (USG) were performed for the patients and results analyzed. For each patient, severity of liver disease was assessed using the Child-Pugh score.

Calibration of the PHES was done using results from 50 healthy volunteers (staff of the hospital and relatives of patients), negative for Hepatitis B and C virus infections, and with normal liver biochemistry and abdominal sonography.

To obtain PHES of participants, each completed 5 psychometric tests: Number Connection Test A (NCT-A), Number Connection Test B (NCT-B), Digit Symbol Test (DST), Line Tracing Test (LTT), and Serial Dotting Test (SDT) after thorough explanation. The results of each test were recorded. A diagnosis of MHE was made if there was a normal MMSE and impairment in the performance of at least 2 of the 5 psychometric tests applied i.e. patients who used more than 2SD of the average time in completing the tests (NCT-A >99 seconds, NCT-B >200 seconds, LTT >93seconds, SDT >124 seconds and DST<41 correct pairs).

Ethical approval

Ethical approval was obtained from the Korle Bu Teaching Hospital Scientific and Technical Committee as well as the Institutional Review Board, Ref. No: KBTH-STCIRB/00096/2021

Statistical analysis

Socio-demographic, lab variables, and APRI scores were analyzed to determine which factors were associated with MHE using descriptive statistics (frequency, percentages, mean, and standard deviation). The proportion of MHE patients in each Child-Pugh Class (CPC) and the association between PHES scores and MHE were also analyzed using the independent t-test. The performance of the diagnostic test (PHES) was evaluated using ROC curves. Statistical significance was set at a p-value of ≤ 0.05. Statistical analysis was performed using STATA 17.

Results

Sociodemographic characteristics of study participants

Out of the 136 participants with liver cirrhosis screened, 83 (61%) were males and 53 (39%) were females. The age of the patients with liver cirrhosis ranged from 19 to 69 years with a greater proportion of patients (30.9%) being in the age range of 46-55 years. All the study participants (patients with liver

Table 1. Demographic characteristics of study participant.

	Sociodemographic	Total n(%)	MHE n(%)	NON-MHE n(%)	P - value
Age group	18-25	8(100.0)	7(87.50)	1(12.50)	0.176
	25-35	24(100.0)	11(45.80)	13(54.20)	
	36-45	36(100.0)	16(44.40)	20(55.60)	
	46-55	42(100.0)	21(50.00)	21(50.00)	
	56-65	20(100.0)	10(50.00)	10(50.00)	
	>65	6(100.0)	5(83.30)	1(16.70)	
	Mean Age ± SD	44.9 ± 11.71	44.79 ±13.19	45.02 ± 9.99	0.91
Gender	Female	53(100.0)	27(50.94)	26(49.06)	0.921
	Male	83(100.0)	43(51.81)	40((48.19)	
Marital Status	Single	25(100.0)	19(76.00)	6(24.00)	0.247
	Married	64(100.0)	37(57.81)	27(42.19)	
	Co-habiting	2(100.0)	2(100.0)	0(0.00)	
	Divorced	6(100.0)	5(83.33)	1(16.67)	
	Widowed	9(100.0)	7(77.78)	2(22.22)	

Highest level of education	None	1(100.0)	1(100.0)	0(0.00)	0.864
	Primary	45(100.0)	24(53.33)	21(46.67)	
	Secondary	64(100.0)	33(51.56)	31(48.44)	
	Tertiary	20(100.0)	10(50.00)	10(50.00)	
	Post-graduate	5(100.0)	2(40.00)	3(60.00)	
Occupation	Retired	39(100.0)	18(46.15)	21(53.85)	0.644
	Public services	20(100.0)	8(40.00)	12(60.00)	
	Self-employed	42(100.0)	24(57.14)	18(42.44)	

cirrhosis) except 1 had some form of formal education. Regarding occupation, almost half of the total number of participants, 67 (49.3%), were working at the time of this study, with the remaining being either students, retired or unemployed. Seventy (70) out of the total 136 patients with liver cirrhosis screened were found to have MHE, comprising 43 (61.4%) males and 27 (38.6%) females, with a male to female ratio of 1.6:1. The prevalence of MHE was 51%. The mean (SD) age of patients with MHE was 44.8 ± 13 years, with the highest proportion and close to a third (30%) of them in the age range of 46-55 years. With regards to education, 24 (34.3%) patients with MHE had primary education, 33 (47.1%), secondary and 12 (17.1%) had tertiary and post-graduate education (Table 1).

Health/Clinical characteristics of participants

The commonest presenting symptoms among all the participants were pedal edema abdominal distension and jaundice as shown in Table 2. Symptoms of pedal edema, abdominal distension, weight loss and anorexia were significantly associated with MHE. 48 (35.3%) of the participants had a history of herbal medication use for various conditions including their current condition. More than a third, 50 (36.8%) also had co morbid conditions and these included hypertension, diabetes mellitus, dyslipidemia, and retroviral infection (Table 2).

Biochemical variables of the study participants

The mean hemoglobin level and platelet count of patients with MHE was 10.7 ± 1.91g/dl and 121.2 ± 46.9 × 109/l respectively. These as well as the mean values of the remaining laboratory parameters measured are shown in Table 3. Anemia (hemoglobin <12g/dl) was present in 17 (24.3%) patients with MHE, thrombocytopenia in 49 (70%) and hypoalbuminemia in majority (80%) of them. The mean APRI score of patients with MHE was 1.86 and 44.3% of them had APRI scores of 2 (Table 3).

Atieology of cirrhosis

The commonest etiologic agent was hepatitis B infection, which was the cause of liver cirrhosis in 66 (48.5%) patients. This was followed by alcoholic liver disease in 42 (30.9%) patients, chronic hepatitis C in 8 (5.9%) patients, autoimmune hepatitis in 3 (2.2%) patients and NAFLD in 1 (0.7%) patient. Five patients had multiple causes, one had schistosomiasis and no aetiology was identified in 10 (7.4%) patients (Figure 1). Aetiology of liver cirrhosis did not show significant correlation with MHE (Table 4).

Severity of liver cirrhosis (Child-pugh classification of patients)

Table 2. Clinical features of study participants.

Presentation	Total n(%)	MHE n(%)	Non MHE n(%)	Sig
Mean Diastolic BP ±SD	76.99 ±10.68	77.39 ±10.08	76.58 ±11.34	0.5
Mean Systolic BP ±SD	123.04 +-13.86	12.28 ± 122.26	123.85 ±15.39	0.65
Pedal edema	59 (100.0)	39 (66.10)	20 (33.90)	0.00*
Abdominal distention	57 (100.0)	42 (73.68)	15 (26.32)	0.00*
Jaundice	39 (100.0)	25 (64.10)	14 (35.90)	0.06
Weight loss	35 (100.0)	29 (82.86)	6 (17.14)	0.00*
Anorexia	28 (100.0)	20 (71.43)	8 (28.57	0.01*
Abdominal mass	8 (100.0)	5 (62.50)	3 (37.50)	0.52
Fever	5 (100.0)	4 (80.00)	1 (20.00)	0.19
Poor sleep	12 (100.0)	6 (50.00)	6 (50.00)	0.91
Other	9 (100.0)	6 (66.67)	3 (33.33)	0.34

Table 3. Biochemical parameter of MHE and NON-MHE patients.

Variable		Total		MHE		NON-MHE		Sig
		Mean	SD	Mean	SD	Mean	SD	
Bilirubin	Total bilirubin	57.41	54.184	61.67	59.49	52.89	47.95	0.34
	Direct bilirubin	33.19	30.081	34.43	32.77	31.88	27.11	0.62
Liver function	AST(IU/L)	83.96	45.614	79.26	42.26	88.95	48.74	0.21
	ALT(IU/L)	69.1	57.555	57.6	51.56	81.3	61.35	0.01*
	ALP	158.9	76.257	165.59	81.91	151.82	69.687	0.29
	GGT	114.91	95.168	133.25	105.08	95.14	79.32	0.02*
	Albumin	31.51	5.697	30.3	5.557	32.79	5.6	0.01*
	Total Protein	72.04	12.898	70.13	14.41	74.05	10.85	0.07

Blood work	Hb(g/dl)	10.55	1.861	10.69	1.91	10.39	1.8	0.34
	WBC	6.73	2.354	7.14	2.43	6.3	2.202	0.03*
	Platelet	124.99	64.687	121.16	46.9	129.05	79.493	0.47
Kidney function	Na+	136.46	12.68	137.14	12.3	135.74	13.11	0.52
	K+	4.16	0.842	4.24	0.88	4.09	0.79	0.3
	BUN	6.43	3.852	6.16	2.6	6.69	4.78	0.43
	Cr	98.29	30.319	97.2	32.31	99.4	28.24	0.66
	INR	1.56	0.55	1.6	0.58	1.54	0.54	0.5
	APRI Score	1.98	1.19	1.86	1.15	2.1	1.22	0.23

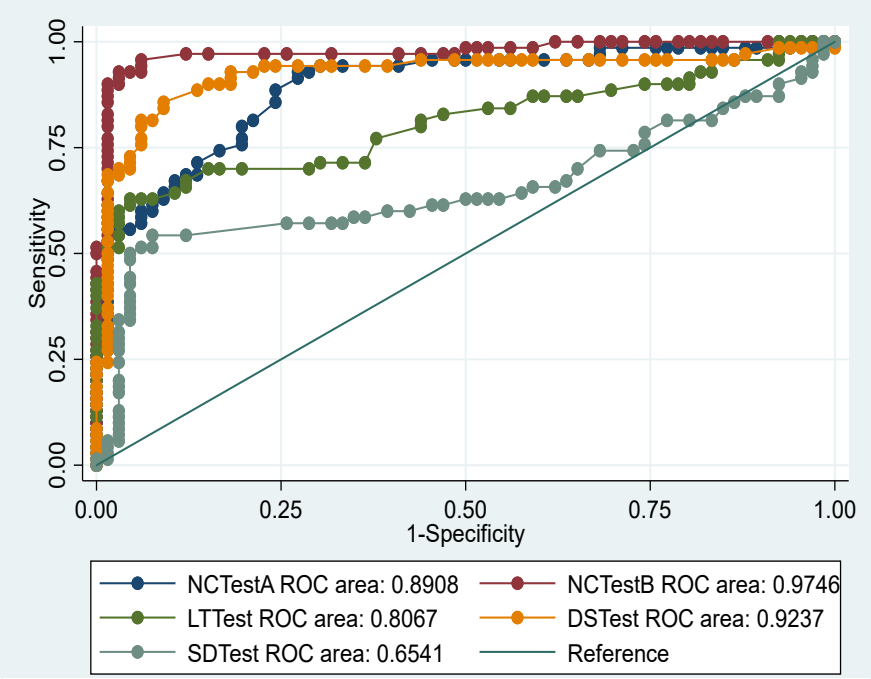

Figure 1. ROC curve for PHES scores.

Table 4. Distribution of aetiology among groups of patients.

Aetiology	Total liver cirrhosis n(%)	MHE n(%)	NON-MHE n(%)	P value
HBV	66(48.53)	32(45.71)	34(51.51)	0.3
Alcohol	42(30.87)	24(34.29)	18(27.27)	0.54
Unknown	10(7.35)	4(5.71)	6(9.09)	0.45
HCV	8(5.88)	5(7.14)	3(4.55)	0.51
Autoimmune	3(2.21)	2(2.86)	1(1.52)	0.65
HBV and Alcohol	3(2.21)	2(2.86)	1(1.52)	0.65
HBV and HCV	2(1.47)	0(0.00)	2(3.03)	0.74
NAFLD	1(0.74)	1(1.43)	0(0.00)	0.71
Other	1().74)	0(0.00)	1(1.52)	0.24

Table 5. Association between child Pugh class and group.

Variable		Total	MHE	Non-MHE	P-value
Child Pugh class	A	32(100.0)	7(21.90)	25(78.10)	<0.000*
	B	64(100.0)	35(54.70)	29(45.30)	
	C	40(100.0)	28(70.00)	12(30.00)	
	Total	136(100.0)	70(51.50)	66(48.50)	

Table 6. Diagnostic performance of PHES test in predicting MHE.

Test	AUC	95% C.I	Standard Error	Observations
NC test A	0.89	0.83-0.95	0.027	135
NC test B	0.97	0.94-1.00	0.013	135
LT test	0.81	0.73-0.88	0.038	135
DS test	0.92	0.87-0.97	0.026	135
SD test	0.65	0.55-0.75	0.049	135

According to the Child Pugh Classification (CPC) system, 7 (10%) of patients with MHE were in CPC-A, 35 (50%) in CPC-B and 28 (40%) in CPC (Table 5).

PHES scores

The prevalence of MHE was 51% (Figure 1). The difference between the PHES of patients with MHE and those without, was statistically significant for all the tests with p value <0.05. This was based on cut-offs of NCT-A >99 seconds, NCT-B >200 seconds, LTT >93 seconds, SDT >124 seconds and DST<41 correct pairs, derived from the normal population. This criterion was met by 70 (51%) patients with liver cirrhosis, who were then diagnosed as having MHE9 (Table 6).

Diagnostic performance of PHES scores

The Table, I provided shows the Area Under the Curve (AUC), 95% confidence interval, standard error, and number of observations for five different tests: NC test A, NC test B, LT test, DS test, and SD test. NC test B and DST were the golden standards for predicting MHE. SDT was the least performing modality.

Discussion

HE is an important and common complication of liver cirrhosis. A rather wide MHE prevalence range of 30%-84% is reported in the literature and often attributed to different diagnostic criteria and different tests used for its recognition [14].

The prevalence of 51% reported in this study is high and consistent with reports from China (50.9%). This means that more than half (51%) of the patients with cirrhosis have cognitive and psychomotor deficits that are not clinically recognizable. This is expected to have negative effects on the day-to-day activities of these patients. Shomerus H and Hamster W and Bajaj JS, et al. have previously reported the negative impact of MHE on both blue and white-collar jobs and driving respectively [15,16]. It is surprising therefore that this study did not find any association between MHE and sociodemographic characteristics such as employment status. There is evidence however that patients with MHE tend to overestimate their abilities and the subtle nature of these deficits may make it non-obvious to employers [17,18].

Equally surprising and inconsistent with some reports in the literature is the lack of any significant association between MHE and etiological agents that have been reported to increase cognitive decline such as hepatitis C infection and alcohol [19].

The prevalence of sarcopenia is reported to be 84% in patients with MHE compared to up to 30% in patients without MHE. This skeletal muscle depletion favours the accumulation of ammonia in blood and the development of HE [20]. The association between weight loss and MHE in this study is therefore consistent with reports in the literature. Another contributory factor could be anorexia which has been reported in patients with MHE and reported in this study [21].

The association between MHE and severity of liver disease has been severally reported [14,22]. This study confirms this association with about 70% of patients in CTP class C having MHE compared to only about 22% in those in CTP class A. Interestingly some independent laboratory parameters typically associated with severe liver cirrhosis i.e. elevated bilirubin, high INR, platelet count, and low sodium were not associated with MHE. This is comparable to findings by Bale A, et al, which showed that whiles CTP scores independently predicted presence of MHE, serum creatinine, sodium, potassium, urea, total bilirubin, AST, ALT and albumin levels did not 8 . The use of single laboratory parameters to predict MHE must therefore be discouraged. At present, there is no single optimal test for the diagnosis of MHE [14].

The association of MHE with some clinical features (abdominal distension, pedal oedema, weight loss and anorexia) and some laboratory parameters (ALT, GGT, albumin and WCC) could be explored for the development of a simple algorithm to assist clinicians screen for MHE.

Uncertainty over which tests to employ ignorance of treatment advantages, and test performance in identifying patients who will benefit from anti-HE treatment are the main causes of the reluctance by practitioners to screen for MHE [14]. Using the 2 most sensitive tests identified in this study, screening for MHE can be simplified, encouraging more practitioners to screen and consequently treat MHE. The PHES test used in this study explores different cognitive domains in patients. The results from this study highlight the varying diagnostic performance of these tests. Together, the best performing tests NCT-B and DST assess psychomotor speed, set shifting, divided attention, visuospatial reasoning and praxis compared with the least performing test that assesses only psychomotor speed. To simplify the diagnosis of MHE for clinicians, the results from this study could become the basis for validation of NCT-N and DST in the Ghanaian population.

Conclusion

MHE is common among patients with liver cirrhosis attending the gastroenterology clinic at KBTH, affecting over half of them. Aetiology of liver cirrhosis is not associated with development of MHE. Child Pugh Class B & C, high serum ALT and ALP were identified as predictors of MHE. NCT-B and DST are the most sensitive psychometric tests applied in this study.

Further studies to validate NCT-B and DST for screening for MHE in patients with liver cirrhosis, particularly those in CPC B & C are recommended. This would allow for early diagnosis and therefore prompt treatment of patients with MHE to prevent the development of overt HE, and also improve their quality of life and overall prognosis.

Limitations

Neuroimaging (brain CT/ MRI) to rule out any coexisting brain pathology which could account for the deficits observed would have been ideal and preferred but was not carried out on account of cost.

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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