Prevalence of and Factors Associated With Minimal Hepatic Encephalopathy in Patients With Cirrhosis of Liver

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Background/objectives: **Minimal hepatic encephalopathy (MHE), though highly prevalent, is a frequently underdiagnosed complication of cirrhosis of the liver. Because lack of time is reported as the major reason for non-testing, identifying patients at high risk of MHE would help in targeting them for screening. We aimed to determine the factors associated with MHE to help identify patient subgroups with a higher risk of MHE for targeted screening.** ***Methods:*** **Patients with cirrhosis of liver presenting between April 2015 and November 2016 were included. Those with a Psychometric Hepatic Encephalopathy Score (PHES) of ≤ -5 points on psychometric testing were diagnosed to have MHE. Various demographic, clinical and laboratory parameters were included in a univariate and later multiple logistic regression models.** ***Results:*** **Of the 180 (male = 166, 92.2%) patients included 94 (52.2%) had MHE. Though serum albumin, serum total bilirubin, serum aspartate aminotransferase, international normalized ration, Child-Turcotte-Pugh and Model-For-End-Stage-Liver-Disease scores were significant on univariate analysis, only CTP score was found to be significantly associated with MHE ($P = 0.002$) on multivariate analysis. A higher CTP class was associated with a higher risk of the presence of MHE. The Odds ratio for having MHE was higher with CTP classes of B ($P \leq 0.001$) and C ($P \leq 0.001$) compared to class A.** ***Conclusions:*** **MHE is a common complication in patients with cirrhosis of liver and higher CTP scores independently predict the presence of MHE. Patients with CTP class B and C have a higher risk of suffering from MHE than CTP class A. Screening of patients in CTP class B and C is likely to increase the MHE detection rates while saving time, although select CTP class A patients may also need screening in view of public safety or poor quality of life.** **(J Clin Exp Hepatol 2018;8:156–161)**

Hepatic encephalopathy (HE), characterized by reversible neuropsychiatric manifestations, is a common complication of cirrhosis of liver but can also occur less commonly in acute liver failure and other causes of portosystemic shunting. In patients with cirrhosis, it is often considered an indicator of poor prognosis, with 1 and 3-year survival after its first occurrence being 42% and 23% respectively in the absence of liver transplantation.[1] The Working Party at the 11th World Congress of Gastroenterology classified HE according to various associated factors like the disease process leading to HE (Types A, B and C), time pattern of its occurrence (episodic, recurrent, and persistent), existence of precipitating factors (precipitated or non-precipitated) and the severity of manifestations.[2] While at one end of the severity spectrum lies coma with readily identifiable clinical signs, minimal hepatic encephalopathy (MHE) occupies the other end. The American Association for Study of Liver disease (AASLD) has defined MHE as the presence of test-dependent or clinical signs of brain dysfunction in patients with cirrhosis who are not disoriented or display asterixis.[3]

Though MHE has a high prevalence in patients with cirrhosis of liver[2] and it affects various aspects of day-to-day activities like driving,[4] sleep[5] and memory[6] its diagnosis presents a challenge to the clinician as it lacks easily identifiable clinical signs. MHE has significant negative impact on activities requiring attention, fine motor skills, memory and visuo-spatial ability.[7] Patients with MHE are more prone to vehicular accidents[8] but themselves lack insight into their handicap[9] and it also has an adverse impact on the health-related quality of life (HRQOL).[10] Groeneweg et al.[10] showed that MHE was responsible for a

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Abbreviations: AASLD: The American Association for Study of Liver disease; ALT: alanine transaminase; AST: aspartate transaminase; C.I.: confidence interval; CTP: Child Turcotte Pugh; DST: digit symbol test; FCT: figure connection test; HE: hepatic encephalopathy; HRQOL: health-related quality of life; INR: international normalized ratio; ISHEN: International Society For Hepatic Encephalopathy and Nitrogen Metabolism; K^+: potassium; Ltt: line tracing test; MELD: Model For End-Stage Liver Disease; MHE: minimal hepatic encephalopathy; Na^+: sodium; NCT: number connection test; OR: odds ratio; PHES: psychometric hepatic encephalopathy score; Q1,Q3: quartile 1 and quartile 3; SD: standard deviation; SDT: serial dotting test; SPSS: Statistics Package for Social Sciences; TIPS: transjugular intrahepatic portosystemic shunt; WBC: white blood cells

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diminished total Sickness impact profile score independent of the severity of liver disease and treatment with lactulose led to the resolution of MHE and improved the HRQOL in these patients. Those with MHE experience a higher frequency of overt HE compared to those without[11] and the risk of death was higher in cirrhotic patients with abnormal psychometric tests.[12] The high prevalence of MHE, its effect on various day to day activities and the difficulty in its diagnosis underscore the importance of screening for this condition in patients with cirrhosis and treating it once identified. Because of the subtle nature of its manifestations, MHE often goes unrecognized by patients, their close associates and even the attending physicians. According to one study, while 75% of physicians caring for patients with liver diseases were aware of MHE, only 6.3% screened all of their patients for MHE and 64.7% never screened or screened less than 10% of patients with cirrhosis.[13] Though MHE can be diagnosed with a simple and inexpensive paper and pencil office-based test nearly 53% of physicians cited lack of time as the main reason for non-testing.[13] Clearly, there is a need to increase the screening practices for MHE as otherwise nearly one out of two patients with cirrhosis will be denied therapy for this complication. Targeted screening of high-risk groups if any will help save time and help in identifying those most in need of therapy. This study was carried out with an aim to characterize the prevalence of MHE in patients with liver cirrhosis and to determine factors associated with MHE to help identify patient subgroups with a higher risk of MHE for targeted screening.

MATERIALS AND METHODS

Patients and Methods

Patients diagnosed with cirrhosis of liver aged between 18 and 75 years presenting to our department between April 2015 and November 2016 were included in the study. Those with overt HE at the time of evaluation or within the previous 6 weeks, those with alcohol intake, gastrointestinal hemorrhage or spontaneous bacterial peritonitis within the previous 6 weeks, those who had undergone transjugular intrahepatic portosystemic shunt (TIPS) or shunt surgery, those with significant cardiac or respiratory diseases, known neurologic disease (Alzheimer's disease, Parkinson's disease etc.), renal failure (serum creatinine > 1.5 mg/dl), electrolyte imbalance (sodium < 125 meq/L, potassium < 3.5 meq/L or >5.2 meq/L), hepatocellular carcinoma, recent use of drugs affecting psychometric performance (antidepressants, antiepileptic, sedatives, psychotropic drugs etc.) or known to improve psychometric performance (rifaximin, probiotics, branched chain amino acids etc.) and those with poor vision were excluded as were pregnant women.

All patients underwent detailed clinical, biochemical and imaging evaluation. The diagnosis of cirrhosis of liver was based on clinical, imaging, laboratory and endoscopic findings, and liver biopsy if available. Investigations for etiology of cirrhosis were performed as per standard recommendations.[14–20] Evaluation for the presence of overt hepatic encephalopathy was performed, based on the West Haven criteria by a senior gastroenterologist.[3]

All enrolled subjects underwent portosystemic encephalopathy (PSE) syndrome test and a psychometric hepatic encephalopathy score (PHES) was calculated. The PSE test was chosen for the study in accordance with recent guidelines by the AASLD as it is a well-studied and well-validated test that can be used in single-center studies provided that normative reference data are available.[3] A version of PSE test modified for the Indian population as recommended by Dhiman et al.[21] was used. This battery consists of five tests—the number connection test A (NCT-A), figure connection test A (FCT-A), serial dotting test (SDT), digit symbol test (DST), and line tracing test (LTT). The LTT gives two scores which are LTT (time) and LTT (error) based on the time taken to complete the test and the number of errors made while doing so respectively. The PSE test has been validated in the Indian population and normative data were constructed for each test using multiple linear regression equations based on age and education.[21] *z*-Scores were calculated for each test and scores higher than +1 were allotted +1 points, those between +1 to −1 were allotted 0 points, those between −1 and −2 were given −1 points, those between −2 and −3, −2 points and those below - 3 were given −3 points. Individual test points were summed up to derive a composite score with a maximum of + 6 and a minimum of −18 points. MHE was diagnosed if PHES was ≤ -5 points.

Statistical Analysis

Descriptive statistics were computed for all continuous variables. Data processing was performed using Statistics Package for Social Sciences (SPSS) version 15. MHE and non MHE groups were compared for multiple factors including etiology of cirrhosis, the size of esophageal varices, various biochemical parameters, Child-Turcotte-Pugh score (CTP) and Model For End-Stage Liver Disease (MELD) scores. Univariate comparisons were performed using the Student-*t* test, Mann–Whitney *U* test or χ^2 test as appropriate. Factors which showed statistically significant association with MHE were analyzed using logistic regression analysis. A *P*-value of less than 0.05 was taken as being statistically significant.

RESULTS

A total of 365 patients were evaluated for inclusion into the study of which 185 patients were excluded because of recent upper gastrointestinal bleed (52, 28.11%), overt HE (16, 8.6%), lactulose or lactitol use for secondary prophylaxis of HE (36, 19.46%), antibiotic use including that for SBP prophylaxis (43, 23.24%), difficult vision

Table 1 Baseline Characteristics of the Study Population.

Age in years (range)	23–76 years
Male/female, *n* (%)	166 (92.2%)/14 (7.7%)
Education	
None/1–10 years/>10 years, *n* (%)	19 (10.6%)/112 (62.2%)/49 (27.2%)
Etiology	
Alcohol, *n* (%)	97 (53.9%)
Cryptogenic cirrhosis, *n* (%)	44 (24.4%)
Chronic hepatitis B infection, *n* (%)	17 (9.4%)
Chronic hepatitis C infection, *n* (%)	8 (4.4%)
Others, *n* (%)	14 (7.8%)
CTP class A/B/C, *n* (%)	75 (41.7%)/82 (45.6%)/23 (12.8%)
MELD score, mean (SD)	12.57 (4.05)

Abbreviations: CTP: Child Turcotte Pugh score; MELD: Model For End-Stage Liver Disease.

(Uncorrected refractory errors, cataract, glasses not available at time of testing—11, 5.95%), renal failure and dyselectrolytemia (19, 10.27%) and hepatocellular carcinoma (8, 4.32%). The remaining 180 patients were evaluated further. Their demographic and biochemical characteristics are shown in Table 1. Ninety-four (52.2%) of the 180 patients screened had MHE on psychometric analysis. PHES and individual test scores in MHE and non-MHE groups are shown in Table 2.

On univariate analysis, MHE was associated with lower serum albumin levels, higher serum bilirubin, serum aspartate amino transferase (AST) levels, international normalized ratio (INR), CTP score and MELD scores (Table 3). A logistic regression analysis was performed using total bilirubin, AST, INR, albumin, CTP score and MELD score as variables. Only CTP score was significantly associated with the presence of MHE ($P = 0.002$) (Table 4). A higher CTP score was associated with a higher risk of the presence of MHE. The Odds ratio for having MHE was significantly higher with CTP classes of B (OR-3.719, $P \leq 0.001$) and C (OR-15.072 $P \leq 0.001$) compared to class A (Table 5).

DISCUSSION

Previous studies have shown a wide variation in the prevalence of MHE in patients with cirrhosis ranging from 35% to 75%[12,21–23] possibly because of the differences in the inclusion and exclusion criteria and also from the differences in the tests used for diagnosis. While a number of psychometric tests have been advocated for the diagnosis of MHE over the years[24] a paper and pencil test battery identified by Weissenborn et al.[25] is widely used and has been endorsed by the International Society For Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN),[26] the Working Party of the 1998 World Congress of Gastroenterology[2] and AASLD as a well validated test in MHE. However, these tests are influenced by the age and educational status of the respondents and application of normative data corrected for age and educational qualification have been recommended.[27] The prevalence of MHE of 52% found in our study shows that this condition is common in cirrhotic patients attending tertiary care hospitals, and is more prevalent than overt HE. This figure is similar to those reported by other recent studies using PSE tests with modifications as mentioned above.[21,23] Use of the figure connection test in place of NCT-B enabled a large portion of patients in our hospital who are unfamiliar with English alphabets to be enrolled into the present study. Age and education specific normative data were used for calculating the PHES to avoid age and education related biases.

Previous studies have shown that various factors like the severity of the liver disease, the presence of varices,[28,29] alcohol as etiology,[29] ammonia levels[30–32] etc. predicted the occurrence of MHE. However, none of these variables demonstrated the ability to predict MHE in this study. When compared with patients in CTP class A, those in classes B and C were at a higher risk of suffering from MHE with an odds ratio of 3.72 and 15.072 ($P \leq 0.001$ for both)

Table 2 PHES and Individual Test Scores in MHE and Non-MHE Group.

Test	No MHE (*n* = 86)		MHE (*n* = 94)	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)
NCT (seconds)	46.01 (8.52)	46 (40, 52)	90.15 (39.85)	81 (59, 104)
FCT (seconds)	63.78 (14.5)	65 (52.75, 72.25)	116.12 (42.44)	102 (88.5, 130.5)
DST (number)	19.26 (8.79)	19 (12, 25)	10.67 (42.44)	9 (7, 13)
SDT (seconds)	47.12 (8.82)	45 (40.75, 52)	70.59 (21.56)	67 (57.75, 82.25)
Ltt TIME (seconds)	107.27 (68.94)	97 (86.75, 110.5)	157.07 (48.707)	154 (123, 189.25)
Ltt ERROR (number)	17.42 (11.94)	17 (9, 25)	30.98 (21.716)	27.5 (12, 45)
PHES	−2.42 (1.63)	−3 (−4, −1)	−10.07 (2.42)	−10 (−12, −8)

Abbreviations: MHE: minimal hepatic encephalopathy; SD: standard deviation; Q1, Q3: Quartile 1 and Quartile 3; NCT: number connection test; FCT: figure connection test; DST: digit symbol test; SDT: serial dotting test; Ltt: line tracing test.

Table 3 Factors Associated With Minimal Hepatic Encephalopathy (MHE) on Univariate Analysis.

Variable	MHE present	MHE absent	*P* value
Hemoglobin in mmol/L, mean (SD)	6.96 (1.12)	7.24 (1.39)	0.125
WBC $\times 10^9$/L cells, median (quartiles)	5.9 (4.6, 8.725)	6.15 (4.775–8.1)	0.213
Platelet count $\times 10^9$/L cells median (quartiles)	108 (71.75, 142.75)	110 (78.25, 170.5)	0.415
Total bilirubin in µmol/L median (quartiles)	36.77 (25.65, 75.33)	24.8 (15.39, 36.34)	<0.001
AST in ukat/L median (quartiles)	1 (0.61, 1.47)	0.81 (0.59. 1.12)	0.011
ALT in ukat/L median (quartiles)	0.46 (0.36, 0.75)	0.53 (0.37, 0.77)	0.372
Serum albumin in g/L, mean (SD)	30.372 (6.695)	35.276 (7.566)	<0.001
INR, mean (SD)	1.381 (0.280)	1.241 (0.196)	<0.001
Urea in mmol/L median (quartiles)	6.07 (4.64, 9.02)	5.71 (4.29, 7.86)	0.181
Creatinine µmol/L mean (SD)	79.31 (22.29)	80.2 (16.04)	0.758
Na^+ mmol/L, mean (SD)	135.04 (4.308)	135.86 (3.786)	0.179
K^+ mmol/L, mean (SD)	4.178 (0.453)	4.251 (0.418)	0.261
CTP score, mean (SD)	7.93 (1.730)	6.38 (1.504)	<0.001
MELD score, mean (SD)	13.86 (4.394)	11.16 (3.132)	<0.001
Variceal size			
None/small/large, *n* (%)	7 (43.7%)/31 (51.7%)/56 (53.8%)	9 (56.3%)/29 (48.3%)/48 (46.2%)	0.749
Etiology of cirrhosis			
Alcohol/cryptogenic/hepatitis B/hepatitis C/others, *n* (%)	52 (53.6%)/23 (52.3%)/ 7 (41.2%)/6 (75%)/6 (42.9%)	45 (46.4%)/21 (47.7%)/ 10 (58.8%)/2 (25%)/8 (57.1%)	0.548

Abbreviations: WBC: white blood cells; AST: aspartate transaminase; ALT: alanine transaminase; INR: international normalized ratio; Na^+: sodium; K^+: potassium; CTP: Child Turcotte Pugh score; MELD: Model For End-Stage Liver Disease.

Table 4 Multiple Logistic Regression Analysis for Predictors of Minimal Hepatic Encephalopathy.

Variable	OR	95% C.I. for EXP (B)		*P* value
		Lower	Upper	
Total bilirubin	1.172	0.872	1.575	0.293
AST	1.001	0.991	1.010	0.91
INR	0.791	0.237	2.638	0.702
Albumin	1.214	0.684	2.156	0.508
CTP score	1.751	1.227	2.501	0.002
MELD score	0.985	0.840	1.157	0.858

Abbreviations: OR: odds ratio; C.I.: confidence interval; AST: aspartate transaminase; INR: international normalized ratio; CTP: Child Turcotte Pugh score; MELD: Model For End-Stage Liver Disease.

Table 5 Distribution of Minimal Hepatic Encephalopathy Among Different Child Turcotte Pugh Classes.

CTP class	MHE absent	MHE present	Odds ratio (CI)	*P* value
Class A	52	23	–	–
Class B	31	51	3.719 (1.916–7.221)	<0.001
Class C	3	20	15.072 (4.071–55.80)	<0.001

Abbreviations: MHE: minimal hepatic encephalopathy; CTP: Child Turcotte Pugh.

respectively. Disagreement still persists in the literature about the ability of CTP score to predict MHE. While many studies have shown that cirrhotic patients with CTP class B and C have a higher prevalence of MHE compared to CTP class A,[29,33,34] a few have not.[35,36] Das et al. reported that though the prevalence of MHE was similar across all CTP classes, the severity of MHE as determined by the number of abnormal psychometric tests was greater in patients with more severe liver disease.[28] While all patients with cirrhosis need to be screened for

MHE, it is clear from our results that the highest benefit of screening will accrue in those with CTP classes of B and C.

The significance of MELD in the prediction of MHE remains controversial too, with some studies showing significant association[36] and others disagreeing.[34,37] The MELD scores were not associated with the occurrence of MHE in the present study. A meta-analysis studying the development of HE in cirrhotic patients after TIPS showed that a high CTP score was associated with increased risk of HE while MELD score failed to predict the same.[38] Yoo et al. studied the relationship between MELD and the severity of HE and found that MELD did not correlate with the severity of HE and the presence of ascites.[39] In a meta-analysis comparing CTP score and MELD scores for predicting mortality Peng et al. found that though MELD and CTP score had similar prognostic values, each of these had some advantage over the other under different conditions.[40] Hence it may be inferred that though both CTP and MELD scores measure the severity of liver disease their ability to predict MHE differs and CTP may be better for predicting the this complication.

Because of its high prevalence it would be ideal to screen all eligible patients with cirrhosis for MHE irrespective of their CTP class. Paucity of time being the major reason reported for not testing for MHE by physicians and gastroenterologists, screening of patients in CTP class B and C will yield the highest results. With this approach, we would save time by screening 41.7% fewer patients but still identify 75.5% of patients with MHE. Nonetheless 24.5% of patients with MHE who belong to CTP class A would be missed by this strategy. Thus, it would be important to identify patients in CTP class A who are at high risk from MHE such as drivers and operators of heavy machinery, as well as those who have poor quality of life which cannot be attributed to other factors.

In summary, MHE is a common complication in patients with cirrhosis of liver. While CTP scores independently predicted the presence of MHE, MELD, serum creatinine, sodium, potassium, blood urea, serum Total bilirubin, AST, ALT and albumin did not. Patients with CTP class B and C had a higher risk of suffering from MHE than CTP class A suggesting that selective screening of patients belonging to CTP class B and C would save time but still identify three-quarters of the patients with MHE.

CONFLICTS OF INTEREST

The authors have none to declare.

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