Critical flickering frequency test: a diagnostic tool for minimal hepatic encephalopathy

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Background Minimal hepatic encephalopathy (MHE) is underestimated. It affects 30–55% of patients with liver cirrhosis and can change their daily functions. Psychometric tests are sensitive in diagnosing MHE, but interpretation is difficult. Availability of a simpler diagnostic tool for MHE is mandatory. Critical flicker frequency (CFF) is a simple diagnostic test.

Aim The aim of this study was to assess the diagnostic accuracy of CFF test for MHE.

Patients and methods A total of 86 patients with cirrhosis with negative history of overt hepatic encephalopathy were included. History, clinical examination, laboratory investigations, and abdominal ultrasonography data were collected. Arabic version of number connection test, serial dotting test, and line tracing test were done. Total psychometric hepatic encephalopathy score (PHES) was used to diagnose MHE. CFF was done for all patients with MHE diagnosis at 39 Hz.

Results Of the 86 patients, 45 (52.3%) had MHE with PHES. Patients with MHE had significantly older age, presentation with jaundice, ascites, lower hemoglobin level, lower serum albumin, prolonged INR, higher Child class and score ($P \leq 0.001$), and higher model of end stage liver disease score ($P = 0.001$) than patients without MHE. In comparison with PHES, CFF has a sensitivity of 91.1 ± 8.32%, specificity of 92.7 ± 7.96%, positive predictive value of 93.2 ± 7.44%, and negative predictive value of 90.4 ± 8.91%. In receiver operating characteristic curve, CFF is excellent in diagnosis of MHE, with area under the curve 0.937 ($P < 0.001$).

Conclusion MHE is common among patients with liver cirrhosis. CFF is a simple, rapid, noninvasive test for diagnosis of MHE, with a very good accuracy at 39 Hz. Eur J Gastroenterol Hepatol 31:1030–1034

Introduction

Minimal hepatic encephalopathy (MHE) describes patients with chronic liver disease or cirrhosis who have no symptoms on clinical or neurological examination, but with deficits in some cognitive areas that can only be measured with neuropsychometric testing [1]. It is an important disorder that may seriously impair daily functioning, quality of life, and driving competency in those patients [2–4]. The prevalence of MHE varies between 30 and 55% in patients with liver cirrhosis, dependent on the diagnostic criteria used [5]. MHE is considered to be clinically relevant for two reasons. First, it could be a proceeding of clinical manifest hepatic encephalopathy. Second, the psychometric deficit found in MHE could have a disadvantaging influence on patients' daily functioning [2]. However, few hepatologists really screen patients for MHE owing to time-consuming neuropsychological and neurophysiological tests [6].

There are many diagnostic tests for MHE, but no universal 'gold standard' test. The Expert Working Group in 1998 suggested that the psychometric hepatic encephalopathy score (PHES) should be considered the gold standard test [1]. However, the final results of the psychometric tests are influenced by the grade of cirrhosis, the educational level and the cultural background of the examined population, as well as subjected to the effect of repeated learning [7]. So, a quick, accurate, objective, cost-effective, and well-validated diagnostic test is an unmet clinical need and would simplify the early management algorithm for this condition [8].

Critical flickering frequency (CFF) was devised originally as an ophthalmological test used to measure visual acuity and to screen for optic nerve lesions [9]. CFF is a reproducible parameter with only little bias by training effects, educational level, and daytime variability [10]. The CFF has been in limited clinical and research use for a decade, but its diagnostic accuracy has been subjected to quantitative review in limited number of studies.

Aim

The aim of this study was to evaluate the CFF test in diagnosis of MHE.

Patients and methods

This prospective cross-sectional study was conducted on 86 cirrhotic patients admitted to Hepatology, Gastroenterology and Infectious Diseases Department, Benha University Hospital, in the period from June 2013 to February 2014, to evaluate CFF test in diagnosis of MHE. The study protocol was approved by Benha Faculty

European Journal of Gastroenterology & Hepatology 2019, 31:1030–1034

Keywords: cirrhosis, critical flickering frequency, hepatitis C virus, minimal hepatic encephalopathy

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Received 6 December 2018 **Accepted** 7 January 2019

of Medicine Ethical Committee. A written informed consent was taken from all patients before enrollment in the study. Diagnosis of cirrhosis was based on presence of liver biopsy examination with stage IV metavir fibrosis or clinical, laboratory, ultrasonography, or endoscopic findings confirming liver cirrhosis.

Patients were excluded from the study if they have present or past history of overt hepatic encephalopathy (OHE); alcohol intake; poorly controlled diabetes mellitus; severe respiratory, cardiac, or renal disease; neurodegenerative disease; oculovisual dysfunction; portosystemic shunt operation; use of psychoactive medication; or illiterate.

All patients were subjected to full history taking through a pre-prepared standard sheet, and clinical examination with special emphasis on signs of liver cell failure. Laboratory investigations including complete blood picture, liver function tests, kidney function tests, and HCV antibodies by third-generation enzyme-linked immune sorbent assay were collected. Abdominal ultrasonography was done to all patients.

All patients were subjected to the psychometric testing as a gold standard for diagnosis of MHE and CFF test at the same day by two different investigators independently. Both investigators were previously trained for applying and interpreting the test result.

Psychometric testing

A battery of four paper-and-pencil-based neuropsychological tests was used. The paper-and-pencil test battery (conventional PHES) consisted of the number connection test A (NCT-A), line tracing test (LTT; time and errors), and serial dotting test (SDT). Test results were considered abnormal when they were outside 1 SD from the mean of a large age-matched control population, using data provided by the manufacturer of the Vienna Test System. Each test is evaluated separately and recorded either on accuracy or time to completion. After the raw value of each test is generated, it is converted into score points using the scoring norms. Using the age of the patient and the score of each subset, we generate the total score for the psychometric test battery. The age-related norms range from '+1' for scores better than 1 SD above the normal mean, to '−3' for the scores more than 3 SDs below the normal mean. The base line performance is assigned a score of '0'. Because the LTT generates two values (time and errors), there are a total of four measurements with a total score ranges from '+ 4' to '−12'. A total value equals or less than '−2' was considered pathological and diagnostic of MHE.

Critical flicker frequency

The test was done using the Hepatonorm analyzer (R&R Medi-Business Freiburg GmbH, Freiburg, Germany) as a test for the CFF detection value. A patient puts the Hepatonorm analyzer headset on his/her eyes; if the patient uses eyeglasses, he/she still can use it while he/she is using the headset. The patient is asked to hold the stop button and press it when he/she observes the change in the illumination frequency. This process is repeated nine times. The investigator holds the control unit with touch screen to observe the frequency result and record it.

The test was done in a quiet, well-illuminated place under our observation after illustration of the test instructions. CFF was considered diagnostic when the cutoff value was less than 39 Hz [11].

Statistical analysis

The sample size was calculated based on an estimation of prevalence of MHE among patients with liver cirrhosis of 50%. Minimum sample size for evaluation of a diagnostic test based on an estimated test sensitivity of 95% and confidence interval of 0.07 was 75 patients with 95% confidence. We included 86 patients. The collected data were summarized in terms of mean ± SD and range for quantitative data and frequency and percentage for qualitative data. Comparisons between the different study groups were carried out using the χ^2-test and Fisher exact test when indicated to compare proportions as appropriate. The two-tailed Student *t*-test (*t*) was used to detect difference in the mean between two parametric data, whereas the Mann–Whitney test (*z*) was used to compare two nonparametric data. Receiver operating characteristic curve (ROC) analysis was used to test the diagnostic accuracy of CFF test in diagnosis of MHE. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve were calculated. Statistical significance was accepted at *P* value up to 0.05. A *P* value less than 0.001 was considered highly significant.

Results

Based on the paper-and-pencil test battery (conventional PHES), we found that of 86 patients with liver cirrhosis, 45 (52.3% with 95% CI 10.56%) had MHE. Table 1 shows comparison between patients with and without MHE regarding demographic and clinical parameters, where patients with MHE have significantly older age, more pallor, jaundice, and ascites.

Regarding laboratory findings, there was a highly statistically significant difference between both groups regarding hemoglobin ($P < 0.001$), red blood cells count ($P < 0.001$), albumin levels ($P < 0.001$), total bilirubin level ($P = 0.003$), prothrombin time (PT) ($P < 0.001$), and INR ($P < 0.001$; Table 2).

Child–Pugh and model of end stage liver disease (MELD) scores [12,13] were calculated, and the two groups were compared, where there is a significant difference between the two groups regarding either scores or Child–Pugh classes (Table 3).

Comparison of patients with and without MHE showed that mean CFF score in MHE was 37.5 ± 1.9 Hz in comparison with patients without MHE (40.7 ± 1.6 Hz)

Table 1. Comparison between patients with and without minimal hepatic encephalopathy regarding demographic and clinical parameters

Parameters	MHE (*N* = 45) [*n* (%)]	No MHE (*N* = 41) [*n* (%)]	*P* value
Age (years)	54.7 ± 8.3	47.1 ± 8.5	**< 0.001**
Sex (male)	28 (62.2)	31 (75.6)	0.2
Jaundice	30 (66.7)	8 (19.5)	**< 0.001**
Pallor	29 (64.4)	13 (31.7)	**0.002**
Hepatomegaly	3 (6.7)	1 (2.4)	0.4
Splenomegaly	23 (52.3)	20 (48.8)	0.8
Ascites	26 (57.8)	5 (12.2)	**< 0.001**

Bold indicates statistically significant *P* values.
MHE, minimal hepatic encephalopathy.

Table 2. Comparison between patients with and without minimal hepatic encephalopathy regarding laboratory parameters

Parameters	MHE ($N=45$)	No MHE ($N=41$)	P value
HB (g/dl)	9.8±1.5	11.4±1.9	**<0.001**
RBCs (10^6/μl)	3.5±0.91	4.2±0.99	**<0.001**
WBCs (10^9/l)	7.3±3.2	6.1±2.77	0.07
Platelets ($\times10^3$/l)	95.6±68.1	129±59.9	0.02
AST (IU/l)	46.2±29.5	38.9±16.8	0.2
Albumin (g/dl)	3±0.5	3.6±0.49	**<0.001**
Total bilirubin (mg/dl)	2±0.99	1.4±0.6	**0.003**
PT (s)	18.3±3.1	15.9±2.4	**<0.001**
INR	1.7±0.3	1.4±0.2	**<0.001**
Serum creatinine (mg/dl)	1.2±0.4	1.1±0.4	0.2
Blood urea (mg/dl)	51.4±22.1	41.5±14.8	0.2

Bold indicates statistically significant P values.
AST, aspartate transferase; HB, hemoglobin; MHE, minimal hepatic encephalopathy; PT, prothrombin time; RBCs, red blood cells; WBC, white blood cells.

Table 3. Comparison between patients with and without minimal hepatic encephalopathy regarding MELD score and Child–Pugh score and class

Parameters	MHE ($N=45$)	No MHE ($N=41$)	P value
MELD score	16.1±5.4	12.2±4.6	**0.001**
Child–Pugh score	8.5±2.5	6.1±1.6	**<0.001**
Child–Pugh class [n (%)]			
A	12 (26.7)	31 (75.6)	**<0.001**
B	15 (33.3)	8 (19.5)	
C	18 (40)	2 (4.9)	

Bold indicates statistically significant P values.
MELD, model of end stage liver disease; MHE, minimal hepatic encephalopathy.

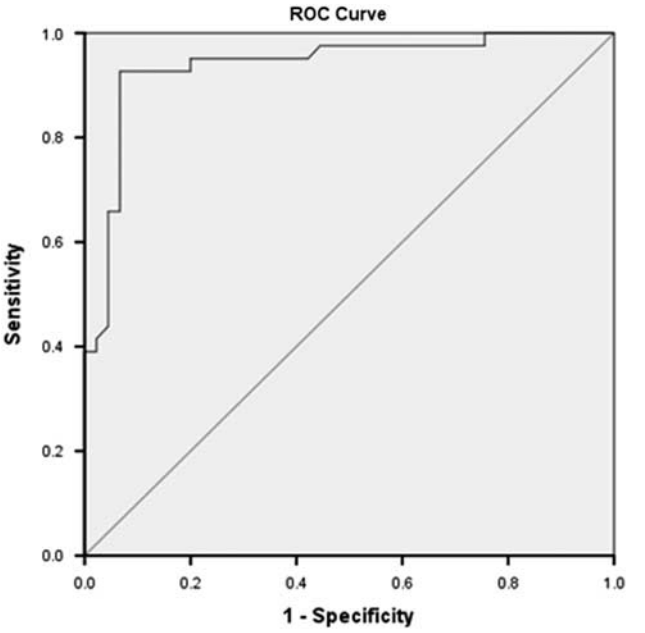

Fig. 1. Receiver operating characteristic curve (ROC) showing sensitivity, specificity, and accuracy of critical flicker frequency in diagnosis of minimal hepatic encephalopathy with area under the curve 0.937.

($P<0.001$). CFF score below 39 Hz was considered positive test for diagnosis of MHE. Based on that cutoff, of the 45 patients with MHE (with PHES), 41 were tested positive, and of 41 patients without MHE (with PHES), 38 were tested negative. CFF test below 39 Hz has a sensitivity of 91.1±8.32% (82.78–99.42), specificity of 92.7±7.96% (84.74–100), PPV of 93.2±7.44% (85.76–100), and NPV of 90.4±8.91% (81.49–99.31). Evaluation of the accuracy of CFF test with the ROC curve showed that the test is excellent in diagnosis MHE, with area under the curve 0.937, with P value less than 0.001 (Fig. 1).

Discussion

MHE, previously known as subclinical or latent encephalopathy is the earliest form of hepatic encephalopathy and can affect up to 80% of cirrhotic patients [14]. By definition, it has no obvious clinical manifestation and is characterized by neurocognitive impairment in attention, vigilance, and integrative function. MHE has been shown to affect daily functioning, quality of life, driving, and overall mortality [15]. The burden of MHE is not obviously apparent. It is often believed to lack a significant effect on patient quality of life or ability to function, and thus, frequently remains undiagnosed. However, studies have shown that it is the leading cause of cognitive dysfunction in cirrhotic patients [4]. Furthermore, MHE is associated with an increased risk of developing OHE and overall mortality [16].

MHE is not detectable by routine physical or neurological examinations, and a specific neuropsychological/neurophysiological test is needed for its diagnosis [17]. The prevalence of MHE varies according to the diagnostic tool used in its detection [18]. The PHES is internationally recommended as the gold standard for the diagnosis of MHE [19]. The PHES is composed of five tests, NCT-A, NCT-B, SDT, LTT, and digit symbol test. PHES can be used to assess motor speed, motor accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction, and memory [20]. The PHES has been standardized in several countries, such as Germany, Italy, Spain, India, Korea, and Mexico [21]. The disadvantages of the test are the occurrence of learning effects, which limits repeatability, and the strong emphasis on fine motor skills. There are also differences as to where the border between normal and pathological should be drawn [17]. So the availability of a simpler and more reliable diagnostic test of MHE is mandatory and makes the bedside diagnosis easier and applicable on a wider scale.

In the present study, 86 HCV cirrhotic patients with negative history of OHE were investigated for the presence of MHE with PHES as a gold standard for diagnosis of MHE. Diagnostic accuracy of CFF was investigated in those patients in comparison with PHES. We diagnosed MHE in 45 patients out of 86 (52.3%) patients without overt encephalopathy by using a test battery consisting of a combination of four psychometric tests (NCT-A, SDT, and LTT with its two values time and errors). This figure estimate that more than half of patients with liver cirrhosis had MHE is considered a red flag sign. Almost a near figure was reported by Dhiman *et al.* [22], who found that 48.5% of cirrhotic patients without overt encephalopathy had MHE using a combination of NCT-A and B and figure connection-A and B. Moreover, this was in agreement with a study by Maldonado-Garza *et al.* [23], who found that the prevalence of MHE to vary between 29.2 and 57.1%.

However, some studies reported a lower figure than our study, such as Tsai *et al.* [24], who found that 28.7% of the studied cirrhotic patients had MHE, and Romero-Gomez *et al.* [25], who found that 30% of the studied cirrhotic patients had MHE. On the contrary, there were studies that reported higher figures, at 71.5 and 84%, respectively [2,26]. The difference in the reported figures is possibly attributed to the difference in degree of cirrhosis among different studies, as patients with Child C cirrhosis are suspected to have higher prevalence of MHE than patients with Child A cirrhosis. The second cause for this variation is the method of diagnosis as some papers used only two psychometric tests and others used the total PHES battery. The third cause is owing to the difference in numbers of patients in each study, which makes the CI different.

In this study, we found that the mean age of patients with MHE was (54.7 ± 8.3 years), which was higher than the mean age of patients without MHE (47.1 ± 8.5 years), with high statistically significant difference between both groups ($P < 0.001$). Most of the published data have found that patients with liver cirrhosis and MHE were significantly older than those without MHE based on PHES tests [21,24]. These findings can be explained by the published data about the neuropsychological performance of patients with liver cirrhosis that can be influenced by age [7,27].

In the present study, there is no significant difference between MHE and non-MHE groups regarding white blood cells, platelets, alanine transferase, or aspartate transferase. However, patients with MHE had statistically significant prolonged PT ($P < 0.001$), INR ($P < 0.001$), lower serum albumin levels ($P < 0.001$), lower hemoglobin levels ($P < 0.001$), and higher total bilirubin levels ($P = 0.003$) than patients without MHE. Previous published data reported that patients with MHE exhibited significantly lower levels of albumin and total protein and prolonged PT, INR [28], and bilirubin level [10] than patients without MHE ($P < 0.001$). However, there was no correlation regarding alanine transferase or aspartate transferase. It appears from these results that patients with laboratory data that indicate advanced hepatic diseases with higher grades of cirrhosis had more MHE than those with lower grades of cirrhosis. This was confirmed by the results that we found that patients with high MELD score or high Child–Pugh score or class had significantly more MHE than those with lower score and class (Table 3). The association of MHE and grade one hepatic encephalopathy (covert hepatic encephalopathy) with higher MELD score was previously published by Greinert *et al.* [29] and Zacharias *et al.* [30]. This information may lead to a recommendation that patients with liver cirrhosis especially those with advanced cirrhosis should be screened for MHE.

The difficulty of application of the PHES for screening of patients leads to searching for another simple diagnostic test for MHE. One of these tests is CFF test, which measures the CFF threshold at which light pulses are perceived as flicker. CFF is a well-established neurophysiological technique that measures the ability of the central nervous system to detect flickering light, and which is directly influenced by cortical activity. The highly statistical significant difference between patients with and without MHE in detection flickering light, which we found here, was previously reported by Dhiman *et al.* [16], who demonstrated that the mean CFF was significantly lower among patients with cirrhosis with evidence of MHE (39.06 ± 3.66 Hz) compared with patients with cirrhosis without MHE (41.39 ± 3.32 Hz) ($P = 0.001$). Similar data were also reported by Kircheis *et al.* [10].

A large meta-analysis was done by Torlot *et al.* [8], which included nine studies with total number of 626 patients and evaluated the CFF test for diagnosis of MHE. There is wide variability in the studies regarding sensitivity and specificity of the test. Sensitivity ranged from 21% [31] to more than 85% [32], and specificity ranged from 72.9 [33] to 100% [11,34]. In this meta-analysis, the CFF only had a moderate pooled sensitivity of 61% (95% CI: 55–67), but a good specificity of 79% (95% CI: 75–83), but the symmetrical ROC curve had an area under receiver operating characteristic curve of 0.84, indicating that CFF was effective in discriminating patients with MHE from those without MHE.

Our evaluation of CFF with a cutoff less than 39 Hz as a diagnostic test for MHE, showed that CFF test had a sensitivity of 91.1 ± 8.32% (82.78–99.42), a specificity of 92.7 ± 7.96% (84.74–100), a PPV of 93.2 ± 7.44% (85.76–100), and a NPV 90.4 ± 8.91% (81.49–99.31), with area under receiver operating characteristic curve of 0.937 and *P* value less than 0.001. Using CFF with cutoff less than 39 Hz appeared very important in prediction of survival and development of OHE [35].

Conclusion

MHE is common among patients with liver cirrhosis. CFF is a simple, rapid, noninvasive test that can be used for diagnosis of MHE with a very good accuracy at a cutoff value of 39 Hz.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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