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ORIGINAL ARTICLE

Validity of Inhibitory Control Test and Critical Flicker Frequency to Diagnose Minimal Hepatic Encephalopathy

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ABSTRACT

AIM: Minimal hepatic encephalopathy (MHE) impairs quality of life and predicts overt hepatic encephalopathy (HE) in cirrhotic patients. Recent studies into the inhibitory control test (ICT) and critical flicker frequency (CFF) tests are encouraging since these tests can increase the rate of MHE diagnosis. We aimed to assess the validity of ICT and CFF in the diagnosis of MHE.

MATERIAL AND METHODS: Out of 68 cirrhotic patients, 48.5% (33 patients) were diagnosed as MHE on the basis of psychometric tests. On these 33 patients, ICT and CFF were applied. 35 healthy subjects served as controls for the ICT and CFF.

RESULTS: Taking > 9 lures as positive ICT according to receiver operator characteristic (ROC) curve, the sensitivity, specificity, PPV and NPV were 90.9%, 37.1%, 57.6%, 81.3% respectively. Cirrhotics with MHE had significantly higher lures (22 ± 7.8 *vs* 11 ± 5.6, $p < 0.001$) or (56% *vs* 28%) and lower target response (90% *vs* 97%) compared with controls. For CFF taking < 37 Hz as cut-off, the sensitivity, specificity, PPV and NPV were 57.5%, 94.3%, 90.5% and 70.2%. We also found that CFF is less time consuming as compare to ICT.

CONCLUSION: ICT and CFF are useful tools to assess MHE. CFF to be less time to consume, less sensitive but more specific than ICT.

Key words: Minimal Hepatic Encephalopathy; Inhibitory Control Test; Critical Flicker Frequency

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INTRODUCTION

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome present in patients with chronic or acute liver disease after exclusion of other brain diseases. According to recent guidelines (AASLD/EASL 2014), hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma[1]. Patients with cirrhosis with normal neurologic and mental examination can present minimal forms of HE, showing intellectual function impairment that cannot be detected through general clinical examination but can be unveiled using specific neuropsychologic and neurophysiologic tests[2]. MHE has significant negative impact on

health-related quality of life and associated with driving impairment, vehicle accidents and reduced survival[3-8]. Testing for MHE is important, as it may progress to overt hepatic encephalopathy, indicate poor quality of life and reduced socioeconomic potential[1]. Diagnostic tests for MHE should be easy to use, valid, less time consuming and reliable. Recent studies into the inhibitory control test and critical flicker frequency tests are encouraging since these tests can increase the rate of MHE diagnosis[9]. In this study, we assessed the validity of ICT and CFF to diagnose MHE in cirrhotics irrespective of its cause.

MATERIALS AND METHODS

Study Design

A single-center, case-control observational study, performed in the department of medicine, division of gastroenterology, Maharaja Yashwant Rao hospital, MGM medical college, Indore, Madhya Pradesh, India on 5 Oct 2012. A total of 68 cirrhotic patients were enrolled who met our inclusion criteria, in which MMSE (Mini Mental Score Examination) and SPT (Standard Psychometric Test) was done. In this study, MMSE ≥ 24 and positive SPT [ie, impairment in the performance of at least two of the following tests: number connection test-A (NCT-A), number connection test-B (NCT-B), block design test (BDT) and digital symbol test (DST)] were taken as gold standard to diagnose MHE as per recommendation by Working party at the 11th World Congress of Gastroenterology, Vienna, 1998[10].

After performing MMSE and SPT, 33 patients had MMSE ≥ 24 and positive SPT and were labeled as MHE positive. Another set of 35 age and education matched healthy volunteers were taken as controls.

Among these 33 patients and 35 controls, ICT and CFF are applied on the same day. An informed consent was taken from all patients and our study is approved by local ethics committee.

Inclusion Criteria: (1) Patients with cirrhosis irrespective of the cause and irrespective of their medication status without overt hepatic encephalopathy or who recovered from hepatic encephalopathy admitted in our wards and patients who attended outpatient department (Division of Gastroenterology, Maharaja Yashwant Rao Hospital, Indore, Madhya Pradesh, India) were enrolled; (2) Patient with basic education level (at least completed 8 years of education). Cirrhosis was diagnosed on the clinical basis, laboratory tests, endoscopic evidence, sonographic findings and liver histology, if available.

Exclusion Criteria: (1) Overt hepatic encephalopathy (Using West Haven criteria); (2) Patients without basic education level; (3) Patients with chronic kidney disease, active gastrointestinal bleed, Wilson's disease and alcohol intake within 3 months; (4) Previous TIPS (Transjugular intrahepatic portosystemic shunt) or shunt surgery; (5) Significant comorbid illness such as heart, respiratory, or renal failure and any neurologic diseases such as Alzheimer's disease, Parkinson's disease, and nonhepatic metabolic encephalopathies; (6) Hepatocellular carcinoma; (7) Patients on psychoactive drugs, such as antidepressants or sedatives.

Critical Flicker Frequency

The CFF is a portable analyzer, with head-mounted goggles into which the patient is asked to look. The controller evokes an intrafoveal light stimulus, red light pulses at preconfigured wavelength, luminance, luminous intensity, and a specified ratio between the visual impulse and the interval starting from a high frequency of 60 Hz and being gradually reduced. At this high frequency, the light appears steady (fused). The light pulse frequency is gradually decreased, which gives the impression that the light is flickering/pulsating. The patient is asked to register when this change happens by pressing a handgrip button, and this determines the CFF threshold. The test is repeated about 8 to 10 times and the average CFF threshold is calculated. The test takes about 15 to 20 minutes to complete.

The CFF was measured in a quiet, semidarkened room without distracting noises. A portable, battery-powered analyzer was used (Hepatonorm Analyzer; R&R Medi-Business Freiburg GmbH, Freiburg, Germany). The analyzer evokes an intrafoveal light stimulus with defined pulses of light at a wavelength of 650 nm, luminance of 270 cd/m^2, and the luminous intensity of 5.3 mcd. It is a simple, easy-to-use, and reliable tool that is independent of education, gender, age, and literacy.

Inhibitory Control Test

The Inhibitory Control Test (ICT) is a computerized test measuring attention and response inhibition. It consists of a continuous stream of letters presented on a computer screen every 500 milliseconds. The examinee is required to respond when certain alternating patterns involving the letters X and Y (ie, targets) are presented. Examinees must be careful not to respond when X and Y are not alternating (ie, lures). Typically, 1 training session and 6 test runs are completed by the patient, lasting 2 minutes each, with a total of 40 lures, 212 targets, and 1728 random letters in between. The percentage of targets and lures responded to, are recorded. Good psychometric testing will depict lower lure response, higher target response.

Statistical analysis

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data. Results on continuous measurements are presented on Mean ± SD and results on categorical measurements are presented in Number (%). The significance is assessed at 5% level of significance. Student *t*-test (two-tailed, independent) has been used to find the significance of study parameters on a continuous scale between two groups on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on the categorical scale between two or more groups. Receiver operating curve was calculated for ICT for the diagnosis of MHE. The probability level of $p < 0.05$ was set for statistical significance. To the best of our knowledge, there is no study that validated these 2 tests ie, ICT and CFF in the same group of patients.

RESULTS

Between November 2011 and October 2012, all patients were screened. A total of 68 cirrhotic patients were enrolled in our center, in which MMSE (Mini Mental State Examination) and SPT (Standard Psychometric Test) was done to diagnose MHE on a single day. MMSE ≥ 24 and positive SPT [ie, impairment in the performance of at least two of the following tests: Number connection test-A (NCT-A), Number connection test-B (NCT-B), Block design test (BDT) and Digital symbol test (DST)] were taken as the gold standard to diagnose MHE. Out of 68 patients, only 33 patients had MMSE ≥ 24 and positive SPT and were labeled as MHE positive. Another set of 35 age and education matched healthy volunteers were taken as controls. Among these 33 cases and 35 controls, CFF and ICT were applied on a single day.

The baseline characteristics of cases and controls are mentioned in Table 1.

Inhibitory Control Test and CFF

A cut-off of >9 lures per person was used to diagnose MHE based on receiver operating characteristic analysis (Figure 1). The receiver operating characteristic curve had an area under the curve of 0.88 (95% CI 0.791-0.97) for MHE diagnosis using lures with the sensitivity of 91% and specificity of 63%. Of the 33 MHE patients, 30 had > 9 lures and 3 did not while among 35 controls 22 had >9 lures, and 13 had ≤ 9 lures.

The sensitivity, specificity, PPV and NPV of ICT are 90.9%, 37.1%, 57.6% and 81.3% respectively. Cirrhotics with MHE had significantly higher lures (22.5 ± 7.9 *vs* 11.1 ± 5.7, $p < 0.001$) or (56% *vs* 28%) and lower target response (190.6 ± 19.7 *vs* 206 ± 7.3, $p < 0.001$) or (90% vs 97%) compared with controls.

For CFF, a cut-off of < 37 Hz was used to diagnose MHE according to ROC curve (Figure 2). The ROC curve had an area under the curve of 0.87 (95% CI 0.83- 0.92) for MHE diagnosis with the sensitivity of 63% and specificity of 94%. Of the 33 patients, 19 patients had mean CFF < 37 Hz, while among controls only two patients had CFF mean < 37 Hz.

The sensitivity, specificity, PPV and NPV of CFF are 57.5%, 94.3%, 90.5 % and 70.2% respectively. CFF mean of MHE were lower (36.7 ± 0.84 *vs* 48.6 ± 3.5, $p < 0.001$) compared to controls. In our study CFF found it to be less sensitive (57.5% *vs* 90.9%), but more specific (94.3% *vs* 37.1%), having higher positive predictive value (90.5% *vs* 57.6%) and lesser negative predictive value (70.2% *vs* 81.3%) than ICT. Also time requirement for ICT and CFF by MHE patients were higher than controls (17.80 ± 1.26 *vs* 16.08 ± 0.91 mins for ICT and 12.40 ± 0.93 *vs* 10.02 ± 1.21 mins for CFF). The results of ICT and CFF are summarised in Table 2.

Table 1 Baseline Characteristics of cases and controls.

	Cases (n = 33)	Controls (n = 35)	P Value
Age (Years)	41.2 ± 10.9	41.5 ± 9.9	0.886
Sex (M: F)	28: 5	21: 14	0.022
Education (Years)	12.1 ± 2.1	12.2 ± 1.7	0.913
Child Score	8.2 ± 1.8	-	-
Child Class (A: B: C:)	7: 19: 07	-	-
MELD score	16.1 ± 4.7	-	-
Etiology			
Alcohol	24	Nil	
Hepatitis B	10	Nil	
Both	4	Nil	
None	3		
AST (in IU/L)	62.3 ± 24.1	40.5 ± 4.8	< 0.001
ALT (in IU/L)	44.5 ± 21.5	39.8 ± 5.8	0.215
Serum Na+ (meqv/L)	136.5 ± 4.5	139.3 ± 1.7	0.002
Serum Bilirubin (mg/dL)	2.3 ± 0.8	1.1 ± 0.14	< 0.001

MELD: Model for End Stage Liver Disease; AST: Aspartate Transaminase; ALT: Alanine Transaminase.

Table 2 Results of Inhibitory control test and critical flicker frequency to diagnose minimal hepatic encephalopathy.

Variables	Cases (n = 33)	Controls (n = 35)	P value
Number of Incorrect Lure Responses	22.5 ± 7.9	11.1 ± 5.7	< 0.001
Number of Correct Lure Inhibitions	17.8 ± 7.7	28.9 ± 5.7	< 0.001
Number of Correct Target Responses	190.6 ± 19.7	206 ± 7.3	< 0.001
Number of Incorrect Target Misses	20.2 ± 18.6	6 ± 7.3	< 0.001
Total Number of Random Responses	9.9 ± 4.5	6.9 ± 3.1	0.002
CFF Mean (Hz)	36.7 ± 0.8	48.6 ± 3.5	< 0.001
Time for ICT (mins)	17.8 ± 1.3	16.1 ± 0.9	< 0.001
Time for CFF (mins)	12.4 ± 0.9	10.0 ± 1.2	< 0.001

DISCUSSION

Diagnostic tests for MHE abound but are usually limited by their availability, financial, or time constraints. Recent studies into the ICT and CFF are encouraging since these tests can increase the rates of MHE diagnosis without requiring a psychologist.

Our study demonstrates that there is variability in sensitivity, specificity, PPV and NPV of ICT and CFF.

The critical flicker frequency (CFF) measures function at the level of the cortex and has a direct correlation with psychometric tests[11]. This test applies the theory that the pathogenesis of HE comprises

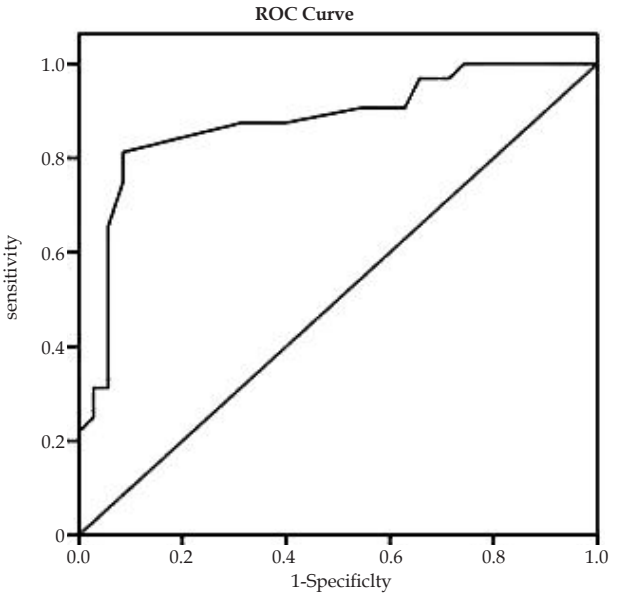

Figure 1 Reciever operating characteristic curve for sensitivity and specificity of ICT in diagnosis of MHE. Taking cut off of 9 lures, the sensitivity was 91% and specificity was 63%. The area under the curve was 0.88 (95% CI 0.791-0.97).

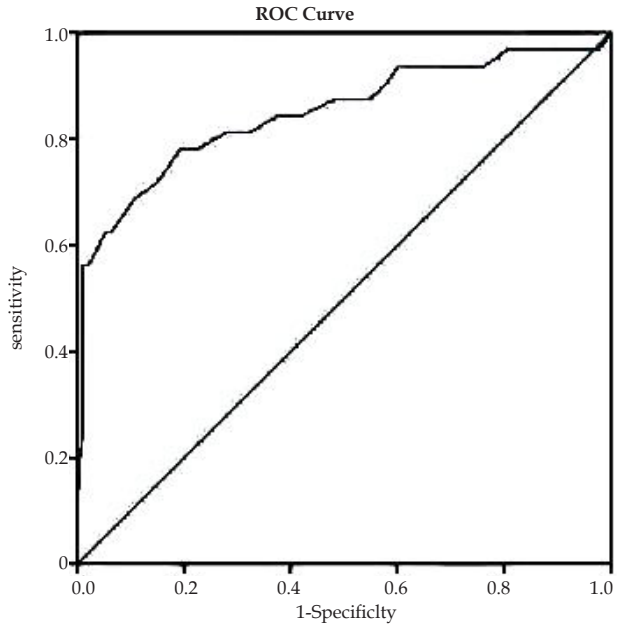

Figure 2 Reciever operating characteristic curve for sensitivity and specificity of CFF in diagnosis of MHE. Taking cut off of < 37 Hz, the sensitivity was 63% and specificity was 94%. The ROC curve had an area under the curve of 0.87 (95% CI 0.83- 0.92) for MHE diagnosis.

low-grade astrocyte swelling, disrupting neuronal communication, this same process occurs in glial cells of the retina[12-14]. The underlying thought is that retinal gliopathy could serve as a marker of cerebral gliopathy occurring in HE, and has been investigated in patients with low-grade HE.

ICT measures response inhibition and attention, basic cognitive domains that are affected in MHE. Bajaj and colleagues extended the use of the test to identify individuals with MHE. The ICT is similar to other go-no-go or continuous performance tests (CPT) and assesses sustained attention as well as the ability to inhibit responses to nontargets.

Lure response is an act of commission, signifying a defect in response inhibition. In the current study, all subjects were instructed to avoid responding to lures in the training session. Patients with MHE responded to a significantly higher number of lures compared with healthy controls.

Jasmohan S Bajaj *et al* [15] in 2008 has taken >5 lures for 87 cirrhotic patients with MHE and 48 cirrhotic patients without MHE in accordance with ROC curve. MHE-positive patients had significantly higher ICT lures (11 *vs* 4, respectively, $p = 0.0001$) and lower targets (92% *vs* 97%, respectively, $p = 0.0001$) compared with MHE-negative patients. The sensitivity and specificity came out to be 87% and 77% respectively. In our study, patients with MHE had significantly higher lures (22 ± 7.8 *vs* 11 ± 5.6) or (56% vs 28%) and lower target response (90% vs 97%) compared with controls.

In a study by Jasmohan S Bajaj *et al* [16] in 2007 when he applied ICT and SPT in 50 non-alcoholic cirrhotics and 50 age/education matched controls, > 5 lures were taken as cut off according to ROC curve for MHE diagnosis with 90% sensitivity and specificity. Cirrhotics with MHE had significantly higher lure (28% *vs* 3%) and lower target response (91% *vs* 96%) compared with those without MHE.

In a two-center study by Amodio P *et al* [17], Italy in 2010, a cut-off of 5 lures was taken to discriminate patients with and without MHE with 88% sensitivity and 77% specificity. A total of 75 cirrhotics and 55 normal healthy controls were included. In centre A and B cirrhosis had higher ICT lures as compared to healthy individuals (23.2 ± 12.8 *vs* 12.9 ± 5.8 at centre A and 11.7 ± 8.1 *vs* 8.5 ± 5.2 at centre B respectively) and lower ICT target accuracy (0.88 ± 0.17 *vs* 0.96 ± 0.03 at centre A and 0.83 ± 0.18 *vs* 0.97 ± 0.11 at centre B respectively). Our results resemble with the Italian study but not with American study. Even though further studies are required to validate these results of ICT.

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[18]. CFF is reliable, simple, easy to apply, and is not influenced by age, education level and sex[19].

The appropriate cut-off to identify abnormal CFF is still not defined. In our study taking < 37Hz as cut off as per ROC curve, the sensitivity, specificity, PPV, and NPV came out to be 57.5%, 94.3%, 90.5% and 70.2%.($p < 0.001$).

In the study by Kircheis *et al*[11], by using a threshold of 39 Hz when comparing healthy subjects to patients with cirrhosis, SHE (Subclinical Hepatic Encephalopathy) patients separated from cirrhotic patients without hepatic encephalopathy with high sensitivity (55%) and specificity (100%). CFFs in cirrhotic patients without HE were not different from those found in noncirrhotic controls. Also, with CFF cut-off value of 39 Hz, a 100% separation of patients with manifest HE from noncirrhotic controls and cirrhotic patients without hepatic encephalopathy was obtained.

Romero-Gomez M *et al*[19] in 2007 used receiver operating characteristic curves which revealed better sensitivity and specificity for the diagnosis of MHE using the threshold of 38 Hz. With a cut off of 38 Hz, the sensitivity was 72.4% and specificity was 77.2%. Also, they found that CFF did not correlate with age, education, and sex.

In a study by Sharma P *et al*[20] in 2007 who applied CFF in 83 cirrhotic patients with MHE, sensitivity, specificity, PPV, and NPV were 96%, 77%, 68% and 98% respectively taking 39Hz as cut off.

In our study, we found that CFF is less time to consume requiring 12.4 mins by cases as compared to ICT which required 17.8 minutes while controls required 10 min for CFF and 16 min for ICT. Also, CFF was easy to perform and understand from the patient's point of view as compared to ICT, based on the questionnaire given to both cases and controls at the end of the study. As per our best knowledge, this is one of the rare studies in which validity of both ICT and CFF were evaluated in the same cohort.

LIMITATIONS

To evaluate the validity of ICT and CFF, cirrhotics without MHE is not taken as controls, instead, healthy controls were taken which may have the influence on the results. As this study included less number of participants, further large studies are required to validate the results.

CONCLUSION

ICT and CFF are useful tests to diagnose MHE. CFF is simple, less time consuming, less sensitive and has less negative predictive value, but more specific and with more positive predictive value than ICT. CFF is easy to perform and understand from the patient's point of view as compared to ICT.

Abbreviations: CFF, Critical Flicker Frequency; ICT, Inhibitory Control Test; MHE, Minimal Hepatic Encephalopathy; MMSE, Mini Mental Score Examination; NPV, Negative Predictive Value; PPV, Positive Predictive Value; ROC, Reciever Operator Characteristics.

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