Inhibitory Control Test, Critical Flicker Frequency, and Psychometric Tests in the Diagnosis of Minimal Hepatic Encephalopathy in Cirrhosis

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ABSTRACT

Background/Aim: Minimal hepatic encephalopathy (MHE) impairs health-related quality of life and driving ability of the patient. Objective: We assessed the utility of the inhibitory control test (ICT), critical flicker frequency (CFF), and psychometry in the diagnosis of MHE. Patients and Methods: Consecutive patients with cirrhosis underwent number connection tests A and B (NCT-A, B), digit symbol test (DST), line tracing test (LTT), serial dot test (SDT), CFF, and ICT at baseline and after four hours. Fifty healthy subjects served as controls for the ICT test. Results: Fifty patients with cirrhosis (43.4 ± 10.2 yrs, M: F 42:8) underwent psychometric tests [NCT-A (48.3 ± 17.7 vs. 42.6 ± 17.3 sec, P = 0.001), NCT-B (85.7 ± 40.1 vs. 90.2 ± 37.0 sec, P = 0.18), DST (23.5 ± 9.3 vs. 23.0 ± 8.7, P = 0.45), LTT (96.6 ± 48.2 vs. 96.8 ± 46.8 sec, P = 0.92), SDT (88.0 ± 39.5 vs. 83.4 ± 37.2 sec, P = 0.02)] at baseline and after four hours. Target accuracy of ICT was lower in patients with cirrhosis compared with controls (88.4 ± 5.6 vs. 95.6 ± 2.1, P = 0.01), whereas ICT lures were higher (18.3 ± 4.2 vs. 10.2 ± 2.8, P = 0.01). Patients with cirrhosis showed a reduction in lures in the second evaluation compared with the first (18.3 ± 4.2 vs. 17.1 ± 4.3, P = 0.003) but no change in target accuracy (88.4 ± 5.6 vs. 88.4 ± 5.3, P = 0.97). Control subjects did not show any change either in lures (10.2 ± 2.8 vs. 10.3 ± 2.1, P = 0.65) or target accuracy (95.6 ± 2.1 vs. 95.5 ± 2.2, P = 0.82). The sensitivity and specificity of ICT test for the diagnosis of MHE at lure rate >16.5 was 88.5 and 56%, respectively. CFF in patients with MHE (38.4 ± 1.8 vs. 38.6 ± 1.5, P = 0.3) and non MHE (40.6 ± 2.2 vs. 40.8 ± 2.2, P = 0.6) did not show any difference after four hours as in controls (41.9 ± 2.4 vs. 42.1 ± 2.0, P = 0.3). Thirty one (31%) patients preferred psychometric tests, 57 (57%) preferred CFF and only 12 (12%) preferred ICT (P = 0.001). Conclusions: ICT, CFF, and psychometric tests are useful tools to assess MHE, and CFF was preferred by this study cohort.

Key Words: Critical flicker frequency, inhibitory control test, psychometric tests

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Minimal hepatic encephalopathy (MHE) is characterized by subtle deficits and psychomotor abnormalities that can only be elicited by specialized psychometric tests.[1] MHE remains an important entity for clinicians to consider because of its negative impact on health-related quality of life of the patient and association with driving impairment and vehicle accidents.[2-7] MHE has also been associated with an increased rate of overt hepatic encephalopathy (HE) and increased mortality in patients with cirrhosis.[8] Hence the need for early identification and treatment of MHE. For the diagnosis of MHE we require tests that are easy to perform, less time consuming, can be done by physicians in their clinics, are reproducible with little learning effect, and not affected by the age or education status of the patient.

Neuropsychological tests for the diagnosis of MHE are established, time-tested tests, and are well characterized. However, they are time consuming and are influenced by age and educational status and need normative data which are available in a few countries only.[9] Critical flicker frequency (CFF) is a well-established neurophysiological
Attempts to improve the sensitivity and reliability of diagnostic tools have been made. The inhibitory control task (ICT), a computerized psychometric test, has been recently proposed as a simple diagnostic tool for MHE in western countries where the level of education is higher. ICT evaluates both sustained attention and the ability to inhibit responses to potentially relevant stimuli. However, in developing countries, the level of education is lower and people are not very computer literate. So in the search for a method that is patient friendly and reproducible, we planned this study to evaluate the ICT, CFF, and psychometric tests in the diagnosis of MHE in patients with cirrhosis.

PATIENTS AND METHODS

Consecutive patients with cirrhosis from April 2011 to September 2011 were included in this study. The diagnosis of liver cirrhosis was based on available history, serologic testing, radiologic imaging, and liver histology when available. Staging of cirrhosis was determined by the Child-Pugh classification. All patients completed a standard preprocedural history and physical examination to establish the current degree of encephalopathy and ascites. All patients with cirrhosis and aged between 18 and 70 years were included in this study. Patients were excluded from the study if they had variceal bleeding within the last 6 weeks, alcohol intake during the past six weeks, hepatocellular carcinoma, previous Transjugular intrahepatic portosystemic shunt (TIPS) or shunt surgery, significant comorbid illness such as heart, respiratory, or renal failure, any neurologic diseases such as Alzheimer’s disease, Parkinson’s disease, or nonhepatic metabolic encephalopathies. Patients on psychoactive drugs, such as antidepressants or sedatives were also excluded. Patients with visual or mental impairment who were unable to complete the psychometric testing, CFF, and ICT were also not included. The study was approved by the ethics committee of the institute, and informed written consent was taken from all patients before enrollment in the study.

Psychometric testing

All patients underwent a combination of psychometric tests including number connection tests A and B (NCT-A and B), digit symbol test (DST), line tracing test (LTT), and serial dot test (SDT). These tests were easy to administer and could be performed in 30-40 minutes. In principle, in NCT patients, there is a need to connect numbers as fast as possible. In the DST, the subjects have to transcribe symbols accurately and quickly corresponding to numbers, looking at a key in a timed manner over 90 seconds. The number of correctly transcribed symbols indicates performance, that is, a low score means poor performance. In the SDT, subjects place dots exactly in the center of ten rows of large circles beginning from each row on the left and working to the right. In LTT, subjects need to draw a line between two lines on the paper and stay between, neither touching nor drawing over the printed lines. The test score is the time required to complete the test, including the time needed to correct any errors. Tests were considered abnormal when test score was more than mean ± 2 SD from the age-and education-matched controls (n = 170).

Measurement of CFF threshold

CFF was done by HEPAtonorm analyzer (R & R Medi-Business Freiburg GmbH, Freiburg, Germany). It was measured in a quiet, semi-darkened room. Patients were first instructed and trained about the procedure. Flicker frequencies were measured eight times and the mean value was calculated. Measurement of the CFF thresholds was done by intrafoveal stimulation with a luminous diode. Decreasing the frequency of the light pulses from 60 Hz downward, the CFF threshold was determined as the frequency when the impression of fused light turned to a flickering one.

Measurement of ICT

In this computer-based test, patients are shown a series of letters and are asked to respond by pressing a mouse key when an X is followed by a Y, or a Y is followed by an X (alternating presentation, termed targets). Patients are instructed not to respond to X following X or Y following Y (nonalternating presentation, termed lures). Cognitive functions required to consistently recognize targets include reaction time, whereas avoidance of lures requires response inhibition, attention, and working memory. High lure and low target response indicate poor psychometric performance. The ICT is administered as a practice test followed by a series of six similar two-minute runs, separated by breaks to allow the subjects to rest. The psychometric evaluation, CFF, and the ICT were performed in a quiet room without distracting noises.

Assessment of HE and MHE

HE was defined according to the West-Haven criteria. MHE was diagnosed if two or more psychometric tests were abnormal (± 2 SD of age-and sex-matched controls) as taken in previous published trials. We used psychometric tests as the gold standard for the diagnosis of MHE as per consensus statement.

Study design

Patients who met the inclusion criteria and were provided written informed consent, were enrolled. All the patients underwent minimental scale examination (MMSE) and if the score was more than 24, were subjected to psychometric tests, NCT-A, B, SDT, DST, LTT, CFF, and ICT at baseline and after four hours to assess the effect of learning on these tests. All these patients were given a questionnaire regarding the choice of tests to be done to
assess for MHE in the future and they were asked to write down their choice in the order of preference. Fifty healthy subjects (age and education matched) were also enrolled and underwent ICT and they acted as controls for the ICT. The study was approved by the institutional ethical board in compliance with the Declaration of Helsinki.

Statistical analysis
Data were expressed as mean ± SD. For a comparison of categorical variables, chi square and Fisher’s exact tests were used, and for continuous variables, a Mann-Whitney test for unpaired data and a Wilcoxon signed rank test for paired data were used, as appropriate. Correlation between psychometric tests, CFF, and ICT was calculated using Spearman’s rank correlation. Receiver operating curve was calculated for ICT for the diagnosis of MHE. The probability level of $P < 0.05$ was set for statistical significance.

RESULTS

Between April 2011 and September 2011, 140 patients with cirrhosis were screened; 50 patients (36%) met the inclusion criteria. The etiology of cirrhosis ($n=50$) was due to alcohol ($n=20$), chronic hepatitis B ($n=12$), chronic hepatitis C ($n=8$), primary biliary cirrhosis ($n=2$), autoimmune hepatitis ($n=2$), and cryptogenic cirrhosis ($n=8$). Ninety patients (64%) were excluded from the study due to history of recent alcohol intake ($n=11$), renal impairment ($n=8$), hepatocellular carcinoma ($n=5$), recent use of drugs affecting psychomotor performance ($n=3$), severe medical problem ($n=12$), and unwillingness to take psychometric tests/CFF/ICT ($n=51, 12:11:28$). Of these 51 patients, 28 patients had no prior exposure to computers. The clinical and demographic characteristics of the patients enrolled are shown in Table 1. Fifty age-and education-matched healthy subjects with no history and biochemical evidence of liver disease served as controls for the ICT.

Results of psychometric tests
All patients could do NCT, SDT, DST, and LTT tests. Of 50 patients with cirrhosis, the results of the psychometric tests done before and after four hours were NCT-A: $48.3 ± 17.7$ vs. $42.6 ± 17.3$ sec, $P = 0.001$; NCT-B: $85.7 ± 40.1$ vs. $90.2 ± 37.0$ sec, $P = 0.18$; DST: $23.5 ± 9.3$ vs. $23.0 ± 8.7$, $P = 0.45$; LTT: $96.6 ± 48.2$ vs. $96.8 ± 46.8$ sec, $P = 0.92$; SDT: $88.0 ± 39.5$ vs. $83.4 ± 37.2$ sec, $P = 0.02$. Overall, the results of the psychometric tests before and after four hours in MHE patients ($n=26$), non-MHE patients ($n=24$), and controls are shown in Table 2. There was no change in time taken to complete the test (NCT, DST, SDT, and LTT) before and after in these patients; on the contrary, NCT-A and SDT showed a reduction in time to complete the tests.

CFF before and after the endoscopy
CFF was significantly lower in patients with MHE as compared to non-MHE patients ($38.4 ± 1.8$ vs. $40.6 ± 2.2$ Hz, $P = 0.001$). CFF repetition in patients with MHE and non-MHE patients did not show any difference after four hours as in controls [Table 3]. Sensitivity and specificity of CFF <39 Hz for the diagnosis of MHE was 77 and 75%, respectively. CFF in patients with cirrhosis was significantly correlated with NCT-A ($r = 0.574$, $P = 0.001$), NCT-B ($r = 0.313$, $P = 0.02$), DST ($r = 0.476$, $P = 0.001$), LTT ($r = 0.360$, $P = 0.01$), and SDT ($r = -0.367$, $P = 0.009$) at baseline.

ICT
The target accuracy of ICT was lower in patients with cirrhosis compared with controls ($88.4 ± 5.6$ vs. $95.6 ± 2.1$, $P = 0.01$), whereas ICT lures were higher ($18.3 ± 4.2$ vs. $10.2 ± 2.8$, $P = 0.01$). Similarly, we found ICT lures to be higher in non-MHE ($16.7 ± 4.5$, $P = 0.01$) and MHE ($19.6 ± 3.5$, $P = 0.01$) patients compared to controls and target accuracy lower in non-MHE ($90.5 ± 4.8$, $P = 0.01$) and

### Table 1: Clinical and demographic profile of patients

| Parameters                  | Patients (n=50) | Controls (n=50) |
|-----------------------------|----------------|----------------|
| Age (yrs)                   | 43.4±10.2      | 40.4±12.4      |
| M:F                         |                |                |
| Education (yrs)             | 11.5±4.6       | 12.2±3.5       |
| Child’s status (A:B:C)      | 11:25:14       |                |
| MELD score                  | 13.8±4.9       | -              |
| MHE %                       | 26 (52%)       | -              |
| AST (IU/L) median (range)   | 45 (22-203)    | 23 (19-35)     |
| ALT (IU/L) median (range)   | 43 (24-108)    | 22 (19-33)     |
| Serum sodium (mmol/L)       | 132.0±4.5      | 138.0±3.5      |
| Variceal size (none: small: large) | 11:24:15        | -              |

MELD: Model for end-stage liver disease, MHE: Minimal hepatic encephalopathy, AST: Aspartate transaminase, ALT: Alanine transaminase

**Figure 1:** Receiver operating curve of inhibitory control test for the diagnosis of minimal hepatic encephalopathy
MHE in cirrhosis

Table 2: Psychometric tests in patients with cirrhosis and controls before and after 4 hours

| Tests          | Non MHE (n=24) | MHE (n=26) | Controls (n=50) |
|---------------|----------------|------------|----------------|
|               | Before | At 4 hr | P value | Before | At 4 hr | P value | Before | At 4 hr | P value |
| NCT-A (sec)   | 33.5±7.1 | 32.1±7.8 | 0.02 | 62.0±12.9 | 52.2±18.2 | 0.06 | 28.5±6.5 | 26.2±5.0 | 0.03 |
| NCT-B (sec)   | 51.8±15.4 | 56.5±15.3 | 0.45 | 117.0±28.5 | 121.2±19.6 | 0.46 | 56.0±18.5 | 59.5±14.3 | 0.57 |
| DST (sec)     | 29.9±8.9 | 28.7±8.6 | 0.97 | 17.5±4.3 | 17.8±4.7 | 0.09 | 33.2±10.5 | 34.5±9.3 | 1.0 |
| SDT (sec)     | 60.2±27.4 | 59.7±27.9 | 0.01 | 113.7±30.7 | 91.0±37.1 | 0.03 | 59.7±10.9 | 57.4±15.2 | 0.02 |
| LTT (sec)     | 68.6±27.8 | 65.0±26.0 | 0.90 | 124.0±47.0 | 126.2±42.5 | 0.46 | 66.5±13.8 | 68.1±17.9 | 0.56 |

NCT: Number connection test, DST: Digit symbol test, SDT: Serial dot test, LTT: Line tracing test, MHE: Minimal hepatic encephalopathy

Table 3: Critical flicker frequency and Inhibitory control test in patients with cirrhosis at baseline and after 4 hours

| Tests          | Non MHE (n=24) | MHE (n=26) | Controls (n=50) |
|---------------|----------------|------------|----------------|
|               | Before | At 4 hr | P value | Before | At 4 hr | P value | Before | At 4 hr | P value |
| CFF (Hz)      | 40.6±2.2 | 40.8±2.2 | 0.60 | 38.4±1.8 | 38.6±1.5 | 0.31 | 41.9±2.4 | 42.1±2.0 | 0.31 |
| ICT lures (number out of 40) | 16.7±4.5 | 16.0±4.2 | 0.07 | 19.6±3.5 | 18.1±4.2 | 0.01 | 10.2±2.8 | 10.3±2.1 | 0.65 |
| ICT targets (% responded to)  | 90.5±4.8 | 88.4±5.8 | 0.19 | 86.4±5.6 | 87.5±4.8 | 0.14 | 95.6±2.1 | 95.5±2.2 | 0.82 |

CFF: Critical flicker frequency, ICT: Inhibitory control test, MHE: Minimal hepatic encephalopathy

MHE (86.4±5.6, P = 0.01) patients compared to controls. Patients with MHE had lower target accuracy and higher lures compared with those of non-MHE patients ([86.4 ± 5.6 vs. 90.5 ± 4.8, P = 0.01] and [19.6 ± 3.5 vs. 16.7 ± 4.5, P = 0.01] respectively). Patients with cirrhosis showed a reduction in lures in the second evaluation after four hours compared with the first (18.5 ± 4.2 vs. 17.1 ± 4.3, P = 0.003) but no change in target accuracy (88.4 ± 5.6 vs. 88.4 ± 5.3, P = 0.97). In contrast, control subjects did not show any change either in lures (10.2 ± 2.8 vs. 10.3 ± 2.1, P = 0.65) or target accuracy (95.6 ± 2.1 vs. 95.5 ± 2.2, P = 0.82). Patients with MHE showed reduction in ICT lures after four hours with no change in target accuracy, whereas non-MHE patients did not show any change in the rate of target lure or target accuracy as in controls [Table 3]. The sensitivity and specificity of ICT test for the diagnosis of MHE at a lure rate >16.5 was 88.5 and 56%, respectively with area under curve 0.695 [confidence interval (CI): 0.54-0.84, P = 0.01] [Figure 1]. Lure rate in patients with cirrhosis at baseline was significantly correlated with NCT-A (0.323, P = 0.02), NCT-B (0.302, P = 0.03), DST (−0.312, P = 0.02), LTT (0.360, P = 0.01), and SDT (0.278, P = 0.05). Similarly target accuracy at baseline in patients with cirrhosis was significantly correlated with NCT-B (−0.453, P = 0.002), LTT (−0.298, P = 0.03), and SDT (−0.373, P = 0.008) but not with NCT-A (−0.172, P = 0.23) and DST (0.265, P = 0.06).

Patient perception of different tests

After completion of the second test, the patients were given a questionnaire regarding which tests would they like to repeat to assess the cognitive function in future. Thirty-one (31%) patients preferred psychometric tests, 57 (57%) preferred CFF, and only 12 (12%) preferred ICT (P = 0.001). In patients with cirrhosis, psychometric tests, CFF and ICT was preferred by 26, 56, and 18%, respectively (P = 0.001), whereas in controls, psychometric tests were preferred by 36%, CFF by 58%, and ICT by 6%, (P = 0.001).

DISCUSSION

In the present study, MHE was present in 52% of the patients with cirrhosis. CFF was preferred by patients as a tool for assessment of MHE and had a sensitivity and specificity of 77 and 75%, respectively, for the diagnosis of MHE. ICT had a sensitivity of 89% and specificity of 56% and was not a preferred test for the evaluation of MHE in this cohort of patients.

The detection of MHE is a relevant health-care issue because of the impact that it has on the quality of life and driving ability. Psychometric tests are well-known tests for the diagnosis of MHE as they are easy to perform and do not require sophisticated instruments. However, they require considerable motor activity and normative data in controls which is not available in most countries. Confining the motor response to simply pressing or not pressing a button seems to be a far better option than pencil-and-paper tests. In recent trials, CFF and ICT have shown to accurately predict MHE and to have a good correlation with psychometric tests as in this study also.

We evaluated ICT as an alternative for the assessment of cognitive function as it interrogates working memory, learning capacity, and response inhibition. We found a significant difference in ICT lure and target accuracy in cirrhotic patients versus controls. In this study, controls (10.2 ± 2.8) had significantly higher lures than the controls (3 ± 2) described by Bajaj et al.,[13] but were comparable with the controls (12.9 ± 5.8) in a study by...
Amodio et al. A higher level of education and familiarity with computers might be a possible explanation. But this signifies that for the use of ICT, every country should have its own reserve of controls who satisfy these criteria. We also found target accuracy to be significantly lower in patients with cirrhosis (with and without MHE) compared to controls which is a measure of poor inhibition and attention ability in patients with cirrhosis. Patients with cirrhosis showed a reduction in lures in the second evaluation after endoscopy compared with the first ($P = 0.003$) but no change in target accuracy ($P = 0.97$). This suggests some learning effect in the inhibition ability in patients with cirrhosis, predominantly in MHE patients. However, none showed any deterioration in attention ability as measured by target accuracy. Compared to psychometric tests and CFF, ICT was less preferred by the patients.

Psychometric tests assess psychomotor function (NCT-A), whereas the NCT-B analyzes divided attention and executive function. The DST is a test of attention and processing speed. Similarly LTT (psychomotor and visuo-spatial) and SDT measure psychomotor abilities. Psychometric tests have been used as a measure of cognitive functions in number of trials. We had also shown earlier that no deterioration was seen in psychometric tests after two hours of endoscopy under propofol in patients with cirrhosis. However, psychometric tests also need normative data which varies from country to country and depends upon the level of education. In our study, we found that NCT-A and SDT showed some learning effect. Psychometry was preferred over ICT in our study.

CFF is a reproducible parameter with little bias for training effects, education, age, time of day, or interexaminee variability. In this study also, we found the same results. Patients with cirrhosis (MHE and non MHE) and controls did not show any learning effect. Patients preferred ICT over psychometry and ICT in our study. The strength of this study is that it is the first study to evaluate ICT, CFF, and psychometric tests for assessing MHE. We found that like psychometric tests, ICT is also influenced by demographic profile and demonstrates the effect of learning. CFF did not require any learning effect and was preferred by patients. This study was a time-bound study and we had not calculated any sample size for the same; so, type II error could not be ruled out while interpreting the results. In conclusion ICT, CFF, and psychometric tests are useful tools to assess MHE, and CFF was preferred by this cohort of patients.

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