Critical flicker frequency is diagnostic of minimal hepatic encephalopathy

Serag Esmat,[1] Nouman El Garem,[1] Hassan Raslan,[2] Mohamed Elfekki,[3] Gihan A Sleem[1]

[1]Department of Internal Medicine, Cairo University, Cairo, Egypt
[2]Department of Internal Medicine, Al Agouza Police Hospital, Giza, Egypt
[3]Department of Internal Medicine, Beni Suef University, Beni Suef, Egypt

Correspondence to
Serag Esmat, Department of Internal Medicine, Faculty of Medicine, Cairo University, Al-Saray Street, El Manial Cairo, Cairo 11562, Egypt; seragesmat@hotmail.com, seragesmat@kasralainy.edu.eg

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ABSTRACT

Minimal hepatic encephalopathy may affect up to 80% of cirrhotic patients, in the absence of overt hepatic encephalopathy. The objective of the study is to evaluate the accuracy of diagnosis of minimal hepatic encephalopathy with critical flicker frequency (CFF). The study was conducted on 180 patients with post hepatitis C liver cirrhosis and on 60 healthy subjects as control. Patients and controls were divided into four groups: group 1 (60), healthy individuals as a control group; group 2 (60), patients with liver cirrhosis (Child class A); group 3 (60), patients with liver cirrhosis (Child class B); and group 4 (60), patients with liver cirrhosis (Child class C). All participants were subjected to estimation of CFF, line drawing test, complete blood picture, liver functions, viral markers, and abdominal ultrasound. CFF detected abnormality in 90% of patients. Accuracy of CFF in differentiation of Child A from normal is 100%, Child B from normal is 100%, Child C from normal is 100%, Child A from Child B is 80%, Child A from Child C is 100% and Child B from Child C is 100%, and it has higher accuracy than line drawing test. CFF is a simple, reliable and accurate method for the diagnosis of minimal hepatic encephalopathy. It is not influenced by the patient level of education.

Significance of this study

What is already known about this subject?

- Minimal hepatic encephalopathy (MHE) may affect up to 80% of cirrhotic patients.
- The prevalence of hepatitis C virus in Egypt is the highest among all countries.
- MHE is only detectable on psychometric or neurophysiological testing.

What are the new findings?

- Critical flicker frequency (CFF) is a highly accurate method for the diagnosis of MHE.
- CFF using the portable analyzer has high accuracy and is a simple and reliable method for the diagnosis of MHE, and it is not influenced by education, easy accessible, and not expensive.
- We believe that it will be very beneficial if used in Egypt for the early diagnosis of MHE especially for those who are planning to get a driving license in order to eliminate car accidents.

How might these results change the focus of research or clinical practice?

- Further studies on the use of portable CFF analyzer for the diagnosis of MHE are needed to validate its use widely.

INTRODUCTION

Hepatitis C displays a worldwide health problem with a prevalence of 3%.[1] Around 80% of infected patients develop chronic hepatitis C which, if untreated, results in liver cirrhosis and may be complicated with hepatocellular carcinoma.[2–5] The prevalence of hepatitis C virus (HCV) in Egypt is around 15% which is the highest among all countries.[6–10] The population in Egypt is more than 90,000,000 which means that around 13 million individuals is infected with HCV which, in turn, leads to a huge number of patients with liver cirrhosis.

Hepatic encephalopathy (HE) is a common and serious complication of liver cirrhosis. HE is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction, after exclusion of other known brain diseases; it is characterized by personality changes, intellectual impairment, and a depressed level of consciousness.[11 12]

Minimal HE (MHE) in patients with liver cirrhosis is defined by the presence of otherwise unexplained cognitive abnormalities, only detectable on psychometric or neurophysiological testing, in the absence of overt HE and may affect up to 80% of cirrhotic patients. Psychomotor slowing, deficits in attention, visual perception, visuoconstructive abilities, and impaired fine motor performances are the key features of MHE.[11 12] MHE affects daily functioning and quality of life; impairs learning capacity; and reduces psychomotor speed, attention, visual perception, and driving ability.[11 12] It is associated with motor vehicle crashes.[13 14]

Predictably, such impairments lead to major difficulties in safely performing routine activities of life, and there are doubts on the patients' fitness to drive as they have psychomotor slowing and cognitive deficits. Various studies have shown variable prevalence of MHE in patients with liver cirrhosis ranging from 25% to 80%.[11 15–18] The increased risk of car accidents in patients with

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Figure 1 Portable Hepatonorm Analyzer.

MHE is related to a decline in cognitive function.[19] Bajaj *et al* reported a higher occurrence of violations and accidents in patients with cirrhosis and MHE compared with healthy persons. The impaired attention and speed of mental processing adversely affect the person's ability to react to unexpected traffic conditions.[20] Therefore, early diagnosis and treatment of MHE are of great importance especially in Egypt.

Subjects and methods

The study included 180 patients with HCV-related liver cirrhosis and 60 healthy subjects as control. The patients were recruited from the outpatient clinics and inpatients of the internal medicine department of Kasr Al Aini Hospital, Cairo University. Patients and controls were divided into four groups: group 1 (60), healthy individuals as a control group; group 2 (60), patients with liver cirrhosis (Child class A); group 3 (60), patients with liver cirrhosis (Child class B); and group 4 (60), patients with liver cirrhosis (Child class C). All participants were subjected to detailed history and clinical examination, estimation of critical flicker frequency (CFF) using the portable Hepatonorm Analyzer (Accelab, Kusterdingen, Germany), line drawing test (LDT), complete blood picture, liver functions (aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, serum albumin, prothrombin time, and prothrombin concentration), viral markers (hepatitis B surface antigen and HCV antibody), and abdominal ultrasound. The diagnosis of cirrhosis was based on physical finding, laboratory investigations, ultrasonographic findings, AST-platelet ratio index and Fibrosis-4 scores, and histopathological findings whenever available. Exclusion criteria included patients with recent gastrointestinal hemorrhage, renal failure, hepatorenal syndrome, alcohol intake, hepatocellular carcinoma, uncontrolled diabetes, severe pulmonary or cardiac complication, and liver cirrhosis due to cause other than HCV. Patients receiving lactulose, rifaximin, or other treatments for HE were also excluded from the study. For those who were candidates for the HCV treatment, we prescribed the treatment for them, but at the time of the study, they were not receiving any treatment for HCV eradication.

Estimation of CFF

We used the portable Hepatonorm Analyzer (figure 1). While the subject is sitting, he wears closed dark goggles, in which he sees a steady red light of 60 Hz. The frequency of this light is gradually decreased, and the subject is instructed to press a button when he has the impression that the steady fused light switches to a flickering one. The process was repeated five times to ensure that the subject understood the procedure. The mean values for each subject were calculated.[21] We used a cut-off value of ≥39.65 Hz to separate patients with MHE from controls and patients with cirrhosis without HE. All study subjects or their legal guardian provided informed consent prior to study enrollment.

The review board and the ethical committee of the Department of Internal Medicine, Faculty of Medicine, Cairo University, approved the study protocol, which was performed according to the Declaration of Helsinki.

STATISTICAL METHODS

Data were statistically described in terms of mean±SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables among the study groups was done using the one-way analysis of variance test with post hoc multiple two-group comparisons. For comparing categorical data, χ^2 test was performed. Fisher's exact test was used instead when the expected frequency is less than 5. Accuracy was represented using the terms sensitivity and specificity. Receiver operating characteristic (ROC) analysis was used to determine the optimum cut-off value for the studied diagnostic markers. p Values less than 0.05 were considered statistically significant. All statistical calculations were done using SPSS V.15 (SPSS, Chicago, Illinois, USA) for Microsoft Windows. The statistical methods of this study were performed and reviewed by a certified biostatistician.

RESULTS

The demographic and biochemical characteristics of the studied groups are shown in table 1.

The prevalence of MHE in our study was 70% in Child A and 100% in Child B and Child C.

CFF and LDT results

We compared the mean values of the CCF and LDT in all groups; there was a highly statistically significant difference among all groups (table 2, figures 2 and 3).

Accuracy of CFF

The sensitivity, specificity, and accuracy of CFF in diagnosing MHE and in differentiation among the four groups were measured by applying the ROC curve (figure 4) to detect the cut-off values with the best sensitivity and specificity (table 3).

The accuracy was 100% in differentiating all groups and 80% in differentiating Child A from Child B.

Accuracy of LDT

The sensitivity, specificity, and accuracy of LDT in diagnosing MHE and in differentiation among the four groups were measured by applying the ROC curve (figure 4) to detect the cut-off values with the best sensitivity and specificity (table 4). The accuracy ranged from 75% to 100% in differentiating all groups and failed to differentiate Child A from Child B.

The accuracy of CFF was much higher than the accuracy of LDT in differentiating all groups.

The educational status of the controls and patients is demonstrated in figure 5.

Table 1 Demographic and biochemical characteristics of the patients and controls

	Control, group 1 (n=60)	Child class A, group 2 (n=60)	Child class B, group 3 (n=60)	Child class C, group 4 (n=60)	Significance between and within groups (p)
Age (year)	50.80±3.80	51±3.25	53±6.12	61.70±7.66	<0.001
Gender (M/F)	36/24	24/36	36/24	30/30	0.346
Hb	12.360±0.87	11.34±1.29	10.01±2.29	8.88±1.59	<0.001
WCC	6010±961.09	5850±18,190.68	5533±24,420.89	6350±18,050.31	0.382
PLT	275,500±321,190.12	171,900±139,780.67	72,170±408,030.65	62,910± 12,434.92	<0.001
PC	98.50±6.45	80.70±4.68	68.20±8.79	44.93±7.89	<0.001
Creatinine	0.65±0.15	1.13±0.34	1.33±0.77	1.57±1.15	<0.001
Albumin (g/dL)	4.40±0.1930	3.64±0.89	2.37±0.37	2.13±0.31	<0.001
AST (IU/L)	26.60±6.35	57.70±23.16	67.70±47.76	76.50±109.21	<0.001
ALT (IU/L)	24±4.39	60.10±31.10	54.80±37.41	68±115.12	<0.001
T.Bil (mg/dL)	0.85±0.14	1.34±1.38	2.86±4.13	3.81±0.92	<0.001

All measures are by mean values±SD except gender.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; Hb, hemoglobin; M, male; PC, prothrombin concentration; PLT, platelet; T.Bil, total bilirubin; WCC, white cell count.

Table 2 Comparison between the mean values of the CCF and LDT in all groups

	Control, group 1 (n=60)	Child class A, group 2 (n=60)	Child class B, group 3 (n=60)	Child class C, group 4 (n=60)	Significance between and within groups (p)
CFF (Hz)	45.60±1.77	37.93±1.34	34.97±2.82	28±1.67	<0.001
LDT (errors/min)	1.3±1.2	6.5±3.5	4.2±3.4	15.9±5.7	<0.001

CFF, critical flicker frequency; LDT, line drawing test.

We performed multivariable analysis to adjust for age and educational status effect. The analysis showed a significant association between CFF and Child-Pugh scores ($p<0.0001$). This association is independent from age or education level ($p>0.05$).

DISCUSSION

In the current study, we included 240 Egyptian subjects: 60 of them were healthy normal individuals as a control group and 180 patients with HCV-related liver cirrhosis control; patients were divided into four groups, and each group includes 60 subjects: control, Child class A, Child class B, and Child class C groups.

Mean laboratory data included hemoglobin, platelets, albumin, and prothrombin concentration which were lower among patients than controls, but total bilirubin, AST, ALT, and creatinine were higher in patients than controls, and there was a high statistically significant difference ($p<0.001$) in most of the data except with white cell count and gender where there was no statistically significant difference among groups.

The prevalence of MHE is high in patients with cirrhosis of liver and varies between 30% and 84%, and it is higher in patients with poor liver function.[21]

The prevalence in our study is somewhat higher: 70% in Child class A group and 100% in Child class B and C groups. This may be attributed to the development of neurological complications in patients with large portosystemic shunts even with good liver function and is generally underdiagnosed.[22]

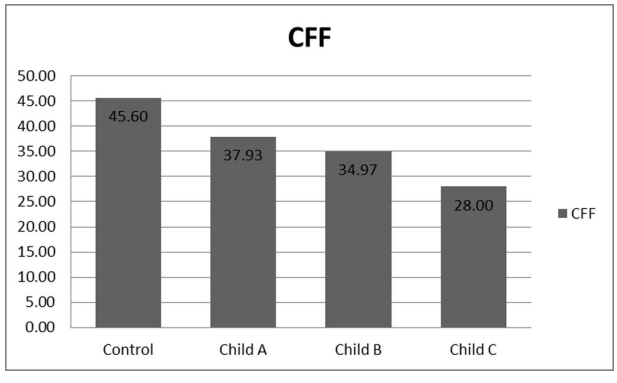

Figure 2 Comparison between the mean values of critical flicker frequency (CFF) (Hz) in control, Child A, Child B, and Child C groups ($p<0.001$).

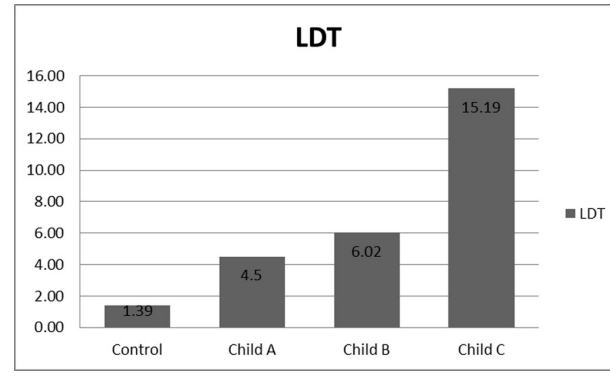

Figure 3 Comparison between the mean values of line drawing test (errors/min) in control, Child A, Child B, and Child C groups ($p<0.001$).

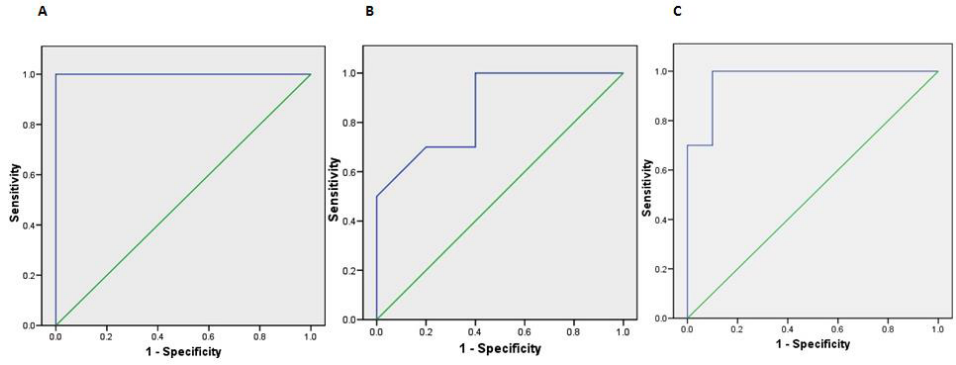

Figure 4 A. Receiver operating characteristic (ROC) curve for critical flicker frequency (CFF) in differentiating Child A from normal. B. ROC Curve for CFF in differentiating Child A from Child B. C. ROC Curve for line drawing test in differentiating Child A from Normal.

Patients with MHE are the focus of several studies because the diagnostic methods used for cognitive evaluation in this population are varied, and there is no consensus regarding the optimum strategy. Various methods have been evaluated for diagnosis of MHE, mainly (A) neurophysiological tests including electroencephalogram, evoked potentials, and CFF; (B) neuropsychological tests including the number connection test, finger connection test, LDT, the digit symbol test, the block design test, and the circle dotting test; and (C) imaging techniques including CT, MRI and magnetic resonance spectroscopy.[11]

Our study was focused to evaluate the diagnosis of MHE with CFF using the portable Hepatonorm Analyzer and the LDT.

CFF is a well-established neurophysiological technique that measures the ability of the central nervous system to detect flickering light, which is directly influenced by cortical activity.[23]

In our study, we found that CFF and LDT correlated strongly with HE severity. Several studies found significant correlation of the mean CFF with the psychometric tests and that CFF together with Child-Pugh class can diagnose the development of MHE.[24] In our study, we found similar results as we found significant correlation between CFF and both Child-Pugh score and the LDT. Kircheis *et al* found that the accuracy of CFF is 100% in separating cirrhotic patients with manifest HE from non-cirrhotic control when a cut-off frequency of 39 Hz is used.[25] In our study, the accuracy of CFF was 100% in differentiating patients with Child class C group from the control group at a cut-off value of 37 Hz.

Other tools such as electroencephalography or exogenously evoked potentials including brainstem-evoked potentials, visual-evoked potentials, and somatosensory-evoked potentials have been widely used for the diagnosis of MHE. However, these tools have lower sensitivity than CFF and require specialized equipment with trained personnel.[24] Sharma *et al* reported that the accuracy of CFF in diagnosis of MHE was 80% with sensitivity and specificity of 65% and 91%, respectively.[26]

In our study, the accuracy of CFF in diagnosis of MHE was higher ranging from 80% to 100% with sensitivity of 100% and specificity ranging from 60% to 100%. The accuracy of CFF in differentiating Child A from normal was 100% when a cut-off value of 41.40 Hz was used, and the accuracy of CFF in differentiating Child B from normal cases is 100% when a cut-off value of 40.30 Hz was used. On the other hand, the accuracy of CFF in differentiating Child A from Child B cases was 80% when a cut-off value of 37.80 was used.

The accuracy of LDT in differentiating Child class A group from normal cases was 85% when a cut-off value of 2.575 error rate/min was used. While the accuracy of LDT in differentiating Child class B group from normal cases was 75% when a cut-off value of 1.69 error rate/min was used.

The accuracy of LDT in differentiating Child class C group from normal cases was 100% when a cut-off value of 5.76 error rate/min was used.

On the other hand, the accuracy of LDT in differentiating Child class C group from Child A cases was 80%, and the accuracy was 90% in differentiating Child class B group from Child class C group, but differentiating between Child class A and B groups failed. Finally, the accuracy of CFF in differentiating the different groups is higher than LDT.

CONCLUSION

CFF using the portable Hepatonorm Analyzer has higher accuracy and is a simple and reliable method for the diagnosis

Table 3 Comparison between the accuracy rates of CFF (Hz) in differentiating the four groups

Differentiating	Cut-off point	Sensitivity (%)	Specificity (%)	(+) PV (%)	(–) PV (%)	Accuracy (%)
Child A from normal	41.40	100	100	100	100	100
Child B from normal	40.30	100	100	100	100	100
Child C from normal	37	100	100	100	100	100
Child A from Child B	37.80	100	60	71.43	100	80
Child B from Child C	33.60	100	100	100	100	100
Child A from Child C	31.65	100	100	100	100	100

CFF, critical flicker frequency; PV, predictive value.

Table 4 Comparison between the accuracy rates of LDT (error rate/min) in differentiating the four groups

Differentiating	Cut-off point	Sensitivity (%)	Specificity (%)	(+) PV (%)	(–) PV (%)	Accuracy (%)
Child A from normal	2.575	90	80	80.82	88.89	85
Child B from normal	1.69	80	70	72.73	77.78	75
Child C from normal	5.765	100	100	100	100	100
Child B from Child C	7.75	100	90	90.90	100	90
Child A from Child C	8.88	90	90	90	90	80

LDT, line drawing test; PV, predictive value.

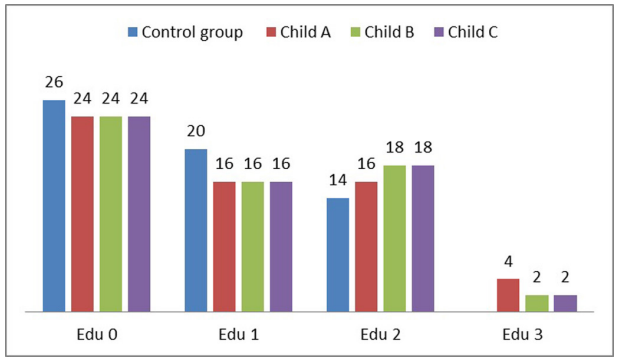

Figure 5 The educational status of the controls and patients (Edu 0, illiterate; Edu 1, finished grade 6 of primary school; Edu 2, finished high school; Edu, college degree).

of MHE, and it is not influenced by education, easy accessible, and not expensive, and we believe that it will be very beneficial if used in Egypt for the early diagnosis of MHE especially for those who are planning to get a driving license in order to eliminate car accidents.

Contributors All authors have contributed in this article and are in agreement with the content of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval Review board of the department of internal medicine, Faculty of Medicine, Cairo University.

Provenance and peer review Not commissioned; externally peer reviewed.

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