Turk J Gastroenterol *2017; 28: 191-6*

Liver

Critical flicker frequency test for diagnosing minimal hepatic encephalopathy in patients with cirrhosis

Banu Demet Özel Coşkun[1], Mustafa Özen[2]

[1]Clinic of Gastroenterology, Kayseri Training and Research Hospital, Kayseri, Turkey
[2]Clinic of Internal Medicine, Kayseri Training and Research Hospital, Kayseri, Turkey

ABSTRACT

Background/Aims: The critical flicker frequency (CFF) and psychometric hepatic encephalopathy score (PHES) are commonly proposed tests for detecting minimal hepatic encephalopathy (MHE); however, no studies have examined their value for detecting MHE in Turkey.

Materials and Methods: A total of 70 patients with cirrhosis without overt HE, 205 controls for PHES, and 100 controls for the CFF test were included. All the patients underwent the PHES and CFF tests during the same session. Psychometric tests comprising number connection test A and B, digit symbol test, serial dotting test, and line drawing test were used. Tests were considered abnormal when test score was more than mean ± 2 standard deviations in comparison with that of the age- and education-matched controls. MHE was diagnosed when ≥2 PHES test were abnormal, and CFF was <39 Hz.

Results: The prevalence of MHE among the 70 patients with cirrhosis, as measured by the CFF and PHES tests, was 41.4% (29) and 30.7% (25), respectively. The mean CFF was significantly lower in patients with cirrhosis having MHE (38.3±1.2 Hz) than in patients with cirrhosis not having MHE (42.6±2.3 Hz; p=0.001) and in controls (44.84 ± 3.7 Hz; p=0.001). With a cutoff value of <39, CFF had a sensitivity of 39%, specificity of 82%, and diagnostic accuracy of 70.6% for detecting MHE.

Conclusion: The CFF test is also a useful method for detecting MHE in xxx patients with cirrhosis. However, the CFF test should be used as an adjunct to the PHES test because of its low sensitivity for detecting MHE.

Keywords: Minimal hepatic encephalopathy, Critical flicker frequency test, Psycometric hepatic encephalopathy score

Original Article

INTRODUCTION

Minimal hepatic encephalopathy (MHE) is the first phase in the clinical spectrum of HE, occurring in up to 30%-84% of patients with cirrhosis (1,2). Patients with MHE have deficits in cognitive functions such as attention, reaction time, vigilance, coordination, and motor function. Minimal hepatic encephalopathy is associated with a decreased quality of life, an increased risk for traffic/work accidents, and death. Minimal hepatic encephalopathy also increases the risk for overt HE (OHE). Thus, MHE must be early diagnosed and treated (3,4).

Minimal hepatic encephalopathy is not detectable by routine clinical and laboratory tests, and specific psychometric/neurophysiological tests are needed for an accurate diagnosis. In 1998, The Expert Working Group suggested that the psychometric hepatic encephalopathy score (PHES) test was the preferred standard for MHE diagnosis. However, patient numeracy, literacy, or language skills may affect the results of the PHES test (5). The critical flicker frequency (CFF) test has been recently proposed as an alternative, which is unaffected by the above mentioned issues and has a high specificity and a moderate sensitivity for predicting MHE (6).

The CFF test is a neurophysiological method that measures the brain function and was used for detecting MHE by Kircheis et al in 2002 (6). The early pathogenetic event of HE is a low-grade swelling in cerebral and retinal glial astrocytes, which cause hyperammonia and increase systemic inflammation. In patients with cir-

Address for Correspondence: Banu Demet Özel Coşkun E-mail: demetcoskun2@gmail.com
Received: October 23, 2016 **Accepted:** February 19, 2017 **Available Online Date:** March 17, 2017

rhosis, the morphological abnormalities in the retinal glial cells are described as hepatic retinopathy. It causes impairments in neuron-glial communication. Based on the hypothesis, retinal gliopathy could be used as a marker of HE. CFF significantly decreased in parallel with the HE severity (7).

The CFF test is performed by placing a portable device on the eyes. During the test, subjects are administered light pulses with decreasing frequency (from ≤60 Hz to 25 Hz) and are requested to press a switch as soon as the feeling of a fused light changes to a flickering light (7,8).

This study aimed to examine the prevalence of MHE in cirrhotic patients and compare the performance of the PHES and CFF tests for the diagnosing MHE. To date, no studies have assessed the usefulness of CFF as diagnostic tool for MHE in Turkish cirrhotic patients.

MATERIALS AND METHODS

This prospective study was conducted in the Gastroenterology Department, Kayseri Training and Research Hospital between Aug 2015 and May 2016. This study has been approved by the Ethics Committee of Erciyes University School of Medicine, and all subjects provided signed written consent forms.

Cirrhotic Patient Group

A total of 85 patients with cirrhosis without OHE were included. The diagnosis of cirrhosis was establishedon the basis of clinical, laboratory, endoscopic, or histopathological findings. The cirrhosis staging was determined according to the Child-Turcotte-Pugh (CTP) class (9). The exclusion criteria were as follows: 1) presence or a history of OHE, 2) gastrointestinal bleeding within 4 weeks), 3) alcohol intake, 4)presence of an infection, 5) use of a psychoactive or antimicrobial medicine, 6) trans hepatic porto systemic shunt (TIPS) or shunt surgery, 7) hepatocellular carcinoma or other malignancies, 8) poorly controlled diabetes mellitus, 9) severe systemic disease (heart and renal failure), 11) neurodegenerative disorders, and 12) oculo-visual dysfunction. The demographic, clinical, and laboratory parameters of the cirrhotic group are presented in Table 1.

Clinical evaluation of OHE was performed with neurological examination according to West-Haven criteria (WHC) and the clinical HE staging scale (5,10). All patients underwent the Mini-Mental State Examination, and in cases where the score was >25 (11), both the PHES and CFF tests were performed during the same session. The tests were performed in a soundless room with appropriate light by the clinical doctor (OM, BDO).

Control Group I (PHES)

We recruited 205 healthy subjects from the general population for generating a normative data for the PHES test. Exclusion criteria were as follows: 1) history of hepatic disease, 2) neuropsychiatric diseases, 3) diabetes mellitus, 4) severe systemic diseases (heart and renal failure), 5) consumption of alcohol or psychotropic drugs, and 6) inability to read. The subjects' age, sex, and education level were recorded. Healthy subjects were divided into four categories according to their age, with equal numbers of males and females (20-29, 30-39, 40-49, and ≥50 years), and each age group was also stratified into three subgroups according to their education levels (≤5, 5-12, and ≥12 education years). The numbers of male and female in each age and education groups were equal.

Table 1. Demographic, clinical, and laboratory parameters of patients with cirrhosis

Baselineparameters	Cirrhosis (n=70)
Sex (female/male)	38/32
Age (years)	58±8
Education (years)	7.2±3.1
WBC ($\times10^3$/L)	5.2±2.1
Hb (g/dL)	12.7±1.9
Platelets ($\times10^9$/L)	127.9±70
ALT (U/L)	43.5±36
AST (U/L)	55.5±37.3
Albumin (g/dL)	3.7±0.8
PT (sc)	15.4±1.8
Child-Turcotte -Pugh Class	
Child A	45 (64.2%)
Child B	15 (21.4%)
Child C	10 (14.2%)
CFF (Hz)	41.2±2.8

WBC: white bloodcell; Hb: hemoglobin; AST: aspartate amino transferase; ALT: alanine amino transferase; PT: prothrombin time; CFF: critical flicker frequency test

Control Group II (CFF)

We recruited 100 healthy subjects to evaluate the effects of age and education level on the CFF test results. The exclusion criteria were similar to those listed above for the control group I. The subjects' age, sex, and education levels were recorded. This control group was used to determine the influence of age and education level on CFF performance.

Psychometric Tests

In this study, we used a battery of psychometric tests, comprising the number connection test (NCTA and B), digit symbol test (DST), serial dotting test (SDT), and line drawing test (LDT). In these tests, the results were measured as NCT-A, NCT-B, SDT, LDT in seconds and DST in points. Tests were considered abnormal when test score was more than mean±2 standart deviations (SD) in comparison with that of the age- and education-matched controls (12,13). In addition, the patients who had ≥2 abnormal psychometric test results were accepted as MHE (6,14).

CFF

The CFF test wasperformed using the HEPAtonorm analyzer (R&R Medi-Business Freiburg GmbH, Freiburg Germany). After the subjects were well-informed regarding the procedure, the CFF test were measured eight times, and the mean score was determined. The whole analysis was completed in 10-15 min. CFF was considered abnormal at <39 Hz (6).

Laboratory Measurements

On the same day as psychometric analysis, blood samples were collected for hematological (whole blood count, prothrombin time, and international normalized ratio INR) and biochemical tests. The laboratory test parameters were measured using standard methodologies. Venous ammonia levels were determine dusing the Blood Ammonia Checker II system (Daiichi Kagaku, Kyoto, Japan).

Statistical Analysis

Normality of data was assessed using the Shapiro-Wilk test. Parametric data were presented as mean±standard deviation (SD). The comparisons between the groups were performed using Student's *t*-test and Mann-Whitney U test. Categorical data were shown as percentages, and the chi-square ($\chi 2$) test was used to define the differences between the groups. Correlation analysis was performed using either Pearson's or Spearman's correlation analyses, depending on data distribution. The diagnostic accuracy, specificity, and sensitivity of the CFF test were assessed by the area under the receiver operating characteristic curves. Statistical analyses were performed using Statistical Package for the Social Sciences 15.0 (SPSS Inc.; Chicago, IL, USA), and $p<0.05$ was considered to be statistically significant.

RESULTS

Control Group I (PHES)

All subjects successfully completed all five tests. The mean age and education level of the control group was 46±10.3 and 8.6±3.03 years, respectively, and 105 subjects were men (51.2%). The mean age did not significantly differ between the male and female subjects. The results of NCT-A, NCT-B, LTT, SDT, and DST were 41.9±18.7, 87.3±27.3, 59.1±14.2, 83.1±11, and 30.7±13.2, respectively. The results of NCT-A, NCT-B, and LDT were inversely correlated with the education levels, whereas those of DST and SDT were positively correlated with the education levels. The results of NCT-A, NCT-B, and LDT were positively correlated with age, whereas those of DST and SDT were inversely correlated with age. Sex was not correlated with the PHES test results. The results of DST and LDT in subjects who were age and had a higher education were better. The mean PHES in the control group was 0.33±2.18 (median, 0; range,–8 to +5) points.

Control Group II (CFF)

All subjects successfully completed the CFF tests. The mean age and education level were 56±5.5 and 8.2±3.2 years, respectively, and 48 subjects were men (48%). The mean age did not differ between the male and female subjects (53.7±10.4 vs.55.1±12.9 years, p=0.65), whereas the mean total years of education level was significantly greater among men than among women (8.8±3.2 vs. 7.2±3.15; p=0.03).

The mean CFF in the control group was 44.84±3.7 Hz. There was no difference in the mean CFF between men and women (43.7±2.96 vs. 43.9±2.6; p=0.819). In the control group, only two values were below the threshold of 39 Hz. There was no correlation between CFF and age (r=–0.100; p=0.4), educational level (r=0.003; p=0.97), or sex (r=0.07; p=0.52).

PHES in the Cirrhotic Group

Fifteen patients were excluded from the study because of the use of lactulose or the inability to write and read. In total, 70 patients with cirrhosis (CTP-A/B/C: 45/15/10) were included in this study. The etiology of cirrhosis was HBV in 35 (50%) patients, HCV in 20 (28.5%), steatohepatitis in six (8.6%), autoimmune hepatitis in three (4.2%), and cryptogenic cirrhosis in five (7.1%). Esophageal varices were present in 40/70 patients (57.1%).

The mean age and education level were 58±8 and 7.2±3.1 years, respectively, and 32 subjects were men (45.7%). The mean age did not differ between men and women (59.4±8.7 vs. 56.5±9.5 years; p=0.15), whereas the number of years of completed education was significantly greater for men than for women (5.9±3.6 vs. 6.8±2.9; p=0.03).

The results of NCT-A, NCT-B, LDT, SDT, and DST were 67.3±29.7, 139.4±55.4, 62.6±20.4, 74.6±19, and 20.07±14.9, respectively. In the cirrhotic group, the results of all PHES tests, except LDT, significantly differed from those in the control group (p<0.001). MHE was detected in 25 (35.7%) patients. Eleven (24.4%) of 45 patients with CTP-A cirrhosis, eight (53.3%) of 15 patients with CTP-B, and six (60%) of 10 patients with CTP-C had MHE (p=0.03).

CFF in the Cirrhosis Group

There was no significant difference in the mean age or sex between the cirrhotic group and control group II (p>0.05), whereas the mean education level was significantly higher in the control group II than in the cirrhotic group (8.2±3.2 vs. 7.2±3.1; p<0.001).

Table 2. Association between PHES and CFF in patients with cirrhosis

	CFF		
PHES	**Normal**	**Abnormal**	**Total**
Normal	34	11	45
Abnormal	7	18	25
Total	41	29	70

PHES: psychometric hepatic encephalopathy score; CFF: critical flicker frequency

Original Article

The mean CFF in the cirrhotic group was 41.2±2.8 Hz. There was no significant difference in CFF between men and women (41.4±2.9 vs. 40.6±2.6; p=0.28). CFF was weakly correlated with age (r=–0.26; p=0.015) and CTP (r=0.26; p=0.016) but not sex (r=–0.19; p=ns) and education level (r=–0.13; p=ns).The mean CFF was significantly lower among patients with cirrhosis having MHE (38.3±1.2 Hz) than among patients with cirrhosis not having MHE (42.6±2.3 Hz; p=0.001) and controls (44.84±3.7 Hz; p=0.001).

In this study, 29 (41.4%) patients with cirrhosis had an abnormal CFF score (<39Hz), whereas 25 (35.7%) patients with cirrhosis had an abnormal PHES. Eleven of 29 patients with an abnormal CFF had a normal PHES, whereas seven of 25 patients with an abnormal PHES had an abnormal CFF score. Table 2 shows that the associations between PHES and CFF. Using PHES as the reference standard, at the cut-off of <39 Hz, CFF had a sensitivity of 39%, specificity of 82%, and diagnostic accuracy of 70.6% for diagnosing MHE. Furthermore, at the cut-off of <38 Hz, CFF had a sensitivity of 21.4%, specificity of 83%, and diagnostic accuracy of 0.72. The diagnostic performances of the different cut-off of CFF for predicting MHE are shown in Table 3.

Critical flicker frequency was correlated with NCT-A (r=–0.451; p<0.01), NCT-B (r=–0.366; p<0.01), LDT (r=–0.41; p<0.002), DST (r=0.31; p<0.01), and SDT (r=–0.34; p<0.01). There was a good correlation between CFF and PHES (r=0.44; p=0.01). The results of the correlations analysis are shown in Table 4.

Comparison of MHE and non-MHE

There was no difference in age, sex, and education level between patients with MHE and those without MHE (p>0.05). Serum AST and albumin levels were significantly lower in patients with MHE than in those without MHE. CFF was not correlated with age (r=–0.18; p=0.35), sex (r=–0.65; p=0.64), educational level (r=0.23; p=0.9), whereas CFF was moderately correlated with the CTP class (r=–0.31; p=0.02). The demographic and laboratory findings of patients with cirrhosis having and those not having MHE are shown in Table 5.

DISCUSSION

The present study confirmed that 1) the prevalence of MHE increased among patients with cirrhosis and that of MHE determined on the basis of PHES and CFF was 35.7% and 41.4%, respectively, and 2) there was a significant correlation between CFF and PHES test results.

The CFF test is a neurophysiological method that evaluates the abilities of the cerebral cortex to identify flickering light (6,7). Sharma et al. (14) and Romero-Gomez et al. (15) have demonstrated that CFF is a simple, reliable, and accurate method for detecting MHE. The appropriate CFF cut-off to identify MHE remains unknown. Kircheis et al. (16), 92 cirrhotic patients were classified as having HE 0, MHE, OHE grade I, and OHE grade II based on the results of the PHES tests and mental state (WHC). Patients who had none or one abnormal PHES test result were defined as HE 0, and patients who had ≥2 abnormal PHES test results were defined as SHE. Patients with an abnormal mental state examination were defined as OHE. The CFF values significantly decreased in parallel with the HE severity and were strongly correlated with all the PHES test, particularly NCT-A and B. When using the cut-off of <39 Hz, patients with MHE were distinguished from HE 0, with a sensitivity of 55% and a specificity of 100% (16). In some studies, an abnormal CFF threshold was set at <38 Hz. Romero-Gomez et al. (15) reported that at this cut-off, CFF had a specificity of 77.2% and a sensitivity of 72.4% for predicting MHE and when using the cutoff of 39 Hz, they observed a lower specificity (61.4%) but a slightly better sensitivity (76.2%). They also reported that CFF of <38 Hz correlated better with a risk for developing OHE than CFF of 39 Hz. In another study, Keircheis et al. (16) also compared the diagnostic value of conventional PHES+CFF using a cut-off of <38 Hz and conventional PHES+CFF using a cut-off of <39 Hz to detect MHE in patients with cirrhosis. In this study, CFF (<39 Hz)+PHES had a greater sensitivity than CFF (<38 Hz)+PHES. While CFF (<38 Hz)+PHES had a sensitivity of 37.8% and a specificity of 89.5%, CFF (<39 Hz)+PHES had a sensitivity of 48.6% and a specificity of 89.5%. Authors have been concluded that PHES+CFF of <38 Hz to diagnose MHE have no advantage based on the specificity but showed a disadvantage regarding sensitivity to detect MHE (16). In the present study, we found that CFF (<39 Hz) had 39% sensitivity and 82% specificity for diagnosing MHE using the PHES test as the standard of diagnosis and a diagnostic accuracy of 0.70, whereas CFF (<38 Hz) had a 21.4% sensitivity, 83% specificity, and diagnostic accuracy of 0.72.We also showed that CFF of <39Hz has a better sensitivity and specificity than CFF of <38 Hz).

Table 3. The diagnostic performances of CFF's different cut-offs in the prediction of MHE

CFF cut-off	AUROC	Specificity	Sensitivity
<38 Hz	72	83	21.4
<39 Hz	70	82	39

CFF: critical flicker frequency test; MHE: minimal hepatic encephalopathy; AUROC: Area under receiver operating

Table 4. Correlation analysesof the CFF test with the PHES test

	CFF	
PHES	**r**	**p**
NCT-A	0.451	0.01
NCT-B	–0.366	0.01
LDT	–0.41	0.002
DST	0.31	0.01
SDT	–0.34	0.01
PHES	0.44	0.01

NCT-A: number connection test-A; NCT-B: number connection test-B; LDT: line drawing test; DST: digit symbol test; SDT: serial dotting test; PHES: psychometric hepatic encephalopathy score; CFF: critical flicker frequency test

Table 5. Demographic, clinical, and laboratory parameters of patients with cirrhosis having MHE and those not having MHE

Patients	No MHE n=45	MHE n=25	p
Age (years)	56±8.4	57±7	0.62
Sex (female/male)	32/24	11/18	0.64
Education(years)	5.5±3.3	5.9±3.3	0.13
WBC	4.9±2	5.5±2.2	0.242
Hb (g/dL)	13±2	12.6±1.9	0.41
Plt ($\times 10^9$/L)	127±80	129±61	0.92
AST (U/L)	55±49	62.6±53	0.08
ALT (U/L)	48±48	49±49	0.25
Albumin (g/dL)	3.9±0.6	3.7±0.5	0.03
PT (sc)	16.2±1.7	17.3±2.1	0.45
CFF (Hz)	42.6±2.3	38.3±1.2	0.00
Child-Pugh Class			
Child A	34	11	
Child B	7	8	0.03
Child C	4	6	

WBC: white blood cell; Hb: hemoglobin; AST: aspartate amino transferase;; ALT: alanine amino transferase; PT: prothrombin time; NH3: ammonium; CFF: critical flicker frequency test; MHE: minimal hepatic encephalopathy

The CFF test has some advantages compared with the PHES test. For example, the PHES test is independent of age, education level, and socioeconomic background (8). Contradicting previous reports, Dhimanet al. (17) reported that CFF was correlated with age in healthy subjects and patients with cirrhosis (r=–0.279 and r=–0.479, respectively), leading the authors to propose that age-matched CFF values should be used for diagnosing MHE. Keircheis et al. (16) also recently reported that there was a significant correlation between CFF and age in both healthy subjects and patients with cirrhosis. In addition, they showed that diagnostic accuracy and sensitivity reduced when age-matched cut-off values were used and concluded that age has no additional predictive value. In present study, we found that CFF was weakly correlated with age (r=0.303; p=0.001) in pa- tients with cirrhosis while CFF was not correlated with age in healthy subjects. Thus, we did not apply age-matched CFF values in healthy subjects.

The prevalence of MHE reportedly varies between 30% and 84% among patients with liver cirrhosis (15,16). These differences in the prevalence of MHE may be because of the variations in the methods used for diagnosing MHE (PHES, CFF, inhibitory control test, electroencephalography, SP300 auditory, or their combinations) and the differences between the patient populations studied. Sharma et al. (18) reported that the prevalence of MHE among 110 patients with cirrhosis (CTP-A/B/C: 39/42/29) was detected to be 65.4% using the CFF test and 68% using the PHES test. Among patients with cirrhosis having MHE in this study, 44% were in CTP-A, 50% were CTP-B, and 76% in CTP-C. Romero-Gomez et al. (15) reported that the prevalence of MHE among 114 patients with cirrhosis (CTP-A/B/C: 57/36/21) was 42% using the CFF test and 30.7% using the PHES test. In this study, we found that the prevalence of MHE by CFF and PHES tests were 41.4% and 35.7%, respectively.

Prior studies have identified several important risk factors for the development of MHE: age, presence of esophageal varices, TIPS or surgical portosystemic shunts, prior episodes of OHE, and severity of liver disease (19-21). Dhimanet al. (17) and Teneja et al.(22) reported a higher frequency of MHE in patients with cirrhosis with CTP-C than those with CTP-A and B. However, Romero-Gomez et al. (15) and Kircheiss et al.(6) reported that there was no association between HE and the severity of liver failure. None of the patients involved in this study had experienced a previous episode of OHE or had undergone TIPS or received surgical porto-systemic shunts. It was observed that MHE was moderately correlated with the CTP class (r=0.303; p=0.03).

This study the some limitations. First, the results of LDT were interpreted with different scoring systems in the literature. While the results of LDT in $PHES_{Italian}$ were interpreted using an error-weight time [w-LDT=LDTt×(1+LDTe/100)], $PHES_{Germany}$ and $PHES_{Indian}$ were interpreted using two separate parameters (LDT_{Time} and LDT_{Error}). In our study, the LDT sum (complete time+error) scoring system was used, similar to that in Spain and Mexico studies. In the Korean study, authors compared calculated PHES scores using three different LDT scoring systems (LDTsum, w-LDT, and LDT_{time}andLDT_{error}) in their own patients with cirrhosis. They reported that the prevalence of MHE in $PHES_{Korean}$, $PHES_{Italian}$, and $PHES_{Spanish}$ were 25.6%, 26.9%, and 27.5%, respectively (23). Second, blood ammonium levels were an important etiological factor in the pathogenesis of MHE. Sharma et al. (14) and Keircheiset al. (6) have also reported that there was a significant correlation between blood ammonium levels and CFF values. But in our study, blood ammonium levels could not be evaluated because of inadequate technical equipment. In addition, CFF test cannot be performed for patients with ophthalmological disorders and red-green blindness. This patient group should be evaluated with other methods.

We found that CFF is a reliable tool for diagnosing MHE. Critical flicker frequency test has several advantages such as easy administration, application by a non-specialist personal, and results that are independent of numeracy, literacy, and age. Critical flicker frequency test should be used as an adjunct to conventional PHES tests because of its low sensitivity for predicting MHE.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.D.Ö.C.; Design - B.D.Ö.C.; Funding - B.D.Ö.C., M.Ö.; Materials - B.D.Ö.C., M.Ö.; Data Collection and/or Processing - B.D.Ö.C., M.Ö.; Analysis and/or Interpretation - B.D.Ö.C.; Literature Review - B.D.Ö.C.; Writer - B.D.Ö.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Hartmann IJ, Groeneweg M, Quero JC, et al. The prognostic significance of subclinical hepatic encephalopathy. Am J Gastroenterol 2000; 95: 2029-34.
2. Poordad FF. Review article: the burden of hepatic encephalopathy. Aliment Pharmacol Ther 2007; 25: 3-9.
3. Montagnese S, Biancardi A, Schiff S, et al. Different biochemical correlates for different neuropsychiatric abnormalities in patients with cirrhosis. Hepatology 2011; 53: 558-66.
4. Bajaj JS, Hafezullah M, Franco J, et al. Inhibitory control test for the diagnosis of minimal hepatic encephalopathy. Gastroenterology 2008; 135: 1591-600.
5. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy-definition, nomenclature, diagnosis, and quantification: final report of the Working Party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-21.
6. Kircheis G, Wettstein M, Timmermann L, Schnitzler A, Häussinger D. Critical flicker frequency for quantification of low grade HE. Hepatology 2002; 35: 357-66.
7. Suraweera D, Sundaram V, Saab S. Evaluation and Management of Hepatic Encephalopathy: Current Status and Future Directions. Gut Liver 2016; 15: 509-19.
8. Torlot FJ, McPhail MJ, Taylor-Robinson SD. Meta-analysis: the diagnostic accuracy of critical flicker frequency in minimal hepatic encephalopathy. Aliment Pharmacol Ther 2013; 37: 527-36.
9. Pugh RNH, Murray-Lyon LM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-9.
10. Li SW, Wang K, Yu YQ, Wang HB, Li YH, Xu JM. Psychometric hepatic encephalopathy score for diagnosis of minimal hepatic encephalopathy in China. World J Gastroenterol 2013; 19: 8745-51.
11. Ortiz M, Cordoba J, Doval E, et al. Development of a clinical hepatic encephalopathy staging scale. Aliment Pharmacol Ther 2007; 15: 859-67.
12. Weissenborn K, Rückert N, Hecker H, Hecker H, Manns MP. The number connection tests A and B: inter individual variability and use for the assessment of early hepatic encephalopathy. J Hepatol 1998; 28: 646-53.
13. Dhiman RK, Saraswat VA, Verma M, Naik SR. Figure connection test: a universal test for assessment of mental state. J Gastroenterol Hepatol 1995; 10: 14-23.
14. Sharma P, Sharma BC, Puri V, Sarin SK. Critical flicker frequency: Diagnostic tool for minimal hepatic encephalopathy. J Hepatol 2007; 47: 67-73.
15. Romero-Gomez M, Cordoba J, Jover R, et al. Value of the critical flicker frequency in patients with minimal hepatic encephalopathy. Hepatology 2007; 45: 879-85.
16. Kircheis G, Hilger N, Häussinger D. Value of critical flicker frequency and psychometric hepatic encephalopathy score in diagnosis of low-grade hepatic encephalopathy. Gastroenterology 2014; 146: 961-9.
17. Dhiman RK, Kurmi R, Thumburu KK, et al. Diagnosis and prognostic significance of minimal hepatic encephalopathy in patients with cirrhosis of liver. Dig Dis Sci 2010; 55: 2381-90.
18. Sharma P, Sharma BC, Puri V, Sarin SK. An open-label randomized controlled trial of lactulose and probiotics in the treatment of minimal hepatic encephalopathy. Eur J Gastroenterol Hepatol 2008; 20: 506-11.
19. Rikkers L, Jenko P, Rudman D, Freides D. Subclinical hepatic encephalopathy: detection, prevalence, and relationship to nitrogen metabolism. Gastroenterology 1978; 75: 462-9.
20. Quero JC, Hartmann IJC, Meulstee J, Hop WC, Schalm SW. The diagnosis of subclinical hepatic encephalopathy in patients with cirrhosis using neuropshychological tests and automated electroencephalogram analysis. Hepatology 1996; 24: 556-60.
21. Dhiman RK, Chawla YK. Minimal hepatic encephalopathy. Indian J Gastroenterol 2009; 28: 5-16.
22. Teneja S, Dhiman RK, Khatri A, et al. Inhibitory Control Test for the Detection of Minimal Hepatic Encephalopathy in Patients with Cirrhosis of Liver. J Clin Exp Hepatol 2012; 2: 306-14.
23. Seo SY, Yim SY, Jung JY, et al. Psychometric Hepatic Encephalopathy Score for the detection of minimal hepatic encephalopathy in Korean patients with liver cirrhosis. J Gastroenterol Hepatol 2012; 27: 1695-704.