Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

The usefulness of critical flicker frequency in the diagnosis and follow-up of covert hepatic encephalopathy treated with Rifaximin-α

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Abstract. Covert hepatic encephalopathy (CHE) affects between 20% and 80% of patients with liver cirrhosis. It has influences on quality of life, driving-related ability, daily routine, and not least on mortality. As CHE is without symptoms, its diagnosis is based on psychometric tests and/or neurophysiological tests like critical flicker frequency (CFF). The primary objective the study is to determine the prevalence of CHE in cirrhotic patients, with no history of overt hepatic encephalopathy OHE using CFF test. A secondary objectives of the study was to identify the impact of CHE on driving abilities within the studied patients and its correlation with CFF results. Last, but not least, another aim of the study was to analyze how the treatment with Rifaximine-α improved CFF results within the respective patients. Material and method: The study was conducted on 26 patients with Child-Pugh class A liver cirrhosis without clinical signs and without history of OHE. CFF is the transition point of an intermittent light source where the flickering light ceases and appears as a continuous light. Frequencies are measured 8 times and the mean value is further calculated, with a standard deviation of less than 1.5. Results: The study was conducted on 26 patients, with a median age of 60.61 years, 61.5% men and 38.5% women. The etiology was mostly viral (58%), followed by ethanol-related etiology (31%). Among patients with CHE, 71% had minor car accidents in the past 3 years, compared with 33% of patients without CHE. Using CFF test, from the total number of patients, 14 were diagnosed with CHE (54%). They were treated with Rifaximin-α 1200 mg/day for 30 days. Treatment response: 35.71% of patients achieved a normalization of the CFF score and treatment was stopped ($p<0.001$); 57.14% have obtained an improvement in the CFF score but without a normalization and treatment was extended. All patients were re-examined after 1 year. After treatment discontinuation, patients with ethanol-related etiology had a rapid unfavourable evolution compared with those with viral etiology ($p=0.049$). All patients refrained from consuming alcohol during the follow-up. Conclusions: The prevalence of CHE in the study group was 54%. Rifaximin-α therapy was effective in 92.86% of patients. Premature discontinuation of treatment with Rifaximin-α decreased the average values of CFF in patients with CHE, particularly in those with ethanol-related etiology. Patients with CHE have a higher risk of getting into car accidents.

Key Words: covert hepatic encephalopathy, critical flicker frequency, Rifaximin-α.

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Introduction

Covert hepatic encephalopathy (CHE) is the mildest form of the spectrum of hepatic encephalopathy affecting the quality of life in terms of health (Ennaifer et al 2014). This condition is characterized by minor cognitive impairment that is difficult to confirm, but which may endanger the health and sometimes even the life of the patient (Córdoba et al 2014). Clinical signs are absent, with deficits in attention, alertness and response capacity, generally activities that require fine motor skills, neurovisual skill and attention (Stinton et al 2013; Prakash et al 2013). Around 20% to 80% of patients with cirrhosis may present this complication (Córdoba et al 2014). There are pathophysiologic changes in brain metabolism different from overt encephalopathy. Thus, if in the case of OHE there is a reduction in blood flow and oxygenation, in patients with CHE and healthy subjects there are no such changes. Magnetic resonance imaging has demonstrated a low degree of swelling, not only in astrocytes but also in the white matter of patients with hepatic encephalopathy (Keiding et al 2013).

As a result of their turmoil, patients with CHE may experience driving difficulty and navigation problems (Bajaj et al 2008; Kircheis et al 2009; Schomerus et al 1995; Schomerus et al 1998; Bajaj et al 2009). Thus, there is an increased risk of incidents and accidents (Bajaj et al 2007; Bajaj et al 2008; Bajaj et al 2009). Testing driving skills is difficult at the border between medicine, psychology and legal implications (Marshal 2008; Dubinsky et al 2009).

Nowadays, doctors are not trained to evaluate driving skills, and cognitive tests alone can not tell the difference between a good driver and one who has driving difficulties (Jasmohan et al 2011). Driving simulation test results in patients with CHE showed driving difficulties and navigation problems, both in terms of exceeding the statutory speed limits and veering to the wrong side, veering off the road and the inability to read road signs (Bajaj et al 2007; Bajaj et al 2008; Saeian et al 2009).

There are no standardized tests for the diagnosis of CHE. Neuropsychometric and neuropsychological testing was used for this purpose along the years (Ferenci et al 2002; Ortiz et al 2005; Bajaj et al 2008).

Critical flicker frequency (CFF) is among the latest proposals to be used for the diagnosis of CHE. This has proven its prognostic value, both in terms of progress towards symptomatic hepatic encephalopathy and mortality (Romero-Gómez et al 2007; Kircheis et al 2009).

In the past, CFF was used to detect drug effect on the central nervous system. In 2002, it was recommended to use it in the diagnosis of CHE and since then, it has been evaluated by several researchers (Kircheis et al 2002). CFF was initially used for testing visual acuity and detecting optic nerve damage.

It is an objective method for a simple and quick assessment. It is reproducible, with fast learning curve, and it does not depend on the level of education or the circadian rhythm. It can be used at the patient's bedside.

The main purpose was to assess the prevalence of CHE in the study group using intermittent critical flicker frequency.

Secondary purposes were to monitor the evolution of patients under treatment with Rifaximin-α and to identify the influence of CHE on driving abilities and its corelation with CFF results.

Material and method

A total of 26 patients diagnosed with Child-Phug class A cirrhosis without clinical signs and no history of hepatic encephalopathy were tested between October 2013 and April 2014. Patients signed the informed consent form and the study protocol was approved by the Ethics Committee.

The diagnosis of liver cirrhosis was based on conventional laboratory tests and ultrasound imaging. The severity was measured using the Child-Pugh Score. The exclusion of overt hepatic encephalopathy was done using clinical criteria and graded according to the West-Haven criteria.

CHE testing was carried out with the consent of patients and consisted of the use of the HEPAtonorm Analyzer 2.0 (Flicker-Fusion Kingdom), manufactured by nevoLAB GmbH (Germany). The method is based on intrafoveal stimulation with a luminous diode. A lens system allowed light accommodation to a virtual picture of light source at 12 meters in the distance. Light pulses with 1:1 ratio between the visual impulse and the interval were used with decreasing frequency in gradual step of 0.5Hz/sec from 60Hz to 25Hz. During this procedure, the patient presses a button when sensing the transition from continuous light to flashing light and the light stimulus disappears. After brief instructions and dark adaptation and training period (5 testing attempts), flicker frequency was measured and the results were saved. Subsequently, the patient is subjected to about 8 measurements with a standard deviation of less than 1.5. CFF analysis is done in a quiet room with constant light quality.

The presence of CHE was validated for a cut-off value of < 39 Hz according to the study conducted by Kircheis in 2002.

Patients with a cut-off value below 39 Hz received daily, 400 mg of Rifaximin-α three times a day, for a period of 4 weeks. Rifaximine-α is the innovative non-absorbable antibiotic licensed also for the treatment of patients with HE and manufactured by Alfa Wassermann, Italy. That was the time for the first reassessment. Treatment discontinuation was prompted in patients who achieved a normalization of the score, while it continued for the others. All patients were re-evaluated after one year. Additionally, anamnesis data were gathered regarding the possession of a driver's license and the existence of minor car accidents.

The rest of the statistical analyses were performed using MedCalc Statistical Software Program Version 16.4.3 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). Normality tests were performed using Kolmogorov-Smirnov test. Quantitative data were described as mean and standard deviation, and qualitative data as frequency and percentage. Repeated measures ANOVA was used to detect any overall differences between related groups. The t test for independent variables was used to detect the differences between unrelated groups. Statistical significance was determined for a p value of < 0.05.

Results

The study was conducted on 26 patients aged between 45 and 76 years, with a median age of 60.61 years, with a standard deviation of 8.64.

Regarding gender distribution, there was a predominance of men (61.5%) over women (38.5%).

The most common cause of the disease was the hepatitis C virus (58%), followed by alcohol (31%).

The prevalence of CHE was assessed for the group studied. Of the 26 patients, 14 (54%) had critical flicker frequency values below 39 Hz and were diagnosed with CHE.

Patients with a normal baseline score, above 39 Hz (8 patients), received no treatment and were reassessed after 1 month. There were minor changes in scores (on average below 1 Hz) compared to baseline.

Patients with CHE were treated with Rifaximin-α (1200 mg/day, divided in three daily administrations) and were reassessed after one month.

Of the 14 patients with CHE, 5 (35.71%) achieved a normalization of the score, i.e. a CFF value of over 39 Hz, and therefore discontinuation of treatment with Rifaximin-α was indicated. An improvement in the score, without reaching the normal value, was obtained in 8 patients (57.14%). One patient had a lower score following treatment with Rifaximin (7.14%).

Patients without CHE had no significant differences between the two CFF evaluations. Patients with CHE had a significant score growth CFF score growth from the first to the second CFF evaluation which was determined by the Rifaximine-α treatment.

The influence of other factors, besides the treatment, was also studied. There were no statistically significant differences in terms of age ($p=0.303$).

There were also no differences in terms of gender ($p=0.339$).

There were no differences in terms of etiology ($p=0.169$).

Patients were followed-up and reassessed after one year. In the group of patients without CHE, 75% had a mean decrease of 1 Hz, without reaching statistical significance ($p=0.317$). The lack of significance was probably due to the small size of the group. This will require confirmation in a larger group of patients. The most obvious decrease was recorded in patients with CHE at baseline and in whom treatment discontinuation was indicated due to normalization of CFF score. These patients had an initial average (mean scores) increase of 1.73 Hz after Rifamine-α

treatment, followed by an average decrease of 1.48 Hz in 60% of tthe respective cases at the end of the follow-up period (1 year). This, however, does not reach statistical significance (p=0.317). Ethanol-related etiology reached statistical significance in terms of CFF score decrease in patients where treatment discontinuation was indicated (p=0.049). All patients refrained from consuming alcohol during the follow-up.

In the group of patients who continued the treatment, there was an average improvement in score of 0.47 Hz in 71.42% of them, one patient died due to the occurrence of HCC, and one showed a decrease in the score of 3.4 Hz, despite the continuation of treatment, without being able to detect another factor that negatively influences patient outcomes.

The influence of CHE on driving-related skills was assessed. Among patients with CHE, 7 possess a driver's license and 5 (71%) of these patients had minor car accidents in the past 3 years. Among patients without CHE, 6 possess a driver's license and 2 (33%) had minor car accidents in the past 3 years. This three-year time reference was considered the average number of years since all patients have been diagnosed with liver cirrhosis. But the group of patients was too small to be subjected to statistical analysis.

There were 4 patients who developed complications (2 - upper gastrointestinal bleeding, 1 - HCC, 1 - liver failure). There were no differences in terms of age, etiology. Three of the four patients were suffering from CHE.

There were three deaths (upper gastrointestinal bleeding, HCC, liver failure). After initial favourable evolution under treatment, the fourth patient, with ethanol-related etiology, suffered from an episode of upper gastrointestinal bleeding, with a significant decrease in the score, without clinical signs of encephalopathy after discontinuation of treatment with Rifaximin-α, without alcohol consumption.

Discussion

This study was conducted in order to detect the prevalence of CHE in patients diagnosed with Child-Pugh class A cirrhosis and no history of HE. Diagnostic methods for CHE are not standardized (Ferenci et al 1998; Ortiz et al 2005; Bajaj et al 2008). Cognitive deficits are minor and difficult to confirm (Córdoba et al 2014), while the absence of clinical signs makes it more difficult to assess patients (Stinton et al 2013; Prakash et al 2013). In the scientific literature, the incidence of CHE varies very widely and affects between 20% and 80% of patients with liver cirrhosis (Stinton et al 2013). The high variability in prevalence is given by the diversity of methods used. Therefore, studies using psychometric tests report a higher frequency of CHE compared with those using critical flicker frequency. The disadvantages of these tests are the need to adapt to the patient's education level, to the age, the existence of a computerized interpretation system, the physical inability of the patient related to the use of hands for writing (Romero-Gómez et al 2007; Kircheis et al 2014). However, most studies have demonstrated the similarity of sensitivity and specificity to other assessment methods.

Regarding the use of ammonia levels in the blood, studies in the literature are contradictory, some demonstrating the effectiveness of the method (Bajaj et al 2008), while others consider it inferior to psychometric tests (Berlioux et al 2014). Given the technical difficulty of the method (blood harvesting, cold transport medium, immediate and individual centrifugation of blood samples, low temperature storage, large kits) which did not overlap with the fact that most of our patients were outpatients, we chose not to use this diagnostic method.

The most recent test used for diagnosis is the critical flicker frequency method. We chose this assessment method because it is simple, fast, independent of the level of education and it has proven its prognostic value over time (Bajaj et al 2008; Romero-Gómez et al 2007).

The prevalence of CHE in the study group was 54%. It is consistent with other data in the literature. Although there are studies that consider a cut-off value of 38 Hz of greater specificity (Romero-Gómez et al 2007), these limits are of great importance in terms of sensitivity and specificity and they are not absolute cut-off values. When using the 38 Hz cut-off value, there is a decrease in sensitivity and some patients are underdiagnosed for the benefit of increasing specificity. In our study, the presence of hepatic encephalopathy was determined for a value below 39 Hz, according to the study presented by Kircheis in 2002.

Patients with CHE were treated with Rifaximin-α, 1200 mg/day divided into three doses over a period of four weeks and then reassessed. Score normalization was achieved in 35.71% of patients, and there was an improvement in the score in 57.14% of patients, without exceeding the 39 Hz cut-off value. Thus, the treatment was effective in 92.86% of patients. One patient experienced a decrease in the score under treatment with Rifaximin-α (7.14%).

The influence of other factors was also assessed in the evolution of the study group. There were no statistically significant differences in terms of age, gender or etiology.

Patients were followed-up and a new test was performed after 1 year. In the group of patients with CHE, 75% had a mean decrease of 1 Hz, without reaching statistical significance. The lack of significance might be due to the small size of the group. This will require confirmation in a larger group of patients. The most obvious decrease was present in patients with CHE at baseline and after treatment discontinuation. After CFF normalization under 30 days of Rifaximine-α treatment, they had an average increase in mean scores of 1.73 Hz, followed by an average decrease after treatment discontinuation of 1.48 Hz in 60% of them, reaching statistical significance in patients with ethanol-related etiology. This emphasizes the importance of maintaining long-term treatment with Rifaximin-α in patients diagnosed with CHE, even in their case the treatment may be stopped due to a favorable evolution of CFF results. Therefore, the focus is on the indication of long-term / indefinite treatment with Rifaximin-α in patients diagnosed with CHE. It should be noted that 1 patient with a negative CFF score at baseline who followed only the interferon-free antiviral treatment achieved sustained virological response and an increase of the CFF score during the follow-up period.

In the group of patients who continued the treatment, there was an average improvement in score of 0.47 Hz in 71.42% of them, one patient died due to the occurrence of HCC, and one showed a 3.4 Hz decrease in the score, despite treatment continuation, without being able to detect another factor that negatively affected patient outcomes.

The influence of CHE on the driving-related ability was assessed. Among patients with CHE, 7 possess a driver's license

and 5 (71%) of these patients had minor car accidents in the past 3 years. Among patients without CHE, 6 possess a driver's license and 2 (33%) had minor car accidents in the past 3 years. However, the group was too small to be subjected to statistical analysis, which could be the aim of a future study on a larger group of patients.

Conclusion

The prevalence of CHE in the study group was 54%. Treatment with Rifaximin-α was effective in 92.86% of patients with CHE, with an improvement in CFF scores. Early discontinuation of treatment with Rifaximin-α led to a decrease in the average CFF values of patients with CHE, particularly in those with ethanol-related etiology. Patients with CHE have a higher risk of getting into minor car accidents.

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Citation	Niculescu CC, Pascu O. The usefulness of critical flicker frequency in the diagnosis and follow-up of covert hepatic encephalopathy treated with Rifaximin-α. HVM Bioflux 2016;8(2):114-118.
Editor	Ştefan C. Vesa
Received	5 June 2016
Accepted	18 June 2016
Published Online	23 June 2016
Funding	None reported
Conflicts/ Competing Interests	None reported