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Diurnal changes of critical flicker frequency in patients with liver cirrhosis and their relationship with sleep disturbances

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ABSTRACT

Background: We aimed to measure the diurnal changes of critical flicker frequency in healthy subjects and cirrhotic patients and to investigate their relationship with sleep disturbance.
Methods: Cirrhotic patients and healthy volunteers were included. All groups completed the Pittsburgh Sleep Quality Index and a simple sleep questionnaire. Sleep disturbance was defined as a Pittsburgh Sleep Quality Index score of >5. Critical flicker frequency was measured twice a day to detect diurnal abnormalities.
Results: Overall, 59 cirrhotic patients (54.2% males, Mean Age 59 ± 11 years) and 18 controls (39.9% males, Mean Age 58 ± 9 years) were included. Sleep disturbances were more common in cirrhotics (66.1%) than controls (38.9%, $p < 0.05$). In cirrhotics, the critical flicker frequency was not related to decompensation. The nocturnal values were higher than the morning values in cirrhotics (64.4%), but not in controls ($p < 0.0001$). Additionally, sleep disturbances were more common in cirrhotics who had higher nocturnal values ($p < 0.05$).
Conclusions: Changes in the diurnal critical flicker frequency were observed in cirrhotics but not in controls. Sleep disturbances in cirrhotics appear to be associated with deviations of the diurnal rhythm of critical flicker frequency rather than with clinical parameters such as the clinical stages of cirrhosis and the Model For End-Stage Liver Disease and Child–Pugh scores.

1. Introduction

Approximately two-thirds of cirrhotic patients suffer from sleep disturbances, which may manifest as being more alert at night than in the morning. Although the reason for these sleep disturbances remains unclear it may be related to minimal hepatic encephalopathy (MHE), which is acknowledged as an early phase of hepatic encephalopathy (HE) [1].

MHE is neither a completely standardized condition nor has a clear clinical significance and detection criteria. As most of the tests to detect MHE depend on the ability of the patient, it is very difficult to standardize them. Therefore, objective tests that do not have interpersonal variability and that can be easily applied are needed. The critical flicker frequency (CFF) measures patient wakefulness and can be used to detect MHE. Being an objective and easily implemented test, CFF is becoming more widely used to detect MHE [2–4]. It is assumed that retinal gliopathy is indicative of cerebral gliopathy in patients with hepatic encephalopathy and CFF is a visual test that is sensitive to such changes in retinal glial cells [4]. Given the advantages of language independence, and being simple to perform and interpret, CFF is suggested for use for detecting MHE rather than psychometric and neurophysiologic tests [5–7]. However, recent data and a meta-analysis showed that CFF has a high specificity and moderate sensitivity for diagnosing minimal hepatic encephalopathy, therefore suggesting that the use of CFF could be an adjunct to psychometric testing [8,9].

We hypothesized that abnormal CFF, as the indicator of MHE, could be associated with sleep disturbances. Therefore, we aimed to investigate the morning to night changes of CFF in cirrhotic patients and healthy subjects, as well as the relationship of these changes and CFF with sleep disturbances.

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2. Patients and methods

2.1. Patient selection

Patients with liver cirrhosis (18–70 years of age) who were admitted to our outpatient clinic between August 2011 and May 2012 were included in the study. Written informed consent was obtained from all participants before enrolment. Patients with a history of overt HE were required to be free from HE findings during the preceding 6 months according to notes of our outpatient clinic and their medical history. Patients with alcoholic cirrhosis were excluded if they were not abstinent for at least 6 months, and patients taking sedatives, hypnotics, selective serotonin reuptake inhibitors, and neuroleptics were excluded. The diagnosis of cirrhosis was based on clinical, biochemical, endoscopic, and radiological findings, while liver biopsies were performed when necessary. The severity of liver disease was assessed using the Child's Pugh grading system and MELD scores. Twenty-two patients who were taking lactulose, L-ornithine, L-aspartate, or antibiotics stopped these medications at least one week prior to testing to avoid affecting the results.

Patients were also classified as decompensated if they had any of the following conditions: ascites, history of hepatic encephalopathy, variceal bleeding, bilirubin level >3 mg/dl in non-biliary cirrhosis (>6 mg/dl in biliary cirrhosis), or INR > 1.9.

Age-matched healthy volunteers were included in the study as the control group. None of the controls had chronic liver or neuropsychiatric disease or abused alcohol. In addition, none of the controls was taking medications known to affect sleep.

2.2. Measurement of sleep disturbances

All patients and controls completed a validated Turkish Form of the Pittsburgh Sleep Quality Index (PSQI) [10,11] and a simple sleep questionnaire (STSQS) [12].

The total PSQI score is between 0 and 21. This validated tool is used to assess sleep quality and sleep disturbances over the preceding month. The questionnaire contains 19 questions that are used to generate seven components, each of which is scored from zero to three, where three represents the negative extreme. These component scores are then summed to provide the total PSQI score (range: 0–21). The PSQI testing takes approximately 10 min to complete and 5 min to score [10].

The STSQS, which was described by Montagnese et al., provides a simple overall assessment of sleep quality rated on a 1–9 analogue scale (1 = best, 9 = worst sleep ever) and allows for the collection of information on habitual sleeping parameters such as bedtime, total sleep time, sleep latency, night awakenings, and waking and arousal times during the preceding month [12]. The STSQS takes 1–2 min to complete without additional time for scoring.

Sleep disturbance was defined as a PSQI score (0–21) of >5 or an STSQS score ≥4.

2.3. Measurement of the critical flicker frequency threshold

The CFF was measured with an HEPAtonorm analyzer (HE-Flicker Diagnostics, Germany). The patients were first trained and instructed on the procedure. By decreasing the frequency of the light pulses from 60 Hz downward, the CFF threshold was determined as the frequency at which the impression of fused light turned to a flickering one. Flicker frequencies were measured 9 times for each measurement, and the mean value was calculated. Measurements below 38.9 Hz were designated as abnormal CFF, based on the CFF results obtained from our unpublished previous study, which is consistent with a German study [13]. The cut-off was calculated as 2 standard deviations below the mean CFF values found in healthy volunteers. The CFF was measured twice a day (at 10 am and at 10 pm) for all cirrhotic patients and controls. The measurements performed at 10 am and 10 pm were defined morning measurement (CFFam) and night measurement (CFFpm), respectively. We then evaluated the differences between CFFam and CFFpm.

The ethics committee approval was received on August 1, 2011 (Registration Number: 11-5/7).

Table 1
Clinical characteristics of 59 cirrhotic patients.

Age	58.8 ± 11.4
Male gender	32 (54.2%)
Time since diagnosis in years (median)	5.95 ± 5.49 (4.0)
Aetiology	
Hepatitis B	24 (40.7%)
Hepatitis C	6 (10.2%)
Alcohol	10 (16.9%)
Other	19 (32.2%)
History of hepatic encephalopathy	8 (13.6%)
Esophageal varices	36 (61%)
Ascites	35 (59.3%)
Child–Pugh class	
A	23 (39.0%)
B	19 (32.2%)
C	17 (28.8%)
Decompensation	38 (64.4%)
Child's–Pugh score	7.7 ± 2.1
MELD score	12.2 ± 4.1

MELD: Model For End-Stage Liver Disease.

2.4. Statistics

The differences between CFFam and CFFpm in compensated and decompensated cirrhotic patients and in healthy volunteers were compared using a general linear repeated-measures model.

Since the number of healthy controls was low, the Mann–Whitney *U* test was used to compare the parametric values between controls and cirrhotic patients.

The possible differences among the nominal data were examined using the chi square test and Fisher's exact test. The Fisher's exact test was applied if the number of samples in any category was ≤5. Otherwise, the chi square test was applied.

The Wilcoxon signed rank test was used to compare the morning and night CFF values of cirrhotic patients and healthy controls.

The patients were also separately analyzed and defined as compensated or decompensated according to the presence of jaundice, ascites, variceal bleeding, and history of HE.

3. Results

Fifty-nine cirrhotic patients (54.2% males, Mean Age: 58 ± 11.4 years) and 18 healthy controls (38.9% males, Mean Age: 57.7 ± 9.2 years) were included in the study. The clinical characteristics of cirrhotic patients are shown in Table 1. Twenty four had hepatitis B virus-related cirrhosis (40.8%) and only 8 had a history of overt HE (13.5%). Thirty eight patients (64.4%) had decompensated cirrhosis and of these 35 had ascites (59.3%). Seventeen patients were in Child–Pugh class C (28.8%), the mean MELD score was 12.2 ± 4.1, and MELD score was ≥15 in 13 patients (22%).

Overall, 22 patients (37%) were receiving anti-HE treatment (lactulose, rifaximine or LOLA) until one week before CFF testing. Fourteen of the 22 patients without history of overt HE were taking these drugs due to forgetfulness or difficulties in concentration, particularly for their business. However, there were no differences in the CFFam or CFFpm measurements between those who did and did not receive anti-HE treatments (data not shown).