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ORIGINAL ARTICLE

Sleep disturbance and daytime sleepiness in patients with cirrhosis: a case control study

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Abstract Sleep disturbance and excessive daytime sleepiness have been reported in patients with hepatic cirrhosis. The objective of this study was to evaluate daytime somnolence and sleep complaints in a group of 178 patients with cirrhosis compared to a control group. Sleep features and excessive daytime sleepiness were evaluated by the Basic Nordic Sleep Questionnaire (BNSQ) and the Epworth Sleepiness Scale (ESS). We collected clinical and laboratory data, neurological assessment and EEG recordings in cirrhotic patients. Patients with cirrhosis complained of more daytime sleepiness ($p<0.005$), sleeping badly at least three times a week ($p<0.005$), difficulties falling asleep ($p<0.01$) and frequent nocturnal awakening ($p<0.005$) than controls. We found a poor correlation between sleep disorders and clinical or laboratory parameters. Our results confirm previous literature reports suggesting a high prevalence of sleep disturbance in patients with cirrhosis. Insomnia and daytime sleepiness are the main complaints. Sleep disorders are probably a multifactorial phenomenon.

Keywords Liver cirrhosis · Insomnia · Daytime somnolence

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Introduction

Sleep disturbance and excessive daytime somnolence are common in patients with cirrhosis [1–4]. In addition, a disturbance of sleep is recognized as one of the early signs of hepatic encephalopathy [5–7]. Reversal of sleep rhythm, drowsiness and lethargy are classic signs of this disease, and their presence and entity are used to define the clinical stages of hepatic encephalopathy [8–11].

The most common feature of the sleep pattern in patients with cirrhosis is fragmented nocturnal sleep caused by frequent nocturnal awakenings, and a daytime functioning affected by frequent episodes of undesired sleepiness and more prolonged napping time [1, 2]. The sleep-wake cycle is also shifted with activity toward the later hours of the day. This is ascribed to the displacement toward later hours in the 24-hour profile of plasma melatonin, common in cirrhosis [12]. However, the existence of a phase delay in cirrhotic patients and its relation with the melatonin rhythm remains controversial [13]. In addition, few data have shown a correlation between sleep impairment and the clinical parameters of liver disease. There are limited data on the true prevalence of sleep disturbance in cirrhotic patients compared with a control group.

For these reasons, we conducted a case control study to assess the prevalence and characteristics of sleep disturbance and excessive daytime sleepiness in patients with cirrhosis compared with a sex and age matched non-cirrhotic population, and determine their correlation with clinical parameters.

Materials and methods

Participants

Patients with cirrhosis

We studied a consecutive series of 178 patients with hepatic cirrhosis. All patients with a diagnosis of non-alcohol-related liver cirrhosis seen at our Neurology Unit were invited to participate in this study. Patients were referred to our Unit either for neurological screening for orthotopic liver transplantation (112 patients) or for any neurological complaint (including hepatic encephalopathy). Patients with post-alcoholic cirrhosis were excluded due to the possible independent influence of ethanol on the central nervous system and quality of sleep.

The patient population included 115 males and 63 females, whose mean age was 52.12 years (ranging from 17 to 71 years) were enrolled. The diagnosis of cirrhosis was based on a compatible clinical history, radiological studies, and liver biopsy when available.

At the time of evaluation, 23.5% were Child-Pugh class A patients, 48.2% class B and 28.3% class C. The aetiology of cirrhosis was viral hepatitis in 78.6% (HBV 18.5%; HCV 53.4%; HBV+HCV 6.7%), autoimmune disease in 9% and diverse causes in 11.4%. Past episodes of hepatic encephalopathy was reported by 24.2% of patients, while 6.2% had current minimal hepatic encephalopathy and 68% had never had episodes of encephalopathy. One hundred and thirty-six patients were on the list for orthotopic liver transplantation.

Healthy controls

A control group was selected from healthy subjects, mostly blood donors at our hospital and employees from our institution. The group included 178 individuals who were sex and age matched with the cirrhotic patients (±1 year). Mean age of normal controls was 52.06 years (ranging from 17 to 72 years).

The study was conducted according to the principles established in Helsinki and approved by the local ethics committee.

Procedures

Neurological assessment

A complete neurological assessment was performed in all patients with cirrhosis, and 113 underwent EEG recording.

Sleep Evaluation

All patients with cirrhosis were assessed by a sleep specialist with a semi-structured 20 minute interview on their sleep habits and complaints. All subjects were administered two standardised questionnaires: the Basic Nordic Sleep Questionnaire (BNSQ) and the Epworth Sleepiness Scale (ESS).

The BNSQ comprises 22 questions investigating sleep habits and complaints of insomnia, difficulty falling asleep, night awakenings, early morning awakening, use of hypnotic drugs, napping habits, daytime sleepiness, snoring and sleep apnoea [14].

We added two questions to better define the severity of daytime sleepiness and the circumstance in which sleepiness occurred. The questions added were: "Do you feel excessively sleepy during the daytime?" with five possible responses (1) never, (2) sometimes after lunch, (3) often or always after lunch, (4) even at other times of the day, and (5) throughout the day; and "Sleepiness is" (1) absent, (2) slight, (3) moderate, (4) severe and (5) very severe. Most of the questions ask for the frequency of the symptom (never or less than once per month, less than once per week, on 1-2 days per week, on 3-5 days per week, daily or almost daily), rather than the severity of the symptom.

The ESS is a standardised scale scoring the level of daytime sleepiness by rating the chance the subject would doze off in eight different real-life situations [15]. All questionnaires were administered by a physician.

All subjects were classified on the basis of their answers to the BNSQ questions as Sleepy (S) if they complained of excessive daytime sleepiness, at least moderate and not only in the postprandial hours at least three times a week, Postprandial Sleepy (PS) if they complained of excessive daytime sleepiness, at least moderate only after lunch at least three times a week, or Not Sleepy (NS) if they did not fit these conditions. Subjects were classified as Insomniacs if they reported sleeping badly or rather badly at least three times a week.

Clinical and laboratory data

We included in the database information on education, employment and routine biochemistry, including albumin and serum bilirubin, prothrombin activity, cholesterol, alkaline phosphatase, blood ammonia, transaminase, γ-glutamyl transpeptidase, γ-globulins, serum triglyceride level, γ-fetoprotein, blood nitrogen and current therapy. We also investigated the presence and severity of ascites, episodes of encephalopathy, gastrointestinal bleeding and jaundice.

Statistical Analysis

We used the *t*-test, variance analysis (ANOVA) and the Wilcoxon-Mann-Whitney test. Data were analysed by the McNemar test. We related all questionnaire answers to blood ammonia value with Pearson's correlation.

Results

Patients with cirrhosis showed a significantly higher prevalence of sleep disturbance than the healthy control group. Twenty-six per cent of patients complained of sleeping badly or almost badly at least three times a week ("insomniacs"), whereas this complaint was infrequent in the healthy subjects (7.9%) ($p<0.005$).

Patients with cirrhosis complaining of "insomnia" reported more often both difficulty initiating and maintaining sleep but they also differed from "non-insomniac" patients with cirrhosis for a higher prevalence of daytime sleepiness ($p<0.001$) and more frequent naps ($p<0.01$). No difference was observed between groups regarding early morning awakening and snoring.

Patients with cirrhosis showed a significantly higher prevalence of daytime sleepiness ($p<0.005$): 18.5% were classified as Sleepy (vs 3.9% of controls), 30.9% were classified as Postprandial Sleepy (vs. 18.5% of controls) and 50.6% were classified as Not Sleepy (vs. 77.5% of controls).

Among patients with cirrhosis 55% referred habitual naps vs 23% of healthy controls and cirrhotic patients reported more prolonged napping time (Table 1). Among cirrhotic patients, the Sleepy group showed worsening parameters of nocturnal sleep quality, such as nocturnal awakening ($p<0.05$), difficulties falling asleep ($p<0.05$), complaint of sleeping badly or almost badly at least three times a week ($p<0.005$) and referred sleep apnoea ($p<0.05$).

Patients with cirrhosis had a mean ESS score of 6.66 (vs 6.17 in healthy controls), and 15.7% of them had a score higher than 10 (vs. 12.9% in healthy controls), but the difference was not statistically significant. The patients with the highest scores, although not pathological, were patients complaining of "insomnia". Among patients with cirrhosis those with current minimal hepatic encephalopathy were more frequently "sleepy" ($p<0.005$) and "insomniac" ($p<0.05$).

No significant difference was observed between Sleepy and Postprandial or Not Sleepy cirrhotic patients with regard to Child-Pugh score, development of ascites, aetiology of cirrhosis, previous encephalopathy and routine biochemistry. The mean value of blood ammonia was 61.79 mcg/dL in Postprandial and Not Sleepy, and 76.88 in Sleepy patients, but the difference was not significant (ANOVA). We divided patients into two groups, according to pathological or normal blood ammonia value (≤ or >80 mcg/dL), and the two groups were compared according to parameters of sleep habits: they did not show significant differences. Moreover, blood ammonia value did not show any significant correlation with parameters of sleep quality.

Bedtime and arising time of patients with cirrhosis and healthy controls were similar. The mean value of bedtime in cirrhotic patients was 11.16 pm vs. 11.53 pm in controls, whereas the mean value of arising time in cirrhotic patients was 7.46 am vs. 7.36 am in controls. Even a comparison between cirrhotic patients with sleep disturbances and those without revealed no differences in these parameters. The mean value of bedtime and arising time in the insomniac cirrhotic group were 11.07 pm and 7.18 am, whereas in the non-insomniac cirrhotic group they were 11.19 pm and 7.15 am.

Discussion

Our study confirms that patients with cirrhosis frequently have sleep disorders. We found a significantly higher prevalence of parameters of poor sleep quality, such as difficulties falling asleep, nocturnal awakenings and complaints of sleeping badly, in patients with cirrhosis than in healthy controls. In addition, daytime functioning of these patients was affected by excessive sleepiness and more prolonged napping time. A higher prevalence of daytime sleepiness disclosed by the BNSQ questionnaire was not accompanied by a significant different in the Epworth Sleepiness Scale (ESS). This may be because the ESS, validated in narcoleptics and OSAS patients, is not sufficiently accurate in estimating sleepiness in an inactive population like patients with cirrhosis [16]. As reported in previous studies, we found a poor correlation between clinical and laboratory parameters and sleep disturbance

Table 1 Sleep characteristics of patient population

	Cirrhotic patients	Healthy controls	*p* value
Sleepy (%)	18.5	3.9	0.005
Post-prandial sleepy (%)	30.9	18.5	0.005
Not sleepy (%)	50.6	77.5	0.005
"Insomniacs" (%)	26	7.9	0.005
Difficulty falling asleep (%)	21	8.5	0.01
Night awakening (%)	71	43	0.005
Early awakening (%)	15	12	n.s.
Hypnotics (%)	4.5	2.3	n.s.
Morning sleepiness (%)	19	12	n.s.
Sleep attacks (%)	6.8	3.4	n.s.
Total sleep time (min)	450	442	n.s.
Snoring (%)	26	35	n.s.
Referred sleep apnoea (%)	4.1	5.4	n.s.
Nap (%)	55	23	0.005
Nap duration (min)	38.8	26.9	0.05

or daytime somnolence [17, 18]. We did not find a phase delay in the sleep patterns of patients with cirrhosis, although the sleep questionnaire we used is not an accurate tool for identifying circadian abnormalities.

Another limitation of our study is the difficulty defining and estimating sleepiness on the basis of subjective patient evaluation. The first problem is to distinguish sleepiness from common symptoms in cirrhosis, like fatigue, tiredness and lack of energy.

Sleepiness could also be linked to the limitations of a chronic disease forcing subjects to lead very sedentary lives, thereby increasing the risk of episodes of undesired sleepiness. In addition, the frequent nocturnal awakenings could be related to increased episodes of nocturia because of diuretic treatment. In this regard, another limitation of our study is the lack of a control group with another chronic disease (e.g. chronic renal failure). Sleep difficulty in patients with cirrhosis could be related to a specific dysregulation of the histamine neurotransmitter system [19, 20], and a comparison with other chronic diseases could yield information useful for estimating the real impact of hepatic failure on sleep pattern and its pathogenesis.

Snoring and reported apnoeas did not significantly differ from healthy controls. However, the finding that snoring was more common in "sleepy" than in "post-prandial sleepy" and "not sleepy" patients with cirrhosis in our cohort could strengthen the hypothesis that somnolence in cirrhotic patients is favoured at least in part by an obstructive apnoea syndrome during sleep [21–23].

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