Research Article

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Active at night, sleepy all day – Sleep disturbances in patients with hepatitis C virus infection

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Background & Aims: More than 50% of patients with chronic hepatitis C with only mild liver disease complain about chronic fatigue, daytime sleepiness and poor sleep quality. The aim of the present study was to characterize and objectify the sleep disturbances in hepatitis C virus-infected patients.

Methods: Twenty-five women who had been infected with hepatitis C virus contaminated anti-D immunoglobulin in 1978/79 and 22 age-matched female healthy controls underwent actigraphy over a period of 5 days to measure motor activity and thereby sleep-wake-rhythm and in addition completed questionnaires for depression, health-related quality of life, fatigue and sleep, and a sleep diary. Liver cirrhosis, a history of neurological or psychiatric disease, history of intravenous drug abuse, shift work, or current medication with effect upon the central nervous system were exclusion criteria.

Results: The patients achieved higher scores for depression, fatigue and sleep disturbances and lower quality of life scores than the healthy controls. Actigraphy showed higher nocturnal activity and worse sleep efficiency in the patients, while the 24-h activity level did not differ between groups. Fatigue and quality of life scores correlated with bad sleep quality and daytime sleepiness.

Conclusions: Our data indicate that chronic fatigue is associated with bad sleep quality and increased nocturnal activity in HCV-infected patients suggesting an alteration of sleep architecture behind fatigue in HCV-associated encephalopathy.

Introduction

About 170 million people worldwide suffer from chronic infection with the hepatitis C virus (HCV), the global prevalence is about 2.35%. In 80% acute hepatitis C infection leads to chronic hepatitis whereas between 1 and 20% – dependent on the presence or absence of risk factors such as older age, male sex, alcohol abuse, or diabetes for example – develop liver cirrhosis [1,2]. An extremely low rate of liver cirrhosis has been observed in the so-called German Anti-D cohort, a group of women who have been infected with HCV contaminated anti-D immunoglobulin in 1978/79 in Eastern Germany. Wiese *et al.* reported that only 2% of 1980 women who underwent a follow-up examination 25 years after the infection showed liver cirrhosis or a pre-cirrhotic stage while 62% "complained of constitutional symptoms such as reduced exertional capacity, weakness and fatigue, abdominal distention, arthralgia, myalgia, or headaches" [2].

Hepatologists are well aware of the extrahepatic manifestations of the HCV-infection and it has been acknowledged recently that the central nervous system is most frequently affected [3]. Symptoms like chronic fatigue, mood disturbances and cognitive dysfunction occur in HCV infected patients with none or only mild liver disease and are accompanied with a reduction of health-related quality of life. The most frequent symptom with more than half of the patients affected is fatigue. Of note, this holds true also in the absence of advanced liver disease or ongoing antiviral therapy with interferon alpha [4]. In detail, chronic HCV infected patients complain about daytime fatigue and poor sleep quality. Up to now these symptoms are not well described in the literature and the pathogenesis is still unclear [5].

The purpose of this study was to characterize the feature and degree of sleep disturbances in HCV-infected patients without relevant liver disease and to clarify the patients' symptoms. Furthermore we were interested to analyze the relationship

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Abbreviations: APRI, aspartate aminotransferase-to-platelet ratio index; PSQI, Pittsburgh sleep quality index; ESS, Epworth sleepiness scale; FIS, fatigue impact scale; BDI, Beck depression inventory; HADS, hospital anxiety and depression scale; SF-36, short-form questionnaire; QoL, quality of life; WASO, wake after sleep onset; cpm, counts per minute; MVPA, moderate to vigorous physical activity; CSF, cerebrospinal fluid; FSS, fatigue severity scale.

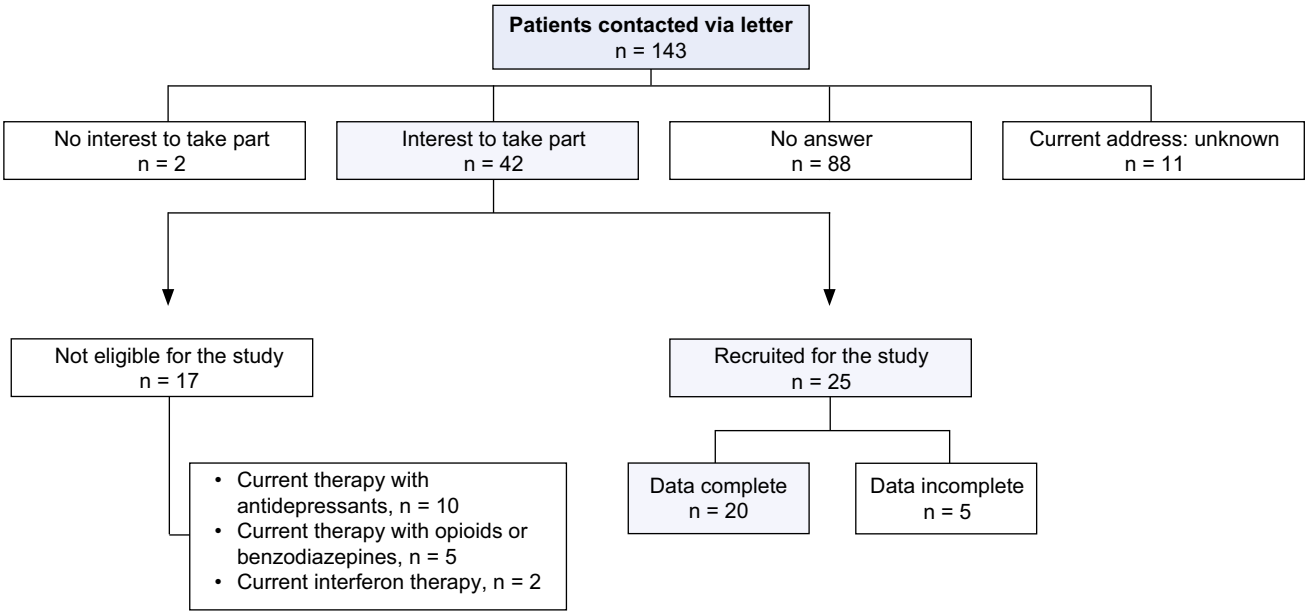

Fig. 1. Flow chart for patient recruitment.

between sleep disturbances, neuropsychiatric symptoms and health-related quality of life.

Patients and methods

Patients and controls

One-hundred-forty-three members of HCV patient support groups for women who had been infected with HCV-contaminated anti-D immunoglobulin in 1978/79 were contacted in writing and asked if they were interested in taking part in the study. These patients were considered especially suitable to study the effect of HCV-infection upon sleep features and quality because neither co-infection, nor substance abuse or other concomitant disorders could probably bias the results. Eleven patients had moved and their current address was not available, two patients refused to take part in the study. Forty-two women answered our letter and showed interest (Fig. 1).

These 42 women were contacted via phone for a structured interview concerning the exclusion criteria such as liver cirrhosis, a history of neurological or psychiatric disease, history of intravenous drug abuse, shift work, or current medication with effect upon the central nervous system. Thereafter 17 patients had to be excluded from the study because of current therapy with antidepressants (n = 10), opioids or benzodiazepine (n = 5) or current interferon therapy (n = 2) (Fig. 1).

Finally, twenty-five women were included into the study. The time span since infection was more than 30 years and the genotype of the virus 1b in all patients. Liver cirrhosis or severe fibrosis was excluded by calculation of the APRI (aspartate aminotransferase-to-platelet ratio index) score [6], by ultrasound of the liver and/or by liver biopsy.

22 age-adjusted female control subjects were recruited from the clinic staff as well as family and friends of working group members applying the same exclusion criteria as for the patients. Patients and controls gave their written informed consent.

The study has been performed according to the 1975 Declaration of Helsinki and has been approved by the local ethics committee.

Questionnaires

The patients and controls completed several questionnaires including the Pittsburgh sleep quality index (PSQI) [7], the Epworth sleepiness scale (ESS) [8], the fatigue impact scale (FIS) [9], the Beck depression inventory (BDI) [10], the hospital anxiety and depression scale (HADS) [11] and the SF-36 [12]. The PSQI is a subjective measure of sleep quality over the previous 4 weeks. The questionnaire consists of 17 items based on components of quality, latency, duration, efficiency, disturbance, use of sleeping medication and daytime dysfunction. The global score varies between 0 and 21. A score $\geqslant 5$ can be considered suggestive of significant sleep disturbance. The ESS intends to measure daytime sleepiness. Each item is rated on a 4-point scale. The global score ranges between 0 and 24, with 10 as a cut-off score for pathological daytime sleepiness. The FIS is a self-report scale to measure the impact of fatigue upon patients' daily living activities. It contains 40 items with a scale from 0 to 4. The total score varies between 0 (no fatigue) and 160 (severe fatigue), we choose 50 as a suggested cut-off for pathological fatigue considering own data from healthy controls from former studies. The BDI is a self report scale to measure depression. The questionnaire contains 21 items and a 4-point response scale, ranging from 0 (minimal) to 3 (severe). The global score ranges from 0 to 63, a score $\geqslant 18$ can be considered as pathologic. The Hospital Anxiety and Depression Scale (HADS) has been developed for use in in-hospital patients with internal disease to assess emotional alterations. It is a 14 items scale, each scored from 0 to 3. The global range varies between 0 and 21 for anxiety and depression, respectively, with a score $\geqslant 11$ indicating anxiety or depression. The Short-Form questionnaire (SF-36) is a survey with 36 questions to measure health-related quality of life (QoL). It provides scores for 8 health domains which can be summarized to a physical and a mental score with a maximum of 400 points for each of the two domains. The cut-off depends on age and sex. The patients' results were evaluated accordingly.

Sleep diary

The patients were requested to fill in a sleep diary to record the "in bed time", time to sleep onset, number of awakenings, "out of bed time", daytime nap, coffee and alcohol consume for the days studied.

Actigraphy

Actigraphy was used to measure motor activity of the subjects throughout a period of 5 days. The actigraph is a small device (38 mm $\times$ 37 mm $\times$ 18 mm, weight 26 g) which is worn on the wrist of the non-dominant hand. We used the accelerometer ActiGraph Monitor GT1M and GT3X (ActiGraph, Pensacola, USA). Both contain a sensor which detects motion with linear piezoelectric accelerometer in a vertical axis [13]. The signal is summarized over epochs of 60 s, and given as counts per minute (cpm). Patients and controls were advised to wear the device from Sunday to Saturday 24 h per day and to only take it off for washing the dishes or taking a shower. The data stored were downloaded to a computer using the ActiLife 5.0 software. Because of the varying sleep-wake-rhythm during the weekend only data covering the time span from Monday 12 pm until Friday 12 pm were considered for further analysis.