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Assessment of excessive daytime sleepiness in cirrhotic patients

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ABSTRACT

Background. It is known that alterations of the sleep-wake cycle are present from the early stages of hepatic encephalopathy (starting with grade I on the West Haven criteria). However, minimal hepatic encephalopathy (which is not included in the West Haven criteria) defines the earliest form of HE, with no obvious clinical manifestations, but with subtle alterations in cognitive domains such as attention, visuo-spatial perception, psychomotor speed and response inhibition.
Aim. To determine if liver cirrhosis in otherwise asymptomatic individuals (without clinically manifest hepatic encephalopathy) is associated with an increased risk of altered sleep rhythm or excessive daytime sleepiness. Additionally, to determine if this risk is correlated with liver disease severity or other clinical and biological parameters.
Material and methods. Cross-sectional study involving 25 adult patients with liver cirrhosis. Patients were evaluated through a standard neurological examination and with the Epworth Sleepiness Scale. Liver disease severity was measured using the MELD and Child-Pugh scores. Blood ammonia levels were also measured.
Results. Mean age of the patients was 50±12 years-old. There was a predominance of males (68%, n=17). Mean MELD score was 17±7 points. Mean Child-Pugh score was 8±2 points. Mean blood ammonia level was 34±17 µg/dL. Subjective daytime somnolence was reported by 24% of patients (n=6). Mean ESS score was 6±5 points. No correlation was noted between the ESS scores and liver disease severity as measured by the Child-Pugh and MELD scores. Only three patients (12%) scored over 10 points on the ESS (none of them obese) and were consequently diagnosed with excessive daytime sleepiness (EDS). This proportion falls into the accepted prevalence of EDS in the general population.
Conclusions. In our study, liver cirrhosis was not associated with a higher prevalence of excessive daytime sleepiness than in the general population.

Keywords: Epworth sleepiness scale, minimal hepatic encephalopathy, liver cirrhosis

Abbreviations (in alphabetical order):

ALD – Alcoholic Liver Disease
HBV – Hepatitis B Virus
HCV – Hepatitis C Virus
HDV – Hepatitis D Virus
HE – Hepatic Encephalopathy
EDS – Excessive Daytime Sleepiness
ESS – Epworth Sleepiness Scale
MELD – Model for End-stage Liver Disease
MHE – Minimal Hepatic Encephalopathy
OSA – Obstructive Sleep Apnea
PHES – Psychometric Hepatic Encephalopathy Score
PSQI – Pittsburgh Sleep Quality Index
REM – Rapid Eye Movement
SDS – Subjective Daytime Somnolence

BACKGROUND AND AIMS

Hepatic encephalopathy (HE) is defined as a reversible syndrome of brain dysfunction in the context of advanced liver disease and/or portosystemic shunting [1,2]. It can manifest as a broad spectrum of neuropsychiatric symptoms, ranging from subclinical alterations (detectable only on neurophysiological or neuropsychological testing), to alterations of cognition and motor function, to coma [3]. The severity of HE is classically graded according to the

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West Haven criteria into four grades (see *Table 1*) [4,5]. As one can notice, alterations of the sleep rhythm are present from the early stages of HE.

The term "minimal hepatic encephalopathy" (MHE) defines the earliest form of HE (not included in the West Haven criteria), which has no obvious clinical manifestations, but is characterized by subtle alterations in cognitive domains such as attention, visuo-spatial perception, psychomotor speed and response inhibition [6]. The prevalence of MHE varies between 47-80% in cirrhotic patients, and has been associated with poor driving performance and impaired health-related quality of life [7,8,9].

Because of the difficulty in diagnosing grade I HE (due to high inter-observer and even intra-observer variability), the current guidelines recommend using the terms **covert HE** (for MHE and grade I HE) and **overt HE** (when referring to grades II-IV) [4,10].

TABLE 1. The West Haven criteria for hepatic encephalopathy

Grade	Manifestations
1	– Shortened attention span – Altered sleep rhythm – Impairment of addition and subtraction – Minor lack of awareness
2	– Disorientation for time – Apathy or lethargy – Inappropriate behavior – Dyspraxia – Asterisks
3	– Disorientation for time and space – Confusion – Bizarre behavior – Somnolence to stupor (responds to stimuli)
4	– Coma (doesn't respond to stimuli)

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OBJECTIVES

Our main objective was to determine if the presence of liver cirrhosis in otherwise asymptomatic individuals (without clinically manifest hepatic encephalopathy) is associated with an increased risk of altered sleep rhythm or excessive daytime sleepiness. Additionally, we wanted to establish if this risk is correlated with liver disease severity or other clinical and biological parameters.

MATERIAL AND METHODS

We performed a cross-sectional study, in which we recruited 25 adult patients diagnosed with liver cirrhosis at the Gastroenterology and Hepatology Department of Fundeni Clinical Institute. All patients were included on the liver transplantation waiting list. Evaluation comprised of a standard neurological examination, and also included an assessment of their sleep-wake cycle and the administration of the Epworth Sleepiness Scale (ESS). For this, we acquired the license for using the Romanian version of the ESS (Version of 22 Jan 18). Assessment of liver dysfunction was measured by using the MELD and Child-Pugh scores.

All recruited patients signed an informed consent form and respected the inclusion and exclusion criteria highlighted in Table 2. Obviously, cirrhotic patients with overt HE, or those previously diagnosed with a sleep disorder (including sleep apnea) were excluded, due to the known alterations of the sleep-wake cycle generated by these disorders. For similar reasons, patients with alcohol intoxication (or alcohol withdrawal), those receiving psychoactive medications, or those with other major neuro-psychiatric comorbidities, were also excluded from this study.

TABLE 2. Inclusion and exclusion criteria used for patients in our study

Exclusion criteria	Inclusion criteria
Overt hepatic encephalopathy	Age > 18 years-old
Previous diagnosis of a sleep disorder	Diagnosis of liver cirrhosis
Previous diagnosis of obstructive/central sleep apnea	
Alcohol intoxication or withdrawal	
Current use of psycho-active medication which may influence the sleep/wake cycle	
Major neuro-psychiatric comorbidities which may alter the sleep/wake cycle (e.g., dementia)	

Relevant medical information (discharge papers, laboratory test results) was accessed using the hospital's informatics system Hipocrate. Patient database was created with Microsoft Office 365 and statistical analysis was done with MedCalc Statistical Software version 18.9. The study protocol was approved by the Ethics Committee of Fundeni Clinical Institute.

RESULTS

Mean age of the patients was 50 ± 12 years-old (range: 30-69 years-old). There was a predominance of males (68%, n=17). The most frequent cirrhosis etiology was chronic hepatitis due to HBV ± HDV (40%, n=10), followed by ALD (32%, n=8), chronic hepatitis due to HCV (24%, n=6) and autoimmune hepatitis (4%, n=1). Mean MELD score was 17±7 points (range: 7-29 points). Mean Child-Pugh score

was 8±2 points (range: 5-12 points). Mean blood ammonia level was 34±17 µg/dL (range: 8-56 µg/dL). About half of the patients (52%, n=13) were also diagnosed with type II diabetes mellitus. The prevalence of obesity was 8% (n=2). Regarding symptoms of the sleep-wake cycle, 28% of the patients (n=7) complained of insomnias, and 24% (n=6) complained of daytime somnolence.

Mean ESS score was 6±5 points (range: 0-19). No correlation was noted between the ESS scores and age (R=0.009, p=0.9) (see *Figure 1*). There were no significant differences between males and females regarding the ESS score (p=0.7). Mean ESS score of patients with insomnia was 8±6 points. There was no statistically significant difference between ESS scores in patients with insomnias and patients without insomnias (p=0.2). Mean ESS score of patients who complained of daytime somnolence was 10±5 points and was significantly higher than in patients with no complaints (p=0.04) (see Figure 2). No significant correlation was noted between ESS scores and severity of liver disease as measured by the MELD (R=0.16, p=0.4) and Child-Pugh scores (R=0.35, p=0.09). Likewise, ESS scores were not correlated with blood ammonia levels (R=0.02, p=0.95). No significant difference was noted between diabetics and non-diabetics regarding the ESS scores (p=0.7). Only three patients (12%) scored over 10 points on the ESS (none of them obese) and were consequently diagnosed with excessive daytime sleepiness.

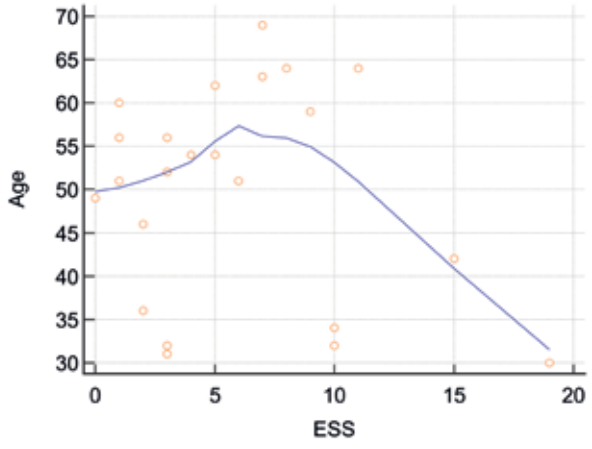

FIGURE 1. Correlation between ESS scores and age of patients

DISCUSSIONS

Excessive daytime sleepiness (EDS) is defined as the inability to maintain wakefulness and alertness during the waking periods of the day, with sleep occurring unintentionally and/or at inappropriate times almost daily for at least three consecutive months [11]. There are many tools available to measure EDS, and the most widely used is the Epworth Sleepiness Scale (ESS) [12,13]. The ESS was introduced in 1991 by Johns MW from the Epworth Hospital in Melbourne (Australia) [14]. The scale consists of a self-administered questionnaire which measures the level of the patient's sleepiness during the day. It consists of 8 questions in which the patient is asked to state the probability (from 0 to 3) of dozing off or falling asleep during certain daily situations. A score above 10 points is indicative of EDS.

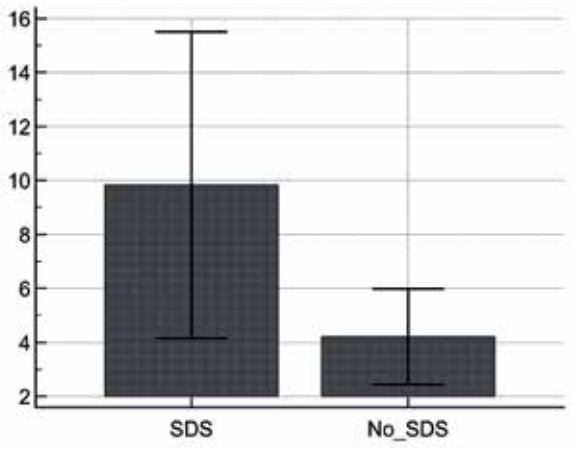

FIGURE 2. ESS comparison between patients with subjective daytime somnolence (SDS) and patients without SDS

Many causes are known to induce or contribute to EDS, including obstructive sleep apnea, narcolepsy, restless legs syndrome, neurodegenerative disorders, brain tumors, paraneoplastic syndromes, obesity-hypoventilation syndrome, psychiatric conditions or the use of alcohol or of certain medications (benzodiazepines, barbiturates, anti-seizure medications) [15]. EDS is estimated to affect about 20% of the general population [16], however the prevalence varies in different papers between 9 – 28%, due to differences in demographic, cultural and geographic factors, but also due to differences in study design and/or sample size [13]. In our study for instance, EDS was diagnosed in 12% of patients. This proportion falls into the accepted prevalence of EDS in the general population.

In cirrhotic patients, the occurrence of sleep disturbances is classically associated with hepatic encephalopathy, however sleep disturbances may be present even in cirrhotic patients without overt HE [17]. One study reported a high percentage of cirrhotic patients without HE (47.7%) who complained of unsatisfactory sleep, as compared to healthy controls (4.5%), and this was further corroborated by the use of actigraphy [18]. Another study concluded that sleep-wake abnormalities were more frequent in cirrhotic patients than in healthy volunteers (with abnormal ESS scores of 21% versus 0%), and that these abnormalities were not correlated with the presence or severity of hepatic encephalopathy [19].

Bajaj et al. established that obstructive sleep apnea (OSA) is a potential cause of daytime sleepiness and a contributor to cognitive dysfunction in liver cirrhosis, and should be considered especially in cirrhotic patients with obesity [20]. Prior episodes of hepatic encephalopathy may synergize with OSA in worsening the sleep architecture. Cirrhotic patients with prior HE and OSA seem to spend more time in the early (non-restorative) stages of sleep, do not have slow wave sleep, and also reach the REM stage sooner, compared to cirrhotic patients with OSA alone [21].

It is noteworthy that patients with OSA have a significantly higher risk of liver disease (especially of cirrhosis, hepatitis C and non-alcoholic fatty liver disease) than the general population, as was highlighted in a cohort study involving over 17000 patients with OSA and over 69000 controls [22]. The prevalence of restless legs syndrome also appears to be significantly higher in patients with chronic liver disease (62% in one study) than in the general population (~10%) [23]. Both OSA and restless legs syndrome are important causes of excessive daytime sleepiness. In one study comprising 200 patients with liver cirrhosis, the prevalence of EDS, OSA, and both EDS and OSA were 29.5%, 42.9% and 13.6%, respectively [24].

Regarding the pathophysiologic mechanisms, some authors have pointed to a central circadian disruption in patients with liver cirrhosis, based on the fact that the peak plasma melatonin/cortisol levels were delayed, and the plasma melatonin response to light was reduced [25]. However, the same authors did not find an association between these circadian abnormalities and impairment of sleep quality. Other authors highlighted the importance of glucose fluctuations in reducing the quality of sleep. In the study performed by Haraguchi et al., glucose fluctuations correlated with the Pittsburgh Sleep Quality Index (PSQI) score and were identified as an independent risk factor for sleep disturbance in cirrhotic patients [26]. The role of ghrelin has been researched in one small study, and an association was established between altered ghrelin secretion (low ghrelin levels) and the loss of slow wave sleep in cirrhotic patients [27].

By performing the PHES, PSQI and ESS on 100 cirrhotic patients, Samanta et al. demonstrated a strong correlation between the presence of MHE and the existence of night time sleep disturbance and excessive daytime sleepiness [28]. Worth mentioning is also the observation that treatment with Rifaximin can improve the sleep architecture (and in particular, the duration of REM sleep, which is an indicator of good sleep quality) in patients with recurrent HE who suffer from poor sleep quality and EDS [29]. A similar conclusion was reached in another study, in which poor sleep quality and EDS were found to be more frequent in cirrhotic patients with MHE (as compared to those without MHE), and sleep disturbances improved after treatment with Lactulose [30]. It should be emphasized that the presence of sleep disturbances and excessive daytime sleepiness is associated with decreased health-related quality of life in cirrhotic patients [19,28,30].

CONCLUSIONS

In our study, liver cirrhosis was not associated with a higher prevalence of excessive daytime sleepiness than in the general population. However, sleep disturbances and, in particular, excessive daytime sleepiness may be more frequent in cirrhotic patients than in healthy subjects, and hence, must be sought and treated according to the underlying cause.

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