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SLEEP TIMING AND CIRCADIAN PREFERENCES IN A SAMPLE OF EGYPTIAN PATIENTS WITH HEPATIC CIRRHOSIS

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Keywords:

hepatic; cirrhosis; sleep; circadian; eveningness

Abstract

OBJECTIVE: to evaluate the sleep timing and circadian preference in a sample of Egyptian patients with hepatic cirrhosis in comparison to healthy individuals

METHODS: Individuals with hepatic cirrhosis (n=50) and healthy controls (n=30) were recruited. Sleep quality, sleep timing parameters and circadian preference were evaluated using the Pittsburgh Sleep Quality Index (PSQI), Sleep Timing Questionnaire (STQ) and The Composite Scale for Morningness (CSM) respectively.

RESULTS: As compared to healthy controls, patients with hepatic cirrhosis reported significantly higher problems in Subjective sleep quality, sleep latency, sleep disturbances, use of sleep medications, and total score of PSQI. They also showed overall more pronounced evening preference in addition to delayed timings for both bedtimes and awakening times in week days but not in weekends.

CONCLUSIONS: Disturbances of both quality and timing of sleep are prominent in hepatic patients. Further larger studies are needed to explore the exact pathophysiological mechanism of such an association.

Introduction

Cirrhosis of the liver is a chronic, diffuse, degenerative disease in which the parenchyma deteriorates, the lobules are infiltrated with fat and structurally altered, dense perilobular connective tissue forms and often areas of regeneration develop. These regeneration nodules have a reduced blood supply resulting in impaired liver function [1] and [2]. Factors that are taken into account to determine the severity of cirrhosis include serum albumin, prothrombin concentration, serum bilirubin, ascites and encephalopathy. A point system known as the Child's-pough-Turcotte score has been designed to determine the severity of cirrhosis. Depending on the total score, patients are classified as class A (early cirrhosis) through class C (advanced cirrhosis) [3].

A disturbance of sleep is recognized as one of the early signs of hepatic encephalopathy. Reversal of sleep rhythm, drowziness and lethargy are classic signs of this disease. Sleep disturbance and excessive daytime somnolence are common in patients with cirrhosis. It was estimated that up to 70% of individuals with cirrhosis (regardless of etiology) experience sleep disturbances [4]. Difficulty falling asleep and a shift in sleep schedule toward the latter part of the night, which might be result in daytime sleepiness, are commonly reported findings in patients with hepatic cirrhosis without encephalopathy [4]. Patients with cirrhosis were also reported to suffer from significantly more frequent daytime sleepiness and habitual napping, nighttime sleep problems, and nocturnal awakenings than

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healthy controls [5]. These sleep disturbances were not related to any clinical or laboratory parameters [5]. Objective measures of sleep quality, such as actigraphy, were utilized to confirm the deterioration of sleep parameters in cirrhotic patients [6]. Sleep deprivation has profoundly negative effects on cognitive function, [7] which is already impaired in the majority of patients with cirrhosis [8]. Ascites was recently reported to be a contributing factor to the development of obstructive sleep apnoea in patients with liver cirrhosis [3].

The circadian rhythm, as exemplified by the sleep/wake cycle, is the outward manifestation of a cell-autonomus 24-hour timing system. Virtually all eukaryotic organisms have endogenous circadian clocks that coordinate the daily periodicity of several physiological and behavioral rhythms and synchronize the organisms to daily environmental cycles [9]. Almost all body processes systematically fluctuate during the 24-hour period and show daily shifts in response to the changes in the period of light and darkness [10]. Core body temperature, hormonal secretion, food intake, sleep/wakefulness and hepatic metabolism are only few examples of the circadian oscillations in the human being [11]. Mounting research evidence demonstrates a significant negative impact of circadian disruption on human health. Strict regulation of hepatic metabolism through circadian-regulated hepatobiliary pathways plays an important role in maintaining maximally efficient nutrient use and storage [12]. An early study reported that patients with cirrhosis had markedly elevated melatonin levels during daytime hours. In addition, the time of onset of melatonin increase and the time at which melatonin levels peaked were consistently and significantly delayed in these patients [13].

The current study aims to evaluate the sleep timing and circadian preference in a sample of Egyptian patients with hepatic cirrhosis in comparison to healthy individuals. We hypothesized that after adjusting for confounding variables, hepatic patients will show significantly more sleep disturbances in addition to evening preference when compared to healthy controls.

Methods

Patients with hepatic cirrhosis were recruited from tropical medicine department in Tanta University hospital, Egypt. Cirrhotic patients were diagnosed clinically, laboratory and by imaging. A control sample that consists of 30 age and sex matched healthy individuals. After acquiring an informed consent, all subjects were subjected to full psychiatric history and mental status examination. Any unexpected risks during the course of the research were cleared to the participants and to the ethical committee of the Faculty of Medicine – Tanta University which approved the study. Subjects with neurological diseases that might affect their cognitive performance, e.g. hepatic encephalopathy, cerebrovascular stroke, and those with substance abuse disorders, were excluded.
The following psychometric tools were utilized:

1. **Fahmy and El-Sherbini scale** [14] was used to collect demographic and socioeconomic data for subject and control families.
2. **Pittsburgh Sleep Quality Index (PSQI)** [15] is an effective instrument used to measure the quality and patterns of sleep in the older adult. PSQI contains 19 self-rated questions and 5 additional questions rated by bed partner or roommate (if available). Only self-rated questions are included in the scoring. The 19 self rated items are combined to form seven "component" scores, each of which has a range of 0-3 points. These components are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. In all cases, a score of "0" indicates no difficulty, while a score of "3" indicates severe difficulty over the last month. The seven component scores are then added to yield one "global" score, with a range of 0-21 points, with "0" indicating no difficulty in sleep and "21" indicating severe difficulties in all areas. An Arabic translated and validated version of the PSQI [16] was utilized.
3. **The Sleep Timing Questionnaire (STQ)** [17] is a reliable valid measure of sleep timing that provides equivalent measurements of sleep to those obtained from a formal sleep diary. It also yields measures of sleep timing regularity and sleep quality [18]. Outcome variables analyzed from the STQ includes the sleep onset latency (SOL), and wake after sleep onset (WASO) calculated in minutes. The STQ also includes questions about actual bedtimes and waking up times that were not included in the analysis. The “usual” night times and morning times, the only times used for this analysis, were considered as the average times for going to bed and waking up respectively. The STQ also examines for the earliest and latest times which

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were not used in our work. To avoid cyclic nature of the numbers usually used to refer to time, all morning times and night times were converted to minutes and subtracted from a fixed time point (midnight in case of morning times and noon in case of night times).

4. **The Composite Scale for Morningness (CSM)** [19, 20] is a validated adaptation of the Horne– Ostberg scale. It is composed of 13 multiple choice sentences used to evaluate whether an individual is a "morning-type" or an "evening-type." A score of morningness/eveningness, which ranges from 13-55, can be easily calculated by adding up the scores of the individual questions. "Evening type" people have lower scores than morning type people. Arabic translated and validated versions of STQ and CSM were used in the study [21].

Statistical Analyses

Between-group demographic and clinical characteristics were compared using chi-square, ANOVA, and non-parametric tests as appropriate. All p-values were based on two-tailed tests with α=0.05. All analyses were performed using the Statistical Analysis System (SAS) version 16.

Results

Ages of the participants ranged from 37-69 (mean=53.4). Of the 80 subjects participating in the study, 38 (47.5%) were females and 42 (52.5%) were males. As shown in table-1, no significant between group differences were reported as regards age or sex. Similarly, no significant differences were reported between patients and controls regarding socioeconomic status (p values $\geq$ 0.05; table-1 and figure 1). Patients with hepatic cirrhosis showed significantly higher scores (indicating more problems) in most of the subscores of Pittsburgh sleep quality index, namely subjective sleep quality, sleep latency, sleep disturbances, use of sleep medications, and total score of PSQI. These differences are all highly significant (p values $\leq$ 0.01; table-2 and figure 2). Patients also showed significantly later usual bedtimes and wake up times in weekends but not in week days. They also reported significantly longer time lost before falling asleep and time lost due to waking up during night. Finally, patients with hepatic cirrhosis reported significantly higher tendency towards evening circadian preference as compared to healthy controls (table 3, figure 3 and 4).

Discussion

The current study aimed to specifically explore sleep timing and circadian preferences in Arabic speaking Egyptian patients with hepatic cirrhosis. Consistent with the literature, [4-6, 8, 12, 13] sleep-timing and circadian preferences were more disturbed in hepatic patients as compared to healthy controls. Our study is the second study to use the Pittsburgh Sleep Quality Index (PSQI) in the assessment of hepatic population. We agreed with the previous study [8] which used the widely know scale in differences in total score and in subscores for sleep latency and disturbances, which both came with significantly higher scores in hepatic group, and subscore for sleep duration, which indicated no significant difference between hepatic patients and control groups in both studies.. On the other hand, the two studies disagreed about four subscores, namely subjective sleep quality, habitual sleep efficiency, use of sleep medications, and daytime sleep dysfunction. These differences could be explained by diffeent etiological factors behind hepatic disease in Egypt and USA.

The Sleep Timing Questionnaire (STQ) was used in this study to confirm and provide approximate estimations (in minutes) for the increased sleep latent periods and periods of time lost due to awakening after sleep onset reported in the PSQI. It was also used as a tool to confirm and quantify the delayed circadian phase reported by the CSM. The delayed timings for both bedtimes and wake up times were reported in hepatic patients as compared to healthy controls only in week days but not in weekends. This finding might be explained by the tendency for late timing in both going to bed and waking up in Holidays among healthy controls.

Finally, it is important to highlight the limitations of this study. First, the small size of the sample might limit the generalization of the results on patients with hepatic cirrhosis. Second, the study design did not control for potential psychiatric disorders, which are known to have a significant impact on sleep quality, in both patients and control. Third, any influence of psychoactive medications on the cognitive and neurophysiological outcomes cannot be ruled out. Fourth, the information collected in this study was obtained only from self-reports; objective measures to evaluate sleep (e.g. actigraphy) were not included. Thus, inaccurate reporting regarding sleep

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preference/disturbances may have occurred and may have in turn contributed to between-group differences. Another limitation of our study is the lack of a control group with another chronic disease (e.g. chronic renal failure).

To our knowledge, this is the first study to specifically explore sleep timing and circadian preferences in Arabic speaking Egyptian patients with hepatic cirrhosis. In conclusion, the present study supports the hypothesis that patients with compensated cirrhosis do suffer from significantly more sleep disturbances in addition to evening preference when compared to healthy controls. Sleep disturbances by themselves have been associated with psychosocial difficulties and they can increase the risk for further psychiatric morbidity [22, 23] in hepatic patients warranting their early identification and management in this population which is not routinely screened for psychiatric disturbances in common practice in Egypt. In addition, our data suggest a possible relationship of compensated cirrhosis and alteration of circadian systems. Recognition of sleep disturbance in cirrhosis and understanding its underlying pathophysiological mechanisms may result in approaches that translate into more comprehensive treatment approaches that take into consideration the improvement of sleep quality and circadian rhythmicity in patients with hepatic cirrhosis.

Compliance with Ethical Standards:

Funding and sources of support: Nil.

Conflict of interest: None declared.

Ethical approval: The study protocol was approved by the ethical committee of faculty of medicine, Tanta University. Informed consent was obtained from each patient before participation in the study.

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Table (1) group differences on demographic variables:

variable	Hepatic Patients (N=50)		Healthy control (N=30)		Statistic	p value
	Mean	(SD)	Mean	(SD)		
Age	53.3	8.1	53.2	7.3	t = 0.2	0.9
Sex (female %)	40		60		x^2 = 3.1	0.8
SES	22.4	3.9	23.8	3.7	t = 1.5	0.1

SES = Socio-economic Status according to Fahmi and El-sherbini scale

Table (2) group differences on subscores and total score of PSQI scale

variable	Hepatic Patients (N=50)		Healthy control (N=30)		Z	p value
	Mean	SD	Mean	SD		
Subjective sleep quality	1.4	0.7	0.9	0.3	-3.6	**≤0.001**
Sleep latency	1.7	0.7	0.6	0.5	-5.8	**≤0.001**
Sleep duration	0.8	0.8	0.5	0.6	-1.2	0.22
Habitual sleep efficiency	0.4	0.7	0.1	0.3	-1.5	0.14
Sleep disturbances	1.9	0.8	0.7	0.8	-5.3	**≤0.001**
Use of sleep medications	0.5	0.8	0.1	0.3	-2.6	**0.01**
Daytime dysfunction	2.5	1.2	1.9	1.0	-1.9	0.06
Total score of PSQI	1.4	0.7	0.9	0.3	-5.8	**≤0.001**

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Table (3) group differences on parameters of STQ scale and morningness score of CSM

variable	Hepatic Patients (N=50)		Healthy control (N=30)		Z	p value
	Mean	SD	Mean	SD		
Usual night time – week day	683.8	60.0	666.0	42.7	-1.86	0.06
Usual night time – week end	768.5	65.2	726.0	42.7	-3.24	**≤0.001**
Usual morning time – week day	455.9	67.3	426.0	92.3	-1.48	0.14
Usual morning time – week end	618.5	83.6	570.0	68.2	-2.21	**0.03**
Time to fall asleep	39.2	25.6	13.5	3.3	-5.78	**≤0.001**
Sleep lost due to waking up during night	33.6	19.8	10.5	2.7	-6.89	**≤0.001**
Morningness/Eveningness score	36.7	5.6	28.7	4.6	t=6.6	**≤0.001**

Figure (1) group differences on demographic variables:

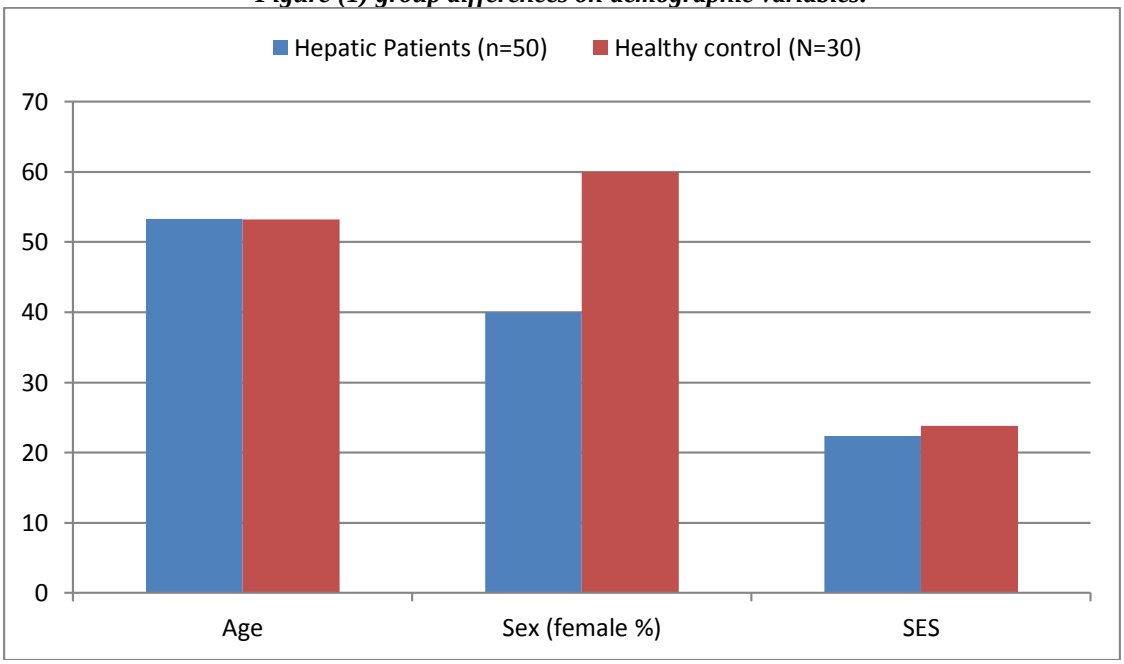

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Figure (2): group differences on subscores and total score of PSQI scale

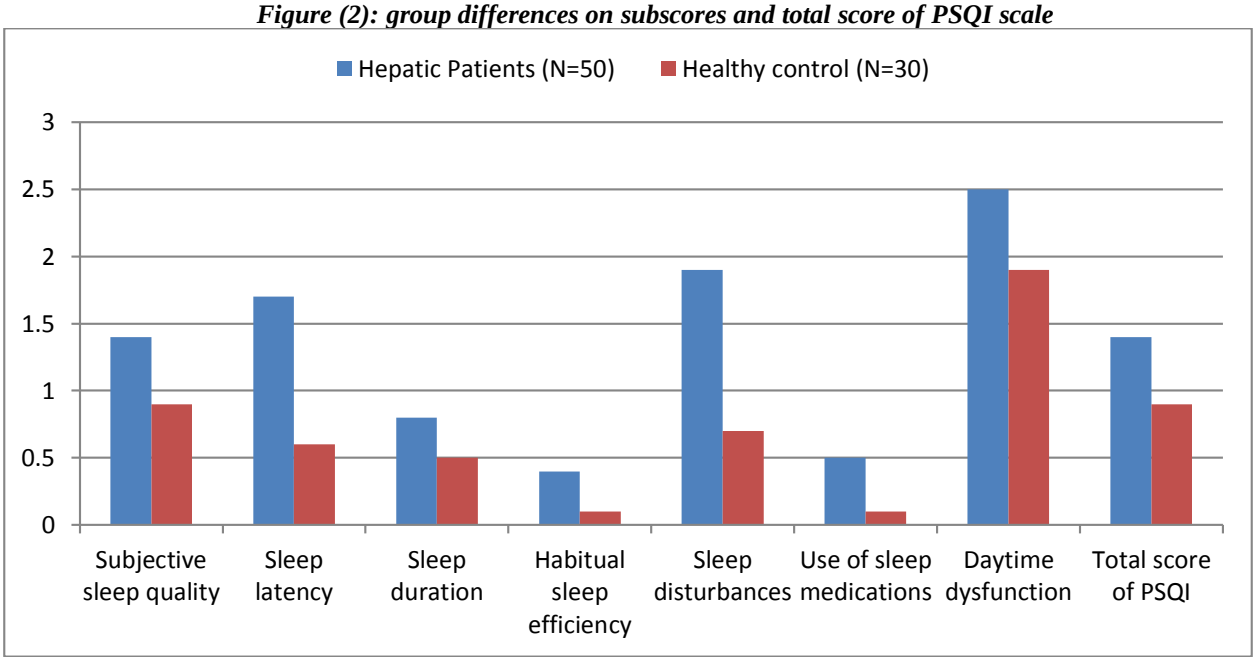

Figure 3: group differences on sleep timing parameters of STQ scale