



The impact of chronic hepatitis C infection on the circadian clock and sleep

Daniel Shouval*

Liver Unit, Hadassah-Hebrew University Hospital, Jerusalem, Israel

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Sleep disturbance with reversal of the day and night cycle is a well known phenomenon in patients with hepatic encephalopathy irrespective of etiology as shown in animal models and in humans [1–3]. Furthermore, insomnia, fatigue, depression, and cognitive impairment are common symptoms in patients with chronic liver disease (CLD) with cirrhosis. During the past 15 years, several studies have been published on the impact of cirrhosis such as primary biliary cirrhosis, non-alcoholic fatty liver disease, and Wilson's disease on the quality of sleep [4–6]. However, it is less known that abnormal sleep patterns have also been documented in up to ~50% of patients with cirrhosis in the absence of overt hepatic encephalopathy or even in patients with CLD without cirrhosis [5]. It is sometimes difficult to differentiate between an organic cause of fatigue and insomnia from psychiatric disorders of variable severity in CLD in general and in chronic hepatitis C patients in particular [7]. Sleep patterns are dictated by 24 h circadian clocks, subjected to light and darkness cycles, which control numerous metabolic activities such as body temperature, blood pressure, melatonin, cortisol and growth hormone levels, urine output as well as mood and cognitive abilities. Such endogenous circadian cycles exist not only in humans but also in animals, plants, algae, bacteria, and fungi [8]. Disruption of clock genes, which control the circadian rhythms, have recently been linked to sleep disorders and have an impact on metabolic activities [9,10]. Sleep and circadian rhythm disruption may have serious consequences on emotional, cognitive, and somatic responses. For example, inadequate sleep may lead to exhaustion, increased irritability, mood fluctuation such as depression, anxiety or anger, reduced concentration, attention deficit disorder, decreased memory, decreased productivity and creativity, drowsiness, unintended sleep, weight gain, metabolic abnormalities such as hyperglycemia, and more [11]. (The interested reader is referred to a recent review entitled "Sleep Disorders in Chronic Liver Disease" [3].)

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* Address: Liver Unit, Hadassah-Hebrew University Hospital, Division of Medicine, Ein-Kerem, P.O. Box 12000, 91120 Jerusalem, Israel. Tel.: +972 026777337; fax: +972 26420338.

E-mail address: Shouval@hadassah.org.il



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In the past two decades, referral of patients with chronic hepatitis C (CHC) is dominating the practice of clinical hepatologist worldwide, yet sleep disturbances in CHC patients without cirrhosis have received relatively little attention [3,12,13]. In the present issue of the journal, Dr. Heeren and co-workers from the Hannover Medical School in Germany report their observations on altered sleep quality in a cohort of CHC patients without overt cirrhosis or classical hepatic encephalopathy [14]. The study cohort (N = 20, mean age 56.8 yr) was recruited from a small subgroup (N = 143) of the original HCV infected 1833 women who received an HCV contaminated anti-D immunoglobulin over three decades ago [15]. Thus twenty anti-HCV positive, genotype 1b patients of whom 12 were still HCV-RNA positive by PCR participated in the study. The control population consisted of 19 age matched healthy females (mean age 55.3 yr). The unique characteristic relevant to the goals of the discussed study is the relatively benign course of CHC without cirrhosis over a period of more than thirty years in this selected group of women who nevertheless complained among other symptoms of weakness, fatigue, and decreased exertional capacity.

The methodology used to assess the various study variables is broad and quite complex. Participants were asked to fill a number of questionnaires including the Pittsburgh Sleep Quality Index measuring sleep quality; the Epworth Sleepiness Scale measuring daytime sleepiness; the Fatigue Impact Scale measuring the impact of fatigue on daily activity; the Back Depression Inventory measuring depression; the Hospital Anxiety and Depression Scale measuring emotional alteration and the SF-36 questionnaire measuring health related quality of life. Furthermore, patients had to fill a sleep diary and use an actigraph which is a wrist worn device for monitoring of motor activity over a period of 24 h/day for 5 days. Obtained scores from the various questionnaires filled by the study and control groups as well as actigraphy scores were compared and a Spearman correlation test was used to evaluate a relationship between fatigue, quality of life, sleep parameters, and actigraphy results.

The major findings of this study indicate that in contrast to healthy controls, patients with a history of chronic hepatitis C virus infection without overt cirrhosis may develop a disrupted circadian rhythm. This so called circadian arrhythmia is associated with an altered sleep pattern, insomnia, fatigue, depression, and reduced quality of life, which correlate with one another.

Focus

Although patients displayed an increased nocturnal activity, no correlation could be established between fatigue and sleep pattern abnormality and 24 h activity level.

Comments: The reported results suggest and confirm previous observations that sleep disruption and its consequences should be regarded as an extra hepatic manifestation of chronic hepatitis C. Furthermore, these symptoms may already be present in patients with mild chronic hepatitis C without clinical evidence for cirrhosis. A previous report found a strong association between reduced survival and sleep disorders in patients with advanced liver disease [16]. The present cohort of patients with relatively mild CHC is already followed for more than 3 decades and so far there is apparently no indication to suspect a worse prognosis despite the reported abnormal sleep pattern. Interestingly, the abnormal sleep pattern was present in both the 12 viremic patients as well as in those 7 patients who were HCV-RNA negative by PCR. In this context it is worthwhile to mention a recent report suggesting that primary and precursor forms of liver specific microRNA (miR122) are regulated in a circadian rhythm in the liver of animals [17]. In the detailed and well referenced discussion of this paper, the authors express their belief that based on previous functional imaging studies, the described symptoms in both HCV-RNA positive and negative patients are the result of an encephalopathy, which is independent of the state of viremia. However, the relatively small sample size and the absence of functional imaging data for the specific study cohort does not enable yet a firm conclusion regarding the role of viremia in the above described symptoms.

Heeren and co-workers' report is the result of an extensive effort which is a case control study and descriptive by nature. The investigators utilized a wide range of methods to reach their conclusions but their results do not provide a clue regarding the mechanism(s) involved in the sleep disturbance and its consequences in CHC and this will remain a goal of future research. Aberrant sleep patterns have previously been linked to central nervous system involvement in persistent HCV infection affecting up to 65% of CHC patients [12,13,18]. It has been suggested that sleep and the circadian system regulate a number of immune functions or *vice versa* [19,20]. For example, the number of undifferentiated naïve T cells and production of pro-inflammatory cytokines peak during early nocturnal sleep while cytotoxic NK cells and anti-inflammatory cytokines peak during day time [19]. The impact of past or present HCV infection on these parameters in the context of sleep disturbances is still unknown. Sleep and the circadian timing systems are driven by a complex interaction between multiple brain regions, neurotransmitters and hormones. Moreover, up to 20 clock genes and their protein products have been linked to control of circadian rhythms through translational-transcriptional feedback loops [8,11]. However the interaction of the hepatitis C virus with these genes and its impact on the molecular clock is still unexplored except for a recent observation *in vitro* that a circadian protein called PER2 interferes in viral replication [21].

In summary, the discussed report provides descriptive evidence that a history of past or present mild chronic hepatitis C virus infection even without clinical evidence for cirrhosis or "traditional" hepatic encephalopathy is associated with an

altered sleep pattern, which has a negative impact on quality of life and well being.

Conflict of interest

The author declared that he does not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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