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Role of Sleep Disturbance in Chronic Hepatitis C Infection

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Abstract Chronic infection with the hepatitis C virus (CHC) is associated with physical and mental symptoms including fatigue and depression that adversely affect quality of life. A related complaint, sleep disturbance, has received little attention in the literature, with the exception of sleep changes noted in cirrhosis and end-stage liver disease. We present an overview of studies indicating sleep problems in patients with CHC, with about 60% to 65% of individuals reporting such complaints. Evidence suggests that impairments in sleep quality exist independent of antiviral therapy with interferon-α and prior to advanced stages of liver disease. Further investigation of sleep disturbance in CHC patients with a mild stage of liver disease may provide important information on disease course as well as allow additional opportunities for patient support.

Keywords Hepatitis C · Sleep · HCV · Liver disease · ESLD

Introduction

Chronic infection with the hepatitis C virus (CHC) in the United States is reported to have peaked at 3.6 million Americans affected; however, the number of individuals with advanced fibrosis is projected to continue to rise until the year 2020 [1]. Clinical investigations of CHC have identified decrements in physical and mental functioning that negatively impact quality of life (QOL) [2–6]. Among these complaints, physical tiredness or fatigue is the most prevalent symptom endorsed by a sample of patients living with CHC [7]. In fact, studies of CHC have shown that up to 97% of individuals with CHC endorse fatigue [4, 6, 8]. A study of 94 CHC patients not receiving antiviral therapy identified predictors of fatigue to include poor social functioning, poor physical functioning, greater depression, and female gender [9]. Although fatigue has been widely reported, one seemingly related factor, sleep disturbance, has received little attention in the literature. Clinical experience suggests that patients with CHC endorse sleeping problems, and large studies of CHC patients undergoing antiviral therapy with interferon (IFN)-α report insomnia as an adverse event endorsed by as many as 30% [10, 11]. However, the nature of sleep problems in CHC remains poorly understood. Exploration of sleep disturbance in patients with CHC may provide important information about the disease course and allow opportunities for additional supportive care of this patient group. Sleep may be particularly important to study in light of the recent finding that survival was strongly associated with sleep disturbance among 156 patients with cirrhosis [12]. We hypothesized that patients with CHC report significant sleeping complaints. Such sleeping problems may occur prior to IFN treatment and in the absence of advanced stages of liver disease.

Method

PubMed and Medline searches using search terms “sleep and hepatitis C” were conducted to identify investigations of sleep disturbance in CHC published in English over the past 10 years (2000 to 2009). Only articles that 1) went beyond simply mentioning the presence or occurrence of

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sleep disturbance and 2) considered sleep problems independent of mood or other psychiatric disorders were reviewed. Because the search revealed a small number of articles on the specific topic of sleep and CHC and previous work has shown that about 50% of patients with cirrhosis reported unsatisfactory sleep [13], the search was expanded to include search terms "sleep and cirrhosis" and "sleep and end-stage liver disease (ESLD)" but excluded articles that clearly focused on a specific cirrhotic patient sample that would not include patients with CHC (eg, primary biliary cirrhosis).

Results

Six articles [7, 14–17, 18•] met criteria for inclusion using search terms "sleep and hepatitis C." Nine additional articles were identified using search terms "sleep and cirrhosis" and "sleep and end-stage liver disease" [19–22, 23•, 24–27]. The majority of literature on sleep problems focused on patients with cirrhosis.

Sleep and Hepatitis C

Clifford et al. [14] examined sleep disturbance, along with depressive and anxious symptoms and cognitive functioning, in 264 patients with HIV, 30 of whom were coinfected with CHC. Sleep problems were investigated using the Pittsburgh Sleep Quality Index (PSQI) [28], a 19-item self-report questionnaire used to study sleep quality over a 1-month interval. A global PSQI score and seven component scores are calculated providing information on subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Patients with both CHC and HIV reported poorer sleep, overall, than patients with HIV only, with significant group differences in sleep quality and marginally significant differences in sleep disturbances. Coinfected patients also reported significantly more depressive symptoms and demonstrated poorer performances on a task of psychomotor speed and working memory than HIV-only patients. There were no differences in anxious symptoms.

Lang et al. [7] surveyed 188 treatment-naive patients with CHC and found that sleep problems were reported by about 65% and were among the top 10 most prevalent symptoms endorsed. Sleep problems were endorsed equally as often by men as women, unlike depression, physical tiredness, mental tiredness, and forgetfulness, which were endorsed more frequently by women. CHC patients additionally rated symptom severity using a visual analogue scale (VAS) ranging from 0 to 10, with higher scores indicating worse severity over the previous 3 months. The median severity score for individuals reporting sleep problems was 8 on the VAS (range 2 to 10), the highest ranked score among the 21 symptoms reported.

Other investigations of sleep disturbances in early stages of disease were focused on the relationship between sleep disturbance and development of major depressive disorder (MDD) during the course of IFN treatment [16, 17]. Researchers measured sleep problems with the PSQI and administered a semistructured clinical interview to diagnose MDD. Results suggested poor sleep quality is associated with subsequent depression during IFN therapy, but depression was not associated with changes in sleep quality [17]. Moreover, sleep quality tended to be better in CHC patients with a particular genotype of the serotonin transporter length promoter region that was associated with a lower rate of MDD, suggesting a possible mediational role of sleep quality in resilience to MDD [16].

Given the lack of research on sleep problems in untreated CHC patients, our group investigated sleep disturbance in 80 consecutive CHC patients seen in a tertiary hepatology clinic [29]. All participants completed the PSQI and Fatigue Severity Scale (FSS) [30], a nine-item self-report questionnaire measuring the impact of fatigue on daily functioning. Information on psychiatric diagnoses and liver disease staging were also collected. Of the 80 CHC patients sampled, about 63% were identified as poor sleepers on the PSQI. Fifty-six (70%) of the participants met criteria for significant self-reported fatigue on the FSS. As expected, a significant relationship was found between the global PSQI and FSS scores (R=0.50, P<0.001). Further analysis revealed no significant differences in sleep complaints endorsed by patients with or without psychiatric diagnoses. Finally, decrements in sleep quality did not differ according to stage of liver disease, suggesting that sleep disturbance is not only a function of advanced stages of liver disease.

In their review article of sleep disturbance in CHC, Sockalingam et al. [18•] also note the paucity of research in this area and describe in detail how to diagnose and treat the most common sleep disorders in CHC, including insomnia, hypersomnia, restless leg syndrome (RLS), and obstructive sleep apnea (OSA). They also review the literature on sleep disturbances in untreated CHC patients, as well as IFN-induced sleep disturbances, identifying 17 articles published on this topic between 1995 and 2008. Potential etiologies of sleep disturbance in CHC also are discussed. However, their review did not discuss 8 of the 14 articles included in the current review [14–17, 21, 22, 23•, 24], and the current review did not discuss diagnosis and treatment of sleep disorders.

Sleep and Cirrhosis

With regard to the articles addressing sleep in cirrhotic and ESLD patients, much of this work viewed sleep disturbance

as part of hepatic encephalopathy (HE), particularly minimal HE. Martino et al. [22], for example, concluded that sleep electroencephalogram (EEG) revealed the existence of minimal HE and that changes of mean dominant frequency were early markers of cerebral dysfunction. Investigators then began to examine OSA as a complication of cirrhosis [19, 25, 26], finding that as the severity of cirrhosis increased, so did the presence of OSA, particularly in patients with Child-Pugh scores in class C [26]. Additionally, patients with ascites were more likely to have OSA, which may be reversed with removal of ascitic fluid [19]. Central sleep apnea, on the other hand, was not observed in a small sample of patients with cirrhosis [21]. Together, these findings suggest symptoms of sleep apnea in patients with cirrhosis may be related to an enlarged abdominal perimeter and changes in systemic hemodynamics and vasoactive systems associated with decompensated cirrhosis, particularly ascites [19].

More recent work has focused on understanding the qualitative aspects of sleep disturbance in patients with cirrhosis and investigating possible treatments. Mostacci et al. [24] reported that patients with cirrhosis complained of significantly more frequent daytime sleepiness and habitual napping, nighttime sleep problems, and nocturnal awakenings than controls, which were not related to clinical or laboratory parameters. Nighttime sleep disturbance, daytime sleepiness, and preference for evening activities also were noted in a study of the relationship between sleep and QOL in 87 patients with cirrhosis [23•]. In this study, almost 70% of patients were classified as "poor sleepers" using the PSQI, and nighttime sleep disturbance and evening preference were independent predictors of poorer QOL. Montagnese et al. [23•] pointed out that nighttime sleep disturbance and daytime sleepiness were not correlated, but that daytime sleepiness was correlated with slowing on EEG, suggesting that daytime sleepiness might be a harbinger of minimal HE whereas nighttime sleep disturbance does not relate to or reflect the presence of HE.

An initial study of the prevalence of RLS in a heterogeneous sample of 141 patients with chronic liver disease seen in an academic-based tertiary care hepatology clinic found that 62% of respondents indicated RLS [20]. Prevalence of RLS did not differ by gender; the only significant difference between patients with and without reported RLS was the presence of neuropathy, which was more commonly reported in patients with RLS. However, 16% of patients with RLS had no identifiable risk factor. In the only treatment study of sleep disturbance in cirrhotic patients, Spahr et al. [27] found that, compared with placebo, hydroxyzine, 25 mg, at bedtime significantly improved patients' self-reported sleep disturbance assessed using a VAS, as well as their objective sleep efficiency as measured by wrist actigraphy. Importantly, performances on neuropsychologic tests were not affected by administration of hydroxyzine. However, one patient developed clinically overt HE, which was reversed with cessation of hydroxyzine, indicating this medication should be used with caution in cirrhotic patients.

Although changes in sleep behavior appear to be common in patients with cirrhosis, the underlying mechanisms are not yet defined and are likely multifactorial. One hypothesis implicates abnormal liver metabolism of plasma melatonin, which is known to play a key role in sleep [15]. Another hypothesis suggests sleep behavior alterations may result from dysregulation of histaminergic neurotransmission in the brain, because histamine is involved in regulation of sleep-wake cycles and vigilance [31]. Still another posits dysregulation of serotonin and corticospinal tracts, particularly in the etiology of RLS [20]. A more detailed review of potential mechanisms for sleep disturbance in cirrhotic patients is beyond the scope of this article, however.

Discussion

Literature on the nature of sleep disturbance in CHC appears quite limited. Initial data from the few available studies suggest a prevalence of sleep complaints of about 60% to 65% [7, 29], with a moderate relationship between poorer sleep quality and greater fatigue [29]. Furthermore, preliminary findings suggest that sleep problems may exist independently of mood and other psychiatric disorders in CHC [29] and may predict the onset of MDD in CHC patients undergoing IFN therapy [17]. It therefore seems prudent that clinicians monitor sleep complaints prior to treatment, because they may have the potential to aggravate symptoms of underlying mood or psychiatric problems, as well as other side effects of antiviral treatment. The literature also strongly points to the fact that sleep disturbance exists prior to the onset of cirrhosis and ESLD, suggesting that HE is not the only factor contributing to sleep problems in patients with chronic liver disease.

Clearly, additional research is needed to characterize sleep problems in noncirrhotic patients with CHC. Future studies on the effects of CHC infection on the brain may provide important information on the nature of sleep disturbance reported by patients with CHC. Growing research suggests that hepatitis C may be neurovirulent, affecting the central nervous system via a "Trojan horse" mechanism [32]. Studies have shown evidence of cognitive deficits in CHC [33], and a recent review summarized neuroimaging research on brain systems potentially affected [34]. It is unknown whether such effects on the brain may play a role in the sleep complaints reported by patients. Future research may benefit from further exploration of this potential relationship.

In cirrhotic patients, sleep disturbance has long been recognized as part of HE, with OSA receiving the most attention by investigators [19, 25, 26]. Recent research has begun to characterize qualitative aspects of sleep complaints in these patients [23•, 24], with one treatment study suggesting hydroxyzine may be of potential benefit [27]. The etiologies of sleep problems in cirrhotic and ESLD patients are likely multifactorial, and may be related to liver metabolism of plasma melatonin, enlarged abdominal perimeter and associated effects, comorbid medical conditions, and/or dysregulation of neurotransmitter systems [15, 19, 20, 31].

Conclusions

In summary, considerably more research studies focused on the role of CHC infection and sleep and its potential effects on the brain are needed. Future research should study patients with mild stages of disease and include objective measures of sleep quality, such as EEG, actigraphy, and/or polysomnography. It is important that future research also assess for sleep quality independent of mood and other psychiatric problems. With increased knowledge about the mechanisms that underlie sleep disturbance in patients with CHC, appropriate treatments can be developed that may improve patient care outcomes and QOL.

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