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Effect of Obstructive Sleep Apnea on the Sleep Architecture in Cirrhosis

Matthew R. Kappus, M.D.[1]; David J. Leszczyszyn, M.D.[2]; Leonard Moses, M.D.[3]; Shekar Raman, M.D.[2]; Douglas M. Heuman, M.D.[1]; Jasmohan S. Bajaj, M.D.[1]

[1]Division of Gastroenterology, Hepatology, and Nutrition, [2]Department of Neurology, [3]Division of Pulmonary Medicine, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA

Study Objectives: Sleep disturbances in cirrhosis are assumed to be due to hepatic encephalopathy (HE). The interaction between cirrhosis, prior HE, and obstructive sleep apnea (OSA) has not been evaluated. We aimed to evaluate the additional effect of cirrhosis with and without prior HE on the sleep architecture and perceived sleep disturbances of OSA patients.

Methods: A case-control review of OSA patients who underwent polysomnography (PSG) in a liver-transplant center was performed. OSA patients with cirrhosis (with/without prior HE) were age-matched 1:1 with OSA patients without cirrhosis. Sleep quality, daytime sleepiness, sleep quality, and sleep architecture was compared between groups.

Results: Forty-nine OSA cirrhotic patients (age 57.4 ± 8.3 years, model for end-stage liver disease (MELD) 8.3 ± 5.4, 51% HCV, 20% prior HE) were age-matched 1:1 to OSA patients without cirrhosis. Apnea-hypopnea index, arousal index, sleep efficiency, daytime sleepiness, and effect of sleepiness on daily activities were similar between OSA patients with/without cirrhosis. Sleep architecture, including %slow wave sleep (SWS), was also not different between the groups. MELD was positively correlated with time in early (N1) stage ($r = 0.4$, $p = 0.03$). All prior HE patients (n = 10) had a shift of the architecture towards early, non-restorative sleep (higher % [N2] stage [66 vs 52%, $p = 0.005$], lower % SWS [0 vs 29%, $p = 0.02$], lower REM latency [95 vs 151 minutes, $p = 0.04$]) compared to the rest. Alcoholic etiology was associated with higher latency to N1/N2 sleep, but no other effect on sleep architecture was seen.

Conclusions: OSA can contribute to sleep disturbance in cirrhosis and should be considered in the differential of sleep disturbances in cirrhosis. Prior HE may synergize with OSA in worsening the sleep architecture.

Keywords: Cirrhosis, hepatic encephalopathy, obstructive sleep apnea, polysomnography

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SCIENTIFIC INVESTIGATIONS

Sleep impairment is one of the leading causes of impaired health-related quality of life in patients with cirrhosis.[1] Due to the interplay of multiple factors such as fatigue, hepatic encephalopathy (HE), and the underlying etiology of liver disease, the pathophysiology of sleep disturbances in cirrhosis remains unclear.[2] An important sleep disorder that can coexist and possibly confound sleep interpretation in cirrhosis is obstructive sleep apnea (OSA).[3] Given the increasing prevalence of obesity and the age-group affected by cirrhosis, the contribution of OSA to sleep disturbances in cirrhosis needs to be investigated.[4-6]

The aim of the study was to evaluate effect of cirrhosis with or without prior HE on sleep architecture in patients with OSA in a case-control design. The *a priori* hypothesis was that the sleep architecture disruption would be severely affected in patients with cirrhosis and OSA compared to those with OSA alone.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Patients with cirrhosis often suffer from hepatic encephalopathy that is assumed to be the leading reason for sleep disturbance in this population. The effect of obstructive sleep apnea, which can co-exist in this population on sleep quality and polysomnography is not clear and could be an under-recognized reason for sleep disturbance.

Study Impact: Obstructive sleep apnea can contribute to sleep disturbance in cirrhosis and should be considered in the differential of sleep disturbances in cirrhosis. Prior hepatic encephalopathy can synergize with obstructive sleep apnea in worsening the sleep architecture in cirrhosis.

MATERIALS AND METHODS

A review of charts of all patients with OSA who underwent polysomnography (PSG) between July 2007 and January 2010 at the McGuire Veterans Affairs Medical Center, a tertiary referral liver transplant center, was performed. All information was obtained in our polysomnography lab, which are interpreted by the same neurologist. Patients were tested in the same fashion, without an adaptation night. The sleep room was equipped with an infrared camera and audio system so that the technologist could communicate with the patient without entering the bedroom. A technologist, trained in the same manner, was available to document relevant information including heart rate, respiratory rate, oxygen saturation, snoring presence, and body position. Physiologic variables were also automatically recorded on a paperless computerized system, followed by scoring for physiologic stages, stages of sleep, and wakeful-

Table 1—Baseline assessment of the groups

	Cirrhosis + OSA	OSA only
Age	57.4 ± 8.3	58.0 ± 8.3
Gender	94%	100%
Body mass index	33.5 ± 4.9	32.3 ± 5.1
Race (Cauc/AA/Other)	57/37/6	51/43/6
Diabetes	43%	35%
Hypertension	89%	88%
Coronary artery disease	29%	27%
Pre-study questionnaire		
Do you snore?	92.0%	100%
Do you stop breathing at night?	62.5%	60.9%
Do you struggle to breathe at night?	71.4%	50%
Do you gasp for air at night?	58.33%	43.5%
Excessive daytime sleepiness?	79.2%	78.3%
Sleepy during driving?	65.2%	58.7%
Sleepy while watching TV?	78.3%	84.8%
Sleepy while sitting quietly?	78.3%	87.0%
Headache in the morning?	41.7%	34.8%
Frequent heartburn?	43.5%	39.1%

There was no significant difference between the groups on any criteria including the pre-study questionnaire.

ness. The same neurologist scores the sleep report in a format that is standard to our VA medical center using both voltage and frequency criteria.

Patients with cirrhosis were defined as those with evidence of cirrhosis by liver biopsy, imaging modality (ultrasound, computed tomography, or magnetic resonance imaging) or endoscopic evidence of gastroesophageal varices. The severity of liver disease using the model for end-stage liver disease score (MELD; a logarithmic score from INR, total bilirubin, and serum creatinine), complications of liver disease, and specifically information about hepatic encephalopathy (HE) and use of HE treatment (lactulose/rifaximin) was recorded.[7] Prior HE was defined as an admission for alteration in mental status requiring therapy initiation. Patients with history of HE were controlled on medication at the time of the polysomnography and questionnaire. We also separately analyzed cirrhotic patients with and without alcohol as their cirrhosis etiology. We recorded information on sleep characteristics, including apnea-hypopnea index, sleep efficiency, number of apneas, hypopneas, and arousals, as well as quantification in time spent in different stages of sleep. The sleep laboratory also administered a pre-study questionnaire inquiring about whether they snored or gasped for air at night, daytime sleepiness (4 questions regarding daytime sleepiness, sleepiness sitting in quiet place, driving or watching TV), morning headaches, and frequent heartburn.

After the identification of those patients with cirrhosis, we randomly chose age-matched control subjects with OSA but without cirrhosis. We first determined age of our patients with OSA, excluding those patients with other forms of sleep disorder and those with no sleep disorder. We also excluded patients with psychoactive medication use or those whose sleep studies were incomplete. We then generated using a random sequence, age-matched patients with OSA without cirrhosis for the case-control comparison in the list of patients with sleep studies between July 2007 and January 2010. The pre-study questionnaire and sleep study details were recorded. Comorbid conditions such as diabetes, hypertension, and coronary disease were also investigated and compared.

Continuous variables such as age, MELD score, time spent in sleep stages, sleep efficiency, and apnea-hypopnea index were recorded and reported as mean with standard deviation. Categorical variables such as the presence or absence of cirrhosis, hypertension, diabetes, coronary disease, use of HE therapy, and gender were compared using the Fisher and χ^2 tests. The data are presented as means ± standard deviation, and $p < 0.05$ was considered significant.

RESULTS

Using the VA database, the charts of patients with sleep studies were reviewed. Of these, 49 patients were found to have cirrhosis. These were age-matched to 49 patients with OSA without evidence of cirrhosis using a random generator. As shown in **Table 1**, there was no difference in the baseline characteristics of patients with and without cirrhosis in demographics or comorbid conditions.

Sleep Questionnaire Responses

There were no significant differences between patients with and without cirrhosis who were asked questions pertaining to daytime sleepiness (4 questions) and sleep quality (6 questions; **Table 1**).

Patients with Cirrhosis

The mean MELD score of patients with cirrhosis was 8.3 ± 5.4, and the majority were Child Class A at the time of the sleep study (92%). The predominant cirrhosis etiology was hepatitis C (HCV) alone (51%), followed by non-alcoholic fatty liver disease (16%), alcohol and HCV (12%), alcohol alone (10%), and others (11%). Twenty percent (10) of cirrhotic patients had prior but currently controlled HE; the same patients also had controlled ascites. Patients with prior HE had similar age (54.9 ± 7.6 vs 58.1 ± 8.4, $p = 0.28$), BMI (33.3 ± 4.3 vs 33.6 ± 5.1, $p = 0.85$), and MELD score (8.7 ± 5.9 vs. 8.2 ± 4.9, $p = 0.81$) compared to cirrhotic patients without prior HE. The MELD score was significant positively correlated with % sleep spent in N1 ($r = 0.4$, $p = 0.03$) but there was no correlation between the sleep latency, apneas, hypopneas, or %time spent in other stages of sleep.

Characteristics of Sleep Stages

The mean sleep efficiency in the cirrhosis group was 75% ± 13%, with a mean apnea-hypopnea index of 22.2 ± 25.0. The mean latency to stage N1 was 24 ± 23 minutes, to N2 30 ± 24 minutes, and to REM 138 ± 34 minutes. The mean % of sleep that consisted of N1 was 11%, N2 57%, slow wave sleep (SWS) 3.4%, and REM 11%. SWS was absent in 67% of cirrhotic patients. This was similar to age-matched patients with OSA without cirrhosis (**Table 2**). The arousal index however was significantly higher in patients with cirrhosis than those with OSA alone.

Table 2—Sleep study comparison between the groups

	OSA + Cirrhosis	OSA only	p value
Total sleep time (minutes)	295 ± 99	308 ± 97	0.52
Latency to N1 (minutes)	24 ± 23	22 ± 22	0.63
Latency to N2 (minutes)	30 ± 24	37 ± 51	0.42
Latency to REM (minutes)	138 ± 89	156 ± 104	0.42
% time in N1	10 ± 8	11 ± 9	0.80
% time in N2	55 ± 17	56 ± 19	0.83
% time in SWS	9 ± 17	31 ± 29	0.18
% time in REM	35 ± 35	44 ± 14	0.13
% with SWS	10	18	0.35
Total wake time after sleep onset (minutes)	68 ± 51	64 ± 54	0.71
Apnea-hypopnea index	22 ± 25	15 ± 12	0.11
Apnea index	6 ± 10	4 ± 5	0.28
Hypopnea index	11 ± 14	10 ± 10	0.53
Arousal index	18 ± 14	12 ± 10	0.03
Sleep efficiency%	75 ± 13	76 ± 19	0.82

There was no significant difference in the sleep quality as well as architecture in patients with OSA with or without cirrhosis apart from a higher arousal index in cirrhotic patients.

Effect of Prior HE on Sleep Architecture

There was no effect of the diagnosis of prior HE on the pre-sleep study questionnaire compared to cirrhotic patients without HE. Compared to cirrhotics with OSA alone, patients with prior HE+OSA spent a significantly higher percent of their sleep study time in early stages of sleep and reached the REM stage sooner (**Table 3**). None of the cirrhotic patients with prior HE had demonstrable SWS sleep, compared to only 33% of non-HE cirrhotic patients (p = 0.021). Prior HE, however, did not increase the apnea index, hypopnea index, or the arousal index.

Effect of Alcoholic Etiology

Twelve patients had an alcoholic etiology of cirrhosis, although all of them had been abstinent from alcohol for > 3 months at the time of the sleep study. There was no significant difference between alcoholic etiology with (n = 4) and without HE (n = 10, p = 0.9) or in the MELD in patients with (8.7) or without an alcoholic etiology of cirrhosis (8.9, p = 0.56). There were also no significant differences in the age, BMI, or presence of diabetes between patients with and without an alcoholic etiology. As displayed in **Table 4**, the only differences in the sleep study values were a significantly higher latency to stages 1 and 2; rest of the architecture was similar to cirrhotic patients without alcoholic etiology.

Table 3—Comparison between cirrhotic patients with and without prior HE

	Cirrhosis with prior HE (n = 10)	Cirrhosis without prior HE (n = 39)	p value
Total sleep time (minutes)	319.5 ± 87.7	287.0 ± 102.0	0.34
Latency to N1 (minutes)	17 ± 13	26 ± 25	0.16
Latency to N2 (minutes)	23 ± 17	32 ± 26	0.21
Latency to REM (minutes)	95.8 ± 57.2	151.2 ± 93.5	0.04
% time in N1	8.4 ± 6.9	10.8 ± 8.2	0.40
% time in N2	65.7 ± 9.8	51.7 ± 17.7	0.005
% time in REM	12 ± 8	9.5 ± 7.5	0.42
% with SWS	0	29	0.021
Total wake time after sleep onset (minutes)	55.6 ± 38.1	71.7 ± 53.6	0.30
Apnea index	10.0 ± 17.2	4.9 ± 7.30	0.38
Hypopnea index	10.2 ± 11.1	11.8 ± 14.7	0.72
Arousal index	14.4 ± 9.4	18.6 ± 15.2	0.30
Sleep efficiency%	75 ± 13	76 ± 19	0.82

All included patients had OSA. Patients with HE had a lower latency to REM and a higher time in early non-restorative N2 sleep than cirrhotic patients without HE. They also did not have any slow wave sleep noted. There was no difference in the arousals, apnea, or hypopneas noted in cirrhotics with HE compared to those without.

Table 4—Comparison between cirrhotic patients with and without prior alcoholic etiology

	Cirrhosis with alcoholic etiology (n = 13)	Cirrhosis without alcoholic etiology (n = 36)	p value
Total sleep time (minutes)	295.5 ± 68.5	291 ± 109	0.88
Latency to N1 (minutes)	37.2 ± 19.7	17.8 ± 19.5	0.01
Latency to N2 (minutes)	43.8 ± 22.5	24.4 ± 20.6	0.02
Latency to REM (minutes)	128.8 ± 83.0	141.9 ± 95.3	0.69
% time in N1	11.2 ± 5.4	10.5 ± 8.9	0.77
% time in N2	48.4 ± 17.0	56.5 ± 17.1	0.21
% time in REM	15.6 ± 9.9	9.0 ± 6.1	0.06
% with SWS	15	11	0.39
Total wake time after sleep onset (minutes)	61.3 ± 44.7	89.5 ± 64.9	0.21
Apnea index	4.6 ± 8.7	7.1 ± 11.3	0.47
Hypopnea index	7.0 ± 8.4	13.6 ± 15.3	0.09
Arousal index	13.7 ± 7.9	19.2 ± 15.9	0.15
Sleep efficiency (%)	69.3 ± 15.5	76.4 ± 12.1	0.19

All included patients had OSA and were abstinent from alcohol for > 3 months.

DISCUSSION

This study was designed to examine the effect of OSA on sleep architecture in the presence of cirrhosis. In order to do this, we utilized the gold standard diagnostic test for examination of OSA, polysomnography (PSG).[8,9] We found that sleep quality in cirrhosis can be affected by the presence of OSA and that the presence of HE synergizes with OSA to worsen the sleep architecture in patients with cirrhosis. The juxtaposition of increasing age of patients with cirrhosis with an overall epidemic of obesity brings OSA into the forefront while evaluating sleep disorders.[4,10] This is important because there is considerable debate as to the origin of sleep disturbances in cirrhosis.[2] Although the "reversal of sleep-wake cycle" is not specifically

included in the original West-Haven criteria,[11] the use of sleep abnormalities as an initial clue to possible HE has permeated clinical teaching and practice. Therefore most sleep disturbances in patients with cirrhosis are attributed to HE unless proven otherwise.[12] However, the study shows that symptoms of sleep disturbances inquired of our patients with OSA, especially those related to daytime sleepiness, did not differ between those with and without cirrhosis. This was also true for those cirrhotic patients who had a previously experienced an HE episode.

Daytime sleepiness questionnaires such as the Epworth Sleepiness Scale have poor specificity as a screen for OSA or other diseases that affect sleep.[13,14] The nonspecific nature of the daytime sleepiness complaints therefore cannot differentiate between cirrhosis-related and OSA-related sleep disturbances if they occur concurrently in a patient with cirrhosis. This overlap can result in a false, symptom-based diagnosis of HE, resulting in initiation of HE-specific therapy. HE therapy would not improve the underlying deficit associated with OSA, which could worsen the cardiorespiratory status of the patients with cirrhosis by delaying restorative OSA treatment. Therefore prior to attributing the sleep disturbances to HE purely based on symptoms, a diagnosis of OSA should be considered.

The absence of SWS in majority of patients in the sample, which was worse in patients with prior HE, is significant because SWS is the phase associated with restfulness in sleep.[15] SWS is adversely affected in OSA and in patients with minimal HE without OSA.[16-18] Since minimal and overt HE are part of the same spectrum of cognitive dysfunction in cirrhosis, SWS abnormalities seen in the minimal stage could be extended onto the overt stage, which included the HE patients in this study.[19]

We found patients who had prior HE requiring therapy with lactulose had an even worse sleep profile than those without HE but with cirrhosis.[12] While these patients did not have active HE at the time of the sleep study, they had remained on lactulose therapy since their last HE episode. While the current design cannot definitively conclude that the prior HE itself is responsible for this absence of SWS and higher REM latency, it may indicate the shift of the sleep profile to early, non-restorative sleep and decreasing the latency to REM. Interestingly, this worsening was noted even in the background of the highly abnormal sleep study results of patients with OSA with cirrhosis. This synergism may lead to the worsening of daytime performance and propagating the vicious circle of fatigue, daytime sleepiness, and nighttime sleep impairment.

The mechanism of the effect of cirrhosis and prior HE on the sleep architecture is not clear, but this effect is likely to be distinct from the pathogenesis of OSA since HE did not increase the arousal, apnea, or hypopnea indexes. We found a lower REM latency, possibly due to the higher sleep deprivation noted in prior HE patients, leading to potential REM rebound.[20,21] The lower tendency to go in SWS may be reflective of the underlying sleep fragmentation in HE.[21] Another layer of complexity occurs with the super-added effect of alcoholic etiology of cirrhosis showing increased latency to onset of sleep. This effect of alcohol on sleep architecture despite abstinence confirms prior investigations and may be another factor in the multi-dimensional effect of obesity, OSA, and HE on the sleep of cirrhotic patients.[22] This effect is not simply due to worsening liver disease since the patients with and without prior HE or alcohol were similar with respect to MELD score.[23] Studies in patients with compensated cirrhosis have alluded to alterations in melatonin, cortisol, and ghrelin secretion rhythms in affected patients that are associated with poor sleep architecture; however, this requires further study in cirrhotic patients with concomitant OSA.[17,24,25]

The denominator in this study only consisted of patients with OSA with or without cirrhosis, who were otherwise not different with respect to baseline demographics, comorbid conditions, or BMI. Therefore, we biased our study towards only finding an extreme effect of cirrhosis on these results. This would explain the lack of effect of MELD on most sleep parameters and only the significant difference in the arousal index between groups. Prior studies have shown an effect of cirrhosis on sleep quality as well as some preliminary observations on sleep architecture even in compensated cirrhosis compared to healthy controls.[2,17,26,27] While OSA was not systematically excluded in some of the studies, it was not considered a confounder. The results of the current study show that simply asking questions regarding daytime sleepiness in patients with cirrhosis may be misleading, and studies enrolling for sleep disorders in cirrhosis should have a baseline evaluation for OSA.

The study was carried out in the population of veterans, in whom obesity, OSA, hepatitis C, and cirrhosis are epidemic.[4,28,29] This is a relatively uniform group whose results could be widely applicable since, apart from the male predominance, the age and etiology of cirrhosis are similar to the general US population. The study is limited by its retrospective nature and the selection bias that could have occurred while referring patients with relatively compensated cirrhosis for sleep studies. Also, the retrospective nature of this study can only offer a glimpse into identifying the clinically distinguishing features between the effect of OSA and cirrhosis on sleep. This study does however lay the foundation for a more complete, prospective study. The inclusion of advanced cirrhotic patients could have magnified the negative impact of cirrhosis on sleep studies. However, the coexistent pruritus and discomfort due to refractory ascites that is often found in these patients would have confounded the ultimate interpretation.[30] While the interpretation of EEG tracings during an acute episode of HE is fraught with the underlying HE-related changes, none of the included patients had mental status changes when the sleep study was performed.[31] This in and of itself is a limitation, in that the effects of HE on sleep may not be adequately observed because of issues of safety.

We conclude that OSA may be a contributor to sleep disturbance in patients with cirrhosis. We also found that patients with prior HE have worse sleep architecture, shifted toward early, non-restorative sleep. Sleep questionnaires inquiring about daytime sleepiness and sleep quality cannot differentiate between OSA and HE in cirrhotic patients. Therefore, before assuming that daytime sleepiness is an early symptom of HE and initiating HE therapy, OSA should be considered in the differential diagnosis. Prospective studies are warranted in studying the effect of OSA on sleep in patients with cirrhosis.

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Address correspondence to: Jasmohan S. Bajaj, M.D., M.S., Division of Gastroenterology, Hepatology, and Nutrition, Virginia Commonwealth University and McGuire VA Medical Center, 1201 Broad Rock Boulevard, Richmond, VA 23249; E-mail: jsbajaj@vcu.edu

DISCLOSURE STATEMENT

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