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ORIGINAL ARTICLE

The Prevalence and Severity of Sleep Disordered Breathing among Patients with Liver Cirrhosis

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ABSTRACT

Background: The relationship between sleep disorders and liver cirrhosis is bidirectional. **Objective:** Assessment of the prevalence and severity of sleep disordered breathing among patients with liver cirrhosis. **Methodology:** A prospective cross-sectional study was carried out on 32 cases with liver cirrhosis during the period from November 2016 to February 2019. For every patient the demographic and clinical data were collected, liver function tests and full night attended polysomnography was done. **Results:** 53.13% of the included patients had sleep apnea, while 6.25% had Cheyne stoke breathing. The mean hypopnea and apnea hypopnea index were substantially higher in patients with liver cirrhosis due to HCV than the other causes of liver cirrhosis (P value 0.007, and 0.022 respectively). Moreover, there was a substantial moderate negative correlation between aminotransferase enzymes and SaO2 nadir including AST (P = 0.029, r value= -0.500) and ALT (P = 0.023, r value= -0.519). **Conclusion:** The prevalence and severity of sleep disordered breathing is high among patients with liver cirrhosis

Keywords: Liver cirrhosis, Sleep apnea, Sleep disordered breathing, Sleep.

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INTRODUCTION

Egypt has a high population density, with a markedly high prevalence of hepatitis C virus (HCV) infection (26%) which is the highest prevalence rate in the world with the incidence rates between 2 and 6 per 1000 every year. 170,000 new cases are predicted to be added every year to the 11.5 million cases suffering from the infection.[1]

Liver cirrhosis is an irreversible destructive hepatic disease in which the healthy liver tissue is replaced by scar tissue which prevents the liver from functioning properly. Liver cirrhosis is associated with a wide group of complications and among the serious comorbidities of liver cirrhosis are sleep disordered breathing (SDB), which became more obvious among cases of liver cirrhosis.[2]

Sleep disordered breathing (SDB) is a spectrum of disorders consisting of upper airway resistance syndrome, snoring, and sleep apnea. Sleep apnea has different patterns; it can be

obstructive, central or mixed.[3] Obstructive sleep apnea syndrome (OSAS) is the most common type of sleep disordered breathing and one of the most important disorders known in the last fifty years. Obstructive sleep apnea syndrome is characterized by upper airway instability during sleep, which leads to recurrent upper airway obstruction resulting in either complete or partial airflow cessation.[4]

The relationship between sleep disorders and liver cirrhosis is bidirectional. Studies demonstrate that obstructive sleep apnea syndrome is associated with raised alanine aminotransferase levels and a trend toward histological evidence of progressive hepatic disease.[5] On the other hand liver cirrhosis cases were notably more likely to report high risk for obstructive sleep apnea syndrome. Those patients with liver cirrhosis secondary to hepatitis C virus infection are at higher risk of excessive daytime sleepiness (EDS) and obstructive sleep apnea syndrome.[6]

In both animal and human studies, chronic intermittent hypoxia has been shown to provoke structural liver injury and elevate the liver enzyme levels including serum alanine aminotransferase and aspartate aminotransferase. In animal studies, exposure to chronic intermittent hypoxia leading to liver steatosis, necrosis, and inflammation with resultant neutrophil accumulation and collagen deposits.[7]

The aim of this study was to assess the prevalence and severity of sleep disordered breathing among patients with liver cirrhosis and to assess the correlation between sleep disordered breathing and aminotransferase enzymes.

MATERIALS AND METHODS

This study is a prospective cross-sectional study was carried out on 32 cases with liver cirrhosis. It was performed in Aswan University Hospital (including Chest Diseases and Tropical Diseases Departments), during the period from November 2016 to February 2019. The patients included in this study were ≥ 18 years old and had liver cirrhosis. Diagnosis of liver cirrhosis was based on radiological features of cirrhosis (course liver echogenic pattern, irregular surface ± reduced size ± attenuated hepatic veins ± enlarged caudate lobe).[6] The patients either admitted to Aswan University hospital or sought medical advice in the outpatient clinic (chest and tropical Diseases clinics).The patients with associated pulmonary diseases such as chronic obstructive pulmonary diseases (COPD), asthma, interstitial lung disease, bronchiectasis were excluded from the study. The study was approved by the Faculty of Medicine Ethics Committee, Aswan University (IRB number: aswu/42/12/15) and an informed written consent was obtained from all the patients.

All the patients subjected to the following:
-Full history taking including history suggestive of sleep disordered breathing and liver cirrhosis.
-Complete clinical examination including hemodynamic data.
-Anthropometric measures: BMI, neck circumference.
-Chest x-ray
-Laboratory investigations: Alanine transaminase (ALT), aspartate aminotransferase (AST).
-Full night attended polysomnography (PSG) was done in the sleep unit of chest department of Aswan University hospital using Polysomnography (Nihon Kohden`s Polysmith, California, USA) with a full 10-20 montage, 8 bipolar inputs, 6 DC channels, bedside impedance checking, designated channels for electrooculogram (EOG), chin, and 3 electroencephalogram (EEG) channels with a dedicated reference. The PSG amplifier has a built-in pressure transducer and Sp_{O2}. The PSG data collected included: apnea hypopnea index (AHI), desaturation index (DI), average oxygen level, minimum oxygen level, time spent below 90% (TST<90). AHI is calculated as the

number of apnea and hypopnea events per hour of sleep. Sleep apnea is diagnosed if AHI score ≥ 5 with sleep apnea symptoms or if AHI ≥ 15 without sleep related symptoms. The severity is defined as mild for AHI score ≥5 - <15/hr, moderate for AHI score ≥15 and ≤30/hr, and severe for AHI score >30/hr.[8]

Statistical analysis:

Statistical analysis was done by SPSS, version 25 (IBM Inc., Armonk, New York, USA). Non-parametric tests were utilized in the current study. The correlation between different parameters was done using Pearson test. P≤ 0.05 deliberated statistically important.

RESULTS

The study enrolled 32 patients with liver cirrhosis. 21 cases (65.6%) were males while, 11 cases (34.4%) were females. The mean age was 56.69 ±14.05. As regard smoking history, smokers were 11 (34.4%), while non-smokers were 21 (65.6%). The mean BMI was 29.07 ± 9.00. The rest of the demographic data and anthropometric measures of the included cases were shown in table (1).

Sleep apnea was recorded in 17 cases (53.13%), while Cheyne stoke breathing was recorded in 2 cases (6.25%). Regarding the type of sleep apnea, obstructive sleep apnea syndrome was present in 12 cases (70.59%) while, central sleep apnea was present in 5 cases (29.41%). As regard the sleep apnea severity, mild and moderate sleep apnea were present in 7 cases (41.18%) for each, while 3 cases only (17.64 %) had severe sleep apnea as shown in table (2).

Cases of liver cirrhosis were categorized according to the etiology into three groups; liver cirrhosis due to HCV, HBV and non viral causes (non alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis and biliary cirrhosis). Comparison of the respiratory events and oxygen saturation during sleep between the cases with diverse causes of liver cirrhosis was demonstrated in table (3). The mean hypopnea and AHI were substantially higher in patients with liver cirrhosis due to HCV than the other causes of liver cirrhosis, (P value 0.007, and 0.022 respectively).

There was a substantial moderate negative correlation between aminotransferase enzymes and SaO2 nadir including AST (P = 0.029, r value= -0.500) and ALT (P = 0.023, r value= -0.519) as shown in figure (1-2).

DISCUSSION

This study demonstrated that 59.38 % of cases with liver cirrhosis had sleep disordered breathing (53.13% sleep apnea and 6.25% CSB) and the most common pattern was obstructive sleep apnea syndrome. In harmony with our results, Elgammal et al. reported that 56.2% of cases with liver cirrhosis substantially had sleep disordered breathing.[2] Similarly; Fares et al. noted that the prevalence of obstructive sleep apnea among 200 patients with liver cirrhosis was 42.9 %.[6]

This study observed that the majority of sleep apnea cases among liver cirrhosis patients were moderate to severe in grading. Similarly; Elgammal et al. revealed that the prevalence of moderate to severe obstructive sleep apnea in patients with liver cirrhosis was 31.2%.[2]

This study concluded that the patients with liver cirrhosis secondary to hepatitis C had a higher AHI than other causes. These results were consistent with Fares et al. who found that hepatitis C virus was the most common etiology of liver cirrhosis (60.2%) and those patients with liver cirrhosis secondary to hepatitis C virus are at higher risk of obstructive sleep apnea than the

other causes.[6] Evon et al. summarized that sleep disorders disrupted up to 60% of untreated patients with chronic hepatitis C virus and is one of the most common symptoms.[9]

In this study there was a negative correlation between the level of oxygen saturation and the levels of liver enzymes, (r = - 0.500, P value= 0.029) for AST and (r= - 0.519, P value= 0.023) for ALT. In harmony with our results, Mohamed et al. found that in cases with obstructive sleep apnea, the liver enzymes levels including ALT and AST were directly correlated with the severity of nocturnal hypoxia but not with AHI or BMI.[10] Also, Li et al. suggested that obstructive sleep apnea was a risk factor for elevated liver enzymes and the severity of obstructive sleep apnea is correlated with liver enzyme levels. Moreover they assumed that nocturnal hypoxia is one of principal causes of liver cell damage in people with obstructive sleep apnea.[11]

The limitations of the study include small sample size due to the lack of expertise technicians and COVID-19 pandemic which affected the number of the cases and the duration of the study. Also most of the patients with liver cirrhosis who admitted to Aswan University Hospital or sought medical advice in the outpatient clinic were suffering from other comorbidities and others developed many complications as encephalopathy and haematemesis which made them unsuitable for sleep study.

CONCLUSION

The prevalence of sleep disordered breathing is high among patients with liver cirrhosis. The most common pattern of sleep disordered breathing among patients who had liver cirrhosis obstructive sleep apnea**.** Those patients with cirrhosis secondary to hepatitis C are at higher risk of obstructive sleep apnea than other causes. Moreover there is a negative correlation between the level of oxygen saturation and the levels of liver enzymes**.**

Abbreviations

AHI: Apnea hypopnea index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI; Body mass index; CSB: Cheyne Stoke breathing; COPD: Chronic obstructive pulmonary diseases; DI: Desaturation index; EDS: Excessive daytime sleepiness; EEG: Electroencephalogram; EOG: Electrooculogram; OSA: Obstructive sleep apnea; SDB: Sleep disordered breathing; PSG: Polysomnography; TST<90: time spent below 90%.

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Ethics approval and consent to participate

The Research Ethics Committee at the Faculty of Medicine, Aswan University, has approved the study (IRB number: aswu/42/12/15) and all patients provided written informed consent before participation.

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Table (1): Demographic data and anthropometric measures of included cases (N= 32).

	Liver cirrhosis (32)	
	No.	%
Gender:		
Male	21	65.6%
Female	11	34.4%
Smoking:		
Non-smoker	21	65.6%
Smoker	11	34.4%
	Mean ± SD	
Age (years)	56.69 ± 14.05	
Weight (kg)	78.56 ± 23.02	
Height (cm)	164.81 ± 6.71	
BMI (kg/m^2)	29.07 ± 9.00	
Neck circumference(cm)	36.81 ± 4.65	
MAP	88.96 ± 11.02	

Data expressed as mean ± SD and number (%). BMI: body mass index, MAP: mean arterial pressure.

Table (2): Sleep disordered breathing among the study population (N= 32).

SDB	Liver cirrhosis (N= 32)	
	N	%
Normal	13	40.62
CSB	2	6.25
Sleep apnea types	17	53.13
Obstructive sleep apnea syndrome	12	70.59
Central sleep apnea	5	29.41
Sleep apnea severity		
Mild	7	41.18
Moderate	7	41.18
Severe	3	17.64

Data expressed as number (%). SDB: sleep disordered breathing, CSB: Cheyne stoke breathing.

Table (3): Comparison of respiratory events and oxygen saturation during sleep between the cases with the diverse causes of liver cirrhosis (N= 32).

	Etiology of liver cirrhosis			P-value
	Non viral hepatitis (N= 10)	HCV (N= 15)	HBV (N= 7)	
Total apnea: Mean ± SD	10.00 ± 9.76	13.40 ± 30.46	2.43 ± 3.87	0.147
Obstructive: Mean ± SD	7.90 ± 10.55	12.67 ± 30.14	1.86 ± 3.29	0.405
Central: Mean ± SD	1.60 ± 2.76	0.60 ± 1.84	0.43 ± 0.53	0.300
Mixed: Mean ± SD	0.50 ± 0.71	0.13 ± 0.35	0.14 ± 0.38	0.226
Hypopnea: Mean ± SD	32.40 ± 31.95	58.13 ± 77.01	1.43 ± 2.44	**0.007***
AHI: Mean ± SD	12.41 ± 10.81	16.45 ± 25.41	2.07 ± 2.74	**0.022***
TST < 90%: Mean ± SD	24.34 ± 33.33	6.23 ± 9.33	4.03 ± 7.57	0.074
SaO_2: Mean ± SD	71.10 ± 14.80	76.47 ± 10.96	79.71 ± 12.67	0.430

Data expressed as mean ± SD. HCV: hepatitis C virus, HBV: hepatitis B virus, AHI: apnea hypopnea index. TST < 90%: percentage of total sleep time spent with SpO_2<*90*%.

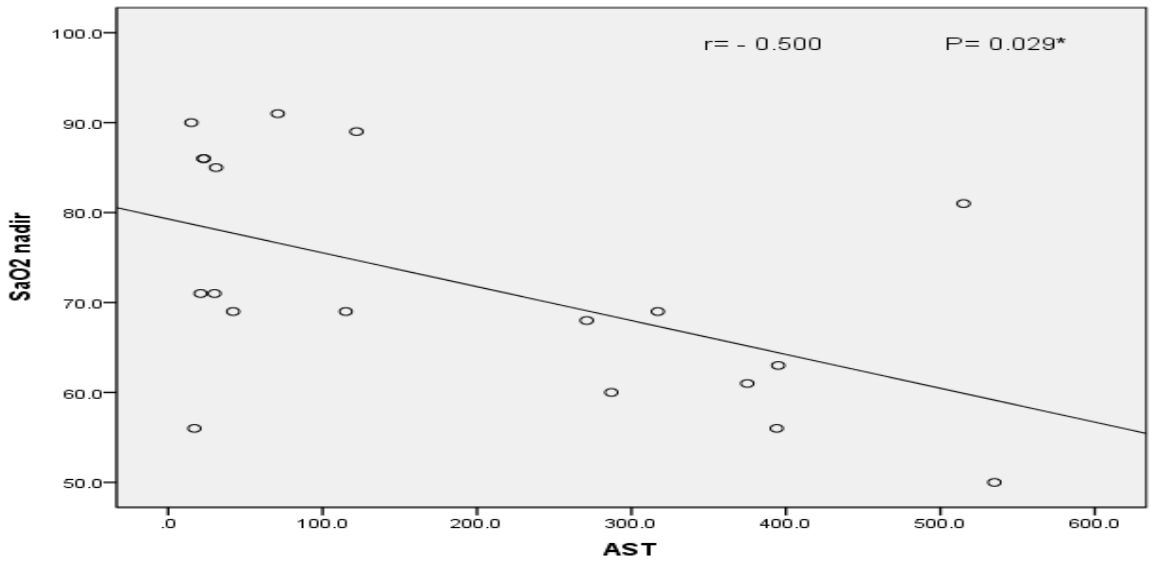

Figure (1): Correlation between AST and SaO2 nadir.

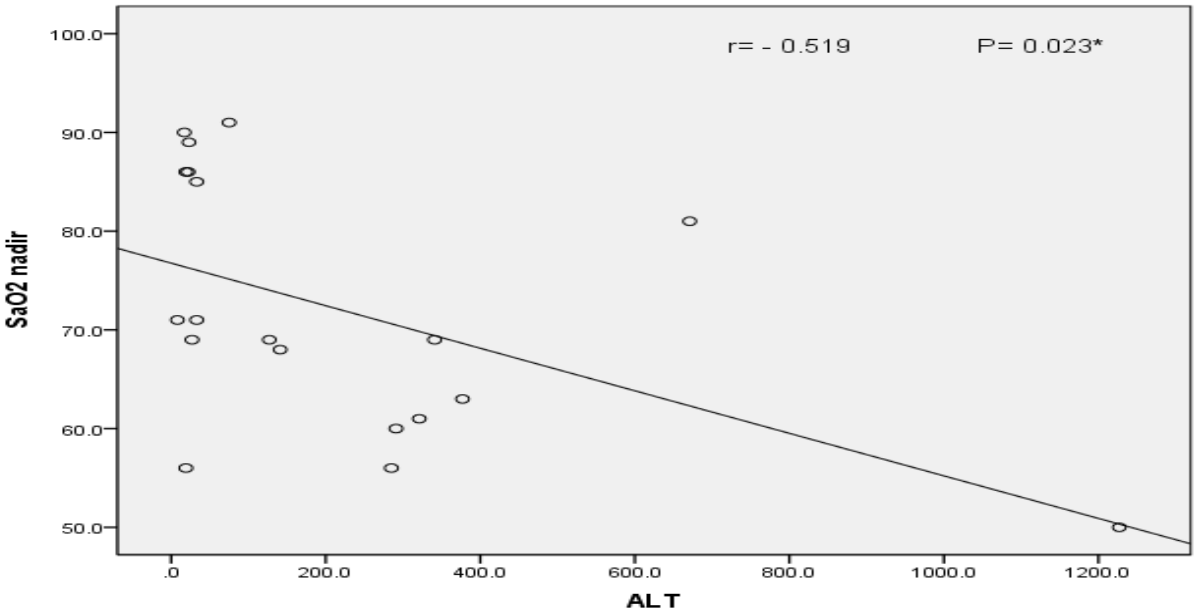

Figure (2): Correlation between ALT and SaO2 nadir.