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ORIGINAL ARTICLE

Sleep parameters in patients with chronic hypersensitivity pneumonitis: a case-control study

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ABSTRACT

Objective: To compare patients with chronic hypersensitivity pneumonitis (cHP) and controls with normal spirometry in terms of their sleep characteristics, as well as to establish the prevalence of obstructive sleep apnea (OSA) and nocturnal hypoxemia. Secondary objectives were to identify factors associated with OSA and nocturnal hypoxemia; to correlate nocturnal hypoxemia with the apnea-hypopnea index (AHI) and lung function, as well as with resting SpO_2, awake SpO_2, and SpO_2 during exercise; and to evaluate the discriminatory power of sleep questionnaires to predict OSA. **Methods:** A total of 40 patients with cHP (cases) were matched for sex, age, and BMI with 80 controls, the ratio of controls to cases therefore being = 2:1. The STOP-Bang questionnaire, the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index, the Berlin questionnaire and the **N**eck circumference, **o**besity, **S**noring, **A**ge, and **S**ex (NoSAS) score were applied to all cases, and both groups underwent full-night polysomnography. **Results:** The patients with cHP had longer sleep latency, lower sleep efficiency, a lower AHI, a lower respiratory disturbance index, fewer central apneas, fewer mixed apneas, and fewer hypopneas than did the controls. The patients with cHP had significantly lower nocturnal SpO_2 values, the percentage of total sleep time spent below an SpO_2 of 90% being higher than in controls (median = 4.2; IQR, 0.4-32.1 vs. median = 1.0; IQR, 0.1-5.8; p = 0.01). There were no significant differences between cases with and without OSA regarding the STOP-Bang questionnaire, NoSAS, and ESS scores. **Conclusions:** The prevalence of OSA in cHP patients (cases) was high, although not higher than that in controls with normal spirometry. In addition, cases had more hypoxemia during sleep than did controls. Our results suggest that sleep questionnaires do not have sufficient discriminatory power to identify OSA in cHP patients.

Keywords: Alveolitis, Extrinsic Allergic; Lung diseases, interstitial; Sleep apnea, obstructive; Hypoxia.

INTRODUCTION

Chronic hypersensitivity pneumonitis (cHP) is an interstitial lung disease (ILD) caused by an exaggerated immune reaction to inhaled antigens found in the environment.[1,2] cHP occurs in susceptible individuals, and its prevalence varies worldwide. Hypersensitivity pneumonitis (HP) is a very common ILD in Brazil.[3] Obstructive sleep apnea (OSA) and ILD have some comorbidities and symptoms in common, such as daytime sleepiness, fatigue, reduced quality of life, and pulmonary hypertension.[4-10] Only a few studies of chronic ILD have examined sleep, despite the fact that sleep disorders appear to be common in ILD patients.[4-8,11-13] In a study including 21 patients with fibrotic HP, the prevalence of OSA was found to be similar between patients with idiopathic pulmonary fibrosis (IPF) and those with cHP (83.3% vs. 76.2%).[11]

The objective of the present study was to compare patients with cHP and controls with normal spirometry in terms of their sleep characteristics, as well as to establish the prevalence of OSA and nocturnal hypoxemia. Secondary objectives were to identify factors associated with OSA and nocturnal hypoxemia; to correlate nocturnal hypoxemia with the apnea-hypopnea index (AHI) and lung function, as well as with resting SpO_2, awake SpO_2, and SpO_2 during exercise; and to evaluate the discriminatory power of sleep questionnaires to predict OSA.

METHODS

Study participants

This was a retrospective case-control study conducted between March of 2016 and December of 2019 at the Federal University of São Paulo, located in the city of

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São Paulo, Brazil. Patients diagnosed with cHP and meeting the inclusion criteria were consecutively included in the study. A total of 154 cHP patients were eligible during the period. Of those, 40 (cases) were selected for inclusion in the study. They were matched for sex, age (± 5 years), and BMI (± 5 kg/m^2) with 80 controls with normal spirometry.[14] The ratio of controls to cases was 2:1. When more than two controls were available for a case, the selection was made by random number generation.

The diagnosis of cHP was based on the criteria suggested by Salisbury et al.[15] Cases were not specifically selected because they had sleep problems or complaints, and controls had no history of lung disease. The exclusion criteria were as follows: age > 80 years; inability to perform spirometry; use of long-term home oxygen therapy or a resting SpO_2 ≤ 89%; a reduced FEV_1/FVC ratio (of < 0.7); ILD exacerbation or progressive ILD; a left ventricular ejection fraction of ≤ 50% on echocardiography; alcoholism; uncontrolled hypothyroidism; systemic diseases that could independently result in pulmonary hypertension; use of hypnotics; and unstable psychiatric disorder. The study was approved by the Research Ethics Committee of the Federal University of São Paulo (Protocol no. 1.162.941), and all participating patients gave written informed consent.

Study protocol

Patients with cHP (cases) underwent biochemical and hematological evaluation; arterial blood gas analysis; HRCT; and echocardiography. The modified Mallampati score and neck circumference were assessed in all cases. The STOP-Bang questionnaire, the Epworth Sleepiness Scale (ESS), the Pittsburgh Sleep Quality Index (PSQI), the Berlin questionnaire, and the Neck circumference, obesity, Snoring, Age, and Sex (NoSAS) score were applied to all cases.[16-20] A high risk of OSA was defined as follows: five or more positive responses to the STOP-Bang questionnaire; two positive responses to the STOP-Bang questionnaire + being male; two positive responses to the STOP-Bang questionnaire + a BMI > 35 kg/m^2; or two positive responses to the STOP-Bang questionnaire + neck circumference ≥ 43 cm (for men) or ≥ 41 cm (for women).

Full-night polysomnography was performed in accordance with current standards.[21] Obstructive apnea was defined as a reduction in airflow ≥ 90% lasting at least 10 s with evidence of persistent respiratory effort. Obstructive hypopnea was defined as a reduction in airflow ≥ 30% for more than 10 s accompanied by ≥ 4% oxygen desaturation and evidence of respiratory effort. Respiratory effort-related arousals were also recorded, being defined as sequences of breaths lasting ≥ 10 s, with increased respiratory effort or flattening of the inspiratory curve, leading to awakening but not meeting the defined criteria for apnea or hypopnea. Nocturnal hypoxemia was defined as the percentage of total sleep time spent below an SpO_2 of 90% (T90). Significant nocturnal hypoxemia was defined as spending 10% or more of the total sleep time below an SpO_2 of 90%.[8] Spirometry and DL_{CO} measurement were performed in accordance with current standards. Oxygen saturation was assessed by oximetry at rest and at the end of a four-minute step test. Desaturation was characterized by a decrease ≥ 4% at the end of the test.

Statistical analysis

The data were expressed as mean ± standard deviation or median (interquartile range). The prevalence of OSA was compared between cases and controls by means of the chi-square test. The normal distribution of the data was assessed with the Shapiro-Wilk test. Between-group comparisons were made with the Mann-Whitney test, given that most of the variables had a nonparametric distribution. Correlations of the AHI with other variables were determined by Spearman's test. In the group of patients with cHP (cases), T90 and the degree of nocturnal hypoxemia were calculated and correlated by means of univariate analysis of pulmonary function test results, PaO_2, $PaCO_2$, sleep questionnaire data, oxygen desaturation at the end of exercise, and polysomnographic parameters. A value of $p < 0.05$ was considered significant.

RESULTS

The general characteristics of the study sample are shown in Table 1. The mean age was 59 years, with a predominance of females (75%). There was no difference between cases and controls in terms of age, sex, or BMI, as expected by the matching criteria. The modified Mallampati score showed that 30 (75%) of the cHP patients were at a high risk of OSA (Mallampati classes III and IV). The results of the pulmonary function tests and arterial blood gas analysis in the patients with cHP are shown in Table 2. There was a mild decrease in FVC and a moderate decrease in DL_{CO}. Mean $PaCO_2$ was in the lower reference range. Twenty-eight (70%) of the patients with cHP experienced oxygen desaturation at the end of exercise. Seventeen (42.5%) of the patients with cHP using corticosteroids at a dose ≥ 20 mg/day were included. When compared with those who were using a lower dose of corticosteroids or who were not receiving corticosteroid therapy, there was no difference in the AHI, BMI, neck circumference, or sleep quality as assessed by the PSQI (data not shown).

The results of polysomnography for both groups are shown in Table 3. The patients with cHP had longer sleep latency and lower sleep efficiency than did those in the control group. The arousal index was higher in the control group. Unexpectedly, the patients with cHP had a lower AHI, a lower respiratory disturbance index, fewer central apneas, fewer mixed apneas, and fewer hypopneas. An AHI ≥ 5 events/hour was common in cases and controls (67.5% vs. 82.5%; $X^2 = 3.44$; $p = 0.06$). Moderate to severe OSA was found in 47.5% of the controls and in 25% of the cases ($X^2 = 5.65$; $p = 0.02$). However, the patients with cHP had significantly

Table 1. General characteristics of cases and controls in the present study.[a]

Variable	Group	
	Control (n = 80)	cHP (n = 40)
Age, years	59.1 ± 11.5	59.3 ± 12.7
Female sex	60 (75)	30 (75)
BMI, kg/m^2	29.6 [25.5-33.6]	29.9 [25.9-35.1]
BMI < 25 kg/m^2	16 (20)	8 (20)
BMI ≥ 25-29.9 kg/m^2	26 (32.5)	13 (32.5)
BMI ≥ 30 kg/m^2	38 (47.5)	19 (47.5)

cHP: chronic hypersensitivity pneumonitis. [a]Data presented as mean ± SD, median [IQR], or n (%).

Table 2. Pulmonary function test results and arterial blood gas analysis results in patients with chronic hypersensitivity pneumonitis (n = 40).[a]

Pulmonary function testing	
FVC, % predicted	70.4 ± 17.9
FEV_1, % predicted	75.0 ± 20.4
FEV_1/FVC	0.84 ± 0.07
DL_{CO}, % predicted (n = 28)	56.9 ± 17.4
Arterial blood gas analysis (n = 37)	
$PaCO_2$, mmHg	36.1 ± 3.7
PaO_2, mmHg	80.1 ± 11.0
SaO_2, %	95.7 ± 1.6

[a]Data are presented as mean ± SD.

lower nocturnal SpO_2 values, the percentage of total sleep time spent below an SpO_2 of 90% being higher than in controls.

The STOP-Bang questionnaire, the NoSAS score, and the Berlin questionnaire showed that 12 (30%), 23 (57.5%), and 24 (60%) of the patients with cHP, respectively, were at a high risk of OSA. There were no significant differences between cases with and without OSA regarding the STOP-Bang questionnaire, NoSAS, and ESS scores. The sensitivity of the NoSAS score for cHP was 55%, with a specificity of 46%. The PSQI was higher in cases than in controls (9; IQR, 7-13 vs. 6; IQR, 4-9.8; $p < 0.01$).

In the cHP group, the AHI was directly correlated with the BMI ($r_s = 0.38$, $p = 0.02$) and T90 ($r_s = 0.67$, $p < 0.01$), as well as being inversely correlated with baseline, mean, and minimum SpO_2 during polysomnography, the correlation being highest with the last of the three ($r_s = -0.70$, $p < 0.001$). In addition, the AHI did not correlate with age, neck circumference, FVC, DL_{CO}, resting SpO_2, or SpO_2 at the end of exercise. Furthermore, T90 correlated inversely with percent predicted DL_{CO} ($p = 0.06$) and, more strongly, with awake SpO_2 at baseline on polysomnography ($r_s = -0.87$, $p < 0.001$; Figure 1). Of the 20 cHP patients with baseline $SpO_2 \geq 93\%$ on polysomnography, only 1 (5%) spent more than 10% of the total sleep time below an SpO_2 of 90%.

DISCUSSION

In the present study, the prevalence of OSA in patients with cHP was high; however, contrary to expectations, it was lower than that in a group of matched controls with normal spirometry, randomly selected from the general population. The reasons for this are obscure. Many problems can occur during the selection of cases and controls in this type of study.[22] In the group of patients with cHP in the present study, the AHI was directly correlated with the BMI, although not with FVC, DL_{CO}, resting SpO_2, or SpO_2 at the end of exercise. As expected, patients with cHP had more hypoxemia during sleep. The present study did not include individuals with markedly compromised lung function or low resting SaO_2. It has been shown that patients with more severe ILD have a higher oxygen desaturation index and a higher AHI.[4]

OSA is an important public health problem, with an increasing prevalence and a high rate of underdiagnosis in patients with ILD. We used sleep questionnaires in an attempt to identify cHP patients who were at an increased risk of OSA and who might benefit from polysomnography. However, we found no correlation between OSA risk as assessed by the questionnaires and a polysomnographic diagnosis of OSA. Therefore, the questionnaires had limited value in predicting OSA in cHP patients. In the present study, we subjectively assessed sleepiness using the ESS. A median ESS score of 5.5 shows that, in general, cHP patients are less sleepy, regardless of the presence of OSA. Although the ESS score has been found to be higher in patients with IPF than in normal controls,[9,23] it was within the normal range in the present study, showing that excessive daytime sleepiness was not significant. Mermigkis et al.[6] showed that only 20% of patients with IPF reported excessive daytime sleepiness. Thus, it is clear that the ESS score is poor at predicting OSA in patients with ILD. Our results confirm that the sleep questionnaires used in the present study have low accuracy in identifying individuals at risk of OSA, regardless of the cutoff point used for the AHI.[24] Polysomnography remains the only tool with sufficient sensitivity and specificity to confirm or exclude a diagnosis of OSA in patients with ILD.

In the present study, the cHP patients reported worse sleep quality than did the controls. Poor sleep quality and its impact on daytime functioning and quality of life can be underestimated in patients with ILD, in whom symptoms such as fatigue, tiredness, and drowsiness can be ascribed to lung disease. Our

Table 3. Polysomnography data and nocturnal oximetry results in cases and controls in the present study.[a]

Polysomnography	Group		p
	Control (n = 80)	cHP (n = 40)	
Sleep efficiency, %	80.6 [73.4-85.3]	76.5 [63.8-82.3]	0.01
Sleep latency, min	8.2 [3.7-16.4]	35 [10.3-57.8]	< 0.01
REM sleep latency, min	89.5 [62.8-140.1]	101.8 [71-162.8]	0.39
Stage 1 sleep, %	11.8 [7.7-20.8]	9.8 [6.3-14.4]	0.04
Stage 2 sleep, %	39.1 [32.8-46.1]	43.5 [34.8-48.2]	0.10
Stage 3 sleep, %	25.4 [19.9-30.7]	28 [21.1-33.7]	0.55
REM sleep (%)	19.5 [14.1-23.4]	18.7 [13.7-24.7]	0.90
Arousal index, events/h	21.9 [15.2-31.0]	14 [8.3-19.3]	< 0.01
Obstructive apnea, n	10 [1.0-30.8]	5.5 [0.3-15.8]	0.26
Central apnea, n	1.0 [0.0-3.0]	0.0 [0.0-1.0]	< 0.01
Mixed apnea, n	0.0 [0.0-3.0]	0.0 [0.0-1.0]	0.01
Hypopnea, n	61.0 [32.0-108.0]	34.5 [23.3-67.5]	0.02
RERA, n	4.0 [1.0-8.8]	2.5 [0.0-8.8]	0.23
Respiratory disturbance index	16.2 [8.3-33.1]	9.1 [6.0-6.0]	0.01
AHI, events/h	14.0 [7.0-31.6]	8.2 [4.0-14.9]	< 0.01
Baseline SpO_2, %	94.7 [93.3-94.9]	93.2 [90.9-94.3]	< 0.01
Mean SpO_2, %	93.9 [92.0-94.9]	92.0 [90.0-93.6]	<0.01
Minimum SpO_2, %	85.0 [80.0-88.0]	83 [78.3-87.0]	0.16
T90	1.0 [0.1-5.8]	4.2 [0.4-32.1]	< 0.01

cHP: chronic hypersensitivity pneumonitis; REM: rapid eye movement; RERA: respiratory effort-related arousal; AHI: apnea-hypopnea index; and T90: percentage of total sleep time spent below an SpO_2 of 90%. [a]Data are presented as median [IQR].

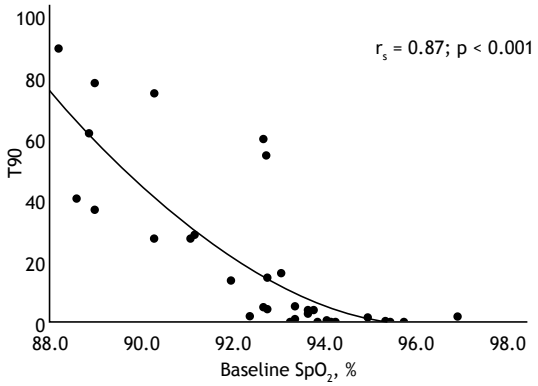

Figure 1. Correlation between baseline SpO_2 and the percentage of total sleep time spent below an SpO_2 of 90% (T90) on polysomnography.

results for cHP patients are similar to those reported by Mermigkis[9] and Krishnan et al.,[23] who found that the quality of sleep as measured by the PSQI was worse in IPF patients than in normal controls, and reduced sleep quality correlated with reduced health-related quality of life. The sleep pattern in patients with cHP is impaired, and we observed changes in sleep architecture, including increased sleep latency, reduced sleep efficiency, and a lower percentage of rapid eye movement (REM) sleep, the last finding having no statistical significance. Previous studies of patients with fibrotic ILD have shown increased non-REM (stage N1 and N2) sleep, reduced slow-wave sleep, and reduced REM sleep.[4,9,25] Several mechanisms can contribute to sleep fragmentation in patients with ILD, including hypoxemia. However, we found that the severity of ILD (as assessed by lung function parameters such as FVC, DL_{CO}, and SpO_2 during exercise or by arterial blood gas analysis) did not correlate with the AHI.

Studies examining sleep in patients with cHP have been few in number and have included patients with ILD of varying etiologies and samples consisting predominantly of patients with IPF, showing a high prevalence of OSA in this population; however, the prevalence of OSA was not compared between cases and healthy controls in those studies.[4-6,8,12,13] The study with the largest number of HP patients showed an OSA prevalence of 69.4% in patients with ILD, of 83.3% in patients with IPF, and of 76.2% in patients with cHP.[11]

In our study, nocturnal hypoxemia correlated significantly and as expected with PaO_2, awake SpO_2 during polysomnography, and DL_{CO}. Awake SpO_2 and SpO_2 during exercise have been shown to correlate significantly but weakly with nocturnal hypoxemia in some studies,[8,10,26,27] but not in others.[28-30] We found no correlation between nocturnal hypoxemia and SpO_2 during exercise. Troy et al.[8] found a significant correlation between T90 and ILD severity markers such as daytime SpO_2, SpO_2 during exercise, and DL_{CO}. Corte et al.[28] found that 78% of patients with nocturnal hypoxemia had no decrease in oxygen saturation after exercise. Therefore, nocturnal hypoxemia cannot be excluded when PaO_2 is normal at rest or during exercise.

The present study has limitations that should be noted. First, the sample size was relatively small, with a predominance of women. In Brazil, however, cHP is more common in women than in men, because indoor exposures are more common in the former than in the latter. Thus, the demographic characteristics of our study population are similar to those reported in the literature.[1] Furthermore, although OSA is more common in men, it becomes more common in postmenopausal women.[31,32] Cases and controls were matched for sex in the present study, meaning that the results cannot be attributed to differences between the sexes. Second, although cHP is common in Brazil, it is often diagnosed at an advanced or progressive stage, and this limits the inclusion of cHP patients. The fact that patients with cHP and hypoxemia during wakefulness or receiving oxygen therapy were not included in the present study is, therefore, another limitation, because the prevalence of OSA could be higher in this population. Third, the fact that the same investigator collected the anthropometric data and administered the questionnaires could have resulted in measurement bias. Finally, the first night effect (when patients are in unfamiliar surroundings) of polysomnography may have also influenced the results. However, given that this effect was common to cases and controls, this limitation becomes less critical.

In summary, the prevalence of OSA in cHP patients (cases) was high, although not higher than in controls with normal spirometry. In addition, cases had more hypoxemia during sleep than did controls. Nocturnal hypoxemia was common and related to baseline oxygen saturation during wakefulness. Our results suggest that sleep questionnaires do not have sufficient discriminatory power to identify OSA in cHP patients.

AUTHOR CONTRIBUTIONS

RBM and CACP: conceptualization; data curation; formal analysis; investigation; project administration; and drafting, reviewing, and editing of the manuscript. LRAB: conceptualization; formal analysis; and reviewing of the manuscript. MRS: reviewing and editing of the manuscript. ABB, ACLR, PSG, and SLKM: data collection. ST: funding acquisition. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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