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Research Article

Sleep Apnea in Individuals with Idiopathic Pulmonary Fibrosis

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Abstract

Introduction: Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lung disease with high mortality. It is characterized by a progressive heterogeneous course, with a median survival of 2.5 to 4.5 years and few treatment options.

IPF is associated with significant comorbidities such as pulmonary hypertension, emphysema, pulmonary lung cancer, pulmonary thromboembolism, coronary artery disease, gastroesophageal reflux disease and obstructive sleep apnea (OSA).

Several studies have reported different incidence frequency of obstructive sleep apnea (OSA) in interstitial lung disease (ILD).

Objectives: The aims of this study were to evaluate the frequency of sleep apnea in 24 stable IPF patients, to describe clinical and home sleep test (HST) features of sleep-related breathing disorders and to analyze the relationship among the indexes HST findings (apnea/ipopnea index - AHI), pulmonary function (forced vital capacity - FVC%, diffusing capacity of the lung for carbon monoxide - DLco) and sleep questionnaires.

Materials and Methods: We synthesized categorical variables as frequencies and percentages and continuous variables as mean and standard deviation (SD). In order to test for differences in characteristics of IPF/OSA group according the gender and severity of OSA scores, One-way analyses of variance and independent sample t-test were performed.

Results: 24 patients were recruited, 22 (91.7%) of which were positive for OSA (mild OSA was detected in 59.1%, moderate in 22.7%, and severe in 18.2%). The mean AHI was 20.7 ± 15.9/h, the mean oxy-haemoglobin saturation was 90.7 ± 2.3% and mean time of oxy-haemoglobin saturation lower than 90% was of 23.5 ± 23.2%. Mean FVC% was 90.1 ± 19.2%, mean DLco was 53.1 ± 16.7%; 15 patients had GAP I. Only one patient presented symptoms suggestive of OSA. The patients presented more events of hypopnea (I/h) than apnea (A/h); this condition was more evident in females than in men. Nocturnal respiratory failure was found associated to OSA in 18%.

Conclusion: In our study, the prevalence of sleep disordered breathing in patients with IPF was very high and the most frequent event was hypopnea. We concluded that the sleep study should be considered as part of the assessment in managing patients with IPF. The therapeutic approach of IPF cannot be limited to the administration of antifibrotic drugs: identification and treatment of complicating comorbidities such as OSA may have a significant impact on patient's survival and quality of life.

Keywords: *Obstructive Sleep Apnea; Idiopathic Pulmonary Fibrosis*

Introduction

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic, progressive, fibrosing interstitial pneumonia. The causes are unknown. It occurs primarily in older adults, it is limited to the lungs, and it is defined by the histopathologic and/or radiologic pattern of Usual Interstitial Pneumonia (UIP). The clinical features are: unexplained chronic dyspnea, cough, bibasilar inspiratory crackles, and/or digital clubbing [1]. IPF is frequently associated with other comorbidities that include emphysema (combined pulmonary fibrosis and emphysema), lung cancer, pulmonary hypertension, sleep apnea, coronary artery disease [2], thromboembolism. The treatment of comorbidities may play a role in the effort to optimize the survival of IPF patients [3,4].

All interstitial lung diseases (ILDs), in particular IPF, often develop progressive daytime hypoxia or desaturation during sleep, with or without associated apnea that may contribute to adverse outcomes. The incidence of obstructive sleep apnea (OSA) and ILDs show different frequency [5-10].

OSA is an increasingly common, chronic, sleep-related breathing disorder, characterized by repetitive episodes of upper airway closure during sleep and by periodic narrowing [11-13].

OSA can appear during the natural course of ILDs, as a consequence of lung function restriction, or it can promote gastroesophageal reflux disease or increase oxidative lung stress through chronic nocturnal intermittent hypoxia: these mechanisms can per se increase the risk of interstitial lung disease [14-16].

In IPF patients, OSA and all the sleep breathing disorders worsen the quality of sleep and increase the mortality rate. The early identification of IPF and comorbidities in patients is one of the most urgent challenges in the effective management of this deadly disease.

There is paucity of studies related to continuous positive airway pressure (CPAP) treatment in this patient group [17-19]: it seems that this therapy improves in daily living activities and quality of sleep and life and good CPAP compliance appears to improve mortality [17].

Objectives of the Study

This observational study aimed to evaluate the frequency of sleep apnea and to analyse the relationships between the indexes of home sleep test (HST) and pulmonary function.

Inclusion criteria were the following: age < 80 years; stable dyspnea; diagnosis of IPF according to ATS/ERS recommendations [1]; stable phase of disease with no exacerbations over the last 3 months. Exclusion criteria were prior diagnosis of OSA and unstable dyspnea, neoplastic diseases.

Materials and Methods

A group of 24 patients with stable, mild and moderate IPF were recruited. All the patients attended HST according to established standards [20]. None of the patients requiring HST at the time of the study received oxygen supplementation. Apneas, hypopneas and apnea-hypopnea index (AHI) were defined according to the American Academy of Sleep Medicine [20]. Other parameters that were analysed were: events and number of events of obstructive apnea (OA) and central apnea (CA), number and events of hypopnea (H), oxygen desaturation index (ODI) and average of arterial saturation (SpO_2 average%) with time of desaturation (T < 90%). OSA was defined as an apnea-hypopnea index (AHI) of > 5 events per hour. The score used for hypopnea (I) respiratory events was the following [20]:

a. The peak signal excursions drop by ≥ 30% of pre-event baseline using nasal pressure (diagnostic study), PAP device flow (titra-

tion study), or an alternative hypopnea sensor (diagnostic study).

b. The duration of the ≥ 30% drop in signal excursion ≥ 10 seconds.

c. A ≥ 3% oxygen desaturation from the pre-event baseline and/or the associated between the event and an arousal.

Subjects were asked to complete the Epworth Sleepiness Scale (ESS) questionnaire for measuring daytime sleepiness and assessing the risk for sleep apnea, snoring index (SI%) [21]. Body mass index (BMI) was calculated.

Pulmonary function testing (PFT) including spirometry (forced vital capacity -FVC%) and measurement of diffusing capacity of the lung for carbon monoxide (DLco) were performed according to ATS/ERS guidelines [22] within 3 months of HST. An assessment of the patients' upper airways was conducted by a IPF physician, a sleep physician, or an IPF nurse practitioner according to the Mallampati (MP) classification for difficult intubation [23]. The GAP index for IPF was calculated [1].

Categorical variables (e.g. gender and snoring assessment) were synthesized as frequencies and percentages. Continuous variables were summarized as mean and standard deviation (SD). In order to test for differences in characteristics of the IPF/OSA group according the gender and severity of OSA scores, one-way analyses of variance and a t-test of an independent sample were performed. The statistical significance was set at p value < 0.05. All the statistical analyses were performed with SPSS 20.0 (SPSS® Inc, Chicago, Illinois).

Results

24 patients were studied (18 males, mean age 68.7 ± 6.2 yrs, mean body mass index 28.1 ± 3.8 kg/m^2, FVC 88 ± 19%; DLco 54 ± 16%).

Sleep disordered breathing was present in 22 patients (Table 1). 15 patients (68.2%) had GAP I and 7 patients (31.8%) had GAP II.

Variables	Mean (± SD)
Age (years)	69.4 ± 5.9
Gender N (%)	
Female	6 (27.3)
Male	16 (72.7)
BMI (Kg/m^2)	28.4 ± 3.9
SI%	6.9 ± 5.5
ESS	9.1 ± 1.2
FVC%	90.1 ± 19.2
DLco%	53.1 ± 16.7
SpO_2	90.7 ± 2.9
T < 90%	23.5 ± 23.2
AHI	20.7 ± 15.9
A/h	47.7 ± 81.4
I/h	95.4 ± 56.9

Table 1: *Characteristics of IPF/OSA group (22 pts).*

Only one patient presented symptoms suggestive of OSA (ESS was normal in 21 patients).

The patients presented more events of hypopnea (I/h) than apnea (A/h) per hour (mean 95.4 ± 56.9 vs. 47.7 ± 81.4); this condition was more evident in females (A/h 16.8 ± 8.1; I/h 119.7 ± 51.0) than in males (A/h 59.2 ± 93.4; I/h 86.3 ± 57.8). IPF men were significantly younger than IPF women. The snoring was more present in females (Table 2). Nocturnal respiratory failure was found in association with OSA in 4 cases (18%), who also had daytime hypoxemia and a worse impairment of DLco (mean 40 ± 10%).

Variables	Female Mean (± SD)	Male Mean (± SD)
Age (years)	73.2 ± 3.3*	68.0 ± 6.2*
SI%	10.6 ± 8.3*	5.5 ± 3.5*
BMI (Kg/m^2)	27.5 ± 4.9	28.7 ± 3.7
ESS	9.2 ± 1.4	9.1 ± 1.2
FVC%	94.7 ± 19.2	88.4 ± 19.5
DLco%	50.7 ± 14.2	53.9 ± 17.8
SpO_2%	90.7 ± 1.4	90.8 ± 2.6
T<90%	20.0 ± 11.4	24.8 ± 26.5
AHI	20.9 ± 15.3	20.5 ± 16.6
A/h	16.8 ± 8.1	59.2 ± 93.4
I/h	119.7 ± 51.0	86.3 ± 57.8

Table 2: *IPF/OSA group (22 pts): evaluation between gender.*
**p < 0.05.*

There was no significant correlation between IPF severity and AHI (Table 3). MP reached 2 in 13 patients (patients with mild OSA) and 3 in 9 patients (patients with moderate and severe OSA).

	Mild OSA (AHI 5 - 15) Mean (± SD)	Moderate OSA (AHI 15 - 30) Mean (± SD)	Severe OSA (AHI > 30) Mean (± SD)
Number pts (%)	13 (59)	5 (22)	4 (18)
ESS	9.2 ± 1.2	8.4 ± 1.1	10.0 ± 1.2
BMI (Kg/m^2)	28.4 ± 2.9	25.8 ± 4.4	31.5 ± 5.3
FVC%	90.5 ± 20.8	84.4 ± 22.6	95.8 ± 7.9
DLco%	54.9 ± 19.6	45.4 ± 9.9	56.8 ± 11.6
SpO_2%	90.7 ± 2.5	91.3 ± 2.0	90.4 ± 2.3
T<90%	22.2 ± 27.3	22.9 ± 20.2	28.3 ± 15.6
A/h	18.2 ± 20.8	28.0 ± 28.7	168.3 ± 140.4
I/h	64.2 ± 35.2	145.6 ± 41.2	134.0 ± 70.1

Table 3: *Characteristics of IPF/OSA group according the severity of OSA.*

Discussion

The main findings of this work are:

1. According to 1984 previous studies, sleep breathing disorders reveal to bee frequent in IPF patients (90% OSA). In some retrospective studies the prevalence either reached 60% or was significantly higher [7,24,25]. The exact mechanism underlying the high prevalence of OSA in patients with IPF has not been established yet. Reduced lung volume has been considered one of the main causes [26]. OSA induces greater oxidative stress and systemic inflammation and accelerates lung structural damage and endothelial remodelling in IPF. Recent clinical and experimental data have shown that intermittent hypoxia is closely associated with disease progression and a worse outcome in IPF [27]. Therefore, OSA is more common in IPF patients than in the general population and early recognition and treatment are crucial.
2. The presence of nocturnal hypoxemia results to be rare due to the mild or moderate severity of OSA affecting most of the patients. The development of nocturnal hypoxemia in patient with IPF was recognized several years ago [28,29]. Sleep hypoxia seems to be associated with episodes of upper airways obstruction. Furthermore, the severity of sleep apnea and nocturnal hypoxia are the main determinants of daytime hypoxemia [30,31]. In our study, 4 patients with nocturnal respiratory failure suffer also from daytime hypoxemia and lung function impairment of lung transfer for carbon monoxide.
3. Hypoventilation is the nocturnal respiratory pattern most represented in our series. Taking into account patients with similar BMI, this condition results to be more common in women than in men.

As in chronic obstructive pulmonary disease [32] IPF patients present alterations in sleep architecture, including decreased sleep efficiency, slow wave sleep and rapid eye movement (REM) sleep, and increased sleep fragmentation. Moreover, sleep related hypoventilations during the vulnerable REM sleep period and obstructive sleep apnea-hypopnea syndrome are frequent, but remain usually under diagnosed. A contribution to an increased ventilation/perfusion mismatch cannot be ruled out. Nocturnal hypoxemia worsens along with the functional impairment and particularly with the deterioration of arterial blood gas tensions. Most likely the scoring criteria used to define the hypopneas should be standardized and adapted to the patient with IPF. The criterion of 30% drop associated with 4% desaturation could lead to an underestimation of the problem, whereas the 3% desaturation associated with 30% diffusion capacity due to the poor capillary alveolus could lead to an overestimation. Probably the best way to define hypopnea in patients with IPF and OSA could be the Chicago criteria, which define hypopnea with a 3% SpO_2 drop associated with a 50% reduction in flow [33,34].

The women observed during the study snored more. Previous studies have reported the factors associated with the differences between men and women in symptoms, characteristics, and severity of OSA [35-38].

Jordan., *et al*. [36] hypothesized that gender differences could be found in the arousal response to apneas. They found that during non-REM sleep men had a higher ventilatory response to apneas than women, but then they developed greater hypoventilation when they went back to sleep, especially in supine position. This prolonged hypoventilation often leads to ventilatory instability upon returning to sleep.

Although this study was conducted in a limited number of patients in only one center, we can say that formal sleep evaluation and HST should be taken into consideration in all patients with IPF given the high prevalence found in our sample.

Conclusion

OSA as an IPF comorbidity may be overlooked by primary care providers and specialists in patients. Evidence from this study indicate that OSA induces IPF severity and results to be closely associated with poor disease outcomes. Early OSA recognition and treatment are crucial in a fatal disease such as IPF.

Finally, given the multiple variables related to scoring and pathology we emphasize the importance of standardization in the scoring of hypopnea in patients with IPF and OSA. All this is essential to optimize the treatment of this new form of overlap syndrome.

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Conflict of Interests

All authors declare that they have no competing interests.

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