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Original Article

Predictive factors of obstructive sleep apnoea in patients with fibrotic lung diseases

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ABSTRACT

Background and aim: Several studies reported a high prevalence of Obstructive Sleep Apnoea (OSA) in patients with Idiopathic Pulmonary Fibrosis (IPF) or restrictive end-stage lung disease (ESLD). Besides the known risk factors for OSA like high Body Mass Index (BMI), reduced static and dynamic volumes for IPF patients and reduced DLCO and low minimal O_2 saturation during sleep for ESLD patients were associated with higher Apnoea-Hypopnoea Index (AHI). The aim of our study was to determine potential predictive factors of OSA in patients with Fibrotic Lung Diseases (FLD).

Materials and methods: In this study, 49 patients with FLD and BMI $\leq$30 kg/m^2 were included. All patients underwent portable cardiorespiratory polysomnography (PSG) and were asked to fill in Epworth Sleepiness Scale (ESS). Their epidemiological, medication and subsidiary exams data were retrieved from their hospital records. Univariate and multivariate correlation models were obtained.

Results: Approximately 70% of patients had an AHI $\geq$5 events/h. In an univariate correlation model, AHI showed a statistically significant correlation with age, BMI, the duration of immunosuppressant treatment, and Forced Expiratory Volume in the first second (FEV1). Only BMI remained an independent predictor of OSA in a multivariate correlation model adjusted for the other statistically meaningful variables.

Conclusions: FLD patients, in general, show a prevalence of OSA superior to that of the general population. Excess of weight might predict a higher risk for OSA in FLD patients. Larger and more homogenous studies are warranted to clarify the associations between OSA severity and lung function impairment and the duration of immunosuppressant treatment.

1. Introduction

Obstructive Sleep Apnoea (OSA) is a common disorder affecting at least 2% and 4% of all adults, women and men, respectively [1]. There are several risk factors for OSA, including obesity, type 2 diabetes, atrial fibrillation, congestive heart failure, treatment refractory hypertension, stroke, nocturnal dysrhythmias, long-distance driving and pulmonary hypertension [2] which is a common complication of some Fibrotic Lung Diseases (FLD) [1]. Some of these risk factors can also be direct or indirect consequences of OSA since this disorder increases the patient's risk for cardiovascular events [2].

FLDs are a heterogeneous group of nosological entities whose general end-stage is pulmonary fibrosis and includes, amongst others: Idiopathic Pulmonary Fibrosis (IPF), Chronic Hypersensitivity Pneumonitis (CHP), Stage IV Sarcoidosis and Connective-tissue associated Interstitial Lung Diseases (ILD) like Rheumatoid Arthritis or Scleroderma. The majority of ILDs are chronic, progressive and present with a restrictive pulmonary pattern. Generally, they have a poor prognosis [3,4], particularly IPF, which is the focus of most of the studies on this theme. The 2011 guidelines on IPF [4] recognize that patients with this disease may have sub-clinical or overt comorbid

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conditions including OSA. That committee considered that at that time, there wasn't enough evidence supporting the use of Continuous Positive Airway Pressure (CPAP) in coexisting IPF and OSA. On the other hand, a multicentric study performed by Mermigkis et al. [5], revealed that good CPAP adherence by IPF patients with OSA contributed to improvement in quality of life, sleep quality, reduction of mortality rates and hospitalizations.

Several studies attempted to measure the prevalence of OSA in patients with IPF. The first was a retrospective study by Mermigkis et al., [5]. The authors found that 11 out of the 18 patients enrolled on the study presented with OSA. The first prospective study on this theme found that 88% of the 50 IPF patients had OSA [6]. Another study by Mermigkis et al. [7], in 34 treatment-naïve patients with newly diagnosed IPF found that 44% had mild OSA and 15% had moderate-to-severe OSA. A 2013 investigation by Pihtili et al. [8], on an heterogenous sample of patients with ILDs (17 patients with IPF, 15 with stage II–III sarcoidosis and 18 with pulmonary fibrosis due to scleroderma) documented a high prevalence of OSA (68%) with different prevalences seen in the different ILD subgroups, namely 82,3% in IPF patients, 66,6% in sarcoidosis patients and 55,5% in scleroderma patients.

Pulmonary fibrosis results from an exaggerated and persistent deposition of extracellular matrix within the lung parenchyma. The abnormal accumulation of scar tissue within the parenchyma characterizes FLD and can be seen in several ILD [1]. The fibrosis leads to a progressive decrease in pulmonary function, predisposing patients to hypoxaemia. In patients with coexisting OSA, the intermittent hypoxia observed during apnoea/hypopnoea events can lead to systemic inflammation and generalized vascular endothelial damage [9,10] that may contribute to the fibrotic process [1].

Accordingly, some studies tried to find a negative correlation between the decline in lung function that characterizes ILD patients and the Apnoea-Hypopnoea Index (AHI) used to define the severity groups of OSA. A large multicentric study registered pulmonary function status impairment and obesity as predictive factors of OSA in IPF patients [11]. Furthermore, Mermigkis et al. [7], found REM AHI to be inversely correlated with Total Lung Capacity (TLC) in a group of 34 treatment-naïve newly diagnosed IPF patients. In addition, Romem et al. [12], found that impaired Diffusion Lung Capacity for Carbon Monoxide (DLCO) and lower saturation during sleep were correlated with higher AHI amongst patients with restrictive end-stage lung disease (ESLD). A more recent prospective study by Gille et al. [13], on 45 newly diagnosed IPF claimed that AHI did not correlate significantly with demographic or physiological data.

Since ILD have a poor prognosis [3,4], the early diagnosis of OSA should be a primary goal for physicians [14] because CPAP treatment in a well-organized sleep centre has shown to improve quality of life and sleep, mortality rates and number of hospitalizations in patients with IPF and OSA [15]. Thus, timely diagnosis and management of OSA in patients with ILD may significantly impact the upper referenced outcomes of these patients. Accordingly, the aim of the present study is to determine potential predictive factors of OSA in patients with FLD through an exhaustive characterization of epidemiologic data, comorbidities, medication, pulmonary function status, blood gas analysis, six-minute walk test, echocardiogram, fibrosis score evaluated through High-Resolution CT Scan (HRCT) and Epworth Sleepiness Scale (ESS).

2. Materials and methods

2.1. Subjects

This study included patients currently followed in the Outpatient clinic of Interstitial Lung Diseases of São João Hospital Centre in Oporto. Of all patients followed, we approached 65 that met the following inclusion criteria: (1) Suffer from a FLD namely IPF, secondary Usual Interstitial Pneumonia (UIP), fibrotic Non-Specific Interstitial Pneumonia (fNSIP) (idiopathic or secondary), Pleuroparenchymal Fibroelastosis, or Stage IV Sarcoidosis documented by HRCT and/or by lung biopsy; (2) Have a stable disease: with no treatment change and no deterioration of FVC (>10%) and/or DLCO (>15%) for the last three months. We excluded patients who had: (1) Known risk factors for sleep disorders (BMI $\geq$ 30 kg/m^2, cranium-facial deformities and benzodiazepine use); (2) Neuromuscular diseases; (3) Severe psychiatric disorders; (4) Other chronic pulmonary diseases; and (5) Previously diagnosed OSA and patients who had medical prescriptions for long-duration oxygen therapy (ambulation liquid oxygen therapy not included).

From the 65 eligible patients, four were unavailable, 10 refused and 51 agreed to participate. The 51 patients enrolled signed the informed consent, underwent polysomnography level III (PSG III) and were asked to fill in the ESS questionnaire. From the 51 sleep studies, two were considered inconclusive and thus, those two patients were excluded from the study. The remaining 49 patients' epidemiological data, co-morbidities, medication, pulmonary function status, blood gas analysis, fibrosis score, echocardiogram and six-minute walk test results were retrieved, in a retrospective way, from their hospital records.

2.2. Polysomnography

The diagnosis of OSA was based on a six-channel overnight PSG III study (ResMed® Embletta™ Gold Portable Testing Device, Broomfield, USA), which included monitoring of heart rate, orinasal airflow by thermistor and cannula, chest wall and abdominal excursion, oxygen saturation by pulse oximetry and a position sensor. All sleep studies were manually scored by experienced sleep technicians and apnoea and hypopnoea were defined according to the criteria of the American Academy of Sleep Medicine (AASM) [2]. We used a 3% desaturation criterion for the definition of hypopneas.

2.3. Pulmonary function tests

Spirometry (Forced Expiratory Volume in the first second (FEV1), FVC and FEV1/FVC ratio), measurement of static lung volumes (TLC, Residual Volume (RV) and RV/TLC ratio by body box plethysmography) and measurement of DLCO by the single-breath technique were performed (Jaeger® Master Screen Body) with the patient in the seated position, according to approved standards [16].

2.4. Six-minute walk test

Six-minute walk test was performed using the protocol approved by the European Respiratory Society (ERS)/American Thoracic Society (ATS) Task Force [17].

2.5. Fibrosis score

The radiological extension (on HRCT) of IPF was evaluated through a fibrosis score, the same used in the Compositae Physiologic Index validation [18].

2.6. Statistical analysis

Data was described as mean and standard deviation (SD) for quantitative variables and was compared using Mann–Whitney or Kruskal–Wallis tests, as appropriate. Categorical variables were described as counts and proportions and compared using the chi-square or Fisher's exact test. To study the association between AHI and the clinical characteristics, Spearman correlation coefficients

were estimated. Multiple regression linear models were also computed. Statistical analysis was performed using SPSS version 24.0 software (SPSS Inc., Chicago, Illinois, USA). All probabilities were two tailed and p values of <0,05 were regarded as significant.

3. Results

The epidemiological, clinical, functional and radiologic characteristics as well as treatment data are shown in Table 1. Of the 49 patients that underwent PSG III, 34 (69,4%) had an AHI $\geq$ 5 events/hour. From those, 22 (64,7%) had mild OSA, 10 (29,4%) had moderate OSA and 2 (5,9%) had severe OSA. The overall PSG results are shown in Table 2. Despite the absence of statistical significance, the prevalence of OSA was higher amongst patients with IPF (10 out of 12–83,3%) compared to patients with CHP (16 out of 21–76,2%), Connective-tissue associated ILD (7 out of 10–70%), Stage IV Sarcoidosis (1 out of 4–25%) and Other ILD's (0 out of 2–0%), namely Pleuropulmonary Fibroelastosis and UIP secondary to Vasculitis.

In an univariate correlation model with all patients included, AHI showed a statistically significant correlation with age, BMI, the duration of immunosuppressant treatment and FEV1 (%) (Fig. 1), as well as the minimum O_2 saturation during sleep and the time spent under 90% of O_2 saturation (T90). In a multivariate correlation model adjusted for age, BMI, duration of immunosuppressant treatment and FEV1 (%), only BMI remained statistically significant.

4. Discussion

In this study we demonstrated not only the high prevalence of OSA in IPF patients (83,3%) but in all patients with FLDs (69,4%). A prevalence of 55,1% was previously reported in patients with restrictive ESLD [12] and the reported prevalence of OSA in IPF patients ranged from 59% to 88% [5–8]. In addition to IPF, patients with other FLDs also had a high prevalence of OSA (CHP – 76,2% and Connective-tissue associated ILD – 70%). The prevalence of OSA in Stage IV Sarcoidosis patients in our study was 25%, in contrast with prevalences ranging from 51,7% to 66,6% found in two studies on patients with Stage I/II/III (non-fibrotic) Sarcoidosis [8,19]. In our opinion, these findings could pave the way to further, more robust research on how and how much each ILD can influence the risk of developing OSA. In addition, those facts should prompt the active search for signs and symptoms of OSA in patients with FLD and screening whenever clinically justifiable.

Our ESS mean score (6,70 ± 5,21) was similar to those found on other studies [5,7,12,20], showing that patients with FLD usually do not report daytime sleepiness [15]; thus investigation showed that IPF patients are more likely to report daytime fatigue rather than daytime sleepiness [15]. These patients need to deal with long-lasting symptoms like dyspnoea and fatigue and, therefore, may perceive abnormal symptoms as normal [15], therefore explaining this contrast with the general population where the ESS was validated and considered as useful tool to access daytime sleepiness [2]. Another possible explanation for these findings is that ILD patients might have a higher threshold of sleepiness possibly due to an increased state of arousal provided by the amplified ventilatory drive that results from their chronic respiratory failure. Nevertheless, the question remains whether ESS is sufficiently sensitive to recognize sleepiness in patients with FLD, or whether objective methods (such as the Multiple Sleep Latency Test (MSLT)) should be used in this research field [15].

In a univariate correlation model, we found a statistically significant correlation between AHI and age, BMI, FEV1 (%), the duration of immunosuppressant treatment, minimum O_2 saturation during sleep and T90. We considered the last two associations as an evidence of the coherence of the results found and of the sample homogeneity regarding sleep variables, proving no other causes of hypoventilation coexist with apnoea/hypopnea events.

Age is not described as a risk factor for OSA in the 2009 AASM guidelines [2] but it can potentially predict the presence of OSA in patients with FLD as showed by our study. A Portuguese study documented a higher prevalence of OSA in males aged 65 to 74 years-old. However, the authors also raised the hypothesis of underdiagnosis of the disorder in younger people [21]. Our results are partially in line with these findings as the mean age of our patients was 67,16 ± 12,18 and may also be explained by the higher number of co-morbidities seen in older patients that can predispose to OSA.

In our study, the mean patients' BMI was 25,60 kg/m^2 as we excluded patients with BMI over 30 kg/m^2. We did that to eliminate a possible confounding factor of OSA as obesity is a well-known risk factor for OSA [2] and to evaluate if even the excess of weight could still be considered a predictive factor for OSA in these patients. We registered an overall predominance of mild OSA (65%) over moderate and severe OSA (combined 35%). On the current available literature

Table 1
Epidemiologic, medication and documentation of ILD severity of all patients enrolled.

Variables	
Age, years	67,16 ± 12,18
Male/female	26/23
BMI, kg/m^2	25,60 ± 2,93
Smoking habits	
Active smoker	4 (8,2%)
Ex-smoker	16 (32,7%)
Non-smoker	29 (59,2%)
UMA	36,38 ± 22,62
Interstitial lung disease	
IPF	12 (24,5%)
Connective-tissue associated ILD	10 (20,4%)
CHP	21 (42,9%)
Stage IV sarcoidosis	4 (8,2%)
Other ILD	2 (4,1%)
Corticosteroids	23 (46,9%)
Duration of corticosteroid treatment, days	925 ± 820,73
Immunosuppressant	19 (38,8%)
Duration of immunosuppressant treatment, days	600 ± 867,73
Pulmonary function status	
FEV1, %	89,26 ± 23,89
FVC, %	86,07 ± 18,89
FEV1/FVC, %	80,34 ± 9,56
TLC, %	84,38 ± 14,84
DLCO, mmol/min/kPa	3,59 ± 1,55
Blood gas analysis	
PaO_2, mmHg	79,61 ± 10,71
$PaCO_2$, mmHg	38,66 ± 5,12
Six-minute walk test	
Desaturation, %	8,27 ± 5,07
Distance, metres	405 ± 124,78
Fibrosis score (HRCT)	10 ± 3
Echocardiogram	
Pulmonary hypertension	6 (17,1%)

Table 2
ESS and polysomnography data of all patients enrolled.

Sleep-related variables	
Epworth sleepiness scale (ESS)	6,70 ± 5,21
Polysomnography	
AHI	11,34 ± 9,86
Apnoeas	4,39 ± 5,10
Hypopneas	6,95 ± 7,34
Respiratory disturbance index (RDI)	11,52 ± 10,72
Minimum O_2 saturation, %	82,96 ± 6,95
Average O_2 saturation, %	92,85 ± 2,85
T90, %	14,37 ± 24,74

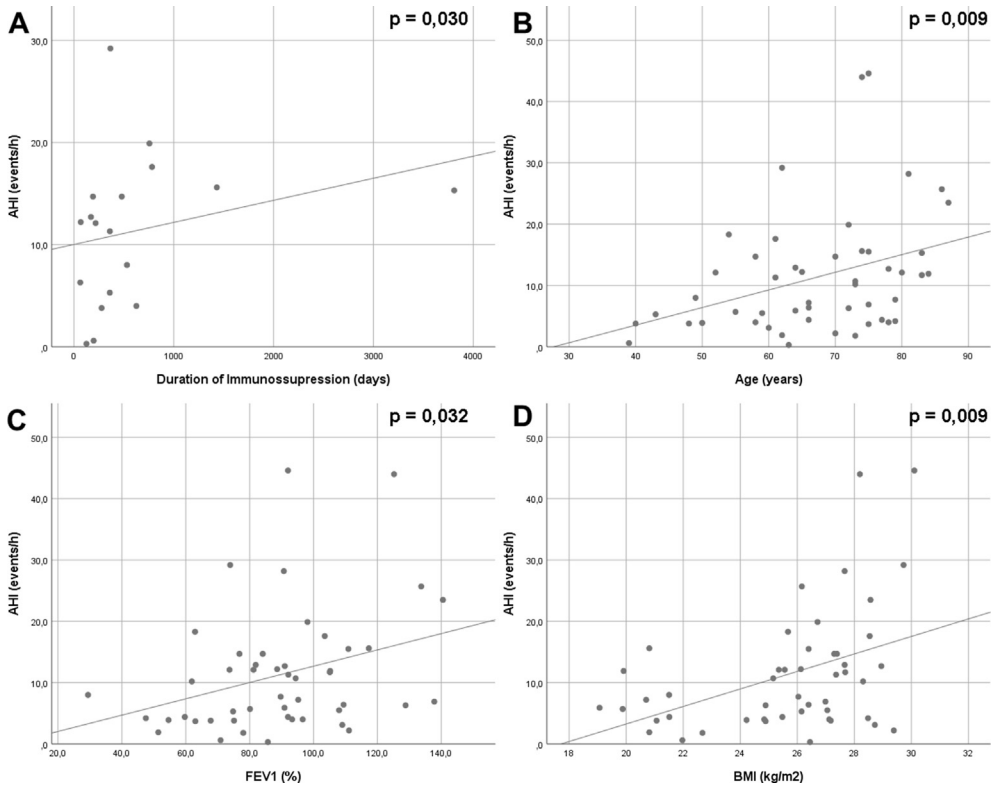

Fig. 1.. Univariate correlation models. Scatter Plot A shows the correlation between AHI and the duration of immunosuppresssant treatment ($p = 0,03$). Scatter Plot B shows the correlation between AHI and age ($p = 0,009$). Scatter Plot C shows the correlation between AHI and FEV1 (1%) ($p = 0,032$). Scatter Plot D shows the correlation between AHI and BMI ($p = 0,009$).

there are no other studies that considered obesity as an exclusion criterion. However, an investigation on 34 newly-diagnosed IPF patients who had a mean BMI similar to ours (27,3 kg/m2) also showed a predominance of mild cases of OSA (mean AHI of 9,4) [7]. Furthermore, on that study, they divided the patients into no OSA, mild OSA and moderate-to-severe OSA groups and presented a descriptive analysis with the moderate-to-severe group having a mean BMI of 30,5 kg/m2 (mean AHI of 24,6 events/h) while the mild OSA group had a mean BMI of 26,6 kg/m2 (mean AHI of 9,2 events/h). We presented similar results concerning the predominance of mild OSA amongst IPF patients but it a slightly higher percentage 66,7%. In contrast, two older studies on IPF patients with mean BMI's over 30 kg/m^2 had 45% [7] and 20% [6] of mild cases, revealing a predominance of moderate-to-severe cases. This heterogeneity of results is partially explained by BMI and corticosteroid treatment differences between the studies, as a high BMI is a known risk factor for OSA [2] and corticosteroid treatment may increase the fat deposition on the neck area, thus increasing the risk of disease [11]. Our IPF patients were either treatment-naïve or treated with antifibrotic drugs (n = 3).

In addition, BMI was the only variable that remained an independent predictive factor for OSA after a multivariate analysis, thus revealing that excess of weight should be taken into account in FLD patients and that OSA should at least be screened in overweight patients with those diseases. Despite the financial and staffing constraints that subsist in our country, screening methods for OSA are widely available and relatively cheap for other countries. Therefore, and given the present results, some might find suitable to screen all patients with FLDs for OSA. To those, possible predictive factors might help to sort patients on eventual waiting lists for sleep exams.

Similarly to our study, Romem et al. [12], found that FEV1 (%) could predict OSA in patients with ESLD. However, they did not specify if that correlation remained significant when the analysis was performed only in patients with restrictive disease. Mermigkis et al. [5], also reported a trend for inverse association between FEV1 values and AHI, and a statistically significant negative correlation between FEV1 values and REM AHI, in IPF patients. Although the mechanism why abnormal lung function can lead to increased prevalence of OSA remains unclear, the reduced upper airway stability and its increased resistance secondary to decreased lung volumes may play an important role in facilitating the collapse of the airway, especially during REM sleep in which the inactivity of respiratory accessory muscles diminishes the residual capacity of the lungs [11,22–25]. In our opinion, the loss of statistical significance in these parameters when a multivariate model was used can be attributed to the small and heterogeneous sample seen in our study, therefore requiring more and larger studies to verify and clarify this association.

In the present study, the duration of immunosuppressant treatment seemed to be correlated with AHI but its significance decreased in a multivariate analysis. This is the first study to report this association. The majority of our patients undergoing immunosuppressant therapy had a connective-tissue associated ILD (like rheumatoid arthritis and scleroderma) or chronic hypersensitivity pneumonitis (CHP). Most of the studies concerning sleep problems in patients with these conditions focus on the sleep deprivation and fragmentation (which lead to poor quality of sleep) caused by other features commonly found on those patients rather than the screening and diagnosis of OSA.

Although different degrees of immunosuppression and different pharmacological agents are applied, there was one study reporting a positive correlation between cumulative tacrolimus exposure and insomnia on this specific subgroup of patients [26] and another one reporting an increased risk of OSA in patients who underwent lung

transplant [27]. The increased risk of OSA documented on this last study was accompanied by an increase of weight, BMI, neck circumference and blood pressure. The increase in neck circumference might indicate larger deposits of fat tissue around the neck which provide a possible explanation to why immunosuppressant treatment might increase the risk of developing OSA.

Furthermore, the loss of statistical significance of this parameter when a multivariate correlation model was used was due to the low number of patients submitted to immunosuppressant treatment ($n = 19$). We can speculate that a study with more patients in those conditions could clarify this association.

Despite the small and heterogeneous sample, we reported an overall high prevalence of OSA as well as in IPF and CHP patients. Excess of weight might predict a higher risk of OSA in patients with FLD. Larger studies with more homogeneous samples are warranted to clarify the associations between AHI and FEV1 and AHI and the duration of immunosuppressant treatment.

Ethical standards

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Conflict of interest

The authors declare that they have no conflict of interest.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.020.

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