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Sleep Apnea Management in "Possible IPF" and "Idiopathic NSIP": A Case-Series

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Abstract

Purpose: The clinical course of patients with possible idiopathic pulmonary fibrosis (IPF) and idiopathic non-specific interstitial pneumonia (NSIP) is not well understood. While these patients are clinically followed for disease progression before rendering therapy, the import of sleep-disordered breathing on the disease course is unknown.

Methods: Retrospective analysis of possible IPF and idiopathic NSIP patients seen at a single center with review of clinical data pertinent to therapy for co-morbid sleep-disordered breathing was done.

Results: 7 patients with possible IPF based upon radiologic possible UIP patterns (5 male and 2 female) and 6 patients with idiopathic NSIP (5 female and 1 male) were followed for an average duration of 40 and 30 months respectively. 6/7 patients with possible IPF required continuous positive airway pressure (CPAP) therapy for sleep-disordered breathing and out of this 5/6 were compliant with therapy. Of idiopathic NSIP patients, 2/6 presented with acute exacerbations. All 6 patients required therapy for OSA out of which 5/6 were treated with CPAP and 1 treated with supplemental oxygen. Patients with possible IPF appeared to stabilize their disease following treatment of OSA and none of the study patients experienced any recurrence of acute exacerbations on CPAP therapy.

Conclusions: OSA can be an important problem in patients with possible IPF and idiopathic NSIP. Treatment with nocturnal CPAP therapy in these patients with concomitant OSA may result in stability of underlying interstitial lung disease.

Keywords: Idiopathic interstitial pneumonias; Idiopathic pulmonary fibrosis; Obstructive sleep apnea; Continuous positive airway pressure

Introduction

Idiopathic interstitial pneumonias represent a difficult group of diseases where the disease evolution is unpredictable and there are no good treatment options. Sleep-related hypoxemia is well-described in patients with interstitial lung disease although benefit of treating OSA on the course of fibrotic disease is unknown [1]. Poor sleep quality in patients with fibrotic disorders especially idiopathic pulmonary fibrosis (IPF) contributes to poor daytime functioning [2,3]. Sleep quality is in IPF patients is affected by nocturnal hypoxemia, the severity of which correlates with daytime measures of physical and social functioning [3].

Besides sleep-related hypoxemia, obstructive sleep apnea (OSA) is also being increasingly recognized in patients with interstitial lung disease (ILD) [4]. While initial reports focused on the high prevalence of OSA in IPF patients [5,6], recent reports indicate that OSA is prevalent in ILD from a variety of etiologies [4,7]. The implications of treating the commonly-encountered OSA in ILD patients are unclear. A benefit of treating OSA on progression of IPF has been shown [8], but similar results are unavailable for other types of ILDs. IPF can be a difficult diagnosis especially if radiologic patterns do meet criteria for UIP on high-resolution chest CT (HRCT) [9]. Such patients with radiologic possible usual interstitial pneumonia (UIP) are not always subjected to a definitive surgical lung biopsy and are followed expectantly. Similar to patients with IPF, patients with another idiopathic interstitial pneumonia – non-specific interstitial pneumonia (NSIP) are difficult management problems especially when occurring without a secondary cause such as underlying rheumatologic disease. In order to understand whether OSA is a significant comorbidity in these idiopathic interstitial pneumonias beside definitive UIP, this study was carried out. A retrospective analysis of patients with idiopathic NSIP and possible IPF (possible UIP by radiology) was done to assess the implications of the diagnosis of OSA and potential benefit of CPAP therapy in non-IPF interstitial lung disease.

Methods

Patient records with diagnoses of IPF, UIP and NSIP seen at Utah Valley Pulmonary Clinic between 2006 and 2011 were reviewed. All patients with defined or undifferentiated connective tissue diseases were excluded based on serology testing that included testing for rheumatoid factor, anti-nuclear antibodies, Jo-1 antibody, Scl-70, SS-A/SS-B antibodies, anti-RNP and evaluation for symptomatology consistent with rheumatoid arthritis, scleroderma, Sjogren's syndrome, polymyositis-dermatomyositis, and mixed connective tissue disease.

Of patients with idiopathic interstitial pneumonias, patients with a definite UIP-pattern on HRCT or on surgical lung biopsy (that suggested the diagnosis of IPF) were excluded. Patients with a possible UIP or an NSIP appearance on the CT scans were selected for further review. Clinical history, radiological abnormalities, and pulmonary function abnormalities at baseline and on follow-up were reviewed including acute exacerbations and use of specific immunosuppressive therapy. Acute exacerbations were defined as an acute clinical change with worsening of dyspnea occurring in less than a 4 week period characterized by new chest radiographic opacities that were not felt to be secondary to infection, embolic disease or heart failure [10]. Chest CT scans were reviewed by a radiologist blinded to the clinical data and radiologic diagnoses of possible UIP and NSIP were accorded based upon 2011 IPF consensus guideline criteria [9].

In order to assess the benefit (or lack of) on the course of the underlying interstitial lung disease from treatment of sleep-disordered breathing, only patients with follow-up PFT and CT scan data for more than one year were included.

Results

13 patients were given diagnoses of possible IPF or NSIP based upon clinical and radiological features (Tables 1 and 2) based on extensive review of records of ILD patients going back 5 years. Out of 57 ILD patients reviewed, only 19 patients met criteria for diagnosis of possible IPF or idiopathic NSIP. Out of these 19 patients, only 13 patients had representative CT abnormalities consistent with possible UIP or idiopathic NSIP and had relevant follow-up data for more than 1 year with CT scans and pulmonary function tests. All patients with chronic interstitial lung disease are typically evaluated for sleep-disordered breathing at this center because of either a clinical history of snoring, abnormal nocturnal oximetry or daytime symptoms of fatigue and/or sleepiness. The reasons for polysomnography (PSG) in each of these patients were not fully documented in their medical records and no screening questionnaires such as STOP-BANG or Epworth Sleep questionnaire were consistently admnistered.

Of the 7 patients with possible IPF (Table 1), only one patient underwent a non-diagnostic transbronchial biopsy. Diagnosis of possible IPF was made solely on basis of CT scan findings of possible UIP (9). Of the 6 patients with idiopathic NSIP (Table 2), four had the diagnosis confirmed on surgical lung biopsy while the other two patients underwent transbronchial biopsies that did not reveal abnormalities inconsistent with NSIP.

Characteristic	Patients with OSA n=5 (AHI mean 38.2)	Patient without OSA n=1	Patient with OSA but not on therapy n=1 (AHI 53)
Age (mean ± SD)	74.6 ± 7.2	71	64
BMI (mean ± SD)	27.2 ± 1.8	21	28.4
Sex	3:2 (M:F)	F	M
Duration of dyspnea (years) (mean ± SD)	4 ± 3.7	No reported dyspnea	1
Duration of PFT follow up (months)	28.2 ± 10.7	25	63
FVC (mean) Initial Final	2.65 ± 0.53 2.58 ± 0.52	2.94 2.85	4.11 3.15
DLCO (mean) Initial Final	13.5 ± 1.74 13.04 ± 1.36	14 12.4	23.2 16.6
CT abnormalities Duration of follow up Mean (range) Significant change	24 (12-45) No (one patient had some worsening of traction bronchiectasis)	63 No	25 No
Medication use Opiates Benzodiazepines Proton-pump inhibitors	3/5 None 3/5	No No No	Yes No Yes

Table 1: Characteristics of patients with possible IPF (Abbreviations: IPF – Idiopathic pulmonary fibrosis; OSA – Obstructive sleep apnea; AHI – Apnea-hypopnea index; BMI – Body mass index; PFT – Pulmonary function test; FVC – Forced vital capacity in liters; DLCO – single breath carbon monoxide diffusion capacity in ml/min/mmHg (CO))

All patients were Caucasian. All were non-smokers except patient 4 in idiopathic NSIP group who had a smoking history of 2 pack-years. The mean age in the possible UIP group was 72.6 years with a male to female ratio of 5:2 (Table 1). In comparison, the mean age in the idiopathic NSIP group was 61.2 years with a female to male ratio of 5:1 (Table 2). The mean duration of dyspnea was longer in patients with possible UIP as compared to those with NSIP due to two of the patients in the NSIP group presenting with acute exacerbations (Tables 1 and 2).

Patient	1	2	3	4	5	6
Age (years)	52	68	50	68	51	78
Sex	F	F	F	F	M	F
BMI	44	27.4	30.2	32.7	35.3	27
Duration of dyspnea (years)	0.75	0.5	0.1	1	2	0.5
Acute exacerbation	Yes	Remote	Yes	No	No	No
Duration of PFT follow up (months)	26	33	40	15	38	58
FVC (liters) Initial Final	2.62 2.52	3.19 2.78	0.92 2.21	2.35 2.13	2.26 2.14	1.9 1.69
DLCO Initial Final	17.2 19.3	11.7 10.4	5.0 16.9	16.6 11.8	16.3 15	12.4 6.4
6 MWT Distance (m) Desaturation below 88%	366 yes	480 yes	443 no	420 yes	480 no	322 no
CT findings Duration of follow up(months) Progression	11 Improved	12 Mild worsening	24 Improved	13 No changes	16 Very mild worsening	54 Worsened
Use of daytime oxygen	Yes	Yes	no	no	no	Yes
Medication use Immunosuppression Proton-pump inhibitors	Azathioprine Yes	Prednisone Yes	Azathioprine No	None Yes	None Yes	Mycopheno-late Yes
AHI	51	12	5	7	9.6	4.7

Table 2: Characteristics of patients with idiopathic NSIP (Abbreviations: NSIP – Nonspecific interstitial pneumonia; AHI – Apnea-hypopnea index; BMI – Body mass index; PFT – Pulmonary function test; FVC – Forced vital capacity in liters; DLCO – single breath carbon monoxide diffusion capacity in ml/min/mmHg (CO); 6MWT – 6 minute walk test.)

Patients with possible IPF were followed for a longer duration with only 1/7 patients showing significant disease progression. 5/7 patients with possible IPF and documented sleep apnea received CPAP therapy and on follow up, showed stability in lung function and CT abnormalities. A similar course was noted in the one patient without evidence of OSA on polysomnography (Table 1). The patient with OSA who refused CPAP therapy showed significant decline in both forced vital capacity and diffusion capacity over a five-year period but did not show any significant progression of disease based on CT appearances (Table 1). None of the patients in the possible UIP group experienced acute exacerbations or significant lower respiratory tract infections. None of the patients used supplemental oxygen during daytime even though two patients showed desaturations below 88% on the six-minute walk test.

2/6 patients with idiopathic NSIP presented with acute exacerbations; these patients presenting with acute exacerbations required hospitalization and underwent surgical lung biopsy and treatment with high-dose steroids. Following clinical improvement on steroids, they were maintained on oral azathioprine therapy for nearly two years after which the azathioprine was tapered off. Two other patients in the NSIP group were treated with immunosuppressive therapy for disease progression based on worsening CT scans, dyspnea and pulmonary function tests. Only 2/6 patients in the idiopathic NSIP group were followed without any evidence of disease progression on CT scans or PFTs. 3/6 patients with idiopathic NSIP required supplemental oxygen during day and night. All patients in the idiopathic NSIP group were diagnosed with OSA. All patients had mild OSA except patient 1 that had severe OSA based on an AHI of 51 (Table 2). Except for patient 6 who had an AHI of 4.7, all other

patients received CPAP therapy in addition to other treatments. None of the patients experienced any acute exacerbations over the duration of follow-up including the ones that presented with acute NSIP exacerbations at initial contact.

Table 3 details the polysomnographic details of patients with possible IPF and idiopathic NSIP. Patients with possible IPF tended to have more severe degree of obstructive sleep apnea (all of them had apnea-hypopnea indices of 15 or more) and majority of them appeared to tolerate CPAP therapy well. Patients with idiopathic NSIP tended to have mild degree of OSA. Consistent with greater severity of OSA, patients with possible IPF tended to have greater sleep fragmentation, decreased REM and slow sleep time and lesser sleep efficiency as compared to idiopathic NSIP patients (Table 3). Significant oximetric desaturation was noted during these PSG studies in both possible IPF and idiopathic NSIP groups (Table 3). Compliance data available on patients after a year of therapy showed that nearly all patients with possible IPF and idiopathic NSIP used CPAP for more than 4 hours a night for more than 90% of the time of the duration of CPAP data download.

	Possible UIP (n=6)	Idiopathic NSIP (n=6)
AHI mean ± SD	36.2 ± 15.3	14.9 ± 17.9
Arousal index mean ± SD	20.2 ± 12.5	9.5 ± 4.7
PLMS index mean ± SD	17.4 ± 29.7	25.3 ± 52.4
Desaturation index mean ± SD (Percentage time below 89%)	28.6 ± 23.4	10.6 ± 20.4
Sleep efficiency mean ± SD (%)	72.5 ± 17.3	77.3 ± 12.2
Sleep stages (Percentage of TST) Stage II (%) Slow wave sleep stage (%) REM stage (%)	65.2 ± 14.2 15.8 ± 12.1 11.3 ± 7.1	56.5 ± 15.5 24.5 ± 12.5 15.9 ± 7.3

Table 3: Polysomnographic details in patients with possible IPF and idiopathic NSIP (Abbreviations: IPF – Idiopathic pulmonary fibrosis; NSIP – Nonspecific interstitial pneumonia; AHI – Apnea-hypopnea index; PLMS – Periodic limb movement; TST – Total sleep time; REM – Rapid eye movement.)

Discussion

During evaluation for ILD, many patients are rendered diagnoses of UIP and NSIP based on CT findings [9,11,12]. If these patients do not meet definitive CT or pathology criteria for UIP, then a diagnosis of possible IPF is considered [9]. Both possible IPF and idiopathic NSIP are difficult management situations where disease course has to be understood before therapeutic decisions can be confidently made [9,12]. While patients with idiopathic NSIP can behave like NSIP secondary to connective tissue disease [13], patients with possible IPF may not evolve like IPF patients and in those not undergoing definitive surgical lung biopsies, watchful expectancy of disease course is done [14].

Given the unpredictable clinical course of IPF and NSIP, there may be potential benefit in addressing co-morbidities in these disorders. The typical comorbidities that occur in these patients are similar to what is seen in IPF patients and include gastro-esophageal reflux disease (GERD), pulmonary hypertension and OSA [15]. Unlike other comorbidities such as GERD [16] and pulmonary hypertension [17], the impact of OSA on ILD is unclear. Given the high prevalence of obstructive sleep apnea in ILD patients, there may be particular benefit from addressing OSA in patients with ILD. Prevalence rate for OSA in one study that included sarcoidosis and scleroderma patients was 68% [4]. For IPF patients, studies have shown OSA prevalence ranging from 59-88% [5,6].

The association of OSA to non-IPF idiopathic interstitial pneumonias is not known. One study examining the association of OSA and GERD in fibrosing lung diseases included 19 fibrotic NSIP patients [7]. We report the first study examining the association of OSA in patients with idiopathic NSIP and possible IPF. This study does not answer the degree of association of OSA in idiopathic interstitial pneumonias because of the small numbers of patients, the selection bias from study population being drawn from a single site and because of inclusion of patients with only established follow-up visits. This descriptive analysis does however demonstrate that OSA can be an important comorbidity in patients with both possible IPF and idiopathic NSIP. To answer the question of prevalence of OSA in idiopathic interstitial pneumonias, a study of unselected IPF and NSIP patients (with and without symptoms of sleep disordered breathing) needs to be performed. The common finding of OSA in idiopathic interstitial pneumonias may be explained in part by the elderly population in which these fibrotic lung diseases are commonly encountered. The prevalence of OSA increases with age [18] and the average age of patients in idiopathic NSIP is in the 50s and of possible IPF in the 70s [9,12]. Secondly, increasing body-mass index (BMI) can predispose to OSA [19] and 4/6 patients with NSIP had BMI>30 that may have increased their propensity to OSA. While the presence of chest restriction in interstitial lung disease can impose higher inspiratory pressure gradients predisposing to dynamic obstruction following upper airway skeletal muscle relaxation during sleep, studies on IPF patients have not consistently shown a relation between measures of chest restriction and AHI [5,6].

The impact of treating OSA in patients with idiopathic interstitial pneumonias has not received attention until recently [5,6,20]. While there may be preliminary evidence that treating OSA in patients with IPF may improve long-term survival [8], such data does not exist for

patients with possible IPF or idiopathic NSIP. Our study suggests that possible IPF patients may benefit from treatment of concomitant OSA. In our treated patients, there was little progression of disease and no acute exacerbations after initiation of CPAP therapy. Moreover, the duration of follow-up of possible IPF patients on CPAP in this study was substantial (Possible IPF patients – 40.2 ± 33.7 months) and no other interventions apart from CPAP and GERD therapy were rendered in these patients. Multiple mechanisms may explain a positive benefit of CPAP on the course of possible IPF. These include a reduction of GERD following CPAP therapy [21] - whether this benefit of CPAP extends to reduction in microaspiration that has been implicated in the injury-fibrosis cascade of IPF is unknown [22]. Secondly, stabilization of the intra-thoracic pressure swings occurring from OSA events may reduce the tractional injury on the peripheral lung lobules that are the seat of IPF progression [23]. Thirdly, positive pressure therapy may exert mechanical effects on the lower lung parenchyma and thereby influence the course of fibrosis. Studies have shown that stiffened lung promotes further contractile fibroblast proliferation that may favor pulmonary fibrosis progression [24]. Fourthly, the effects on chronic intermittent hypoxia or sustained hypoxia on course of lung fibrosis are unknown although there is burgeoning evidence on the effect of hypoxia on allergen-induced airway inflammation in rats [25].

This longitudinal study did not show a significant impact on the progression of idiopathic NSIP from OSA therapy. In our series, out of 6 patients with idiopathic NSIP, 2 presented with acute exacerbations while 2 others exhibited progressive disease and therefore these patients received immunosuppressive for halting disease progression. Idiopathic NSIP patients tend to be younger with a female predominance and excepting for one patient, all the NSIP patients in this study had mild OSA. Unlike possible UIP, idiopathic NSIP may have different pathogenetic mechanisms and this group may tend to behave like NSIP secondary to connective tissue disease [12,13]. While the benefits of treating mild OSA in idiopathic NSIP can be debated, no acute exacerbations were observed in the NSIP patients compliant with CPAP therapy.

Conclusion

This study reveals that OSA has to potential to affect the course of patients with idiopathic interstitial lung disease other than IPF. Patients with the radiologic pattern of possible UIP are a difficult population of patients especially if a surgical biopsy to definitively diagnose IPF cannot be done. Given that possible IPF is a difficult problem in the elderly for which no therapeutic alternatives are available, therapy of comorbid OSA offers the benefit to affect disease course favorably. Larger multicenter studies exploring the complex relationship between fibrotic lung disease and OSA are required to understand the benefits that can be obtained from CPAP therapy in these patients.

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