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Original Article

Frequency of Obstructive Sleep Apnea in Stage I and II Sarcoidosis Subjects Who Had No Corticosteroid Therapy

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Abstract

OBJECTIVES: The number of studies on the frequency of obstructive sleep apnea (OSA) in subjects with sarcoidosis is low. Therefore, we aimed to investigate the frequency and predictors of OSA in subjects with clinically stable stage I and II sarcoidosis who were not taking corticosteroid and/or immunosuppressive drugs. We also evaluated restless legs syndrome (RLS) and periodic leg movements in sleep (PLMS).

MATERIALS AND METHODS: Subjects with clinically stable stage I and II sarcoidosis and not receiving corticosteroid and/or immunosuppressive therapy were included in the study. Upper airway examination, lung function tests (forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], diffusing capacity of the lungs for carbon monoxide [DLCO]), and polysomnography were performed on all subjects. In addition, subjects' Epworth Sleepiness Scale (ESS) scores and the Pittsburgh Sleep Quality Index (PSQI) were recorded.

RESULTS: Of the total number of 46 sarcoidosis subjects (35 women, 11 men; age: 44.4±10.7 years; body mass index (BMI): 29.3±5 kg/m2), 28 (60.9%) were detected with OSA (67.8% mild OSA). The recorded ESS score of the subjects was low (2.6±3.2), whereas the sleep quality was poor in 36.9% of these subjects. Rapid eye movements (REM) related OSA was diagnosed in 14.2% of the OSA subjects. Age was the only factor related to OSA diagnosis in a logistic regression analysis (p=0.048). None of the subjects were diagnosed with RLS and PLMS.

CONCLUSION: OSA is common in stage I and II sarcoidosis subjects who did not receive corticosteroid therapy. The frequency of OSA diagnosis increases as the age of the subjects increases. Therefore, sarcoidosis subjects should be evaluated for OSA throughout the follow-up.

KEYWORDS: Obstructive sleep apnea, sarcoidosis, polysomnography, restless legs syndrome, periodic leg movements in sleep

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INTRODUCTION

The prevalence of obstructive sleep apnea (OSA) in the general population was reported to be between 2% and 4% [1, 2]. The OSA frequency in patients with interstitial lung diseases was reported to be between 17% and 88% [3-5]. However, the majority of the previous studies investigated OSA in patients with idiopathic pulmonary fibrosis. There are few studies about OSA in patients with sarcoidosis and most of the studies included subjects who were receiving corticosteroid treatment which may be a factor to increase the risk of OSA [6-10]. Therefore, the studies that clearly outline the OSA frequency in patients with sarcoidosis are not high in number. Motivated by this, we aimed to design a prospective study to determine the OSA frequency in subjects with stable stage I and II sarcoidosis, who did not receive corticosteroid and/or immunosuppressive treatments. In addition, we aimed to investigate the relationship between OSA and labial biopsy positivity, lung function test results, and stage of the disease. Furthermore, we also evaluated the restless legs syndrome (RLS) and periodic leg movements in sleep (PLMS).

MATERIALS AND METHODS

This prospective study was conducted at İstanbul University, Department of Pulmonary Diseases, Sleep Laboratory. The study included 18- to 70-year-old subjects who were diagnosed with stage I and II sarcoidoses during the last year and never received immunosuppressive therapy. All subjects were informed about the study and the informed consent was obtained. The study was performed according to the principles of the Helsinki Declaration and was approved by the İstanbul University Institutional Board (2013/173).

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The exclusion criteria for the study were receiving treatment with corticosteroids and/or other immunosuppressive agents, prediagnosed neuromuscular disease or severe psychiatric disease, chronic kidney disease, heart failure, lower respiratory tract infection in the last month, and usage of drugs that are proved to affect sleep architecture (benzodiazepine, narcotic drugs, antihistamines).

Demographics, body mass index (BMI), cigarette usage, anthropometrics (neck-waist-hip circumferences, waist/hip ratio), significant comorbidities (hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, gastroesophageal reflux, etc.), extrapulmonary involvement of sarcoidosis, sleep-related symptoms, labial biopsy results of each subject were recorded. The BMI was calculated using Khosla and Lowe's Formula (weight/height^2). Subjects with BMI ≥30 kg/m^2 were considered obese. Stages of sarcoidosis were determined by chest x-ray [11]. Upper airway examination was performed on all subjects.

Spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO) test were performed (ZAN 74N) following the approved standards [12]. Spirometric measurements (forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC ratio) were documented in alignment with the predicted value. The FEV_1/FVC >80% and FVC <80% is categorized to be a restriction, and FEV_1/FVC <70% is categorized to be obstruction. DLCO <80% is classified as pathologic.

The Epworth Sleepiness Scale (ESS) questionnaire was filled by the subjects, and the ESS score of ≥10 was regarded as an innovative value for excessive daytime sleepiness [13]. The Pittsburgh Sleep Quality Index (PSQI) questionnaire was used for evaluating subjective sleep quality. The PSQI total score of >5 indicated poor sleep quality [14].

Polysomnographic Evaluation

Polysomnography was performed using Compumedics E device. The sleep stages and respiratory events were scored according to the AASM 2012 guidelines [15]. Obstructive apnea was defined as a cessation of airflow ≥90% compared with baseline for ≥10 seconds when there was evidence of persistent respiratory effort. Hypopnea was defined as an amplitude reduction of ≥30% in airflow for ≥10 seconds that was associated with an oxygen desaturation of ≥3% or with arousal. Polysomnography records were scored by a trained technician and interpreted by a sleep specialist. OSA was diagnosed if the apnea-hypopnea index (AHI) was ≥5/hour along with the presence of a characteristic sleep apnea symptom. The OSA severity was categorized as mild (AHI: 5-14/hour), moderate (AHI: 15-29/hour), or severe (AHI ≥30/hour). Rapid eye movements (REM) induced OSA was diagnosed when total AHI was ≥5/hour and the ratio of REM AHI to non-REM AHI was ≥2 [16]. Diagnostic criteria of positional OSA were defined with the scores of total AHI ≥5/hour, supine AHI/nonsupine AHI ≥2 [17]. PLMS and RLS were scored following the AASM guidelines (1).

MAIN POINTS

- Obstructive sleep apnea (OSA) is common in subjects with clinically stable stage I and II sarcoidosis who did not receive corticosteroid and/or immunosuppressive therapy. Of all patients 28 (60.9%) were detected with OSA (67.8% mild OSA).
- The frequency of OSA diagnosis increases as the age of the subjects increases.
- Rapid eye movements (REM) related OSA was diagnosed in 14.2% of the OSA subjects. None of the subjects were diagnosed with RLS and PLMS.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 21.0 software (IBM SPSS Corp.; Armonk, NY, USA). The subject characteristics are presented with descriptive statistics as the means±standard deviation (SD) or median (interquartile ranges) for nonnormally distributed variables or frequency (percentage) for categorical variables. The concordance of a normal distribution of all continuous variables was calculated using the Shapiro-Wilk test. If the data were not normally distributed, we used nonparametric tests for the dependent variables. Comparisons between groups were carried out using the Mann-Whitney U test or Student's *t*-test. Categorical variables were compared using Chi-squared test. The Spearman correlation coefficient was used to examine the relationship between ESS score, PSQI, pulmonary function tests, clinical data, and polysomnographic data. A logistic regression analysis was used to determine the related factors of OSA. A p-value less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 46 subjects (76.1% women, 23.9% men; mean age 44.4±10.7 years) were enrolled in the study. Of these subjects, 58.7% (n=27) had stage I and 41.3% (n=19) had stage II sarcoidosis. Mean BMI was 29.3±5 kg/m^2 (18-41). Half of the (54.3%, n=25) subjects were obese (BMI ≥30 kg/m^2) and 80% of these obese subjects were women. Characteristics of all subjects are given in Table 1. Smoking history was reported in 28.3% (n=13) of the subjects (mean: 11.7 pack/year) and 12 of them were ex-smokers.

Majority of the subjects (91.3%, n=42) had sarcoidosis diagnosis proven by a biopsy. Only four subjects (8.7%) were diagnosed according to typical clinical and radiological features. Labial biopsy was present in 43 subjects (93.5%) and 23.3% (n=10) of them revealed granulomatous inflammation. Diagnostic methods are presented in Table 2.

Extrapulmonary involvement of sarcoidosis was presented in 28.2% (n=13) of the subjects (skin, parotid, bone, adrenal gland, brain, eye). Comorbidities were reported in 58% (n=27) of the subjects. These comorbidities were hypertension (n=9), major depression (n=6), diabetes mellitus (n=6), hypothyroidism (n=4), and asthma (n=1). All subjects were under treatment and were stable for comorbidities.

Spirometric measurements were normal in the majority of the subjects (91.3%, n=42). Two subjects had a minimally restrictive pattern and two subjects had an obstructive pattern. Subjects with the obstructive pattern were women and had

Table 1. Characteristics of sarcoidosis subjects

	All subjects (n=46)	Women (n=35)	Men (n=11)	p
Age (year)	44.4±10.7 (23-64)	45.8±10.8	39.8±9.1	0.104
Body mass index (kg/m^2)	29.3±5.0 (18-41)	29.3±5.3	29±4.1	0.886
Duration of disease (month)	6.5±4.5 (1-12)	6.6±4.4	6.1±4.8	0.906
Neck circumference (cm)	35.7±2.9 (29-42)	34.8±2.4	38.5±2.5	<0.001
Waist / Hip ratio	0.85±0.05 (0.71-0.98)	0.83±0.4	0.91±0.04	<0.001

Table 2. Diagnostic methods of sarcoidosis in all subjects

	Number of subjects
Bronchoscopy (TBB, TBNA)	16 (34.7%)
Mediastinoscopy	13 (28.2%)
Clinical and radiological	4 (8.7%)
Skin biopsy	3 (6.5%)
Labial biopsy	3 (6.5%)
Bronchoscopy + labial biopsy	3 (6.5%)
Mediastinoscopy + labial biopsy	2 (4.3%)
Parotid gland biopsy + labial biopsy	1 (2.2%)
Skin biopsy + labial biopsy	1 (2.2%)

TBB: transbronchial biopsy; TBNA: transbronchial needle aspiration

no smoking history. DLCO was < 80% (range: 64%-77%) in nine of the subjects.

Most common findings of ear-nose-throat examination were septal deviation (28.2%), concha hypertrophy (13%), stage I and II tonsillar hypertrophy (100%). More than half of the subjects (58.6%) had Mallampati score III and IV.

At least one of the characteristic OSA symptoms (snoring, witnessed apnea or excessive daytime sleepiness) was present in 84.8% of the subjects. Most common symptom was snoring (69.5%). Witnessed apnea was present in only one subject. Mean ESS score was 2.6±3.2 (0-15) and only one of the subjects had excessive daytime sleepiness. Mean PSQI score was 4.8±3.2 (0-14) and 36.9% (n=17) of the subjects had poor sleep quality. There was a correlation between the PSQI score and ESS score, snoring, excessive daytime sleepiness, and unsatisfied sleep (r=0.422, p=0.003; r=0.437, p=0.002; r=0.337, p=0.022; and r=0.309, p=0.037, respectively). RLS was not found in any of the subjects.

Polysomnographic Data

All Subjects

Percentage of REM sleep decreased. Most of the respiratory events were hypopneas. In addition, arousal index increased. Mean AHI and ODI were higher during REM. Of all the subjects 60.9% (n=28) had OSA (Table 3). Ten of the remaining 18 subjects (55.6%) had primary snoring (AHI <5/hour with snoring). PLMS was not found in any of the subjects.

Subjects with OSA

REM sleep was decreased in the subjects with OSA. Percentage of sleep stages was in a normal range. Most of the respiratory events were hypopneas. Arousal index was increased. Mean AHI and ODI were higher during REM (Table 3).

Table 3. Polysomnographic parameters of all subjects and OSA subjects

	All subjects	OSA subjects
TST (min)	461.8±48.63	457.4±43.7
Sleep efficiency (%)	87.4±8.8	87.5±8.1
Light sleep (N1 + N2) (%)	61.2±10.7	60.4±10.7
Deep sleep (N3) (%)	27±11.1	28.5±12.0
REM (%)	11.7±5.4	11.2±5.5
Arousal index	18.9±7.4	21.4±7.0
AHI/hour	10.7±13.8	16.3±15.4
ODI	11.9±11.8	16.6±12.9
Mean SpO_2 (%)	94.5±2.1	93.8±2.2
Minimum SpO_2	86.3±5.3	83.7±28.9
Sleep time with SpO_2 <%90	4.8±12.6	7.6±15.6
PLM index	0.23±0.7	0.12±0.46

TST: total sleep time; REM: rapid eye movements; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; SpO2: oxygen saturation calculated by pulse oxymeter; PLMS: periodic leg movements in sleep

The OSA frequency was 54.5% (n=6/11) in men and 62.8% (n=22/35, p=0.728) in women. Obesity was present in 57% (n=16) of the subjects with OSA. However, the OSA frequency was similar between obese and nonobese subjects (64% vs 57.1%, p=0.764, respectively). The OSA frequency was also similar in subjects with and without granulomatous inflammation on labial biopsy (50% vs 66%, p>0.05, respectively). Nineteen (67.8% 19/28) of subjects had mild OSA. Moderate and severe OSA rates were 21.4% and 10.7%, respectively. Two subjects had REM-related OSA and two subjects were diagnosed with REM-related and positional OSA. Mean ESS score was 2.6±3.6 and PSQI score was 5.5±3.4. Only one of the subjects had ESS of >10.

Arousal index of all sarcoidosis subjects with OSA was ≥10/hour. Percentage of total sleep time with SpO_2 <90% was >20% in four of the subjects with OSA (range; 23%–57%). Two of these subjects had mild OSA, one had moderate OSA, and one of them had severe OSA.

Sarcoidosis subjects with and without OSA were similar in case of demographic characteristics, upper airway examination findings, labial biopsy results, pulmonary function tests,

ESS, and PSQI scores (Table 4). Waist circumference was significantly higher in the OSA group (p=0.029).

ODI and percentage of total sleep time spent with SpO_2 <90% were significantly higher for the group of subjects diagnosed with OSA.

The OSA frequency was positively correlated with age, neck and waist circumference, ODI, arousal index and negatively correlated with SpO_2 (r=0.463, p=0.001; r=0.316, p=0.032; r=0.309, p=0.036; r=0.748, p=0.000; r=0.492, p=0.001; r=-0.496, p<0.001, respectively). AHI was not significantly correlated with pulmonary function test variables. There was a negative correlation between ODI and FEV_1 (%) (r=-0.319, p=0.031). Sleep time spent with SpO_2<90% showed a negative correlation with FVC (%), FEV_1 (%), and FEV_1/FVC ratio (r=-0.325, p=0.028; r=-0.422, p=0.003; r=-0.404, p=0.005, respectively). There was a positive correlation between SpO_2 and FEV_1 (%), and SpO_2 and FEV_1/FVC ratio (r=0.339, p=0.021; r=0.427, p=0.003, respectively). A positive correlation was found between minimum SpO_2 and FVC (%), FEV_1 (%), FEV_1/FVC, DLCO (r=0.396, p=0.006; r=0.507, p<0.001; r =0.565, p<0.001; r =0.324, p=0.028, respectively). There was no relation between sarcoidosis stage and OSA diagnosis. There was a positive correlation between diabetes mellitus and OSA (r=0.311, p=0.036). In addition, there was a relationship between diabetes mellitus and stage of sarcoidosis (r=0.293, p=0.048), which was not verified with other comorbidities. When the clinical parameters (age, gender, waist/hip circumference ratio, BMI, FVC, FEV_1, DLCO, ESS score, PSQI score) were put into the logistic regression, only age was related with OSA in sarcoidosis subjects (p=0.048) (Table 5).

DISCUSSION

Few studies are evaluating the prevalence of OSA in subjects diagnosed with sarcoidosis. These studies revealed that the OSA frequency in patients with sarcoidosis is higher than the prevalence of OSA among population. Our study reveals that the OSA frequency in subjects with sarcoidosis is significantly high (60.9%).

In our study, we found that the most common symptom of OSA is snoring. A higher frequency of upper airway pathologies may be the reason for this. Although the OSA frequency was high, witnessed apnea was less than expected. Excessive daytime sleepiness is one of the common symptoms of OSA. However, the ESS score is not a good predictor for OSA and did not correlate with AHI [18]. Regardless of OSA, excessive daytime sleepiness is as well as common in sarcoidosis subjects independent of OSA [19]. In a study, 62 subjects with sarcoidosis were compared with 1,005 adults without sarcoidosis who were referred for polysomnography due to suspicion of OSA. Although the frequency of moderate and severe OSA was lower in subjects with sarcoidosis than controls (51% vs 71%), both ESS score and excessive daytime sleepiness were significantly higher in subjects with sarcoidosis (ESS score:11, excessive daytime sleepiness: 34%)

Table 4. Demographics parameters, upper airway examination, positivity of labial biopsy, pulmonary functions, ESS and PSQI of OSA and non-OSA subjects

	OSA subjects (n=28)	Non - OSA subjects (n=18)	p
Age (year)	47.8±9.3	38.9±10.5	0.004
Gender (Women/men)	22/6	13/5	0.440
BMI (kg/m^2)	30.3±4.4	27.6±5.6	0.079
Neck circumference (cm)	35.8±2.8	35.5±3.2	0.769
Waist / Hip rate	0.86±0.1	0.84±0.1	0.297
Cigarettes (pack/year)	18.3±25.3	4.08±2.5	0.187
Tonsillar Hypertrophy I (%)	85.7	83.3	0.570
Tonsillar Hypertrophy II (%)	14.2	16.6	0.570
Mallampati III-IV (%)	57.1	61.1	0.518
Septal Deviation (%)	28.5	27.7	0.613
Stage I sarcoidosis (%) / Stage II sarcoidosis (%)	57.1 / 42.8	61.1 / 38.8	0.518
Comorbidity (%)	71.4	50	0.174
Sleep complaints (at least one) (%)	100	83.3	0.570
Positive labial biopsy (%)	17.8	27.7	0.277
FVC (%)	99.3±15.8	102.4±16.7	0.533
FEV1 (%)	94.3±18.7	98.3±13.8	0.441
FEV1 / FVC	80.5±6.1	82.1±3.9	0.290
DLCO (%)	97±22.4	95.2±10.3	0.712
ESS score	2.6±3.6	2.5±2.5	0.875
PSQI total score	5.5±3.4	3.8±2.5	0.076

BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity of the lungs for carbon monoxide; ESS: Epworth Sleepiness Scale; PSQI: Pittsburgh sleep quality index

Table 5. Factors related with OSA in regression analysis

Factors	β	Standard error	p	95% Confidence interval	
				Lower bound	Upper bound
Age	-0.016	0.008	0.048	-0.032	0.000
Gender	0.015	0.254	0.954	-0.500	0.530
Waist/hip circumference	0.183	1.862	0.922	-3.959	3.594
BMI	-0.19	0.014	0.191	-0.049	0.010
FVC	-0.005	0.012	0.998	-0.025	0.025
FEV1	0.005	0.012	0.676	-0.020	0.030
DLCO	-0.003	0.006	0.560	-0.015	0.008
ESS score	0.008	0.024	0.753	-0.041	0.056
PSQI score	-0.033	0.025	0.200	-0.084	0.018

[19]. In our study, the OSA frequency was recorded to be high, but mean ESS score was low in subjects with sarcoidosis. Excessive daytime sleepiness was found in only one of the subjects. The ESS score threshold may differ according to gender and cultural features. In women, it was reported that ESS sensitivity was lower and threshold of daytime sleepiness was different [20]. In our study, there was women dominance and OSA severity was mostly mild. This may be the factor to explain low ESS scores. Although the ESS score was low, the sleep quality was poor in 36.9% of our subjects. There was a moderate correlation between ESS score and PSQI total score but two questionnaires were insufficient to predict OSA.

In general population, OSA and snoring were reported more frequent in men [21]. However, in most of the previous studies that evaluated OSA frequency in sarcoidosis, majority of subjects (>60%) were women [5, 7-9]. Similarly, the majority of our subjects were women. In contrast to the study by Turner et al. [7], the incidence of OSA in women and men was similar to our study.

OSA incidence increases with age. Mean age of sarcoidosis subjects with OSA has been reported between 44 and 51 years [5, 8, 9]. In our study, the mean age was 44.4±10.7 years. However, the age of the subjects with OSA was significantly higher than subjects without OSA. Age was found to be the only related parameter with OSA in our study.

Obesity is a risk factor for OSA. Most of the previous studies did not exclude obese subjects while evaluating OSA in idiopathic pulmonary fibrosis and sarcoidosis (3,8,19). Patterson et al. [19] found the OSA frequency to be 52% in sarcoidosis subjects with a mean BMI of 38 kg/m^2. In another study, the mean BMI was 37.5 kg/m^2 and OSA rate was 83% (8). In the study by Bingol et al. [9], BMI ≥30 kg/m^2 is considered as an exclusion criterion and OSA rate was 51.7%. Obesity was not an exclusion criterion of our study. More than half of our subjects were obese. However, the OSA frequency was similar between the obese and nonobese sarcoidosis subjects. The OSA frequency was also high in nonobese subjects with sarcoidosis.

Corticosteroids may increase the risk of OSA by causing obesity and upper airway muscle weakness. Previous studies reported that mean AHI was higher in subjects who were using corticosteroids but the OSA frequency was similar in the subjects irrespective of the use of corticosteroids [8, 9]. This study excludes the subjects using corticosteroids and other immunosuppressive drugs.

It is reported that light sleep increased, deep sleep and REM sleep decreased in subjects with interstitial lung diseases [3-5, 22]. In sarcoidosis subjects, respiratory events and desaturations were found more common in REM sleep [9, 19]. In our study, REM sleep decreased in all subjects and OSA subjects. Respiratory events and desaturations were significant during REM sleep.

Although the OSA frequency was high in interstitial lung diseases and sarcoidosis, most of the subjects have mild OSA [5, 9]. Similarly, most of our subjects had mild OSA. The reason for this may be the higher number of women in our study. Some studies showed that OSA severity is mostly mild in women compared to men [23, 24]. Previous studies reported a high frequency of REM-related OSA (52.9% in the study by Pihtili et al. [5] and 40% in the study by Bingol et al. [9]) in interstitial lung diseases and sarcoidosis. In contrast to the reported findings in the literature, we found a low frequency of REM-related OSA.

Decreased lung volumes in interstitial lung diseases may be a predictor for OSA [4]. Decreased lung volumes can reduce upper airway stability and increase resistance due to decreased traction on the upper way [25]. Mermigkis et al. [3] reported that there is a negative correlation between AHI and FVC in idiopathic pulmonary fibrosis. In that study, it was reported that total lung capacity showed a negative correlation with REM-AHI. In another study, Mermigkis et al. [26] reported that there is a positive correlation between DLCO and mean nocturnal saturation in subjects with idiopathic pulmonary fibrosis. However, the relationship between pulmonary functions and AHI has not been shown in the studies by Lancaster and Pihtili [4, 5]. Further, no relationship was detected between polysomnographic parameters and pulmonary function tests in the study by Bingol et al. [9] which evaluated only the subjects diagnosed with sarcoidosis. Our study revealed a correlation between pulmonary function tests and nocturnal oxygenation parameters (mean SpO_2, minimum SpO_2). In addition, a positive correlation was found between DLCO and arousal index. However, no correlation was found between AHI and pulmonary function tests.

The reason our study showed a weak correlation between pulmonary functions and sleep parameters might be that we included only the subjects with stage I and II sarcoidosis. Majority of our subjects had stage I sarcoidosis and pulmonary functions were mostly normal.

Factors predisposing to upper airway collapse and OSA include upper airway lesions. There are case reports of laryngeal sarcoidosis affecting the supraglottic larynx causing OSA. It is as well possible that sarcoid lesions in the tongue and epiglottis cause OSA [27, 28]. In our study, all of the subjects had upper airway examination but none of them had a suspicion for sarcoidosis involvement, so a biopsy was not regarded necessary. However, it should be kept in mind that sarcoidosis involvement of upper airways may still be present in the absence of macroscopic findings. Although oropharyngeal biopsy was not taken, most of our subjects had a labial biopsy. We hypothesized that labial involvement may be associated with upper airway involvement in sarcoidosis. However, we could not find a relationship between positive labial biopsy and the presence of OSA. Possibly this relationship could not be detected because the number of subjects was small. We could not have the chance to compare our results with the results of any other research since there were no other studies that evaluate the relationship between granulomatous inflammation on labial biopsy and OSA presence.

There is only one study reporting a high frequency of RLS and PLMS in sarcoidosis [10]. PLMS was found in 41% and RLS was found in 52% of subjects in that study. Neither PLMS nor RLS was detected in our study.

Strengths of our study are excluding subjects with advanced disease, including subjects who had no treatment except for nonsteroidal anti-inflammatory drugs, performing upper airway examination of all subjects, and being the first study to evaluate the relationship between OSA and labial biopsy.

Including subjects with early stages of sarcoidosis who were not using corticosteroids limited our sample size. On the other hand, not excluding subjects with obesity is a selection bias. In our study group, there was a high frequency of upper airway pathologies but none of them had macroscopic findings of sarcoidosis involvement. It should be kept in mind that sarcoidosis involvement of upper airways may still be present in the absence of macroscopic findings. So that not performing oropharyngeal biopsy was another limitation of our study. Additionally, the frequency of upper airway pathologies was similar between subjects with and without OSA. We did not include healthy control subjects, but the OSA frequency in middle-aged healthy women in the population was not high.

In conclusion, the OSA frequency was found high in subjects with clinically stable stage I and II sarcoidosis who do not receive corticosteroid and/or other immunosuppressive therapy. Age was the only parameter related to OSA. There was no relationship between labial biopsy positivity and OSA. Neither PLMS nor RLS was detected in our subjects.

Ethics Committee Approval: Ethics Committee approval for the study was obtained from the İstanbul University Institutional Board (2013/173).

Informed Consent: Written informed consent was obtained from the patients.

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