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SCIENTIFIC INVESTIGATIONS

The prevalence of obstructive sleep apnea in sarcoidosis and its impact on sleepiness, fatigue, and sleep-associated quality of life: a cross-sectional study with matched controls (the OSASA study)

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Study Objectives: Patients with sarcoidosis experience fatigue and excessive daytime sleepiness (EDS). However, the underlying pathomechanism is unclear. Studies suggested undiagnosed obstructive sleep apnea (OSA) to be an important contributor, but reliable data on prevalence and impact of OSA in sarcoidosis are scarce.

Methods: 71 adult patients with sarcoidosis, 1-to-1 matched to 71 adult controls according to sex, age, and body mass index were included. Participants underwent structured interviews (including Epworth Sleepiness Scale [ESS], Fatigue Assessment Scale [FAS], and Functional Outcome of Sleep Questionnaire [FOSQ-30]) and level-3 respiratory polygraphy. OSA was defined as apnea-hypopnea index ≥ 5 events/h. Prevalence of OSA was assessed and possible risk factors for OSA in sarcoidosis were investigated.

Results: Mild OSA (AHI ≥ 5 events/h) was prevalent in 32 (45%) sarcoidosis patients vs 22 (31%) controls (P = .040). Sarcoidosis patients presented higher ESS compared with matched controls (P = .037). FAS scores (median [quartile] of 21.5 [16, 27.5]) indicated fatigue in sarcoidosis patients. Patients with EDS (ESS ≥ 11) presented reduced FOSQ-30 results (median [quartile] of 16.7 [15.2, 17.8]). ESS, FAS, and FOSQ were not associated with AHI in sarcoidosis patients. Body mass index, sex, neck circumference, and NoSAS score were predictors for OSA in sarcoidosis.

Conclusions: The risk for mild OSA is 2.5-fold higher in sarcoidosis patients compared with matched controls. OSA seems not to be the reason for increased sleepiness or fatigue in sarcoidosis. Risk factors such as body mass index, sex, neck circumference, and NoSAS score can be used to screen for OSA in sarcoidosis patients.

Clinical Trial Registration: Registry: ClinicalTrials.gov; Name: Obstructive Sleep Apnoea in Sarcoidosis (OSASA); URL: https://clinicaltrials.gov/ct2/history/NCT04156789?V_2=View; Identifier: NCT04156789.

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BRIEF SUMMARY

Current Knowledge/Study Rationale: This is the first study investigating the prevalence of obstructive sleep apnea (OSA) in sarcoidosis patients compared with age-, sex-, and body mass index–matched controls, as a possible pathomechanism for the enhanced sleepiness and fatigue in these patients.

Study Impact: A 2.5-fold higher risk for OSA was shown in sarcoidosis. However, it seems not to be the reason for the increased sleepiness or fatigue in these patients.

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown origin, affecting all racial and ethnic groups and occurring at all ages.[1] Fatigue and excessive daytime sleepiness (EDS) are common symptoms in patients with sarcoidosis. In a large study population of over 1100 patients with sarcoidosis, 27% of patients presented severe fatigue or severe EDS using standardized examination tools such as the Epworth Sleepiness Scale (ESS) or the Fatigue Assessment Scale (FAS).[2] Fatigue and sleepiness are strongly associated with decreased quality of life and work capacity.[3] While the term "fatigue" is sometimes misused to describe also increased daytime sleepiness, these are 2 distinct clinical conditions. Distinguishing both is clinically relevant because etiology and treatment of these conditions may differ significantly.[4,5] The underlying pathomechanisms of fatigue in patients with sarcoidosis are not well understood and are likely to be multifactorial, encompassing active inflammation, metabolic disorders such as diabetes mellitus, anemia, thyroid dysfunction, small fiber neuropathy, or psychosocial conditions, such as depression, anxiety, sleep disturbance, and stress.[6] In addition, systemic treatment regimens used to treat sarcoidosis such as corticosteroids can be associated with increased fatigue.[7] In contrast, EDS might be caused by circadian rhythm disturbances,

psychiatric disorders, or sleep-disordered breathing (SDB).[2] The most prevalent form of SDB in the general population is obstructive sleep apnea (OSA), affecting up to 9% of women and 24% of men in the general population aged 30–60 years.[8] There is evidence that OSA might be an important trigger of EDS in patients with sarcoidosis.[9] Granulomatous inflammation in the upper airways, steroid-associated weight gain, and hypotonicity of the upper airway due to sarcoidosis-associated myopathy or neuropathy have been discussed as potential pathogenic mechanisms.[10,11] The prevalence of OSA in sarcoidosis is still unclear, ranging widely from 17% to 67% in previous studies.[9,12,13] The obvious differences between these reported prevalence rates are possibly due to small numbers of study participants, differences between the study cohorts in terms of age, sex, and body mass index (BMI), as well as missing or poorly matched control groups. However, since specific treatment strategies (eg, continuous positive airway pressure [CPAP] therapy) are available, the early diagnosis of OSA in sarcoidosis could play an important role in improving sleepiness and consecutively quality of life for those patients.[14] As a result, stronger evidence regarding the prevalence of OSA in patients with sarcoidosis may be of clinical importance. The primary objective of this study was to assess the prevalence of OSA in patients with sarcoidosis compared with a matched control group in Switzerland. The secondary objective was the investigation of possible clinical predictors for OSA in patients with sarcoidosis.

METHODS

Participants

Patients with sarcoidosis were recruited from 2 different sources: (1) via visits at the University Hospital Zurich and (2) via the sarcoidosis database of the University Hospital Zurich. Hence, patients with sarcoidosis were contacted directly by their treating physician, through a letter, or a personal phone call. Only patients with sarcoidosis diagnosed according to international American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (ATS/ERS/WASOG) guidelines were included.[15] Patients with sarcoidosis and controls were 1-to-1 matched in terms of sex, age (±5 years), and BMI (±5 kg/m^2). The formation of the control group was performed in 2 steps. In a first step, we used data of matched controls obtained from previous studies of our research group.[16] In a second step, control patients were recruited through word-of mouth recommendations and posters that were displayed only in the University Hospital Zurich. The control patients were partially included from former prevalence studies from our group (DOI: 10.1159/000502892 and 10.1136/thoraxjnl-2016-209560). The recruitment of the control group was continued until all patients with sarcoidosis were matched 1-to-1. Participants were not offered any material compensation for their voluntary agreement to take part in this study. All inclusion and exclusion criteria can be seen in the **Inclusion and Exclusion Criteria** in supplemental material.

The study was conducted in accordance with the Declaration of Helsinki and all participants gave written informed consent to participate. The Ethics Committee of the Canton of Zurich approved the study (BASEC-Nr 2019-01604) and the study is registered at www.ClinicalTrials.gov (NCT04156789).

Measurements

Sleep-related questionnaires

Epworth Sleepiness Scale. The ESS is a very short questionnaire intended to measure daytime sleepiness. The score comprises 8 questions on which the participant is asked to rate his or her probability of falling asleep in different situations. EDS was considered with scores ≥ 11 points.[17]

Fatigue Assessment Scale. The FAS is a self-reported questionnaire containing 10 specific fatigue questions that have been validated in patients with sarcoidosis.[6] Each item of the FAS is answered using a 5-point, Likert-type scale ranging from 1 ("never") to 5 ("always"). The FAS score ranges from 10 to 50. FAS scores between 10 and 21 indicate no fatigue and FAS scores from 22 to 50 indicate substantial fatigue. The minimal important difference (MID) is at least 4 points.[6]

Functional Outcomes of Sleep Questionnaire. The FOSQ-30 provides a specific status measure designed to evaluate the impact of disorders of excessive sleepiness on activities of daily living. It is frequently used as a measure of sleep-specific health-related quality of life. The participants are asked to rate the difficulty of performing a given activity on a 4-point scale (no difficulty to extreme difficulty). In 30 items, the FOSQ-30 assesses difficulty due to sleepiness in performing activities of daily living and recreational activities, which are categorized into the following 5 subscales: (1) activity level (9 items), (2) vigilance (7 items), (3) intimacy and sexual relationships (4 items), (4) general productivity (8 items), and (5) social outcomes (2 items). Subscale scores are summed up to produce a global score. The score ranges from 5 to 20 points. Higher scores indicate better functional status. A total score of < 17.9 points has been suggested as a cutoff for impaired sleep-specific quality of life.[14]

NoSAS score. The NoSAS score is a simple score enabling the identification of patients at risk of SDB. The score also helps physicians to decide which patients need further investigations. To do so, neck circumference, BMI, sex, age, and snoring have been evaluated as the scoring criteria. The score ranges from 0 to 17 points, allocates 3 points for a BMI between 25 and 29.9 kg/m^2 or 5 points for a BMI > 30 kg/m^2, 4 points for neck circumference > 40 cm, 4 points for being over 55 years old, 2 points for snoring, and 2 points for being male.[18] The patient has a high probability of SDB if their NoSAS score is 8 or higher.

Laboratory values

In the sarcoidosis group, the serum inflammation markers C-reactive protein (CRP), soluble interleukin-2 receptor (sIL-2R), and neopterin in addition to the serum disease activity marker angiotensin-converting enzyme (ACE) were measured at study visit or within 4 weeks prior to the study visit.

Spirometry and carbon monoxide diffusion capacity

Forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) in liters and percentage predicted were evaluated.

The measurement of carbo monoxide uptake was performed by a single-breath technique. Patients underwent pulmonary function testing and transfer factor of the lung for carbon monoxide (TLCO) measurement according to ATS/ERS guidelines.[19,20]

Home-based sleep study

A home-based sleep study was performed using the ApneaLink Plus device (ResMed Corporation, Poway, CA). This overnight respiratory polygraphy is a noninvasive medical examination technique, routinely applied to detect sleep-related breathing disorders. The participants were instructed in the usage of the device, so that they could install it on their own for the study night. The device records the patient's nasal respiratory pressure signal as a surrogate of nasal flow, respiratory movements by a thoracic impedance belt, and finger pulse oximetry. A blinded person not involved in the study scored the results of the sleep studies according to the current American Academy of Sleep Medicine (AASM) guidelines.[21] Apneas are defined as a cessation of airflow lasting > 10 seconds and hypopneas as a reduction in airflow of at least 30% lasting > 10 seconds, associated with a drop in oxygen saturation of ≥ 3%. OSA severity was quantified as the number of apneas/hypopneas per hour (apnea-hypopnea index [AHI]) and oxygen desaturations ≥ 3% per hour of sleep study (oxygen desaturation index [ODI]). AHI thresholds according to the AASM Task Force of AHI ≥ 5, ≥ 15, and ≥ 30 events/h will be used to define mild, moderate, and severe OSA, respectively.[22]

Data analysis and statistics

All results are shown as median (25%–75% quartiles) unless otherwise stated. Variables were tested for normal distribution using Shapiro-Wilk test. To detect an absolute difference in prevalence of approximately 15% with a power of 80%, assuming the prevalence in the control arm of 3%, 71 patients with sarcoidosis and 71 controls had to be measured. Differences in the sleep characteristics of patients with sarcoidosis and controls were analyzed by independent *t* tests, Wilcoxon rank-sum test and chi-square tests, as deemed appropriate. Conditional logistic regression analysis was used to compare the prevalence of OSA and EDS by matched pairs of sarcoidosis and control patients. Logistic regression analysis was used to assess possible risk factors for OSA in sarcoidosis.

Statistical analysis was performed with STATA 16.1 (StataCorp, College Station, TX). A 2-sided *P* value of < .05 was considered statistically significant.

RESULTS

Study participants

The study flow is presented in **Figure 1**. In total, 71 patients with histologically proven sarcoidosis and 71 controls, matched for age, sex, and BMI, were included in the final analysis. Patient characteristics are shown in **Table 1**. **Table 2** presents the specific characteristics of patients with sarcoidosis. Pulmonary involvement was present in 97% of the patients, while 69% showed extrapulmonary sarcoidosis. According to Scadding,[23] the majority of patients with sarcoidosis were diagnosed with stage II sarcoidosis, while only 3% showed pulmonary fibrosis (stage IV). Neither the serum inflammation markers (sIL-2R or neopterin) nor ACE were elevated. While FVC, FEV_1, and FEV_1:FVC were in normal limits (median [quartile] 94% predicted [pred.] [87–108], 91% pred. [82–106], 79% [72–82]), TLCO was slightly reduced (78% pred. [66.5–86.5]).

Prevalence of OSA, EDS, and fatigue

The prevalence of mild OSA (defined as AHI ≥ 5 events/h) was 45% (32 patients) in patients with sarcoidosis and 31% (22 patients) in matched controls (odds ratio [OR] 2.67; 95% confidence interval [CI] 1.04–6.81; *P* = .040). Moderate OSA (AHI ≥ 15 events/h) and severe OSA (AHI ≥ 30 events/h) were found in 9 (13%) patients with sarcoidosis vs 6 (8%) controls (OR 2.00; 95% CI 0.50–8.00; *P* = .327) and in 2 (3%) patients with sarcoidosis vs 1 (1%) control (OR 2.00; 95% CI 0.18–22.06; *P* = .571), respectively. ESS was higher in the sarcoidosis group as compared with the control group (median [quartile] ESS of 9 [6–11] vs 7 [4–9]; *P* = .037). Twenty-six (36%) patients with sarcoidosis and 16 (23%) controls showed ESS scores higher than 10 (OR 2.43; 95% CI 1.01–5.86; *P* = .048). The FAS in patients with sarcoidosis was a median (quartile) of 21.5 (16–27.5) points, indicating increased fatigue on a group level. Thirty-nine patients with sarcoidosis (55%) reported FAS scores ≥ 21 points. Sixteen (22%) of the patients with sarcoidosis reported concomitant sleepiness and fatigue. The sleep-specific quality of life measured by the total FOSQ-30 score was a median (quartile) of 18.1 (16.9–19.7) in all patients with sarcoidosis, while those with EDS (ESS ≥ 11) presented a median (quartile) FOSQ-30 score of 16.7 (15.2–17.8) (**Table 3**). In patients with sarcoidosis, there was a moderate, negative correlation between ESS and FOSQ-30 (*r* = –.57). ESS, FAS, and FOSQ-30 were not associated with AHI in patients with sarcoidosis (coefficient [Coef.] –0.22; 95% CI –0.70 to 0.27; *P* = .378; Coef. –0.10; 95% CI –0.42 to 0.22; *P* = .539; Coef. 1.00; 95% CI –0.31 to 2.32; *P* = .134). Scadding stadium, extrapulmonary sarcoidosis, CRP, and the biomarker ACE, neopterin and sIL2-R showed no association with FAS or ESS in patients with sarcoidosis (**Table S1** in the supplemental material).

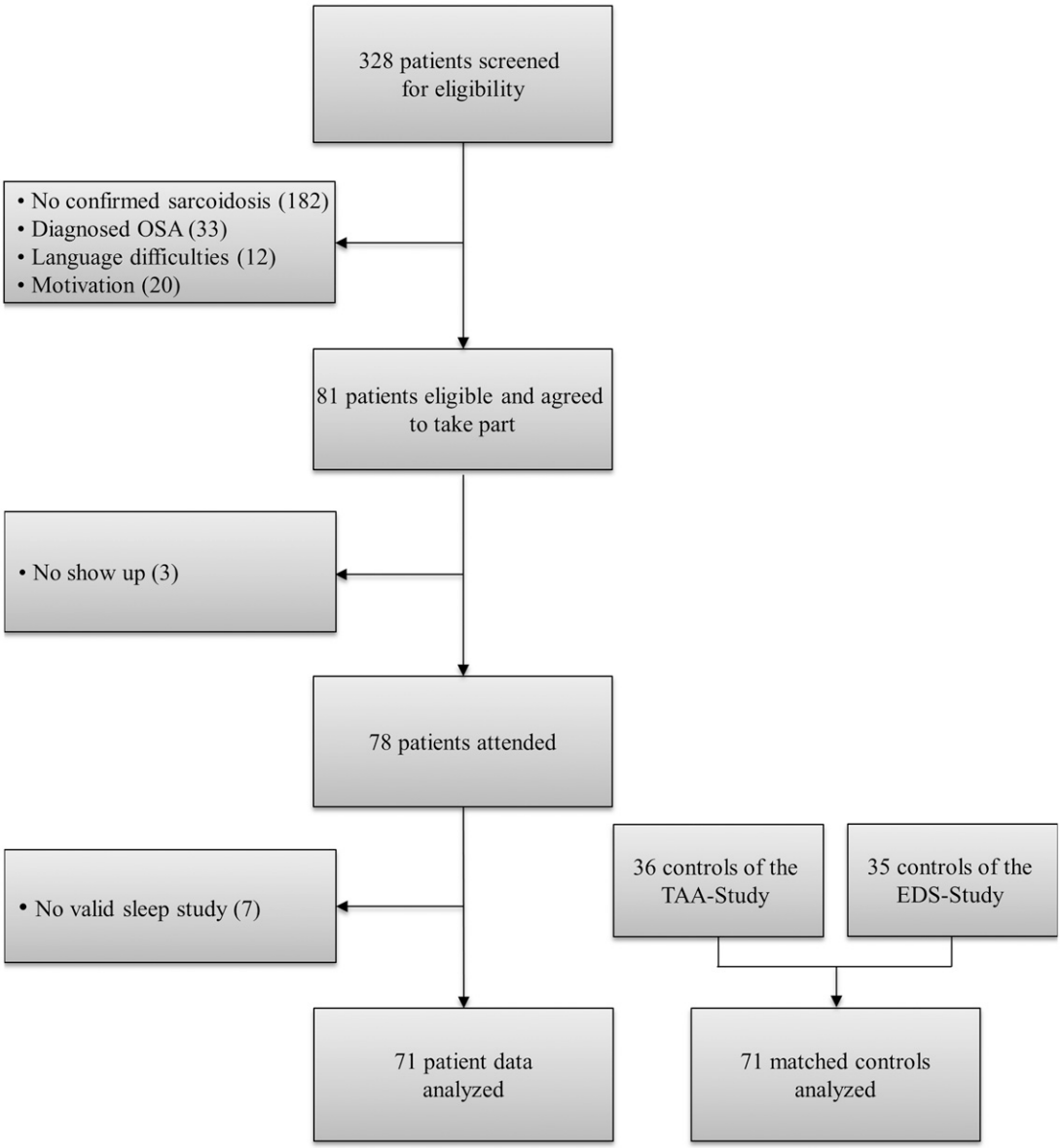
Sleep study parameters

Patients with sarcoidosis showed significantly higher respiratory event rates at night compared with matched controls with an AHI of 4.0 (1.3–9.3) compared with 2.5 (0.9–5.6) events/h (*P* = .047) and an ODI of 6.3 (2.3–13.8) compared with 2.2 (0.9–5.1) events/h (*P* < .001) (**Figure 2**). **Table 4** shows the remaining sleep study parameters.

Risk factors for OSA in sarcoidosis

The univariate logistic regression analysis of predefined possible risk factors showed that sex, BMI, neck circumference, and NoSAS score were positively associated with OSA in patients with sarcoidosis (OR 3.16; 95% CI 1.18–8.45; *P* = .022; OR 1.17; 95% CI 1.02–1.33; *P* = .022; OR 1.20; 95% CI 1.06–1.37; *P* = .005; OR 1.41; 95% CI 1.18–1.68; *P* < .001, respectively). Neither age, steroid use, Scadding stages, or inflammatory

Figure 1—Study flow.



EDS = Ehlers-Danlos Syndromes, OSA = obstructive sleep apnea, TAA = Thoracic aortic aneurysm.

markers, nor pulmonary function values including TLCO (% pred.) and FEV_1 (% pred.) were associated with OSA.

DISCUSSION

Fatigue and EDS are common clinical conditions in patients with sarcoidosis, leading to decreased quality of life and impaired work capacity.[2,3] Previous studies suggested that an increased prevalence of OSA might play an important role in the pathomechanism of these clinical conditions.[9] However, the number of studies addressing the prevalence of OSA in sarcoidosis is limited. Mavroudi et al[24] conducted a parallel cohort study including 21 patients with sarcoidosis with Scadding stage II/III. Mild OSA could be diagnosed in 52.4% of patients. Bingol and colleagues[25] analyzed 29 patients with sarcoidosis and diagnosed OSA in 51% of cases. Verbraecken et al[12] diagnosed OSA in 44% of 46 patients with chronic sarcoidosis. Mari et al[11] diagnosed OSA in 88% in a cohort of 68 patients with sarcoidosis using a level III home sleep apnea testing device. Eventually, the generalizability of these 4 studies is limited due to the small sample sizes or a missing control group. To date, the largest prospective study was conducted by Turner et al,[9] revealing an OSA prevalence of 17% in 83 patients with sarcoidosis compared with 3% in 91 controls.[9] Of note, the controls in the previous studies were not matched by age, sex, or BMI. Our study revealed a remarkably higher prevalence of mild OSA in patients with sarcoidosis and matched controls of

Table 1—Participant characteristics.

	Controls (n = 71)	Sarcoidosis (n = 71)
Age, y	51 (45–59)	50 (41–59)
Female/male, n (%)	33/38 (46/54)	33/38 (46/54)
Height, cm	174 (167–180)	172 (164–179)
Weight, kg	77 (67.0–88.5)	77 (65.0–88.0)
BMI, kg/m^2	25.4 (23.2–27.1)	25.7 (23.0–28.6)
Neck circumference, cm	38 (34–41)	38 (34–41)
Arterial hypertension, n (%)	17 (24)	10 (14)
Metabolic syndrome, n (%)	1 (1)	0 (0)
Diabetes, n (%)	3 (4)	0 (0)
Coronary artery disease, n (%)	10 (14)	3 (4)
Otolaryngological disease, n (%)	0 (0)	14 (20)

Values are median (25%–75% quartile) unless otherwise stated. BMI = body mass index.

Table 2—Characteristics of patients with sarcoidosis (n = 71).

	Values
Time since diagnosis, mo	33 (16–66)
Scadding stage, n (%)	
1	16 (23)
2	50 (72)
3	3 (4)
4	2 (3)
Pulmonary sarcoidosis, n (%)	69 (97)
Extrapulmonary sarcoidosis, n (%)	49 (69)
Cardiac sarcoidosis, n (%)	21 (30)
Neurosarcoidosis, n (%)	2 (3)
Ocular sarcoidosis, n (%)	8 (11)
Cutaneous sarcoidosis, n (%)	14 (20)
Lupus pernio, n (%)	3 (4)
SURT, n (%)	4 (6)
Renal sarcoidosis, n (%)	3 (4)
Spleen sarcoidosis, n (%)	5 (7)
Other manifestations, n (%)	30 (42)
Prednisone treatment, n (%)	24 (34)
Prednisone dosage (range), mg	1.25–40
Immunosuppressive treatment other than corticosteroids, n (%)	25 (35)
TSH, mU/L [0.30–3.18]	1.24 (0.92–1.94)
CRP, mg/L [< 5.0]	1.2 (0.6–2.5)
ACE, U/L [19.8–70.2]	43.1 (27.7–60.3)
Neopterin, ng/mL [< 2.5]	2.24 (1.79–3.04)
sIL-2R, pg/mL [< 477.0]	290.7 (224.4–396.5)
FVC, % pred.	94 (87–108)
FEV_1, % pred.	91 (82–106)
FEV_1:FVC, %	79 (72–82)
TLCO, % pred.	78 (66.5–86.5)

Values are median (25%–75% quartile) unless otherwise stated. Values in brackets are normal values. ACE = angiotensin converting enzyme, CRP = C-reactive protein, FEV_1 = forced expiratory volume during the first second, FVC = forced vital capacity, pred. = predicted, sIL-2R = soluble interleukin-2 receptor, SURT = sarcoidosis of the upper respiratory tract, TLCO = transfer factor of the lung for carbon monoxide, TSH = thyroid stimulating hormone.

45% and 31%, respectively, indicating a 2.5-fold higher risk for OSA in patients with sarcoidosis. The reason for the different prevalence rates might be that Turner et al performed polysomnography only in patients with an ESS of > 10. In fact, this approach mirrors the prevalence of OSA syndrome rather than the prevalence of patients with OSA (AHI > 5 events/h).[22] While some studies found also increased prevalence of moderate to severe OSA in patients with sarcoidosis, with rates up to 55%,[11] our findings suggest that the prevalence of moderate and severe OSA is not increased in patients with sarcoidosis. Reasons for this might be younger age, lower BMI, a lower number of patients treated with corticosteroids, and possibly patients with less severe sarcoidosis given the relatively low serum inflammation markers in our study.

The prevalence rate of mild OSA in our control group was high compared with rates deriving from other epidemiological studies in the general population, presenting rates of 9% in women and 24% in men.[8] Most of our control group were patients recruited in the cardiology and pulmonology departments of the University Hospital Zurich. Looking at the patients' characteristics, we ought to assume that our control group is not as healthy as the general population. Some of the comorbidities of the control group—eg, heart failure, cardiovascular disease, or obstructive ventilations disorders—are also associated with increased OSA prevalence.[26] This might have led to a selection bias, possibly responsible for the high OSA prevalence in our control group. Therefore, the true difference in prevalence and the risk for OSA might be even higher in the sarcoidosis group compared with the matched controls.

Fatigue is a common problem in patients with autoimmune diseases and affects 50%7[27] to 80%[28] of patients with sarcoidosis. Similarly, we found that 55% of the patients in our sarcoidosis group experienced fatigue, with FAS scores higher than 21 points. Although a patient may equate fatigue with sleepiness, these are 2 distinct clinical conditions. EDS should be considered as propensity to fall asleep during usual wakefulness hours, whereas fatigue may be expressed by feelings of apathy or weariness.[2] The pathomechanisms explaining fatigue in patients with sarcoidosis are not well understood and are likely to be multifactorial, including active inflammation, sleep disturbance, depression, and small fiber neuropathy.[6] In addition, systemic treatment regimens used to treat sarcoidosis such as corticosteroids can be associated with increased fatigue.[7] While epidemiological studies in the general population revealed a high prevalence of EDS (ESS ≥ 11) of up to 23%,[29] the prevalence seems to be even higher in patients with sarcoidosis.[5] However, data of prospective case-control studies are missing. In our study, the prevalence of EDS in patients with sarcoidosis

Table 3—Parameter of sleepiness, fatigue, and quality of life in patients with sarcoidosis (n = 71).

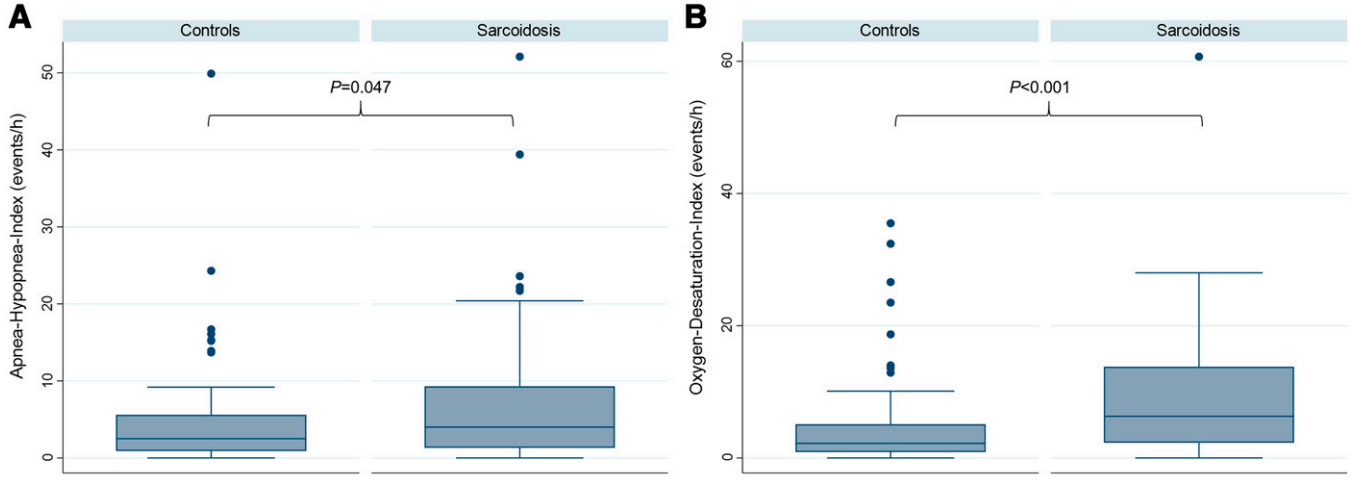
	Values
ESS, points	9 (6–11)
FAS, points	21.5 (16–27.5)
ESS > 10 points, n (%)	26 (36)
FAS > 21 points, n (%)	39 (55)
FOSQ-30	
FOSQ-30 total score of all patients, points	18.1 (16.9–19.7)
FOSQ-30 total score of patients with EDS, points	16.7 (15.2–17.8)
FOSQ-30 total score of patients without EDS, points	19.0 (17.6–19.8)

Values are median (25%–75% quartiles) unless otherwise stated. EDS = excessive daytime sleepiness, ESS = Epworth Sleepiness Scale, FAS = Fatigue Assessment Scale, FOSQ-30 = Functional Outcome of Sleep Questionnaire.

was 36% compared with 23% in the control group, supporting the findings of the study by Patterson et al.[5] The fact that 55% (n = 16) of the patients with sarcoidosis with EDS also reported increased fatigue could be proof of concomitant prevalence, similar etiology, or simply the challenge of distinguishing these conditions even in a study setting. While sleepiness is the cardinal symptom of OSA in the general population, AHI was not associated with increased sleepiness or fatigue in patients with sarcoidosis, supporting the idea that OSA might not play a major role in the pathophysiological mechanism of these symptoms in patients with sarcoidosis. In any case, patients with sarcoidosis with EDS presented a notable impairment of sleep-related quality of life measured by the FOSQ-30, underlining the importance of diagnosing underlying, aggravating conditions that might increase sleepiness and fatigue in those patients. While our results suggest no association of OSA with sleepiness and fatigue, Mari et al showed improved sleepiness (ESS change from baseline by 2.8; 95% CI 2.3–4.5 points) and fatigue (6.3; 95% CI 4.7–8.9) after CPAP treatment in 20 patients with sarcoidosis who have mild to severe OSA.[11] While over 50% of patients with sarcoidosis in this study had moderate to severe OSA, only 13% of the patients with sarcoidosis in our study had moderate to severe OSA. It is possible that more severe forms of OSA contribute more to increased FAS and ESS scores. Consecutively, a decent therapy in the form of CPAP therapy might be able to improve sleepiness and fatigue in those patients.

The underlying pathomechanism for the increased rates of nocturnal respiratory event rates is not clear. However, several hypotheses are discussed. Turner et al[9] found that patients with neurosarcoidosis and lupus pernio are at increased risk for concomitant OSA syndrome. Another hypothesis suggests that inflammatory involvement of the upper airways may lead to impairment of the upper airway patency.[30] Sarcoidosis of the upper airways occurs in 2–3% of patients with sarcoidosis.[31] It seems to be noteworthy that this hypothesis is based only on small sample sizes; hence, statistical power and clinical evidence are low. Since our sarcoidosis group only comprises a small number of patients with neurosarcoidosis, sarcoidosis of the upper airways, and lupus pernio, these findings cannot be assessed. Another theory suggests that the use of corticosteroids with the risk of weight gain might be responsible for higher OSA prevalence in patients with sarcoidosis.[10] Nevertheless, 1 study investigating the OSA prevalence in patients with sarcoidosis treated with systemic corticosteroids compared with controls treated also with corticosteroids for reasons other than sarcoidosis showed no statistical difference.[9] Accordingly, our study results did not show any association of steroid use and OSA prevalence. Observations in patients with interstitial lung diseases describe reduced caudal traction on the upper airway, enhancing collapsibility of the upper airways

Figure 2—Boxplots of AHI **(A)** and ODI **(B)** by patients with sarcoidosis and matched controls.



The threshold for obstructive sleep apnea is marked by the pointed line. Median (quartile) ODI was higher in the sarcoidosis group compared with the matched controls with 6.3 (2.3–13.8) vs 2.2 (0.9–5.1) events/h, P = .003. Median (quartile) AHI was comparable between the 2 groups with 4.0 (1.3/9.3) vs 2.5 (0.9/5.6) events/h, P = .110. AHI = apnea-hypopnea index, ODI = oxygen desaturation index.

Table 4—Comparison of sleep variables in both groups.

	Controls (n = 71)	Sarcoidosis (n = 71)	*P*
Duration of sleep recording, h	6:08 (5:01–7:07)	6:47 (5:10–7:51)	.035
AHI, events/h	2.5 (0.9–5.6)	4.0 (1.3–9.3)	.045
ODI, events/h	2.2 (0.9–5.1)	6.3 (2.3–13.8)	<.001
Number of apneas per night	4 (1–14)	3 (1–10)	.841
Number of hypopneas per night	10 (3–18)	18.5 (7–45)	.002
Obstructive apneas, %	52 (0–86)	50 (0–77)	.449
Central apneas, %	11 (0–47)	10 (0–50)	.483
ESS, points	7 (4–9)	9 (6–11)	.037
Time SpO_2 < 90%, min	5 (0–23)	5 (0–29)	.660
Time SpO_2 < 85%, min	0 (0–0)	0 (0–0)	.850
Time SpO_2 < 80%, min	0 (0–0)	0 (0–0)	.992
SpO_2 mean, %	93 (92–94)	93 (91–94)	.220

Values are median (25%–75% quartile) unless otherwise stated. AHI = apnea-hypopnea index, ESS = Epworth Sleepiness Scale, ODI = oxygen desaturation index, SpO_2 = peripheral oxygen saturation.

or ventilatory control system instability that could lead to extensive ventilation due to heightened chemo-responsiveness and subsequent increased respiratory events during sleep.[32] This hypothesis is supported by Bingol et al[25] who found significantly higher AHI and ODI in patients with sarcoidosis with parenchymal involvement. Our patients with sarcoidosis showed decreased TLCO on a group level, which could be due to parenchymal lung involvement. Nevertheless, neither TLCO nor the Scadding stage were associated with OSA prevalence. There are established risk factors for increased prevalence of OSA in the general population—for example, male sex, increased BMI, older age, higher neck circumference or waist-to-hip ratio, as well as craniofacial and upper airway abnormalities.[33] In concordance, we found that BMI, male sex, and higher neck circumference were also positively associated with an increased risk for OSA in patients with sarcoidosis. Hence, it does not come as a surprise that the NoSAS score was also positively associated with OSA prevalence in patients with sarcoidosis. The NoSAS score is a well-established screening tool for SDB in the general population, encompassing height, weight, age, sex, snoring status, and neck circumference as screening variables.[18] Our data suggest that the NoSAS score might also work as a screening tool for OSA in patients with sarcoidosis, but validation studies are necessary to confirm this hypothesis. Serum inflammation marker and serum ACE measured were not associated with OSA prevalence, leading to the conclusion that the systemic inflammation may not be responsible for the increased OSA prevalence. These biomarkers were also not associated with EDS and fatigue.

There are some limitations to this study. The study was performed as a single-center study and therefore could harbor the potential of selection bias. Moreover, the recruitment of the control group took place at the university hospital, leading to the inclusion of more comorbid patients and possibly therefore a higher prevalence of OSA in the matched control group than described in the literature. This might underestimate the true difference in the prevalence and the risk for OSA. The sleep studies were performed using a home sleep apnea testing (HSAT) device without detecting electroencephalographic changes during sleep. Consequently, arousals that might increase the AHI were not detected, leading to a potential underestimation of nocturnal respiratory event rates in this study. Third, the sarcoidosis group consisted of treated and untreated patients. Thus, a possible mitigation of any effect due to treatment of sarcoidosis cannot be excluded. This is supported by the fact that the serum inflammation markers and ACE were not significantly increased in the sarcoidosis group, suggesting that mainly adequately treated patients were included in this study.

CONCLUSIONS

The prevalence of mild OSA is considerably higher in patients with sarcoidosis compared with matched controls, although moderate and severe OSA was similar in both groups. In patients with sarcoidosis, AHI was neither associated with increased sleepiness nor with fatigue, suggesting that OSA might not contribute meaningfully to these symptoms. Larger multicenter studies are necessary to confirm these findings.

ABBREVIATIONS

ACE, angiotensin converting enzyme
AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
EDS, excessive daytime sleepiness
ESS, Epworth Sleepiness Scale
FAS, Fatigue Assessment Scale
FEV_1, forced expiratory volume during the first second
FOSQ-30, Functional Outcome of Sleep Questionnaire
FVC, forced vital capacity

ODI, oxygen desaturation index
OR, odds ratio
OSA, obstructive sleep apnea
pred., predicted
SDB, sleep-disordered breathing
SpO_2, peripheral oxygen saturation
TLCO, transfer factor of the lung for carbon monoxide

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