Fatigue and Excessive Daytime Sleepiness in Sarcoidosis: Prevalence, Predictors, and Relationships between the Two Symptoms

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Keywords

Sarcoidosis · Fatigue · Excessive daytime sleepiness · Dyspnea · Depression · Anxiety · Multivariate predictors

Abstract

Background: Fatigue is common among patients with sarcoidosis. The etiology of this problem is unknown and multifactorial. Fatigue can be confounded with excessive daytime sleepiness (EDS). Fatigue and sleepiness have rarely been studied simultaneously in sarcoidosis patients. **Objectives:** The aim of this study was the confounder-adjusted estimation of risks for severe fatigue and EDS in a large population of sarcoidosis patients and the development of multivariate predictors from this population. **Methods:** 1,197 German sarcoidosis patients were examined using the Epworth Sleepiness Scale (ESS), the Fatigue Assessment Scale (FAS), the Hospital Anxiety and Depression Scale (HADS), and the Medical Research Council (MRC) dyspnea scale. **Results:** 16.5% (123 patients) had EDS (ESS ≥ 16), 16.4% had severe fatigue (FAS ≥ 35), and 6.3% had both extreme findings. In a multivariate logistic regression model, predictors of the risk of EDS were a history of sleep apnea (odds ratio [OR] 2.46, 95% confidence interval [CI] 1.5–3.9), dyspnea MRC grade ≥ 2 (OR 2.29, 95% CI 1.5–3.5), and organ involve-

ment of 4–7 organs (OR 1.60, 95% CI 1.1–2.4). Significantly associated with higher risk of severe fatigue were the following: conspicuous depression (OR 5.95, 95% CI 4.1–8.7), conspicuous anxiety (OR 2.38, 95% CI 1.6–3.4), and muscle pain (OR 1.92, 95% CI 1.32–2.75). The logit models for severe fatigue with and without simultaneous EDS differed only slightly. **Conclusion:** An extreme form of fatigue and/or sleepiness was found in 27% of all sarcoidosis patients questioned. Because there is a certain overlap, both should be examined simultaneously to allow for a combined assessment.

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Introduction

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by the formation of epithelioid granulomas in affected organs. Incidence rates vary with age, gender, race, and geographical location. Sarcoidosis can affect all organs, but most patients present with pulmonary involvement and respiratory symptoms, such as dyspnea and persistent cough [1]. 30–50% of all sarcoidosis patients show extrapulmonary disease localizations [2, 3]. Sarcoidosis patients also suffer from a

wide spectrum of nonspecific symptoms, such as fatigue, weight loss, fever, night sweats, arthralgia, muscle pain, exercise limitations, and cognitive failure [4, 5].

Fatigue appears to be a frequent and characteristic feature of sarcoidosis and negatively affects quality of life [6]. Recent studies commonly use the Fatigue Assessment Scale (FAS) to measure the severity of fatigue, with reported frequencies of 50–85% for fatigue in sarcoidosis [4, 5, 7]. The etiology of this problem is largely unknown and usually multifactorial. A possible cause of fatigue in sarcoidosis patients is systemic inflammation. Other causes for a “reversible” fatigue may be metabolic disorders, such as diabetes mellitus, anemia, or thyroid dysfunction; psychosocial conditions, such as depression, anxiety, and stress; and treatment-induced fatigue, such as a complication of corticosteroid therapy [5]. A small-fiber neuropathy with chronic pain, which is more frequently observed in sarcoidosis patients, can also contribute to the development of fatigue [8].

Fatigue can also be the consequence of a nonrestorative sleep due to sleep apnea, restless legs syndrome, or insomnia [9, 10]. The prevalence of these sleep disorders is increased in sarcoidosis compared to the general population [11–13]. Patients with sleep apnea or insomnia commonly have a co-occurrence of insufficient sleep and excessive daytime sleepiness [14]. The term fatigue is often used incorrectly for excessive daytime sleepiness. Although there is an overlap between fatigue and excessive daytime sleepiness, these terms describe different symptoms. A patient with excessive daytime sleepiness will fall asleep in monotonous situations, whereas an individual with fatigue may express feelings of apathy or weariness rather than falling asleep [15].

Excessive daytime sleepiness may be the result of a number of extrinsic factors, such as poor sleep hygiene and psychotropic medication, or intrinsic causes, such as primary sleep disorders, circadian rhythm disturbances, psychiatric disorders, and physical illnesses [15]. The questionnaire most frequently used to assess sleepiness is the Epworth Sleepiness Scale (ESS).

Several epidemiological studies have determined a prevalence of excessive daytime sleepiness between 10.8 and 23% in the general population with an ESS >10 [16, 17]. Individuals with medical disorders, especially patients with rheumatic diseases or chronic obstructive pulmonary disease, have a higher prevalence of excessive daytime sleepiness than the general population [18–20]. Patterson et al. [13] observed that >50% of sarcoidosis patients had an ESS score >10 in a retrospective study.

Since fatigue can have very different causes, there is no standard therapy. Sleep disorders with the symptom excessive daytime sleepiness are a well-treatable cause of fatigue in sarcoidosis. It is, therefore, very important and clinically relevant to differentiate excessive daytime sleepiness from fatigue symptoms. For the initiation of a targeted therapy, it is desirable to have more information on possible other risk factors for fatigue and excessive daytime sleepiness and their combinations. This would also facilitate early detection of possible patients at risk. So far, it is unclear when fatigue needs to be treated. Fatigue and daytime sleepiness in sarcoidosis patients were generally studied separately and not correlated with the extent of severity of sarcoidosis. Previous work of our group demonstrated the extent of fatigue in sarcoidosis patients compared to the general population [21].

In this study, we report a confounder-adjusted estimation of risks for severe fatigue and excessive daytime sleepiness in a large population of sarcoidosis patients. The objectives of this study were:

- to determine the prevalence of severe fatigue and excessive daytime sleepiness in sarcoidosis patients;
- to investigate possible links between severe fatigue and excessive daytime sleepiness;
- to describe possible relationships between fatigue or sleepiness and clinical parameters, including anxiety and depression; and
- to derive multivariate predictors of fatigue and sleepiness in sarcoidosis patients.

Methods

Sample of Study Population

The study was conducted in collaboration with the German Sarcoidosis Society between July and September 2009. All members received a specially developed questionnaire together with a regular newsletter. This questionnaire included the ESS, the FAS, and the Hospital Anxiety and Depression Scale (HADS). In addition, we determined dyspnea with the Medical Research Council (MRC) dyspnea scale and recorded the number of organs affected by sarcoidosis as well as comorbidities. A total of 1,270 members (31%) returned the questionnaires together with an informed consent sheet authored by the Sarcoidosis Association; 73 questionnaires were not included because of missing data; 1,197 questionnaires were evaluated. The Ethics Committee of the University of Leipzig reviewed and approved the study.

Questionnaires

Epworth Sleepiness Scale

The ESS is an 8-item self-completion questionnaire which quantifies on a 4-point scale the perceived severity of daytime sleepiness and insomnia-related interference with daytime functioning in common situations of daily living [22]. The ESS total

score is the sum of ratings for the 8 items and ranges from 0 to 24. Values >10 are considered to indicate significant daytime sleepiness and values ≥16 indicate excessive daytime sleepiness.

Fatigue Assessment Scale
Initially developed by De Vries et al. [23], the FAS is a well-validated and reliable scale to measure fatigue in sarcoidosis. The questionnaire consists of 2 subscales with 5 questions each on the physical and mental aspects of fatigue. There are 5 answer options ranging from “never” to “always,” and the total score range is 10–50. Scores <22 indicate no fatigue; scores between 22 and 34 indicate mild-to-moderate fatigue, and scores ≥35 indicate severe fatigue [6].

Hospital Anxiety and Depression Scale
The HADS was developed by Zigmond and Snaith [24] in order to estimate anxiety and depression in somatically ill patients. The self-reporting validated instrument includes 14 items. A score of 8–10 is an indicator of the possible presence of anxiety and/or depression; a score of ≥11 is conspicuous, and the presence of anxiety or depression is likely.

MRC Dyspnea Scale
The MRC dyspnea scale is used to classify the severity of self-reported dyspnea in daily activities. Patients were categorized into 1 of 5 levels ranging from level 1 (“normal”) to level 5 (“too breathless to leave the house”) [25].

Statistical Analyses
Univariate odds ratios were computed, and statistically optimal multivariate logistic regression models were developed for the risks of excessive daytime sleepiness and severe fatigue by a stepwise model choice. The models were internally validated by Hosmer-Lemeshow goodness of fit tests and by analyses of the receiver operating characteristics (ROC) curve with and without Bootstrap cross-validation of the estimation of the AUC (area under the ROC curve). SAS version 9.4 was used for all analyses.

Results

The sociodemographic and clinical characteristics of the patients are shown in Table 1. Women were slightly older than men. Twenty percent lived without a partner, among them twice as many women (23.6%) as men (12.1%). The lungs of most sarcoidosis patients were affected (90.7%). Other organ manifestations were the skin (24.5%), lymphatic nodes (20.8%), eyes (16.0%), liver (11.8%), muscles (9.4%), nerves (9.0%), bones (8.8%), heart (7.9%), kidneys (5.0%), and others (15.9%). In 1,027 patients (85.8%), the diagnosis of sarcoidosis was histologically confirmed. In women, extrapulmonary involvement was more common than in men, and more organs were affected. Corticosteroid therapy was somewhat more common in men than in women.

Table 1. Sociodemographic and clinical characteristics

	Total group (n = 1,197)	Men (n = 414)	Women (n = 783)
Age, years	54.3±11.6	54.0±10.9	54.5±12.0
Age groups			
≤40 years	129 (10.8)	34 (8.2)	95 (12.1)
41–50 years	359 (30.0)	144 (34.8)	215 (27.5)
51–60 years	350 (29.2)	119 (28.7)	231 (29.5)
61–70 years	247 (20.6)	83 (20.0)	164 (20.9)
≥71 years	112 (9.4)	34 (8.2)	78 (10.0)
Partnership			
Living with a partner	950 (79.4)	361 (87.2)	589 (75.2)
Living without a partner	235 (19.6)	50 (12.1)	185 (23.6)
No information	12 (1.0)	3 (0.7)	9 (1.1)
BMI	27.6±5.7	27.2±4.4	27.8±6.3
Time since diagnosis, years	12.8±10.6	13.6±10.8	12.5±10.5
Use of corticosteroids	542 (45.3)	203 (49.0)	339 (43.3)
Organ involvement			
Only lung	413 (34.5)	160 (38.6)	253 (32.3)
Extrapulmonary	784 (65.5)	254 (61.3)	530 (67.7)
≥3 organs	384 (32.1)	117 (28.3)	267 (34.1)

Values are means ± standard deviations or n (%). BMI, body mass index (calculated as kg/m²).

Frequency of Fatigue, Daytime Sleepiness, and Anxiety and Depression by Severity
For daytime sleepiness (ESS), fatigue (FAS), and anxiety and depression (HADS) severity grades exist, which have been used to dichotomize the data [6, 22, 24]. We, therefore, classified all patients according to these categories (Table 2). Extreme manifestations of fatigue (FAS ≥35) were found in 16.4%, and extreme daytime sleepiness (ESS ≥16) was found in 16.5% of the examined sarcoidosis patients. For fatigue, an average of 26.2 ± 7.9 points was achieved on the FAS and 10.4 ± 4.9 points for daytime sleepiness on the ESS.

Formation of Subgroups with Excessive Daytime Sleepiness and Severe Fatigue
There is only a slight connection between excessive daytime sleepiness and fatigue (R² = 0.20); thus, a prediction of excessive daytime sleepiness from fatigue and vice versa is not possible. It is, therefore, useful to study excessive daytime sleepiness and fatigue as independent factors.

Four patient groups were formed to estimate the risks for excessive daytime sleepiness and severe fatigue. Group

Table 2. Classification of patients according to severity for fatigue, daytime sleepiness, and depression and anxiety

	Patients
<i>Fatigue</i>	
No fatigue (FAS 0–21)	30.3%
Mild fatigue (FAS 22–34)	53.3%
Severe fatigue (FAS 35–50)	16.4%
<i>Daytime sleepiness</i>	
No sleepiness (ESS 0–10)	50.0%
Moderate sleepiness (ESS 11–15)	33.5%
Excessive sleepiness (ESS ≥16)	16.5%
<i>Depression</i>	
No depression (HADS 0–7)	58.1%
Possible depression (HADS 8–10)	22.2%
Conspicuous depression (HADS ≥11)	19.7%
<i>Anxiety</i>	
No anxiety (HADS 0–7)	50.0%
Possible anxiety (HADS 8–10)	23.0%
Conspicuous anxiety (HADS ≥11)	27.0%

FAS, Fatigue Assessment Scale; ESS, Epworth Sleepiness Scale; HADS, Hospital Anxiety and Depression Scale.

1 (ESS <16 and FAS <35) consisted of 878 patients (73.3%) in whom neither fatigue nor daytime sleepiness showed excessive levels. Group 2 (ESS ≥16 and FAS <35) consisted of 122 patients (16.5%) with excessive daytime sleepiness, and group 3 (ESS <16 and FAS ≥35) included 123 patients (16.4%) with severe fatigue. Seventy-four patients (6.3%) of group 4 (ESS ≥16 and FAS ≥35) were characterized as having both severe fatigue and excessive daytime sleepiness. A ranking of the 4 groups cannot be performed; therefore, 3 binary prediction models for excessive daytime sleepiness and severe fatigue were developed individually and in combination.

Risk Assessment for Excessive Daytime Sleepiness and Severe Fatigue

Univariate Odds Ratios for the Risk of Excessive Daytime Sleepiness and Severe Fatigue

A description of the possible explanatory variables, including their univariate odds ratios, for the risk of excessive daytime sleepiness and severe fatigue is shown in Table 3. In the univariate analyses, a significantly increased risk for excessive daytime sleepiness was found for the following factors: body mass index ≥35, sleep apnea, dyspnea with a severity of MRC grade 2 to MRC grades 4–5, muscle pain, conspicuous anxiety, and conspicuous de-

pression. A significantly increased risk of severe fatigue was found for conspicuous depression, conspicuous anxiety, dyspnea according to MRC grade ≥3, and muscle pain.

Multivariate Logit Models for Excessive Daytime Sleepiness and Severe Fatigue

The statistically optimal multivariate logit models for excessive daytime sleepiness and severe fatigue are presented in Table 4. The associated odds ratios can be viewed as confounder-adjusted estimates for the risk of excessive daytime sleepiness or severe fatigue. Confounders are all variables contained in the logit model. Based on the extent of the described model goodness values, these logit models are to be regarded as predictors with sufficient internal validity. An increase in the odds ratios with increasing dyspnea levels and numbers of involved organs shows a minor accentuation of the somatic components in the model for excessive daytime sleepiness and might indicate a possible influence of disease severity.

With conspicuous depression and conspicuous anxiety, 2 psychological components are represented in the multivariate logit model for severe fatigue in a special way. They were significantly more frequent ($p < 0.0001$) in groups with severe fatigue than in the group of sarcoidosis patients without severe fatigue and daytime sleepiness (Fig. 1b). In groups with severe fatigue, more than half of the patients reported conspicuous anxiety and/or depression on the HADS questionnaire, which is reflected in the multivariate logit model for severe fatigue. Patients in the groups with severe fatigue (FAS ≥35) complained more frequently of muscle pain than patients in the group without severe fatigue and excessive daytime sleepiness (Fig. 1a). In the group with combined severe fatigue and excessive daytime sleepiness, 74% reported muscle pain. The prevalence was significantly increased both compared to the group with excessive daytime sleepiness alone ($p = 0.0327$) as well as compared to the group without severe fatigue and excessive daytime sleepiness ($p < 0.0001$).

Severe Fatigue in Combination with Excessive Daytime Sleepiness

In 74 sarcoidosis patients, we observed excessive daytime sleepiness combined with severe fatigue. Table 5 shows a summary of the possible explanatory variables, including their univariate odds ratios, for the risk of this constellation. A significantly increased risk of severe fatigue in combination with excessive daytime sleepiness was found for conspicuous depression, conspicuous anx-

Table 3. Univariate ORs for the risk of excessive daytime sleepiness (ESS ≥ 16) and for the risk of severe fatigue (FAS ≥ 35)

Variables	Total sample, <i>n</i> (%)	Excessive daytime sleepiness				Severe fatigue			
		ESS ≥ 16 , <i>n</i> (%)	OR	95% CI	<i>p</i> (χ^2 test)	FAS ≥ 35 , <i>n</i> (%)	OR	95% CI	<i>p</i> (χ^2 test)
Sex									
Male (ref.)	414 (35)	59 (14)	1			69 (17)	1		
Female	783 (65)	138 (18)	1.29	0.92–1.79	0.1344	127 (16)	0.97	0.70–1.33	0.8424
Age group									
≤ 40 years (ref.)	129 (11)	18 (14)	1			25 (19)	1		
41–50 years	359 (30)	58 (16)	1.19	0.67–2.11	0.5540	59 (16)	0.82	0.49–1.37	0.4472
51–60 years	350 (29)	77 (22)	1.74	0.99–3.04	0.0501	66 (19)	0.97	0.58–1.61	0.8971
61–70 years	247 (21)	36 (15)	1.05	0.57–1.94	0.8704	35 (14)	0.69	0.39–1.21	0.1903
≥ 71 years	112 (9.4)	8 (7.1)	0.47	0.20–1.14	0.0892	11 (9.8)	0.45	0.21–0.97	0.0379
Marital status (missing: <i>n</i> = 12)									
Married (ref.)	950 (80)	162 (17)	1			155 (16)	1		
Living alone	235 (20)	32 (14)	0.77	0.51–1.15	0.2025	39 (17)	1.02	0.69–1.50	0.9173
Employment status									
Employed or in education (ref.)	419 (35)	73 (17)	1			54 (13)	1		
Part-time or short-time worker	227 (19)	36 (16)	0.89	0.58–1.38	0.6125	33 (15)	1.15	0.72–1.83	0.5576
Missing or student	29 (2.4)	3 (10)	0.55	0.16–1.86	0.3261	6 (21)	1.76	0.69–4.53	0.2329
Unemployed	66 (5.5)	8 (12)	0.65	0.30–1.43	0.2832	16 (24)	2.16	1.15–4.07	0.0147
Retired	456 (38)	77 (17)	0.96	0.68–1.37	0.8334	87 (19)	1.59	1.10–2.31	0.0128
BMI group									
< 25 (ref.)	421 (35)	54 (13)	1			62 (15)	1		
25 to < 30	456 (38)	70 (15)	1.23	0.84–1.81	0.2838	63 (14)	0.93	0.64–1.36	0.6998
30 to < 35	200 (17)	39 (20)	1.65	1.05–2.59	0.0294	41 (21)	1.49	0.96–2.31	0.0707
≥ 35	120 (10)	34 (28)	2.69	1.65–4.38	< 0.0001	30 (25)	1.93	1.18–3.16	0.0082
Muscle pain									
No (ref.)	630 (53)	75 (12)	1			68 (11)	1		
Yes	567 (47)	122 (22)	2.03	1.48–2.78	< 0.0001	128 (23)	2.41	1.75–3.32	< 0.0001
Organ involvement									
≤ 3 organs (ref.)	1,014 (85)	149 (15)	1			153 (15)	1		
4–7 organs	177 (15)	45 (25)	1.98	1.35–2.90	0.0004	42 (24)	1.75	1.19–2.58	0.0042
≥ 8 organs	6 (0.5)	3 (50)	5.81	1.16–29.04	0.0155	1 (17)	1.13	0.13–9.70	0.9143
Arterial hypertension									
No (ref.)	745 (62)	113 (15)	1			110 (15)	1		
Yes	452 (38)	84 (19)	1.28	0.94–1.74	0.1223	86 (19)	1.36	0.99–1.85	0.0534
Diabetes mellitus									
No (ref.)	1,063 (89)	170 (16)	1			171 (16)	1		
Yes	134 (11)	27 (20)	1.33	0.84–2.08	0.2214	25 (19)	1.20	0.75–1.90	0.4486
Thyroid disorder									
No (ref.)	877 (73)	138 (16)	1			136 (16)	1		
Yes	320 (27)	59 (18)	1.21	0.87–1.69	0.2645	60 (19)	1.26	0.90–1.76	0.1797
Sleep apnea									
No (ref.)	1,093 (91)	159 (15)	1			167 (15)	1		
Yes	104 (8.7)	38 (37)	3.38	2.19–5.22	< 0.0001	29 (28)	2.14	1.35–3.39	0.0009
Sleep apnea with therapy									
No (ref.)	1,145 (96)	177 (15)	1			182 (16)	1		
Yes	52 (4.3)	20 (38)	3.42	1.91–6.11	< 0.0001	14 (27)	1.95	1.04–3.67	0.0356
Restless legs									
No (ref.)	1,011 (84)	157 (16)	1			151 (15)	1		
Yes	186 (16)	40 (22)	1.49	1.01–2.20	0.0434	45 (24)	1.82	1.25–2.65	0.0017
Pulmonary hypertension									
No (ref.)	1,159 (97)	186 (16)	1			184 (16)	1		
Yes	38 (3.2)	11 (29)	2.13	1.04–4.37	0.0348	12 (32)	2.45	1.21–4.93	0.0101
Dyspnea (MRC)									
MRC 1 (ref.)	449 (38)	36 (8.0)	1			49 (11)	1		
MRC 2	478 (40)	83 (17)	2.41	1.59–3.65	< 0.0001	65 (14)	1.28	0.87–1.91	0.2135
MRC 3	179 (15)	45 (25)	3.85	2.38–6.22	< 0.0001	48 (27)	2.99	1.92–4.66	< 0.0001
MRC 4–5	91 (7.6)	33 (36)	6.53	3.78–11.27	< 0.0001	34 (37)	4.87	2.90–8.17	< 0.0001

Table 3 (continued)

Variables	Total sample, n (%)	Excessive daytime sleepiness				Severe fatigue			
		ESS ≥16, n (%)	OR	95% CI	p (χ ² test)	FAS ≥35, n (%)	OR	95% CI	p (χ ² test)
Anxiety (HADS)									
0–10 (ref.)	871 (73)	116 (13)	1			85 (9.8)	1		
≥11	326 (27)	81 (25)	2.15	1.57–2.96	<0.0001	111 (34)	4.77	3.47–6.58	<0.0001
Depression (HADS)									
0–10 (ref.)	961 (80)	129 (13)	1			83 (8.6)	1		
≥11	236 (20)	68 (29)	2.61	1.86–3.66	<0.0001	113 (48)	9.72	6.91–13.66	<0.0001
Use of corticosteroids									
No (ref.)	763 (64)	122 (16)	1	0.80–1.50		123 (16)	1		
Yes	434 (36)	75 (17)	1.10		0.5623	73 (17)	1.05	0.77–1.44	0.7531

All *p* values are unadjusted. ESS, Epworth Sleepiness Scale; FAS, Fatigue Assessment Scale; OR, odds ratio; CI, confidence interval; BMI, body mass index; MRC, Medical Research Council scale; HADS, Hospital Anxiety and Depression Scale.

Table 4. Multivariate logit models for excessive daytime sleepiness and severe fatigue

Variables	Excessive daytime sleepiness				Severe fatigue			
	regression coefficient	SE	OR (95% CI)	<i>p</i>	regression coefficient	SE	OR (95% CI)	<i>p</i>
Intercept	−2.6276	0.1913			−2.9939	0.2096		
Age group (ref. <60 years)								
61–70 years	−0.5779	0.2206	0.56 (0.36–0.87)	0.0088	−0.4331	0.2366	0.65 (0.41–1.03)	0.0672
≥71 years	−1.3841	0.4032	0.25 (0.11–0.55)	0.0006	−0.9378	0.3772	0.39 (0.19–0.82)	0.0129
Organ involvement (ref. ≤3 organs)								
4–7 organs	0.4689	0.2085	1.60 (1.06–2.41)	0.0245				
≥8 organs	1.5671	0.8461	4.79 (0.91–25.16)	0.0640				
Sleep apnea								
Yes	0.8986	0.2409	2.46 (1.53–3.94)	0.0002				
Muscle pain					0.6450	0.1865	1.92 (1.32–2.75)	0.0005
Yes								
Dyspnea (MRC) (ref. MRC 1)								
MRC 2	0.8286	0.2169	2.29 (1.50–3.50)	0.0001	0.0850	0.2224	1.09 (0.70–1.68)	0.7024
MRC 3	1.1800	0.2603	3.25 (1.95–5.42)	<0.0001	0.5977	0.2646	1.82 (1.08–3.05)	0.0239
MRC 4–5	1.8177	0.3146	6.16 (3.32–11.42)	<0.0001	1.2869	0.3190	3.62 (1.94–6.77)	<0.0001
Anxiety (HADS)								
≥11	0.4731	0.1879	1.61 (1.11–2.32)	0.0118	0.8651	0.1906	2.38 (1.64–3.45)	<0.0001
Depression (HADS)								
≥11	0.4171	0.2025	1.52 (1.02–2.26)	0.0395	1.7835	0.1938	5.95 (4.07–8.70)	<0.0001

Model for excessive daytime sleepiness: the AUC was estimated to be 0.732 (Bootstrap-cross-validated 0.699). With *p* = 0.1647 (Hosmer-Lemeshow goodness of fit test), the model has a good fit; the Nagelkerke *R*² is 0.1549. Model for severe fatigue: the AUC was estimated to be 0.824 (Bootstrap-cross-validated 0.810). With *p* = 0.5975 (Hosmer-Lemeshow goodness of fit test), the model has a good fit; the Nagelkerke *R*² is 0.3098. SE, standard error; OR, odds ratio; CI, confidence interval; MRC, Medical Research Council scale; HADS, Hospital Anxiety and Depression Scale; AUC, area under the ROC curve.

xiety, dyspnea from MRC grade 3 to MRC grades 4–5, and for muscle pain. Table 6 describes the associated statistically optimal multivariate logit model.

As with the other 2 models, this logit model is also considered to be an internally sufficiently valid predictor due to the reported model quality data. In the model for severe fatigue combined with excessive daytime sleepiness,

both severe dyspnea (MRC grades 4–5) and the combination of conspicuous anxiety and depression have a particular influence on the risk. In terms of predictability, models 2 and 3 are almost equally good. After a bootstrap cross-validation for a more realistic assessment than by simple reclassification, the AUCs are 0.70 (model 1), 0.81 (model 2), and 0.82 (model 3).

Fig. 1. Prevalence of muscle pain (**a**) and conspicuous anxiety and depression (**b**) in the 4 groups with and without severe fatigue and excessive daytime sleepiness. Significant differences were analyzed with the χ^2 test and are Bonferroni adjusted. The significance level is shown. ESS, Epworth Sleepiness Scale; FAS, Fatigue Assessment Scale. * Only for depression; ** only for anxiety.

Discussion

In this study, we analyzed daytime sleepiness and fatigue in sarcoidosis patients simultaneously for the first time. We found a prevalence of 16% for the simultaneous occurrence of excessive daytime sleepiness (ESS ≥ 16) and severe fatigue (FAS ≥ 35). 26.6% of patients reported either excessive daytime sleepiness and/or severe fatigue. In Parkinson disease patients, Marinus et al. [26] reported a prevalence of 11.3% for excessive daytime sleepiness (ESS ≥ 16). Hawley et al. [27] found a prevalence of 8% in psychiatric patients with an ESS score of ≥ 16 compared to 3% in healthy controls. A recent study by Sander et al. [17] revealed 2.8% excessive daytime sleepiness in the general population. The prevalence of excessive daytime sleepiness reported in sar-

coidosis in this study appears to be quite high compared to these reports.

Our findings of the severity of fatigue in sarcoidosis are consistent with previous results (e.g., [6]). These authors reported that in 145 Croatian sarcoidosis patients, 15% had severe fatigue (FAS 35–50), 42% had mild-to-moderate fatigue (FAS 22–34), and 43% had no fatigue (FAS 10–21). De Kleijn et al. [28] described 3 types of fatigue: mild fatigue, intermittent fatigue, and all-day fatigue. Those patients defined as having all-day fatigue, characterized by a mean FAS of 36 (19% of 434 patients), are patients comparable to those with severe fatigue in our study. The proportions of severe fatigue (FAS ≥ 35) are similar in all 3 studies, so it must be assumed that the characteristics of all-day fatigue described by De Kleijn et al. [28] also apply to our patients with severe fatigue.

Table 5. Univariate ORs for the risk of excessive daytime sleepiness in combination with severe fatigue

Variables	Total sample, <i>n</i> (%)	FAS ≥ 35 and ESS ≥ 16 , <i>n</i> (%)	OR	95% CI	<i>p</i> (χ^2 test)
Sex					
Male (ref.)	414 (35)	22 (5.3)			
Female	783 (65)	52 (6.6)	1.27	0.76–2.12	0.3645
Age group					
≤ 40 years (ref.)	129 (11)	9 (7.0)			
41–50 years	359 (30)	20 (5.6)	0.79	0.35–1.77	0.5624
51–60 years	350 (29)	30 (8.6)	1.25	0.58–2.71	0.5713
61–70 years	247 (21)	12 (4.9)	0.68	0.28–1.66	0.3957
≥ 71 years	112 (9.4)	3 (2.7)	0.37	0.10–1.39	0.1260
Marital status (missing: <i>n</i> = 12)					
Married (ref.)	950 (80)	57 (6.0)			
Living alone	235 (20)	17 (7.2)	1.22	0.70–2.14	0.4839
Employment status					
Employed or in education (ref.)	419 (35)	21 (5.0)			
Part-time or short-time worker	227 (19)	15 (6.6)	1.34	0.68–2.66	0.3986
Missing or student	29 (2.4)	1 (3.4)	0.68	0.09–5.22	0.7063
Unemployed	66 (5.5)	4 (6.1)	1.22	0.41–3.68	0.7202
Retired	456 (38)	33 (7.2)	1.48	0.84–2.60	0.1719
BMI group					
<25 (ref.)	421 (35)	21 (5.0)			
25 to <30	456 (38)	19 (4.2)	0.83	0.44–1.56	0.5602
30 to <35	200 (17)	18 (9.0)	1.88	0.98–3.62	0.0542
≥ 35	120 (10)	16 (13)	2.93	1.48–5.81	0.0014
Muscle pain					
No (ref.)	630 (53)	19 (3.0)			
Yes	567 (47)	55 (9.7)	3.45	2.02–5.90	<0.0001
Organ involvement					
≤ 3 organs (ref.)	1,014 (85)	52 (5.1)			
4–7 organs	177 (15)	22 (12)	2.63	1.55–4.45	0.0002
≥ 8 organs	6 (0.5)	0 (0.0)			
Arterial hypertension					
No (ref.)	745 (62)	40 (5.4)			
Yes	452 (38)	34 (7.5)	1.43	0.89–2.30	0.1338
Diabetes mellitus					
No (ref.)	1,063 (89)	64 (6.0)			
Yes	134 (11)	10 (7.5)	1.26	0.63–2.52	0.5137
Thyroid disorder					
No (ref.)	877 (73)	55 (6.3)			
Yes	320 (27)	19 (5.9)	0.94	0.55–1.62	0.8319
Sleep apnea					
No (ref.)	1,093 (91)	61 (5.6)			
Yes	104 (8.7)	13 (13)	2.42	1.28–4.56	0.0051
Sleep apnea with therapy					
No (ref.)	1,145 (96)	65 (5.7)			
Yes	52 (4.3)	9 (17)	3.48	1.63–7.44	0.0007
Restless legs					
No (ref.)	1,011 (84)	54 (5.3)			
Yes	186 (16)	20 (11)	2.14	1.25–3.66	0.0049
Pulmonary hypertension					
No (ref.)	1,159 (97)	67 (5.8)			
Yes	38 (3.2)	7 (18)	3.68	1.56–8.67	0.0015

Table 5 (continued)

Variables	Total sample, <i>n</i> (%)	FAS ≥ 35 and ESS ≥ 16 , <i>n</i> (%)	OR	95% CI	<i>p</i> (χ^2 test)
Dyspnea (MRC)					
MRC 1 (ref.)	449 (38)	10 (2.2)			
MRC 2	478 (40)	27 (5.6)	2.63	1.26–5.49	0.0078
MRC 3	179 (15)	20 (11)	5.52	2.53–12.05	<0.0001
MRC 4–5	91 (7.6)	17 (19)	10.09	4.45–22.88	<0.0001
Anxiety (HADS)					
0–10 (ref.)	871 (73)	29 (3.3)			
≥ 11	326 (27)	45 (14)	4.65	2.86–7.56	<0.0001
Depression (HADS)					
0–10 (ref.)	961 (80)	26 (2.7)			
≥ 11	236 (20)	48 (20)	9.18	5.56–15.17	<0.0001
Use of corticosteroids					
No (ref.)	763 (64)	47 (6.2)			
Yes	434 (36)	27 (6.2)	1.01	0.62–1.65	0.9662

All *p* values are unadjusted. ESS, Epworth Sleepiness Scale; FAS, Fatigue Assessment Scale; OR, odds ratio; CI, confidence interval; BMI, body mass index; MRC, Medical Research Council scale; HADS, Hospital Anxiety and Depression Scale.

In all 3 models, gender was not an independent risk factor for the prediction of excessive daytime sleepiness or severe fatigue. However, it still had significant correlations with factors contained in the logit models. Female sarcoidosis patients reported a greater number of involved organs and more dyspnea of MRC grades 2 and 3. In comparison to male sarcoidosis patients, a history of sleep apnea was less common, and fewer patients had high values for depression on the HADS. There are significant correlations with age, for example, for dyspnea or anxiety, but it is unclear whether there is an age-related risk reduction. It is also possible that the age effect is transmitted by other risk factors.

Severity of dyspnea was a predictor of both excessive sleepiness and severe fatigue in this study. The influence of dyspnea on daytime sleepiness was more pronounced than its influence on fatigue. There is an increased risk for extreme daytime sleepiness even with less severe dyspnea. Dyspnea is an indicator of the severity of sarcoidosis [29], and a high MRC grade is interpreted as an expression of a stronger impairment of the patient. Then again, fatigue and dyspnea were reduced by a physical training program for 13 weeks [30]. Cavalcante et al. [31] found in chronic obstructive pulmonary disease patients that a high degree of dyspnea on the MRC scale was an independent risk factor for poor subjective sleep quality on the Pittsburgh Sleep Quality Index (PSQI) and was, at the same time, positively correlated with the severity of fatigue.

In the case of the sarcoidosis patients in our study, an average of 2.2 ± 1.4 organs were involved, and involvement of >3 organs was associated with an increased risk of developing excessive daytime sleepiness. Extrapulmonary involvement usually indicates a more severe manifestation of sarcoidosis and involves increased dyspnea and fatigue compared to patients with pulmonary involvement only [32]. Extrapulmonary involvement is observed more frequently in women [33].

A history of sleep apnea increased the risk for the development of excessive daytime sleepiness in sarcoidosis patients. Obstructive sleep apnea syndrome was reported in our study by 8.7% of all patients and by 19.8% of patients with excessive daytime sleepiness (ESS ≥ 16). The prevalence of obstructive sleep apnea syndrome in other sarcoidosis studies was between 17 and 51.7%, while the prevalence in the general population was 2–4% [11–13, 34]. In sleep apnea, the symptom of daytime sleepiness is usually regarded as typical, but fatigue is another frequent symptom. Again, this is particularly true for women [35].

In particular, the presence of conspicuous depression as well as conspicuous anxiety contributes to the increased risk of developing severe fatigue. This is also evident in our multivariate prediction model for excessive daytime sleepiness with concomitant presence of severe fatigue. De Kleijn et al. [36] reported that the prevalence of depressive symptoms and anxiety was greater in patients with all-day fatigue compared to the patients of the

Table 6. Multivariate logit model for excessive daytime sleepiness combined with severe fatigue

Variables	Regression coefficient	SE	OR (95% CI)	<i>p</i>
Intercept	-4.7882	0.4016		
Age group (ref. <60 years)				
61–70 years	-0.6190	0.3579	0.54 (0.28–1.09)	0.0837
≥71 years	-1.2972	0.6385	0.27 (0.08–0.96)	0.0422
Muscle pain				
Yes	0.8928	0.2933	2.44 (1.37–4.34)	0.0023
Dyspnea (MRC) (ref. MRC 1)				
MRC 2	0.8141	0.3901	2.26 (1.05–4.85)	0.0369
MRC 3	1.0754	0.4282	2.93 (1.27–6.78)	0.0120
MRC 4–5	1.9188	0.4624	6.81 (2.75–16.87)	<0.0001
Anxiety (HADS)				
≥11	0.7118	0.2863	2.04 (1.16–3.57)	0.0129
Depression (HADS)				
≥11	1.6031	0.2924	4.97 (2.80–8.81)	<0.0001

The AUC was estimated to be 0.846 (Bootstrap-cross-validated 0.820). With $p = 0.6077$ (Hosmer-Lemeshow goodness of fit test), the model has a good fit; the Nagelkerke R^2 is 0.2643. SE, standard error; OR, odds ratio; CI, confidence interval; MRC, Medical Research Council scale; HADS, Hospital Anxiety and Depression Scale; AUC, area under the ROC curve.

other 2 fatigue groups. They concluded that the nature of fatigue in sarcoidosis patients moderates relationships between fatigue and anxiety or depression. Moreover, patients with all-day fatigue suffered most from psychological problems [28]. It has, therefore, been suggested by various authors that patients with all-day fatigue should benefit from supportive psychological treatment [5, 28, 36].

Muscle pain is among the most common complaints of sarcoidosis patients but is often unspecific and contributes to an increased risk of developing severe fatigue. Sarcoidosis patients with fatigue reported greater exercise intolerance and muscle pain compared to patients without fatigue [37]. Fatigue was a strong and independent predictor of physical activity in patients with idiopathic pulmonary fibrosis [38].

In 2 recent studies of women with fibromyalgia, physical fitness was inversely associated with the level of anxiety, but on the other hand, it was independently associated with pain and fatigue [39, 40]. In the group of sarcoidosis patients with severe fatigue, >50% complained of conspicuous anxiety (Fig. 1b), demonstrating similarities to (secondary) fibromyalgia. We conclude from our data that the nature of fatigue in sarcoidosis patients moderates not only the relationships between fatigue and anxiety or depression but also the frequency of complaints

about pain. Sedating pain medications can be another cause of fatigue in patients with chronic pain [8]. However, there are no data on the use of drugs for pain therapy in the investigated sarcoidosis patients.

In line with the results of others [41], our findings suggest an overlap between daytime sleepiness and fatigue when using self-assessment procedures alone. We, therefore, recommend either to diagnose both at the same time or to verify daytime sleepiness by additional objective investigations (such as the Multiple Wakefulness Test).

At the same time, a distinction between severe fatigue and excessive daytime sleepiness is useful in clinical practice. Sleep apnea is a predictor of excessive daytime sleepiness in sarcoidosis patients. The results of the present study demonstrate the need to investigate the presence of sleep-related breathing disorders in sarcoidosis patients and to treat them according to the guidelines. So far, there have been no prospective stratified and controlled studies on the effect of a therapy of sleep disturbances (such as obstructive sleep apnea) on fatigue in sarcoidosis patients. The implementation of such studies is of great importance, as by increasing the attention paid to sleep problems, the quality of life of sarcoidosis patients can also be improved.

This study has also shown that depression and anxiety are important predictors of severe fatigue. The presence

of anxiety and depression in sarcoidosis patients should, therefore, always be actively investigated in order not to underestimate the presence of mood disorders as in other chronic diseases [42, 43]. On the other hand, an additional psychological disorder, such as depression or anxiety, should be considered in all patients who complain of severe fatigue, and specific diagnostics should always be carried out. To the best of our knowledge, there are currently no prospective randomized and controlled studies of how the therapy of anxiety and depression can affect fatigue in patients with sarcoidosis.

Limitations

The present study is a cross-sectional study, so a statement about causal relationships is not possible. All data are based on the subjective data of the patients in the questionnaire; lung function parameters were not collected. It is possible that the prevalence of restless leg syndrome and sleep apnea syndrome in targeted diagnostics will be significantly higher than that reported in the patients' history.

Summary and Conclusion

We here observed a 27% fraction of sarcoidosis patients with extreme daytime sleepiness and/or severe fatigue which should be further diagnosed and treated. The 3 multivariate logit models demonstrate that there is an

overlap between fatigue and sleepiness, but it is also necessary to differentiate between the 2 conditions. This was achieved in this study by simultaneously using 3 questionnaires.

Depression and anxiety as well as muscle pain were predictors of the development of severe fatigue, whereas sleep apnea and the number of affected organs increased the risk of excessive daytime sleepiness. Severity of dyspnea is a strong predictor of both fatigue and sleepiness. Since fatigue usually has a multifactorial cause, risk factors should also be examined and treated in combination. The specific combinations of risk factors will allow choosing specific therapeutic interventions in order to improve the quality of life of sarcoidosis patients. Further studies are needed to determine the relationship between fatigue and sleepiness in sarcoidosis.

Acknowledgement

The authors thank the German Sarcoidosis Association for its financial and moral support.

Financial Disclosure and Conflicts of Interest

The authors declare that they have no conflicts of interest.

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