Factors Associated With Fatigue in Sarcoidosis

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BACKGROUND: Fatigue is a frequent symptom of patients with sarcoidosis. The origin of fatigue associated with sarcoidosis is unclear. The aim of this study was to assess the impact of affected organs, medication, and comorbidity on fatigue related to sarcoidosis. METHOD: In collaboration with the German Sarcoidosis Society, a sample of 1,197 subjects diagnosed with sarcoidosis was examined. The participants completed a questionnaire that contained the Fatigue Assessment Scale and the Multidimensional Fatigue Inventory. RESULTS: In this study, muscles, bones, and nerves were most strongly associated with fatigue. Patients receiving prednisolone showed heightened fatigue levels. However, the association between the duration of prednisolone therapy and fatigue was weak. The concomitant diseases, pulmonary hypertension and sleep apnea, showed the greatest impact elevating fatigue (effect sizes d > 0.50). In the combined regression analysis, comorbidity was the most important predictor of fatigue. CONCLUSIONS: It is important to consider that multiple clinical factors, especially comorbidities, contribute to the high degrees of fatigue in sarcoidosis. *Key words: comorbidity; fatigue; organs; sarcoidosis.* [Respir Care 2014;59(7):1086–1094.

Introduction

Sarcoidosis is a systemic granulomatous disease. Although the disease may involve almost every organ of the body, the lung is predominantly affected. Patients have a broad spectrum of symptoms. Frequently observed, specific clinical features are shortness of breath, cough, and chest pain (pulmonary)[1]; cranial nerve palsy (neurological); and erythema nodosum, maculopapular lesion, or lupus pernio (dermatological).[1-3] Nonspecific symptoms are chronic fatigue, weight loss, night sweats, fever, and malaise.[3-5]

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Fatigue is one of the most common symptoms in sarcoidosis,[6] and it impairs quality of life.[7,8] In a previous study by this group, the level of fatigue within the same cohort with sarcoidosis was compared to that in the general population. The Fatigue Assessment Scale (FAS) and the Multidimensional Fatigue Inventory (MFI) tests were used. Patients with sarcoidosis showed higher levels of fatigue, with younger patients experiencing greater fatigue than older ones.[9] However, the reasons for higher fatigue levels in patients with sarcoidosis are unknown. Clinical parameters show inconsistent correlation with elevated fatigue levels.[10] The affected organs might be of critical importance since patients with pulmonary and extrapulmonary disseminated sarcoidosis have higher fatigue levels than patients with pulmonary sarcoidosis.[11]

Comorbidity may contribute to fatigue levels. Examples include restless legs syndrome, which leads to disturbed and superficial sleep with subsequent fatigue, insomnia, and daytime somnolence.[12,13] Obstructive sleep apnea correlates with poorer quality of life with respect to sleep, fatigue, and energy levels.[14,15] Body mass index has been proven to be an independent predictor of fatigue in patients with obstructive sleep apnea.[15-17] Metabolic and endocrinological disorders (eg, diabetes mellitus and thyroid disorder) are also significantly associated with fatigue[18]

and may play a role in the development of fatigue in patients with sarcoidosis. Pulmonary hypertension (PHT) is often observed in advanced sarcoidosis, and it contributes to increased mortality and poor prognosis.[19] Patients with PHT have a significantly shorter 6-min walk distance and higher levels of fatigue than patients without PHT.[20] Further complicating conclusive analysis, treatment options of sarcoidosis may themselves impact fatigue development. In particular, prednisolone has been shown to have a nearly linear correlation with sleeping problems.[21]

Although there are several studies examining specific putative reasons for elevated fatigue levels in sarcoidosis, many of them are based on relative small sample sizes.[22] Furthermore, the association between comorbidity and fatigue has been mentioned only in case reports.[23] Hence, in the current study, we intended to comprehensively test several factors associated with fatigue in sarcoidosis.

QUICK LOOK

Current knowledge

Sarcoidosis is a systemic granulomatous disease that impacts primarily the lungs. Fatigue is a frequent symptom of patients suffering from sarcoidosis. The origin of this fatigue is unclear.

What this paper contributes to our knowledge

Multiple clinical factors, especially comorbidities, contribute to the high degrees of fatigue in sarcoidosis. Affected organs, comorbidity, and medications demonstrated a significant and an independent influence on fatigue.

Methods

Sample

The study was performed in collaboration with the German Sarcoidosis Society. In 2009, all members of the society (n = 4,100) were requested to complete a questionnaire concerning demographic characteristics, affected organs, medications, symptoms, and comorbidities. Fatigue was assessed with 2 standardized questionnaires (see next section). The questionnaire was delivered to the members by post with an accompanying letter, a consent form, and a return envelope. The response rate was 31%. A total of 73 questionnaires were excluded from analysis because the respondents wrote their names on the questionnaire (contradicting the pseudonymization procedure) and/or had too many missing values. The final analysis was based on 1,197 questionnaires. The study was reviewed and approved by the Ethics Committee of the University of Leipzig. In a previous study with the same sample of patients, the fatigue levels of the study participants were compared with those of the general populations, and age and gender differences were calculated.

Questionnaire

Regarding affected organs, 10 specific organs covering the most commonly affected sites were included in the questionnaire (lungs, heart, skin, muscle, nerves, eyes, bones, kidneys, lymphatic nodes, and liver) and a category "other organs." Participants were requested to indicate whether the organs were currently affected or not by checking on a box either "yes" or "no." Multiple answers were possible. Medication was assessed with the same method. Medication categories were prednisolone, azathioprine, methotrexate, cyclophosphamide, and oxygen, including the duration (in years) of prednisolone therapy. Participants were asked to state their current medications. Comorbidity was assessed in the same way. The list included diabetes, congestive heart disease, thyroid dysfunction, sleep apnea, restless legs syndrome, and PHT, and for each of the diseases, the subjects had to indicate whether they currently had the disease or not. In all evaluated items, participants had to indicate their present state, not the past.

FAS

The FAS is the most frequently used fatigue questionnaire in sarcoidosis.[22,24] Initially developed by De Vries et al,[25] it is a well-validated and reliable scale.[22] The questionnaire consists of 2 subscales, 5 questions each on the physical and mental aspect of fatigue. There are 5 answer options ranging from "never" to "always." An example for physical subscales is "I get tired very quickly." A cutoff score of 22+ is a widely accepted criterion for elevated fatigue.[25]

MFI

The MFI was developed by Smets et al.[26] This fatigue scale is widely used in patients with cancer, chronic fatigue syndrome, and chronic inflammatory diseases.[27-29] It is well validated[29] with an internal consistency (Cronbach's α) ranging from 0.79 to 0.93.[27]

The MFI consists of 5 subscales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each subscale covers 4 items with 5 answer options (1 "yes, true" to 5 "no, not true"). An example would be: "Thinking requires effort." According to Kuhnt et al,[30] the 75th percentile (53+) was used as the cutoff value for high fatigue.

Statistical Analysis

Group differences in mean values of fatigue scores were calculated with *t* tests. Effect sizes (d) were calculated according to Cohen.[31] Cohen's d is a commonly used value to evaluate the magnitude of differences regardless of the sample size. It is defined as the mean score difference of 2 groups divided by the pooled SD. For each organ category, the mean fatigue differences between subjects with and without affected organs were calculated and indicated as effect sizes (d). Furthermore, the number of organ categories was calculated for each subject (mean: 2.1 organ categories) and participants with multiple affected organs (3 and more) were compared with participants with 1 or 2 affected organs.

Especially in studies with large number of participants, the effect size is a better measure than the significance level because even small differences in mean values can reach significance simply due to sample size. A d value of 0.2 or less is interpreted as small, a d value of 0.5 is classified as medium, and a d value of 0.8 is a large effect. Significant differences do not necessarily render clinical important effects. Therefore, d values provide a better judgment concerning clinical importance of group differences. Several researchers consider an effect size of 0.5 (half SD) clinically important.[32] According to this criterion, an FAS difference of 4 points and an MFI difference of 8 points are assumed to be clinically important since the FAS and MFI SDs are about 8 and 16, respectively. However, even smaller differences than d = 0.50 may be relevant from an epidemiological point of view.

The hypothesized predicting factors of fatigue may be interrelated. Since the inclusion of all single organs, medications, and comorbidities would result in too many predictors for multivariate analyses, we restricted the analysis to the numbers of affected organs, medications, and concomitant diseases together with age and gender. Previous studies showed effects of age and gender on fatigue. Women generally report more fatigue than males. Therefore, age and gender were included in the multivariate analyses. Multiple regression analyses (method = enter) were performed to test the association between multiple predictors and the outcome (fatigue). Multiple R coefficients describe the correlation between the optimal linear combination of the predictors with the outcome. The regression coefficient "B" describes the predictive strength of the independent variable as follows. On average, the fatigue score (dependent variable) differed by X amount for every 1 unit increase in Y predictor while keeping the others constant. "Beta" is the standardized partial regression coefficient, ranging between −1.0 and 1.0. It can be interpreted as the correlation coefficient of the respective variable in the regression analysis with multiple predictors. All calculations were performed with SPSS 17.0 (SPSS, Chicago, Illinois).

Table 1. Demographic Characteristics and Mean Fatigue Scores

	Total (n = 1197)	Males (n = 414)	Females (n = 783)
Demographic data			
Sex, %		34.6	65.4
Age, mean ± SD, y	54.3 ± 11.6	53.9 ± 10.9	54.5 ± 12.0
Fatigue data			
FAS score, mean ± SD	26.3 ± 7.9	25.2 ± 8.4	26.8 ± 7.6
FAS above cutoff 22+, %	69.7	62.1	73.7
MFI score, mean ± SD	60.5 ± 17.2	58.0 ± 18.1	61.8 ± 16.5
MFI above cutoff 53+, %	67.9	62.3	70.9

FAS = Fatigue Assessment Scale
MFI = Multidimensional Fatigue Inventory

Results

The mean age of the study sample (n = 1,197) was 54.3 y (Table 1), and 65.4% were females. In the German Sarcoidosis Society, the mean age of all members was 55.9 y, and 60.0% were females. Both questionnaires confirmed high percentages of participants with fatigue; mean fatigue scores are illustrated in Table 1. Females were more affected than males (P = .02).

Affected Organs

In Table 2, several univariate results of mean fatigue scores for each kind of affected organ are presented. The organs are arranged according to the frequency of occurrence.

The lungs were the most frequently reported site of sarcoidosis manifestation (91%). To evaluate the impact of additional affected areas, the group of participants with pulmonary manifestation was divided into 2 subsamples, pulmonary alone and pulmonary plus extrapulmonary.

Both questionnaires yielded similar results as shown in Table 2. The greatest differences were found for muscles, bones, and nerves related to fatigue levels (P < .001). The lungs, skin, lymph nodes, and eyes were the organs most reported to be affected by sarcoidosis and showed relatively small group mean differences in fatigue. Participants with 3 or more affected organs reported more fatigue (FAS: d = 0.39; MFI: d = 0.31) than participants with 1 or 2 affected organs (P < .001). Extrapulmonary involvement in addition to pulmonary manifestation correlates with a higher fatigue level (FAS: d = 0.28; MFI: d = 0.30, P < .001).

Table 2. Association of Affected Organs and Fatigue

Organs	*n*	FAS			MFI		
		Mean ± SD	d	*P*	Mean ± SD	d	*P*
Lungs							
Yes	1,086	26.2 ± 7.9			60.5 ± 17.3		
No	111	26.5 ± 7.4	0.04	.73	60.5 ± 15.9	0.00	.25
Skin							
Yes	293	26.1 ± 8.0			60.6 ± 16.7		
No	904	26.6 ± 7.2	0.07	.34	61.1 ± 17.3	0.09	.21
Lymphatic nodes							
Yes	249	26.6 ± 7.8			61.1 ± 16.9		
No	948	26.2 ± 7.9	0.05	.47	60.3 ± 17.3	0.05	.50
Eyes							
Yes	191	26.7 ± 7.3			61.8 ± 17.1		
No	1,006	26.2 ± 7.9	0.07	.37	60.2 ± 17.2	0.09	.22
Liver							
Yes	141	28.1 ± 7.9			62.9 ± 17.5		
No	1,056	25.9 ± 7.8	0.28	.02	60.1 ± 17.1	0.16	.067
Muscles							
Yes	113	29.9 ± 7.8			67.2 ± 15.4		
No	1,084	25.9 ± 7.8	0.51	< .001	59.8 ± 17.2	0.45	< .001
Nerves							
Yes	108	29.1 ± 8.4			65.6 ± 16.8		
No	1,089	25.9 ± 7.8	0.40	< .001	59.9 ± 17.1	0.34	< .001
Bones							
Yes	105	29.7 ± 7.5			66.1 ± 16.1		
No	1,092	25.9 ± 7.8	0.50	< .001	59.9 ± 17.1	0.37	< .001
Heart							
Yes	95	28.4 ± 8.0			64.6 ± 16.1		
No	1,102	26.1 ± 7.8	0.29	.004	60.1 ± 17.2	0.27	.01
Kidneys							
Yes	60	28.5 ± 7.3			64.5 ± 16.1		
No	1,037	26.1 ± 7.9	0.32	.02	60.3 ± 17.2	0.25	.066
Other							
Yes	191	28.4 ± 7.1			64.4 ± 15.4		
No	1,006	25.8 ± 7.9	0.35	< .001	59.7 ± 17.4	0.28	.001
No. of organs							
< 3	813	25.3 ± 7.7			58.8 ± 17.2		
≥ 3	384	28.3 ± 7.8	0.39	< .001	64.1 ± 16.6	0.31	< .001

FAS = Fatigue Assessment Scale
MFI = Multidimensional Fatigue Inventory
d = Cohen's effect size

Medication

The relationship between medication and fatigue is displayed in Table 3. Prednisolone was the predominant therapy (45.3%), followed by the immune modulator azathioprine (5%) and methotrexate (2.8%). All medications were associated with higher fatigue levels, with methotrexate showing the greatest impact on fatigue (FAS: d = 0.44, $P = .006$; MFI: d = 0.42, $P = 0.02$). The mean duration of prednisolone therapy was 5.7 years.

Multidrug treatment is possible. Most subjects were on none ($n = 619$) or one ($n = 578$) medication. Patients receiving at least 2 medications ($n = 77$) reported higher fatigue levels in FAS than those with zero or one kind of medication.

Comorbidity

The frequencies of concomitant diseases were as follows (Table 4): arterial hypertension (37.9%), thyroid disease (26.9%), obesity (26.7%), restless legs syndrome (15.7%), diabetes mellitus (11.2%), sleep apnea (8.8%), and PHT (3.2%). All comorbidities were associated with

Table 3. Association of Medication and Fatigue

Medication	*n*	FAS			MFI		
		Mean ± SD	d	*P*		d	*P*
Prednisolone							
Yes	542	27.1 ± 7.8			62.8 ± 17,1		
No	655	25.5 ± 7.9	0.20	< .001	58.5 ± 17.0	0.25	< .001
Azathioprine							
Yes	60	27.5 ± 8.1			62.3 ± 16.4		
No	1,137	26.2 ± 7.9	0.16	.23	60.4 ± 17.2	0.11	.40
Methotrexate							
Yes	34	29.9 ± 9.3			67.4 ± 17.0		
No	1,163	26.1 ± 7.8	0.44	.006	60.3 ± 17.2	0.42	.02
No. of medications							
≤ 1	1,120	26.1 ± 7.8			60.3 ± 17.2		
> 1	77	28.2 ± 8.5	0.26	.037	63.6 ± 16.5	0.19	.95

FAS = Fatigue Assessment Scale
MFI = Multidimensional Fatigue Inventory
d = Cohen's effect size

Table 4. Association of Comorbidity and Fatigue

Comorbidity	*n*	FAS			MFI		
		Mean ± SD	d	*P*	Mean ± SD	d	*P*
Arterial hypertension							
Yes	452	27.1 ± 8.0			63.4 ± 16.8		
No	738	25.7 ± 7.7	0.19	.002	58.6 ± 17.3	0.28	< .001
Disease of thyroid gland							
Yes	320	26.8 ± 8.1			61.9 ± 16.4		
No	869	26.0 ± 7.9	0.11	.10	59.5 ± 17.2	0.10	.053
Obesity (BMI ≥ 30)							
Yes	320	28.3 ± 8.0			65.5 ± 16.3		
No	875	25.5 ± 7.7	0.35	< .001	58.7 ± 17.2	0.41	< .001
Restless legs syndrome							
Yes	186	28.8 ± 7.7			65.9 ± 16.5		
No	998	25.8 ± 7.9	0.38	< .001	59.5 ± 17.2	0.38	< .001
Diabetes mellitus							
Yes	134	27.7 ± 8.0			66.3 ± 16.0		
No	1,060	26.1 ± 7.8	0.21	.02	59.7 ± 17.2	0.39	< .001
Sleep apnea							
Yes	104	31.0 ± 7.8			70.1 ± 14.6		
No	1,084	25.8 ± 7.8	0.68	< .001	59.5 ± 17.2	0.67	< .001
Pulmonary hypertension							
Yes	38	30.2 ± 8.1			72.6 ± 13.5		
No	1,138	26.1 ± 7.8	0.52	< .001	59.9 ± 17.2	0.83	< .001
No. of concomitant diseases							
< 3	1,002	25.7 ± 7.7			58.9 ± 17.1		
≥ 3	195	29.2 ± 7.9	0.45	< .001	68.2 ± 15.4	0.57	< .001

FAS = Fatigue Assessment Scale
MFI = Multidimensional Fatigue Inventory
d = Cohen's effect size
BMI = body mass index

Table 5. Demographic and Medical Factors as Predictors of Fatigue

	B	SE (B)	β	P
FAS (R = 0.28)				
Affected organs (sum)	0.69	0.165	0.122	< .001
Comorbidity (sum)	1.41	0.229	0.186	< .001
Medication (sum)	1.09	0.345	0.092	.002
Age	−0.09	0.020	−0.128	< .001
Sex (female)	1.09	0.475	0.066	.02
MFI (R = 0.29)				
Affected organs (sum)	1.20	0.361	0.097	< .001
Comorbidity (sum)	3.47	0.501	0.210	< .001
Medication (sum)	2.85	0.754	0.109	< .001
Age	−0.06	0.045	−0.043	.15
Sex (female)	2.59	1.040	0.071	.01

B = regression coefficient
SE (B) = standard error of B
β = partial regression coefficient
FAS = Fatigue Assessment Scale
R = multiple regression coefficient
MFI = Multidimensional Fatigue Inventory

higher fatigue levels (Table 4). Sleep apnea and PHT were most strongly related to fatigue (d > 0.50), followed by obesity and restless legs syndrome. Arterial hypertension, the most frequent concomitant disease, reached effect sizes of d = 0.19 (FAS) and d = 0.28 (MFI), which is also statistically significant (P = .002). One-hundred ninety-five participants (16.3%) reported 3 or more comorbidities, and these participants reported the highest fatigue values (FAS: d = 0.45; MFI: d = 0.57, P < .001).

Multiple Regression Analyses

Affected organs, medications, and comorbidities may be interrelated. In addition, these factors may be age- and/or gender-specific. Therefore, the effects given in Tables 2–4 may depend on these mutual relationships. Multiple regression analyses were used to test the independent statistical influence of the different factors on fatigue. Table 5 shows that the 3 components (affected organs, medication, and comorbidity) significantly contributed to the prediction of fatigue. Comorbidity was most strongly associated with fatigue, with β scores of ~0.20. The influence of gender on fatigue levels was statistically significant (higher fatigue scores for females compared to males) but only on the 5% level of variance.

While the FAS showed a significant age effect (P < .001), the MFI failed to confirm that effect (P = .01). The multiple R values of 0.28 and 0.29 correspond to an explained variance of ~8%. Sleep apnea and PHT were the conditions with the greatest effects on fatigue in the univariate analyses. To test these effects in a multivariate model, we also performed multivariate regression analyses with the predictors of Table 5 combined with these 2 conditions (sleep apnea and PHT). The MFI results were B = 6.09, β = 0.10, and P = .002 for sleep apnea and B = 7.14, β = 0.07, and P = .01 for PHT. The corresponding FAS coefficients were B = 3.94, β = 0.14, and P = .001 for sleep apnea and B = 2.15, β = 0.05, and P = .10 for PHT.

Discussion

In this study, the association of fatigue in patients with sarcoidosis concerning different manifestations sites, medications, and comorbidities has been studied. Levels of fatigue were measured with MFI and FAS tests. It was found that patients with additional manifestation sites of pulmonary sarcoidosis have higher levels of fatigue than those with only pulmonary diseases. Furthermore, the comorbidities of PHT and sleep apnea showed the greatest effects on fatigue in multivariate analysis. Patients who were being treated with prednisolone were significantly above the cutoff values for the MFI and the FAS. However, these results were obtained in univariate analyses and may be, at least in part, due to confounding.

The question of whether the burden or localization of the disease contributes to fatigue levels is highly interesting. In a 2-way approach, we initially identified the muscles, bones, and nerves to show the highest effect sizes in direct association. Surprisingly, these manifestation sites were not among the most affected. Higher MFI and FAS values were also found with lung involvement, but effect sizes were less. Sarcoidosis induces inflammatory reactions, leading to the formation of granulomata and nonspecific reaction of tissue. The pathology of increased fatigue[11] related to lung involvement is unclear. Restrictive/obstructive manifestation or a reduction of diffusion capacity might be induced[33] by the disease, leading to decreased blood oxygenation and a consecutive increase in fatigue.

Concerning nonpulmonary manifestation sites, sarcoidosis involvement of the musculoskeletal system may present as myalgia[4] or lytic bone lesions,[34] leading to physical inactivity, lack of exercise, worsening of performance, and deconditioning in physical capacity.[35,36] Manifestation in the heart muscle may cause reduced myocardial contraction strength, blocks,[37] or arrhythmias,[38] resulting in lower cardiac output, dyspnea, and fatigue. In respect to this, localization of sarcoidotic lesions plays an important role. With the strong association of extrapulmonary sarcoidotic manifestation, it was reasonable to examine the additional effects of these sites to pulmonary diseases. It was shown that those patients with pulmonary and extrapulmonary sarcoidosis reported higher fatigue levels than those with only the lungs affected. This has also been shown by Gvozdenovic et al[11] and suggests a possible additive effect to the symptom of fatigue. Furthermore, not only the lo-

calization but also the burden of the disease, seen as numbers of affected organs, showed an influence on the level of fatigue, as patients with 3 or more affected organs reported significantly more fatigue than those with fewer than 3 affected organs.

Manifestation sites of the disease may not play the only role, as we found that certain comorbidities were also strongly associated with increased fatigue levels. Above all, sleep apnea, occurring in 9% of the sample, showed the strongest effect sizes in direct association. Sleep apnea is an interruption of sleep due to the collapse of upper airways, leading to hypoxic episodes. Possible causes might be constitutional reasons, such as obesity, laryngeal manifestation of sarcoidosis, and neurosarcoidosis. A well-documented association of sleep apnea with higher body mass index levels[39] exists that correlated with higher self-reported fatigue in our study. Interestingly, obesity and diabetes not only seem associated via sleep apnea with fatigue[17] but also depict independent influencing factors. Because sleep apnea causes hypoxic episodes, the fatigue due to obesity and diabetes might be mediated through psychological distress and elevated levels of interleukin-6 secreted by adipose cells.[40]

Concerning the effect of restless legs syndrome, the disturbance of sleep stages and sleep fragmentation, leading to daytime somnolence and fatigue, might offer an explanation to greater fatigue in patients with this syndrome. The most common reported comorbidity, arterial hypertension, contributed little amount to fatigue levels. Interestingly, the impairment of the thyroid showed no impact on overall fatigue due to sarcoidosis since the effect sizes of thyroid gland diseases on fatigue were low.

The relationship between medication and fatigue is comparable to that found between affected organs and fatigue. It is generally accepted that chemotherapy induces fatigue.[41] However, the different compounds seem to have an inter-individual association of variable strength. Different effects of prednisolone have been previously documented in the literature.[25] According to Drent et al,[4] prednisolone may induce muscle weakness, leading to a collapse of upper airway muscles and therefore yielding fatigue. Whether this direct effect of prednisolone increases fatigue in patients with sarcoidosis or the higher activity of disease, which makes the treatment with prednisolone necessary, is not quite clear and should be considered in further investigations. The same should be considered for treatment with methotrexate. As this drug is commonly used in escalating therapy, the different effects on fatigue are hard to differentiate.

The analysis of direct associations yielded certain factors to be connected to the level of fatigue, but some additional aspects for interpretation have to be considered. Affected organs can occur in multiple combinations. The most frequently affected organ (lung) seems to have a negligible and nonsignificant association with fatigue since patients with and without lung involvement show similar fatigue levels. Here, one must take into account that more subjects in the control group (patients without lung involvement) have other sites affected. Involvement of muscles, bones, and nerves is relatively uncommon ($< 10\%$ prevalence each) compared to the respiratory system. For these organs, the d values in Table 2 are appropriate measures to indicate the strength of association since the differences between the groups concerning the other organs are smaller. Therefore, it is also useful to calculate the number of affected organs. The same is true for concomitant diseases. Multiple combinations are possible. As in the analysis of affected organs, the most frequent concomitant diseases (hypertension and diseases of the thyroid gland) show lower effect sizes than the (rare) diseases PHT and sleep apnea. The above-mentioned problems of the univariate analyses (multiple combinations of affected organs, concomitant diseases, and medication) call for a multivariate analysis. Table 5 shows that comorbidity is the most important independent factor (highest β values) associated with fatigue. While sleep apnea was an independent factor even in the multivariate analyses, PHT failed to reach statistical significance in the multivariate context even though the univariate effect was also high. This may be due to the small prevalence (3%) of PHT.

The limitations of this study should be acknowledged. The study was based on self-reported data and not on clinical examination. Furthermore, due to the voluntary participation in this study, a response bias cannot be excluded. Selection bias can also be an additional source of errors. In our sample, females were slightly overrepresented (65% in the sample vs 60% in the society), but there were only small age differences between respondents and non-respondents. Therefore, concerning these demographic factors, the sample can be assumed to be fairly representative of the members of the society. However, the society might not represent all patients with fatigue. The correlations found in this study are of statistical significance. A 2-step approach, first univariate correlations and then multivariate correlations, was used to identify possible predictors of fatigue. The predictors found do not indicate causative relationships but describe statistical connections. The study includes multiple univariate statistical tests. Therefore, because of the problem of multiple testing, some effects may be due to chance. As a consequence, we restrict the interpretation to those effects that occur in both questionnaires with significance levels of .01. The rates of comorbidity correspond to those reported in other studies. Finally, affected organs, treatment, comorbidity, and age are interrelated. Tables 2–4 report univariate group differences. Combined analyses, taking into account certain combinations of affected organs or combinations of comorbidity, provided a deeper insight into the predictors of fatigue.

It might be useful to examine certain typical combinations of affected organs and comorbidity.

In conclusion, we reconfirm that fatigue is a major problem in patients with sarcoidosis. The highest mean fatigue levels were reported for patients with sarcoidosis in muscles, bones, and nerves, whereas pulmonary sarcoidosis was associated with a lesser amount of fatigue. In addition, patients affected with pulmonary and extrapulmonary manifestation sites showed higher fatigue levels.

In terms of treatments, we found prednisolone, as well as methotrexate, to be strongly associated with fatigue levels in patients with sarcoidosis. The same was found for the concomitant diseases sleep apnea and PHT. However, in the multivariate analysis, only sleep apnea showed a strong effect and should therefore be carefully considered and treated.

The total burden of multiple affected organs in combination with the number of medications and concomitant diseases was examined in an integrated approach. An increase in the number of affected organs, an intensified therapy, and an increased burden of concomitant diseases are associated with increased fatigue levels.

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