RESEARCH ARTICLE

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The Clinical Correlations of Fatigue in Patients with Sarcoidosis

ABSTRACT

Objective: Fatigue is considered a frequent and characteristic feature of sarcoidosis. This study was designed to determine the prevalence of fatigue in patients with sarcoidosis and to determine its potential clinical correlations in relation to symptom severity.

Methods: A total of 56 sarcoidosis patients were included. Data on patient demographics, anthropometrics, disease characteristics, pulmonary function tests, 6-min walking distance (6MWD), blood biochemistry and hemogram findings were retrieved from hospital records. Psychometric instruments involved fatigue assessment scale (FAS), Beck Depression Inventory (BDI) and Short Form-36 (SF-36) for health-related QOL (HRQOL).

Results: Mean±SD patient age was 50.9±11.9 years. Of 56 patients, 44 were females and 12 were males. When compared to FAS score <22 and FAS score ≥22-34 subgroups, FAS score ≥35 (severe fatigue) subgroup was associated with significantly higher patient age and significantly lower SF-36 physical health scores. Total FAS scores were correlated positively with age (r=0.349, p=0.008) and BDI scores (r=0.515, p<0.001), while negatively with MIP (r=-0.321, p=0.019) and SF-36 physical health (r=-0.402, p=0.003) and mental health (r=-0.351, p=0.009) scores. BDI score (OR 1.146, 95% CI: 1.020 to 1.288, p=0.021) was determined to be the single independent predictor of increased likelihood of a patient with sarcoidosis to have FAS score ≥22.

Conclusions: Our findings emphasize that deterioration in respiratory functions may contribute to development of fatigue among sarcoidosis patients, and besides the fatigue, depressive symptoms and anxiety should also be an integral part of the multidisciplinary management of sarcoidosis patients.

Keywords: Fatigue Assessment Scale (FAS), Fatigue, Health Quality, Sarcoidosis.

Sarkoidoz Hastalarında Yorgunluğu Etkileyen Klinik Etkenler

ÖZET

Amaç: Yorgunluk, sarkoidozun sık ve karakteristik bir özelliği olarak kabul edilir. Bu çalışma, sarkoidozlu hastalarda yorgunluk prevalansını belirlemek ve semptom şiddeti ile ilişkili potansiyel klinik korelasyonlarını belirlemek için tasarlanmıştır.

Gereç ve Yöntem: Toplam 56 sarkoidoz hastası dahil edildi. Hastane kayıtlarından hasta demografisi, antropometri, hastalık özellikleri, solunum fonksiyon testleri, 6 dakikalık yürüme mesafesi (6DYM), kan biyokimyası ve hemogram bulgularına ilişkin veriler elde edildi. Psikometrik araçlar, sağlıkla ilgili yaşam kalitesi (HRQOL) için yorgunluk değerlendirme ölçeği (YDÖ), Beck Depresyon Ölçeği (BDÖ) ve Kısa Form-36 (SF-36) kullanıldı.

Bulgular: Ortalama ± SS hasta yaşı 50.9 ± 11.9 yıldı. 56 hastanın 44'ü kadın, 12'si erkekti. YDÖ skoru <22 ve YDÖ skoru ≥22-34 alt grupları ile karşılaştırıldığında, YDÖ skoru ≥35 (şiddetli yorgunluk) alt grubu, daha yüksek hasta yaşı (p = 0.037) ve anlamlı olarak daha düşük SF-36 fiziksel sağlık skorları (p = 0.029) ile anlamlı bulundu. Toplam YDÖ skorları yaş (r = 0.349, p = 0.008) ve BDÖ skorları (r = 0.515, p <0.001) ile pozitif korelasyon gösteriyor iken; MIP (r = -0.321, p = 0.019) ve SF-36 fiziksel sağlık (r = -0.402, p = 0.003) ve mental sağlık(r = -0.351, p = 0.009) puanları sağlık ile negatif korelasyon gösteriyordu. BDÖ skorunun (OR 1.146,% 95 CI: 1.020 - 1.288, p = 0.021), sarkoidoz hastalarının YDÖ skorunun ≥22 olması olasılığının artmasının tek bağımsız prediktörü olduğu belirlendi.

Sonuç: Bulgularımız, solunum fonksiyonlarındaki bozulmanın sarkoidoz hastalarında yorgunluğun gelişimine katkıda bulunabileceğini ve yorgunluğun yanı sıra depresif belirtiler ve anksiyetenin sarkoidoz hastalarının multidisipliner yönetiminin ayrılmaz bir parçası olması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Yorgunluk Değerlendirme Ölçeği (YDÖ), Sarkoidoz, Yaşam Kalitesi, Yorgunluk

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disorder that may affect any organ system, while it affects lungs in more than 90% of cases (1,2). In the clinical course of sarcoidosis, there exists not only the organ-specific involvement and related dysfunction but also rather nonspecific symptoms (3). Hence, sarcoidosis patients may suffer from a wide spectrum of nonspecific symptoms, such as fatigue, weight loss, fever, night sweats, arthralgia, muscle pain, exercise limitation and cognitive failure (4,5).

Fatigue is considered a frequent and characteristic feature of sarcoidosis, as associated with significant negative impact on the patients' quality of life (QOL) depending on the severity that ranges from mild to persistent and disabling symptoms (6,7). The exact etiology of fatigue in patients with sarcoidosis remains largely unknown, while is considered to be multifactorial with potential contribution of comorbidities, treatments and psychological factors in addition to chronic systemic inflammation (6,8). Amongst the factors suggested to be associated with occurrence of fatigue in active disease are systemic inflammation, muscle involvement, extra-pulmonary locations, comorbidities, pulmonary hypertension, impaired lung function, steroids and other drugs used for the treatment of sarcoidosis and psychological factors (6).

Many patients continue to experience fatigue despite receiving an adequate sarcoidosis treatment (8). In addition, despite a comprehensive search for treatable clinical causes of fatigue, complaints of fatigue are not correlated with clinical parameters of disease activity in most patients (8).

This study was therefore designed to determine the prevalence of fatigue in patients with sarcoidosis and to determine its potential clinical correlations in relation to symptom severity.

MATERIAL AND METHODS

Study Population: A total of 56 sarcoidosis outpatients being followed up at a tertiary-care center were included in this study.

The permission was obtained from our institutional ethics committee for the use of patient data for publication purposes (Date of Approval: 18.03.2019; Reference number/Protocol No:2019/73).

Assessments: Data on patient demographics (age, gender), anthropometrics [body mass index (BMI, kg/m^2), waist circumference (cm) and hip circumference (cm)], disease characteristics (duration of disease, radiographic stage, treatments), pulmonary function tests [% predicted values for forced vital capacity (FVC), forced expiratory volume at 1 second (FEV1), DLCO/VA (transfer coefficient), maximal inspiratory pressure (MIP) and total lung capacity (TLC)], 6-min walking distance (6MWD), blood biochemistry and hemogram findings were retrieved from hospital records. Psychometric instruments involved fatigue assessment scale (FAS), Beck Depression Inventory (BDI) and Short Form-36 (SF-36) for health-related QOL (HRQOL).

Fatigue Assessment Scale: The FAS is a 10-item validated and reliable scale, developed by De Vries et al. being used to assess fatigue in sarcoidosis patients. Each item is scored based on a 5-point Likert scale ranging from "never" to "always," and the total score range is 10–50. Scores <22 indicate absence of fatigue, while scores between 22 and 34 indicate mild-to-moderate fatigue, and scores ≥ 35 indicate severe fatigue (7,9). The Turkish version of the questionnaire used was obtained from https://wasog.org/dynamic/media/78/documents/Questionairres/fas_tur_anon.html.

Beck Depression Inventory: BDI is a 21-item self-reporting questionnaire for evaluating the level and change in severity of depression based on physical, emotional, cognitive and motivational symptoms. Each item is scored on a 4-point scale from 0 (symptom absent) to 3 (severe symptoms), while the total score achieved by adding the highest ratings for all 21 items ranges from 0 to 63 with higher scores indicating greater symptom severity (10).

Statistical Analysis: Statistical analysis was made using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY). Kruskal-Wallis H test was used to compare the continuous variables between FAS subgroups. Correlation of FAS scores with BDS, SF-36 physical and mental health scores and pulmonary function test parameters were analyzed via Pearson correlation analysis. Binary logistic regression analysis was performed to determine factors predicting presence of FAS scores ≥22 in sarcoidosis patients. Data were expressed as mean± standard deviation (SD), median (interquartile range, IQR) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics: Mean±SD patient age was 50.9±11.9 years. Of 56 patients, 44 (79%) were females and 12 (21%) were males. Overall, stage 1, 2 and 3 sarcoidosis was evident in 6 (10.7%), 46 (82.1%) and 4 (7.1%) patients, respectively. Considering steroid treatment, 32 patients were treatment-native, 18 patients had previous treatment and 6 patients were under steroid therapy (Table 1).

Considering pulmonary function tests, mean±SD % predicted values were 101.1±14.8 for FVC, 94.3±16.8 for FEV1, 91.6±21.6 for DLCO/VA, -79.6±24.4 for MIP and 91.5±19.4 for TLC, while mean±SD 6MWD was 405.2±85.5 m (Table 1).

FAS assessment revealed absence of fatigue (FAS score <22) in 21.4% of patients, while mild-to-moderate fatigue (FAS score ≥22-34) was noted in 62.5% of patients and severe fatigue (FAS score ≥35) in 16.1% of patients (Table 1).

Nearly half of the patients were in the mild depression group according BDI scores, while mean±SD SF-36 scores were 64.1±21.9 for the physical health domain and 63.0±23.2 for the mental health domain (Table 1).

Table 1. Demographic and clinical characteristics (n=56)

Patients characteristics	
Gender (Male/Female)	44/12
Age (year), mean±SD	50.9 ± 11.9
BMI (kg/m^2), mean±SD	31.3 ± 4.8
Disease characteristics	mean±SD
Duration of disease (year)	4.4 ± 4.2
Radiographic stage	n(%)
1	6 (10.7)
2	46 (82.1)
3	4 (7.1)
Respiratory parameters (% predicted value)	**mean±SD**
FVC	101.1 ± 14.8
FEV1	94.3 ± 16.8
DLCO/VA	91.6 ± 21.6
MIP	-79.6 ± 24.4
TLC	91.5 ± 19.4
6MWD	405.2 ± 85.5
Fatigue assessment (FAS scores)	**n(%)**
FAS score <22	12 (21.4)
FAS score 22-34	35 (62.5)
FAS score ≥35	9 (16.1)
Beck Depression Inventory	**n(%)**
No depression	16 (28.6)
Mildly depressed	26 (46.4)
Moderately depressed	11 (19.6)
Severely depressed	3 (5.4)
SF-36 scores	**mean±SD**
Physical health	64.1 ± 21.9
Mental health	63.0 ± 23.2
Steroid use	**n(%)**
Never	32 (57.1)
Previously used	18 (32.1)
Still using	6 (10.7)

BMI: Body mass index, FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: Transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity; 6MWD: 6-min walk distance; FAS: Fatigue assessment scale; SF-36: 36-item short form survey

Study Parameters with respect to FAS Subgroups: When compared to FAS score <22 and FAS score ≥22-34 subgroups, FAS score ≥35 (severe fatigue) subgroup was associated with significantly higher patient age (median 60.0 vs. 53.5 and 53.0 years, respectively, p=0.037) and significantly lower SF-36 physical health scores (median 51.8 vs. 83.5 and 70.0, respectively, p=0.029) (Table 2). A non-significant tendency for higher BDI scores along with lower SF-36 mental health scores and lower MIP and 6MWD values were noted in FAS score ≥35 subgroup as compared with other FAS subgroups (Table 2).

Correlation of Total FAS Score with Study Parameters: Total FAS scores were correlated positively with age (r=0.349, p=0.008) and BDI scores (r=0.515, p<0.001), while negatively with MIP (r=-0.321, p=0.019) and SF-36 physical health (r=-0.402, p=0.003) and mental health (r=-0.351, p=0.009) scores. No significant difference was noted in pulmonary function test parameters between FAS sub-groups (Table 3).

Multivariate Analysis of Risk Factors Predicting presence of FAS scores ≥22: BDI score (OR 1.146, 95% CI: 1.020 to 1.288, p=0.021) was determined to be the single independent predictor of increased likelihood of a patient with sarcoidosis to have FAS score ≥22.

Table 2. Physical and clinical characteristics according to FAS subgroups

	FAS subgroups			
Variables	**FAS <22 (n=12)**	**FAS ≥22-34 (n=35)**	**FAS ≥35 (n=9)**	**p value**
Age (year)	53.5 (49.2 – 57.0)	53.0 (37.0 – 56.0)	60.0 (56.0 – 66.0)	0.037
Body mass index (kg/m^2)	34.0 (30.0 - 36.5)	30.0 (27.0 – 35.0)	33.0 (29.0 – 35.2)	0.093
Waist circumference (cm)	107.5 (90.7-115.7)	101.0 (94.0-108.0)	98.0 (94.2-115.0)	0.656
Hip circumference (cm)	112.5 (100.5-121.7)	106.0(102.0-117.0)	107.5(101.2-121.2)	0.751
Beck depression inventory score	10.5 (2.0 – 15.2)	12.5 (9.0 – 19.2)	19.0 (13.0 -30.5)	0.054
SF-36 physical health score	83.5 (57.7 – 89.2)	70.0 (51.0 – 82.8)	51.8 (38.6 – 55.1)	**0.029**
SF-36 mental health score	82.3 (55.1 – 92.8)	69.7 (43.8 – 82.1)	42.7 (38.3 – 76.7)	0.506
6-min walk distance (m)	426.5 (378.7-503.0)	416.5 (333.0-471.0)	385.0 (355.0-420.0)	0.254
FVC (% predicted)	105.5 (98.0 -.114.7)	101.0 (88.0 - 107.0)	98.0 (93.5 – 111.5)	0.352
FEV1 (%predicted)	105.5 (94.0 -108.0)	90.0 (81.0 – 104.0)	93.0 (83.0 – 102.0)	0.119
DLCO/VA(%predicted)	99.5 (84.0 – 106.7)	91.0 (86.2 – 102.2)	96.5 (32.7 – 110.7)	0.505
MIP (%predicted)	87.0 (73.0 – 94.5)	83.5 (60.5 – 101.2)	68.0 (36.0 – 75.0)	0.135
TLC (%predicted)	92.0 (77.0 – 99.5)	86.0 (78.5 – 99.0)	100.0 (85.5 – 115.0)	0.305

Data are shown as median (25-75% quartile).

SF-36: Short form -36; FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity

Table 3. Correlation of FAS total score with study variables

Variables	FAS total score	
	r	p
Age (year)	0.349	**0.008**
Body mass index (kg/m^2)	0.020	0.883
6-min walk distance (m)	-0.268	0.058
FVC (%predicted)	-0.149	0.273
FEV1 (%predicted)	-0.242	0.072
DLCO/VA(%predicted)	-0.230	0.108
MIP (%predicted)	-0.321	**0.019**
TLC (%predicted)	0.127	0.354
Beck depression inventory score	0.515	<0.001
SF-36 physical health score	-0.402	**0.003**
SF-36 mental health score	-0.351	**0.009**

SF-36: Short form -36; FVC: Forced vital capacity; FEV1: Forced expiratory volume at 1 sec; DLCO/VA: transfer coefficient; MIP: Maximal inspiratory pressure; TLC: Total lung capacity; r:correlation coefficient
Pearson correlation analysis

DISCUSSION

Our findings revealed significantly lower SF-36 physical health scores along with tendency for higher BDI scores, lower SF-36 mental health scores and lower MIP and 6MWD values in patients with severe fatigue when compared to those with mild-to-moderate fatigue or without fatigue. Logistic regression analysis revealed significantly higher likelihood of having fatigue among sarcoidosis patients with increase in BDI scores (OR, 1.146).

The findings in the current study indicated high prevalence of fatigue (78.6% overall, mild-to-moderate in 62.5% and severe in 16.1%) among sarcoidosis patients. This seems consistent with data from a past study in 145 Croatian sarcoidosis patients, indicated mild-to-moderate fatigue in 42% of patients and severe fatigue (FAS scores 35-50) in 15% of patients with lack of fatigue (FAS scores 10–21) in 43% of sarcoidosis patients (6).

There are few reports pointing out the possible link between fatigue and depression (11). Goracci et al. (12) indicated high rates of psychiatric comorbidity in sarcoidosis patients and its potential contribution to a poorer quality of life. De Klejn et al. (13) reported anxiety and depressive symptoms to be significant predictors of high fatigue scores and thus the likelihood of fatigue to be related to co-morbid depression and anxiety in patients suffering from active sarcoidosis. However, the impact of underlying depression on fatigue has not been studied in patients with sarcoidosis in clinical remission (11). In a study by Chang et al. (14) among 176 sarcoidosis patients, the rate of depression was reported to be 60%. In our study, depression was noted in 71.4% according to BDI score (≥9), while BDI score was determined to be a significant independent predictor of having FAS scores ≥22.

There are studies on the relationship between sarcoidosis and QOL (15,16). The satisfaction with life is considered an outcome with special relevance among patients with a potentially chronic disease like sarcoidosis, as it is affected directly and indirectly by health and disease, or HRQOL (17). In a study by Cox et al. (18) in 111 sarcoidosis patients, assessment of QOL with St. George Respiratory Questionnaire (SGRQ) revealed a decrease in quality of life.

In another study among sarcoidosis patients by Michielsen et al. (7), authors indicated association of fatigue with all QOL domains and the likelihood of fatigue measured by the FAS to be a good indicator of QOL in sarcoidosis patients. In the current study, SF-36 physical health scores were significantly lower in patients with FAS scores ≥ 35 alongside a significant negative correlation of FAS scores with both mental and physical component scores of SF-36. Accordingly, our findings seems to indicate that the likelihood of poor QOL in patients with sarcoidosis to be due to fatigue-related symptoms.

Fatigue and general weakness may be the reason why patients with sarcoidosis frequently experience exercise intolerance, a symptom also noted frequently in other chronic inflammatory states, such as chronic fatigue syndrome (19-21). In a study by Baydur et al. the relation between plasma cytokine levels and fatigue in sarcoidosis patients was assessed by a multifactorial inventory instrument (22). Comparing the plasma cytokine concentrations before and immediately after cardiopulmonary exercise testing in sarcoidosis patients and control subjects, authors reported a relationship between fatigue and plasma IL-1b concentrations in sarcoidosis patients treated with immunomodulating drugs (22).

The association of fatigue with decreased muscle strength and exercise intolerance has consistently been reported by studies among sarcoidosis patients (11,23). In a study by Karadalli et al., 15 sarcoidosis patients who received inspiratory muscle training (IMT) for 6 weeks were compared with the control group and authors reported the association of IMT with improved functional and maximal exercise capacity and respiratory muscle strength and decreased severity of fatigue and dyspnea perception among patients in the early stages of sarcoidosis (24). Likewise, our findings revealed a negative correlation between FAS severity and MIP, emphasizing the likelihood of IMT training to decrease the FAS score and improve the QOL among the sarcoidosis patients.

Skeletal muscle involvement can occur in sarcoidosis, while myositis with significant elevation of the muscle enzymes in the blood stream is relatively rare. If respiratory muscles are involved, it can lead to respiratory failure (25,26). In a prospective study of 34 sarcoidosis patients with pulmonary disease, peak inspiratory muscle pressure (PImax) was reported to be significantly lower than the control group (27). Muscle strength

has been shown to affect the 6MWD (28). In a study by Baughman et al. in 142 sarcoidosis patients, measurement of 6MWD over a 6-week period revealed more than half of patients to have a 6MWD of less than 400m and 32 (22%) patients to walk less than 300 m, along with a correlation between FAS scores and 6MWD (29,30). Similarly, a negative correlation between FAS score and 6MWT was also noted in our study.

The most important limitation of the study is a relatively small sample size. Another limitation is the fact that the symptoms were self-reported, which could lead to bias. However, the burden of sarcoidosis is determined by the experience of the patients themselves. One of the limitations of our study is; it was not evaluated whether the patient's job, being married or having children, which would affect the quality of life of the patients.

In conclusion, our findings indicate fatigue to be a prevalent symptom in sarcoidosis. This emphasizes the need for developing a good questionnaire to assess fatigue in sarcoidosis patients given that no medical parameters are yet available to objectively assess the fatigue. FAS scores in our sarcoidosis patients showed a significant positive correlation with BDI and a strong negative correlation with MIP along with a negative but non-significant correlation with PFT. Accordingly, our findings emphasize that deterioration in respiratory functions may contribute to development of fatigue among sarcoidosis patients, and besides the fatigue, depressive symptoms and anxiety should also be an integral part of the multidisciplinary management of sarcoidosis patients.

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