Chapter 7

Nature of fatigue moderates the relationships between fatigue and depressive symptoms and anxiety in sarcoidosis

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Submitted

Abstract

Background
Fatigue, depressive symptoms and anxiety are frequently reported in sarcoidosis. However, the relationship between these debilitating symptoms is unclear. Therefore, the purpose of this prospective follow-up study was to identify the prevalence of depressive symptoms and anxiety in sarcoidosis patients, stratified for the nature of fatigue. In addition, we examined whether depressive symptoms and anxiety predicted fatigue.

Methods
Prospectively, sarcoidosis outpatients (n = 274) from Maastricht University Medical Centre were included. Clinical data were obtained from medical records. At baseline, patients completed the Fatigue Assessment Scale (FAS), the Center for Epidemiological Studies-Depression Scale (CES-D), and the State and Trait Anxiety Inventory (STAI). After 6, 12 and 18 months patients completed the FAS again.

Results
Concomitant fatigue (FAS > 21) and high trait anxiety (STAI > 39) was frequently reported (35-36%). The combination of fatigue and high levels of depressive symptoms (CES-D > 16) was reported in 43 to 46%. Combined high trait anxiety and high levels of depressive symptoms were reported in 31% of the patients. These percentages were higher in patients with All Day Fatigue, compared to patients with Intermittent, or Mild Fatigue. Both anxiety and depressive symptoms were significant predictors of high fatigue scores.

Limitations
All patients were recruited in a tertiary referral centre. Therefore, the results may not be generalizable to sarcoidosis patients in general.

Conclusions
The nature of fatigue moderates the relationships between fatigue and anxiety and depressive symptoms in sarcoidosis. Hence, beside fatigue, depressive symptoms and anxiety should be an integral part of the multidisciplinary management of sarcoidosis patients.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown etiology. The clinical manifestations are highly variable and often non-specific, depending on the intensity of the inflammation and the organ systems affected. Virtually every organ can be involved, but most patients present with pulmonary, ocular, or cutaneous involvement. Pulmonary sarcoidosis is the second most common respiratory disease in young adults (<40 years) after asthma[1-3].

Apart from lung-related symptoms (e.g., coughing, breathlessness and dyspnea on exertion), patients may suffer from a wide spectrum of rather non-specific disabling symptoms like arthralgia, muscle pain, general weakness, muscle weakness, exercise limitations, fatigue and cognitive failure[4-8]. Sarcoidosis-related symptoms may become chronic and affect the patients' quality of life (QOL)[5]. Fatigue is a pervasive, difficult and one of the most common and disabling symptoms[9] for patients with sarcoidosis. It contributes considerably to an impaired quality of life[5] and appears across all manifestations of the disease, even in patients believed to be disease-free[7]. As this is a substantial problem in sarcoidosis, fatigue has been reported by up to 80% of patients, fatigue is one of the most important issues in the management of sarcoidosis patients.

Besides fatigue, psychological symptoms such as depressive symptoms and anxiety have been reported in 17% to 66% of the patients with sarcoidosis[4,10-17]. In fact, patients with sarcoidosis had higher depression[18] and anxiety scores[14] than healthy subjects[19]. Furthermore, especially depressive symptoms and, to a lesser degree, anxiety, have been found to be associated with fatigue in sarcoidosis[7,13,20,21].

Understanding the nature of the relationships between fatigue, depressive symptoms and anxiety, however, remains still unclear. Several explanations are possible: fatigue may be a symptom of psychological distressed patients; or fatigue, anxiety and depressive symptoms co-occur. Also, the relationship of fatigue with depressive symptoms and anxiety may differ by the nature of fatigue. The co-occurrence of these symptoms may be explained by sickness behavior induced by the release of cytokines[22]. A cardinal feature of sarcoidosis is the presence of cytokines that are involved in the initiation and maintenance of granulomas[23]. Cytokines are believed to induce sickness behavior such as malaise, pain, fatigue, depressed mood, and impaired concentration[6,24-27].

The purpose of this prospective follow-up study was to identify the prevalence of depressive symptoms and anxiety in sarcoidosis patients, stratified for the nature of fatigue. In addition, we examined whether depressive symptoms and anxiety predict fatigue.

Methods

Participants

All sarcoidosis outpatients (n = 588) of the ild care center of the department of Respiratory Medicine of the Maastricht University Medical Centre, a tertiary referral center in the Netherlands, were asked to participate. Patients were diagnosed with sarcoidosis based on consistent clinical features, and bronchoalveolar lavage fluid analysis results, according to the World Association of Sarcoidosis and Other Granulomatous Disorders guidelines[1]. The exclusion criteria were poor expression in the Dutch language (n = 3), relevant co-morbidity, such as malignancy (n = 7), dementia (n = 1), and a history of psychiatric illness (n = 2). The Medical Ethical committee approved the study protocol and written informed consent was obtained from all patients.

Procedure

The patients received information about the study by mail and were asked to return an informed consent form when they were willing to participate in the study. Patients who agreed to participate received the first set of questionnaires in May 2007 and were asked to return the completed set to the hospital in an enclosed envelope. Each 6 months during an 18-months period, patients received a subsequent set of questionnaires with an envelope. The most common reason for not completing the set of questionnaires was 'insufficient time'. The data were collected by the ild care team. The Medical Ethical Committee of the MUMC+ (MEC 07-4-015) approved the study protocol and written informed consent was obtained from all patients.

Measures

Clinical data

Relevant clinical data, such as time since diagnosis, organ involvement, medication, lung function measurements, and chest radiographs were obtained from the patients' medical files. Lung function measurements, including forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), were measured with a pneumotachograph. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single breathe method. Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV: with signs of pulmonary fibrosis, loss of volume, hilar retraction and bullae.

Fatigue

The Fatigue Assessment Scale (FAS) was measured at baseline, 6, 12 and 18 months follow-up. The FAS is a 10-item self-report fatigue questionnaire. The response scale is a five-point scale (1 never to 5 always); scores on the FAS can range from 10 to 50.

The reliability and validity of the FAS appeared to be good in sarcoidosis patients. Percentages of fatigued patients were calculated by dividing FAS scores 10 to 21 (not fatigued) and FAS scores 22 to 50 (fatigued)[28,29]. Recently, three types of fatigue were defined in sarcoidosis[20]. The following types were described: 1) Mild Fatigue: patients with mild or no complaints of fatigue, 2) Intermittent Fatigue: patients with complaints of fatigue that varied during the day, and 3) All Day Fatigue: patients who felt fatigued the whole day.

Depressive symptoms

At baseline the patients completed the Center for Epidemiological Studies-Depression Scale (CES-D). The CES-D is a 20-item scale designed to measure the presence and degree of depressive symptoms. Scores of 16 or above are an indication of a depressive disorder. Reliability and criterion validity appear to be good[30,31]. Based on their CESD score patients were divided into 'not depressed' (0-15) and 'indicative for depression' (16-60)[30].

Anxiety

At baseline the patients completed the State and Trait Anxiety Inventory (STAI) to measure trait anxiety. Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. The trait scale consists of 20 statements and asks people to describe how they generally feel. The psychometric characteristics of the Dutch version of this questionnaire are well established and considered good. High trait anxiety was defined as a score of 40 or above, based on Dutch norm score. Patients with a STAI trait score 40-80 were referred to as 'anxious patients' and patients with a score of 20-39 were referred to as 'non-anxious patients[32].

Statistical procedure

Participants and dropouts were compared on age, sex, time since diagnosis, medication, multisystemic involvement, lung function test, radiographic staging, depressive symptoms, anxiety, and fatigue by means of t-tests for continuous variables or Chi-square tests for categorical variables when appropriate.

Based on a previous study, patients were divided into groups of Mild Fatigue (MF), Intermittent Fatigue (IF), and All Day Fatigue (ADF)[20]. Percentages of anxious patients, depressive patients and fatigued patients were calculated for the total group and for the nature of fatigue separately.

Furthermore, univariate regression analyses were performed to examine the relationship between fatigue (as measured by the FAS) and depressive symptoms (as measured by the CES-D), and the relationship between fatigue and anxiety (as measured by the STAI). These regression analyses were calculated for the total group, and for the nature of fatigue separately.

A p value < 0.05 was considered statistically significant. All data were analyzed using Statistical Package Social Science[33].

Results

This follow-up study included 274 patients. In Table 7.1 the baseline characteristics are shown of the patients who completed the study after 18 months, as well as the patients who dropped-out (n = 169). At baseline no significant differences were found between the characteristics of the participants and dropouts.

Table 7.1 Baseline characteristics of sarcoidosis patients [a]

	Participants (n = 274)	Drop-outs (n = 169)	*P* [b]
Female	46%	46%	ns
Age in years	48.7 ± 10.9	47.0 ± 11.5	ns
Radiographic stage: 0/I/II/III/IV	45/7/22/11/15%	33/11/28/15/13%	ns
Multisystemic involvement	49%	46%	ns
Time since diagnosis in years	8.2 ± 8.1	6.8 ± 7.1	ns
FEV_1, % predicted value	89.6 ± 22.6	88.4 ± 21.7	ns
FVC, % predicted value	99.3 ± 19.6	97.7 ± 20.1	ns
DLCO, % predicted value	81.7 ± 17.8	81.1 ± 17.0	ns
Prednisone use	33%	40%	ns
Immunosuppressant use [c]	19%	15%	ns
Anti-TNF-α use [d]	7%	3%	ns
Pain medication	33%	28%	ns
Antidepressants	7%	6%	ns
Sleep medication	7%	9%	ns
Fatigue Assessment Scale score	29.5 ± 8.5	29.1 ± 8.4	ns
Trait Anxiety score	40.0 ± 10.4	40.7 ± 10.8	ns
Depressive symptoms score	14.2 ± 9.2	14.9 ± 10.4	ns

[a] Data are expressed in percentages or as means ± standard deviation if appropriate. [b] Comparison between drop-outs and participants; [c] Methothrexate and Azathioprine; [d] Infliximab and Adalimumab. anti-TNF-α = anti-Tumor Necrosis Factor-alpha; DLCO = Diffuse capacity of the lung for carbon monoxide; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity.

The number and percentages of fatigued and non-fatigued patients who did or did not score above the CES-D score indicative for a depression are shown in Table 7.2. Concomitance of high levels of depressive symptoms (CES-D>16) and fatigue (FAS>21) ranged from 34-36% in the total group. Concomitance of high levels of depressive symptoms and fatigue in subgroups subdivided according to the nature of fatigue ranged from 10-13% (MF patients), 40-41% (IF patients), and 52-54% (ADF patients) over the four measurement points.

Table 7.2 Relationship between fatigue and depressive symptoms, stratified for nature of fatigue [a]

CESD score indicative for depression [b]	Baseline		6 months		12 months		18 months	
	Not fatigued	Fatigued	Not fatigued	Fatigued	Not fatigued	Fatigued	Not fatigued	Fatigued
All patients								
No	47 (17.7)	120 (45.1)	47 (17.7)	121 (45.7)	48 (17.8)	122 (45.4)	42 (15.6)	128 (47.6)
Yes	7 (2.6)	92 (34.6)	7 (2.6)	90 (34.0)	4 (1.5)	95 (35.3)	2 (0.7)	97 (36.1)
Mild fatigue patients								
No	33 (46.5)	27 (38.0)	33 (45.8)	28 (38.9)	35 (48.6)	26 (36.1)	30 (41.7)	31 (43.1)
Yes	4 (5.6)	7 (9.9)	4 (5.6)	7 (9.7)	2 (2.8)	9 (12.5)	2 (2.8)	9 (12.5)
Intermittent fatigue patients								
No	13 (9.2)	69 (48.9)	14 (9.9)	68 (48.2)	13 (9.1)	71 (49.7)	12 (8.4)	72 (50.3)
Yes	3 (2.1)	56 (39.7)	3 (2.1)	56 (39.7)	1 (0.7)	58 (40.6)	0 (0)	59 (41.3)
All day fatigue patients								
No	1 (1.9)	24 (44.4)	0 (0)	25 (48.1)	0 (0)	25 (46.3)	0 (0)	25 (46.3)
Yes	0 (0)	29 (53.7)	0 (0)	27 (51.9)	1 (1.9)	28 (51.9)	0 (0)	29 (53.7)

[a] Data are expressed as number (percentage) of fatigued and not fatigued patients, cutoff Fatigue Assessment Scale (FAS) > 21 fatigued; [b] Indication for depression: Center for Epidemiological Studies-Depression Scale (CES-D) score at baseline >16.

Table 7.3 Relationship between fatigue and anxiety, stratified for nature of fatigue [a]

High trait anxiety [b]	Baseline		6 months		12 months		18 months	
	Not fatigued	Fatigued	Not fatigued	Fatigued	Not fatigued	Fatigued	Not fatigued	Fatigued
All patients								
No	43 (16.2)	99 (37.2)	48 (18.2)	94 (35.6)	48 (17.8)	96 (35.7)	42 (15.6)	102 (37.9)
Yes	9 (3.4)	115 (43.2)	4 (1.5)	118 (44.7)	4 (1.5)	121 (45.0)	2 (0.7)	123 (45.7)
Mild fatigue patients								
No	30 (42.9)	25 (35.7)	31 (44.3)	23 (32.9)	35 (49.3)	20 (28.2)	30 (42.3)	25 (35.2)
Yes	5 (7.1)	10 (14.3)	4 (5.7)	12 (17.1)	2 (2.8)	14 (19.7)	2 (2.8)	14 (19.7)
Intermittent fatigue patients								
No	12 (8.5)	56 (39.4)	17 (12.0)	52 (36.6)	12 (8.3)	58 (40.3)	12 (8.3)	58 (40.3)
Yes	4 (2.8)	70 (49.3)	0 (0)	73 (51.4)	2 (1.4)	72 (50.0)	0 (0)	74 (51.4)
All Day Fatigue patients								
No	1 (1.9)	18 (33.3)	0 (0)	19 (36.5)	1 (1.9)	18 (33.3)	0 (0)	19 (35.2)
Yes	0 (0)	35 (64.8)	0 (0)	33 (63.5)	0 (0)	35 (66.0)	0 (0)	35 (64.8)

[a] Data are expressed as number (percentage) of fatigued and not fatigued patients, cutoff Fatigue Assessment Scale (FAS) > 21 fatigued; [b] High trait anxiety: State and Trait Anxiety Inventory (STAI) score at baseline >39.

The numbers and percentages of fatigued and non fatigued patients who did or did not score above the STAI score indicative for high trait anxiety (STAI>39) are presented in Table 7.3. Concomitance of high trait anxiety and fatigue ranged from 43-46% in the total group. The The range of concomitance of high trait anxiety and fatigue was 14-20% (MF patients), 49-51% (IF patients), and 64-66% (ADF patients), over the 4 measurements points.

In Table 7.4 the number of patients who had both high trait anxiety and a CESD score indicative for depressive symptoms are presented. This table shows that 44% of the ADF patients had an indication of depression and high trait anxiety. This combination was present in 35% of the IF patients and in 13% of the MF patients. The percentages of patients with high trait anxiety without an indication for depression were higher than the percentages of depression alone.

Table 7.4 Frequencies of co-existing high trait anxiety and indication for depression, stratified for nature of fatigue at baseline[a]

CESD score indicative for depression[c]	High Trait Anxiety[b]	
	No	Yes
All patients		
No	127 (47.9)	40 (15.1)
Yes	16 (6.0)	82 (30.9)
Mild Fatigue patients		
No	53 (76.8)	6 (8.7)
Yes	1 (1.4)	9 (13.0)
Intermittent fatigue patients		
No	60 (42.3)	23 (16.2)
Yes	10 (7.0)	49 (34.5)
All Day Fatigue patients		
No	14 (25.9)	11 (20.4)
Yes	5 (9.3)	24 (44.4)

[a] Data are expressed as number (percentage); [b] High trait anxiety: State and Trait Anxiety Inventory (STAI) score at baseline > 39; [c] Indication for depression: Center for Epidemiological Studies-Depression Scale (CES-D) score at baseline > 16.

The results of the univariate regression analyses are presented in Table 7.5. Depressive symptoms and trait anxiety were positive predictors of fatigue at baseline and follow-up. In addition, this relationship remained significant within each nature of fatigue. Moreover, the R^2 indicates that depressive symptoms and anxiety explained more variance of fatigue at baseline and at 6 months in the ADF group, in comparison to the IF and MF patients.

Table 7.5 Depressive symptoms and anxiety predict fatigue at baseline and follow-up [a]

Fatigue	Baseline		6 months		12 months		18 months	
	β	R^2	*β*	R^2	*β*	R^2	*β*	R^2
All patients								
Depressive symptoms	0.62 ***	0.38	0.59 ***	0.35	0.55 ***	0.30	0.51 ***	0.26
Trait anxiety	0.55 ***	0.30	0.54 ***	0.30	0.51 ***	0.26	0.43 ***	0.19
Mild fatigue patients								
Depressive symptoms	0.52 ***	0.27	0.45 ***	0.19	0.51 ***	0.26	0.44 ***	0.19
Trait anxiety	0.41 ***	0.17	0.40 ***	0.16	0.49 ***	0.24	0.31 ***	0.12
Intermittent fatigue patients								
Depressive symptoms	0.50 ***	0.25	0.49 ***	0.23	0.44 ***	0.19	0.39 ***	0.15
Trait anxiety	0.43 ***	0.19	0.44 **	0.20	0.35 ***	0.12	0.34 **	0.09
All day fatigue patients								
Depressive symptoms	0.62 ***	0.38	0.61 ***	0.37	0.46 ***	0.21	0.38 ***	0.15
Trait anxiety	0.55 ***	0.30	0.54 ***	0.28	0.42 ***	0.18	0.29 *	0.08

[a] Univariate linear regression analyses *β;* standardized regression weight R^2; explained variance
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Discussion

To the best of our knowledge this is the first study evaluating the prevalence of depressive symptoms and anxiety in relationship to fatigue and its nature in sarcoidosis. In the present study, fatigue was often reported with concurrent depressive symptoms (34-36%) and anxiety (43-46%). Moreover, about one third of the patients (31%) reported high trait anxiety simultaneously with high levels of depressive symptoms at baseline. Both anxiety and depressive symptoms were significant predictors of high fatigue scores at baseline and follow-up. Furthermore, the results showed that the nature of fatigue moderated the relationships between fatigue and depressive symptoms as well as anxiety. These relationships were stronger among the patients with ADF compared to patients with IF and MF.

The association between depressive symptoms and fatigue and anxiety and fatigue in the total group found in the present study is in agreement with earlier the results of earlier studies[7,21]. The results are also in line with findings in other chronic diseases, including cancer[34,35], diabetes, chronic obstructive lung disease, cardiac disease, and rheumatoid arthritis[36]. In the latter study it was suggested that the relationship between depressive symptoms and fatigue is bidirectional. Depressive symptoms may indirectly lead to more symptoms, because depressive symptoms are associated with poor self care in patients with chronic diseases in general[36]. Furthermore, physical symptoms may result in functional impairment, which in turn may increase the burden on the patient's life and provoke depression[36]. In the current study, most patients are chronically ill, i.e., the mean time since diagnosis was 8 years. Possibly,

functional impairment associated with chronic sarcoidosis evokes depressive symptoms.

The relationship between depressive symptoms and fatigue may be explained by a cytokine imbalance in sarcoidosis, which initiates an inflammatory immune response in sarcoidosis[27]. Pro inflammatory cytokines coordinate the inflammatory response to infection, as well as acting on the brain, hereby triggering sickness behaviors, including anhedonia, and fatigue[22]. These sickness behaviors help patients to cope with their illness successfully. However, in some cases, cytokine-induced sickness behaviors may be so severe resulting in social withdrawal which also underlies all depressive symptomatology[37]. The cytokine imbalance also found in patients with depression[38], underlines the theory of sickness behavior.

Anxiety, fatigue and depressive symptoms are associated with a significant burden on the patient's life. These symptoms are, therefore, important targets for therapy. Previously, treatment with anti-TNF-α was associated with a reduction of fatigue in small studies[6,39,40]. In addition, methylphenidate and the stimulant d-methylphenidate were reported as treatment of sarcoidosis-associated fatigue[41,42]. Furthermore, treatment of symptoms of fatigue may indirectly decrease depressive symptoms[43]. Improvements in fatigue were significantly associated with reductions in anxiety and depression among anemic patients[44]. In this latter study it was postulated that for patients with anemia, fatigue can be improved or reversed with darbepoetin alfa therapy[44]. In addition, previous research showed that pharmacological[45] and psychological[46] treatment are effective in a variety of functional somatic and other unexplained physical syndromes. Further research is required to investigate the effectiveness of pharmacological and psychological treatment of depressive symptoms and anxiety in patients with sarcoidosis.

A limitation of the current study is that all patients were recruited in a tertiary referral centre. Therefore, the results may not be generalizable to every sarcoidosis patient. In addition, because of the small sample size in the subgroups, statistical analyses were not feasible for these subgroups. Strengths of the study are the longitudinal design and the large sample size.

In conclusion, this study showed that fatigue and its nature moderates anxiety and depressive symptoms in sarcoidosis. Concomitant fatigue and depressive symptoms and/or anxiety were most common in patients with All Day Fatigue (ADF). Moreover, anxiety and depressive symptoms predicted fatigue across time in sarcoidosis. Hence, besides fatigue, depressive symptoms and anxiety should be an integral part of the multidisciplinary management of sarcoidosis patients, especially in ADF patients.

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