

Chapter 6

Symptoms predicting fatigue in
sarcoidosis: a prospective follow-up study

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Submitted

Abstract

Background

Fatigue is a frequent and severe problem in sarcoidosis. Knowledge concerning correlates for the development of fatigue and possible interrelationships are lacking.

Purpose

A conceptual model of fatigue was developed and tested.

Methods

Sarcoidosis outpatients (n = 292) of Maastricht University Medical Centre, completed questionnaires regarding trait anxiety, depressive symptoms, cognitive failure, dyspnea, social support and Small Fiber Neuropathy (SFN) at baseline. At 12 months follow-up, fatigue was assessed. Sex, age, and time since diagnosis were taken from medical records. Pathways were estimated by means of path analyses in AMOS.

Results

Cognitive failure, depressive symptoms, symptoms suspected of SFN, and dyspnea, were positive predictors of fatigue. Fit indices of the model were good.

Conclusions

The model is valid for explaining variation in fatigue. Cognitive failure and depressive symptoms were the most important predictors of fatigue. These symptoms should be taken seriously and included in the management of sarcoidosis patients.

Introduction

Sarcoidosis is a multisystemic disease of unknown cause, characterized by the accumulation of granulomas. The lungs are most frequently involved, but the lymph nodes, skin, eyes, muscles, heart, and joints also may be affected. Various symptoms are reported, depending on organ involvement and inflammatory activity¹. Besides the symptoms related to specific organs, patients also often report fatigue².

Fatigue is the most frequently reported symptom in the sarcoidosis population in the Netherlands². Moreover, fatigue has a substantial impact on the patient's quality of life (QOL)³. Furthermore, it is important to examine the potential factors that maintain fatigue in sarcoidosis. This may be accomplished by understanding clinical, psychological, and social predictors of fatigue in patients with sarcoidosis.

Previous research showed that cognitive failure⁴, depressive symptoms⁵, dyspnea⁶, being female^{7,8}, and symptoms associated with Small Fiber Neuropathy (SFN)⁹ are related to fatigue. More specifically, patients who reported All Day Fatigue reported more symptoms of SFN, compared to patients with Mild Fatigue and Intermittent Fatigue⁹.

The primary limitations of previous research were the cross-sectional design¹⁰ and segmented examination of the variables, instead of simultaneously. Consequently, the knowledge concerning correlates for the development of fatigue and possible interrelationships is still incomplete.

Therefore, a conceptual model of fatigue, based on the model of Taylor and Aspinwall¹¹, was developed and tested. This conceptual model is represented in Figure 6.1. Clinical variables were not incorporated in this model, because previous studies showed no consistent significant relationships between the Fatigue Assessment Scale (FAS) and widely used medical data in sarcoidosis¹⁰. Time since diagnosis, sex and age were incorporated into this model to control for background variation. Trait anxiety was expected to predict stressors, social support, and fatigue. This is supported by research on fatigue and trait anxiety in other chronic diseases, such as breast cancer¹². Finally, several studies showed that social support has therapeutic effects on both psychological and physical health^{13,14}. Therefore, the aim of this study was to evaluate whether stressors and social support are predictors of fatigue.

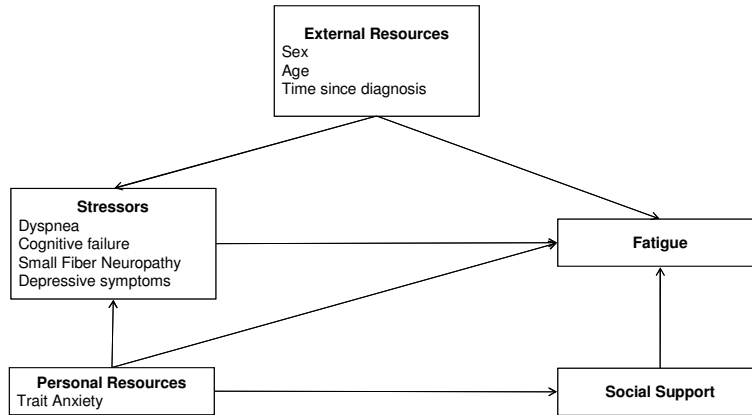


Figure 6.1 Initial conceptual model of fatigue in sarcoidosis^a.

^a Error terms are omitted in this Figure. All predictors were measured at baseline and fatigue at 12 months follow-up

Methods

Participants

All sarcoidosis outpatients 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 guidelines¹⁵. 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 ($n = 2$). Thirteen patients were found to be non-eligible and 133 patients refused to participate. The remaining 348 patients participated at baseline. After 12 months 292 patients remained in the study.

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. After 12-months, 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

External resources and background variables

The following variables were taken as exogeneous: gender (0 = male, 1 = female), age, and time since diagnosis.

Personal resource

At baseline the patients completed the State and Trait Anxiety Inventory (STAI)¹⁶ 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 above 40, based on Dutch norm scores¹⁶.

Stressors

At baseline the patients completed the Center for Epidemiological Studies-Depression Scale (CES-D)¹⁷, the Small Fiber Neuropathy Screenings List (SFNSL)¹⁸, and the Cognitive Failure Questionnaire (CFQ)¹⁹. In addition, patients were asked to rate the Borg Dyspnea Index (BDI)²⁰. The CES-D¹⁷ 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 good²¹. The SFNSL is a short and easy to administer questionnaire to screen for symptoms related to Small Fiber Neuropathy (SFN). It is a 21-item self-administered measure of symptomatology related to SFN. The response scale is a five-point scale (0 never to 4 always); scores on the SFNSL can range from 0 to 84. The cut-off score of the SFNSL is 11. A score below 11 indicates no or a few symptoms related to SFN, a score of 11-48 indicates probably or highly likely SFN, a score above 48 is indicative of SFN¹⁸. The CFQ is a self-report questionnaire consisting of 25 items assessing impairment in attention, perception, memory and motor functioning in everyday life¹⁹. The total CFQ score was calculated by summing up all items, with the total score ranging from 0–100. A higher score indicated more subjective cognitive impairment. The BDI is a self-rated scale for dyspnea. Scores ranges from 0 (unimpairment) to 10 (severe impairment)²⁰.

Social support

At baseline the patients completed the Perceived Social Support Scale (PSSS)²². The total score of the 12-item version of the PSSS was used to assess general perception of social support. The rating scales ranged from 1, very strongly disagree, to 7, very

strongly agree. The PSSS has good reliability and validity in patients undergoing coronary angiography²³ and was translated in Dutch²².

Health outcome

The Fatigue Assessment Scale (FAS)²⁴ was completed at baseline, and at 6 and 12 months follow-up. The FAS is a 10-item self-report fatigue questionnaire. Besides a total fatigue score, the FAS can be divided into a mental fatigue score as well as a physical fatigue score. 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^{24,25}.

Statistical procedure

In order to test the conceptual model, presented in Figure 6.1, Structural Equation Modeling (SEM) analyses were performed using AMOS. The dependent variable FAS at 12 months was regressed on the explanatory baseline variables, i.e., external resources, stressors, trait anxiety, and social support. An additional model was regressed at 6 months follow-up.

In the present study 3% of the total number of values was missing, and 60 (19%) patients had missing data on at least one of the variables. A missing values analysis was performed to test whether the missing variables were Missing Completely At Random (MCAR). The little MCAR test was not significant ($\chi^2 = 119.88$, $df = 110$, $p = 0.25$), indicating that the missing data did not exhibit a systematic pattern. Subsequently, the data were analyzed by means of the software package AMOS 18.0²⁶, which allows for the full information maximum likelihood (FIML) estimation of the model parameters when the data are incomplete.

A backward elimination strategy was used in order to achieve a parsimonious model. This elimination strategy was based on the evaluation of the critical ratio of the individual parameters, yielded by AMOS. The critical ratio for a parameter is estimated by dividing the estimated value by its standard error. Independent variables in the model were retained when the absolute value of their critical ratio was larger than 2.0. This critical ratio equals a significance test at the 5% level. The following fit indices were reported: chi-square goodness-of-fit (CMIN), the comparative fit index (CFI), the Tucker–Lewis index (TLI), and the root-mean-square error of approximation (RMSEA)^{27,28}. Values for CFI and TLI of 0.90 represents good fit and 0.95 represents excellent fit^{27,29}. RMSEA values of 0.05 indicate a close fit, 0.08 a reasonable fit, and 0.10 a poor fit³⁰.

Results

Table 6.1 summarizes baseline characteristics of the participants of the present study. The mean fatigue score was at baseline $M = 29.6$ ($SD = 8.4$), and at 12 months follow-up, the mean fatigue score was $M = 30.1$ ($SD = 7.7$). The mean mental fatigue score

was at baseline $M = 12.7$ ($SD = 4.4$) and at 12 months follow-up, the mean mental fatigue score was $M = 13.7$ ($SD = 4.2$). The mean physical fatigue score was at baseline $M = 16.7$ ($SD = 4.6$), and at 12 months follow-up, the mean physical fatigue score was $M = 16.5$, ($SD = 4.2$).

Table 6.1 Baseline characteristics.

	Participants (n = 292)
Demographics	
Male	157 (53.8%)
Age	48.3 ± 11.0
Medical variables	
Time since diagnosis	8.1 ± 8.2
Radiographic stages: 0/ I / II / III / IV	130 (45%) / 20 (7%) / 65 (22%) / 32 (11%) / 43 (15%)
Symptoms	
FVC	99.4 ± 19.3
FEV ₁	89.9 ± 22.4
DLCO	81.8 ± 17.9
Medication	
Prednisone ^a	95 (32.5%)
Immunosuppressants ^b	54 (18.5%)
anti-TNF- α ^c	21 (7.2%)
Pain killers	92 (31.5%)
Antidepressants	20 (6.8%)
Sleep medication	20 (6.8%)
SFNSL score	24.6 ± 15.7
BDI score	2.6 ± 2.0
FAS score	29.5 ± 8.4
FAS mental score	12.7 ± 4.5
FAS physical score	16.7 ± 4.6
Psychological variables	
CESD score	14.1 ± 9.2
PSSS score	62.6 ± 13.4
STAI score	40.1 ± 10.2
CFQ score	37.5 ± 15.5

Data are presented as means ± standard deviation or in frequencies (percentages)

^a Prednisone (5-40 mg orally daily); ^b Methotrexate (5-15 mg once a week, orally together with 5 mg folic acid once a week orally); or Azathioprine (50-100 mg daily, orally); ^c Infliximab (5 mg/kg, every 4 weeks intravenously) or Adalimumab (40-80 mg once a week subcutaneously). anti-TNF- α = anti-Tumor Necrosis Factor-alpha; BDI = Borg Dyspnea Index; CESD = Center for Epidemiological Studies-Depression Scale; CFQ = Cognitive Failure Questionnaire; DLCO = Diffuse capacity of the lung for carbon monoxide; FAS = Fatigue Assessment Scale; FEV₁ = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity; PSSS = Perceived Social Support Scale; SFNSL = Small Fiber Neuropathy Screenings List; STAI = State and Trait Anxiety Inventory.

In Table 6.2 the correlation matrix between the baseline variables and fatigue at 12 months fatigue is shown. All variables, except age and time since diagnosis, were related to fatigue. Cognitive failure and depressive symptoms were strongly related to mental fatigue and moderately related to physical fatigue. In contrast, symptoms suspected of SFN were more strongly related to physical fatigue and moderately related to mental fatigue.

Table 6.2 Pearson's correlations between variables at baseline and fatigue at follow-up.

	FAS score ^a	FAS mental score ^a	FAS physical score ^a
Sex	-0.12*	-0.11	-0.11
Age	-0.04	-0.02	-0.05
Time since diagnosis	-0.03	-0.03	-0.03
BDI score	0.20**	0.17**	0.20**
STAI score	0.43**	0.44**	0.36**
PSSS score	-0.20**	-0.21**	-0.15**
SFNSL score	0.46**	0.39**	0.49**
CESD score	0.50**	0.51**	0.42**
CFQ score	0.53**	0.53**	0.45**

^a at 12 months follow-up; * $p < 0.05$ level; ** $p < 0.01$ level

BDI = Borg Dyspnea Index; CESD = Center for Epidemiological Studies-Depression Scale; CFQ = Cognitive Failure Questionnaire; FAS = Fatigue Assessment Scale; PSSS = Perceived Social Support Scale; SFNSL = Small Fiber Neuropathy Screenings List; STAI = State and Trait Anxiety Inventory.

In a first analysis, the initial conceptual path model as described in the methods yielded an acceptable fit. The value of the test statistic CMIN was equal to 23.24 with 11 degrees of freedom ($p = 0.02$). The results revealed that the absolute values of the critical ratios of 15 out of the 26 path coefficients were smaller than 2.0. Removing these parameters one by one yielded a second reduced model with a better fit: the value of CMIN was equal to 33.84 with 25 degrees of freedom ($p = 0.11$). The remaining 12 parameters in this model had all critical ratios absolutely larger than 2.0. Therefore, this reduced model could not be simplified further without worsening the fit.

The path analyses yielded good fit indices: TLI = 0.97, CFI = 0.99, and RMSEA = 0.04 (CI 0.00-0.06). The model explained 37% of the variance in fatigue.

The statistically significant path coefficients are provided in Figure 6.2. Patients who reported high levels of cognitive failure ($\beta = 0.31$), depressive symptoms ($\beta = 0.26$), symptoms suspected of SFN ($\beta = 0.16$), and dyspnea ($\beta = 0.10$) reported high levels of fatigue. Neither time since diagnosis, sex, age, social support nor trait anxiety predicted fatigue. Regarding the background variables, only age predicted dyspnea, and cognitive failure. Older patients reported dyspnea ($\beta = 0.12$) more often than younger ones, and younger patients reported cognitive failure ($\beta = -0.12$) more often than older ones. In addition, sex predicted symptoms suspected of SFN and cognitive failure. Females reported more symptoms suspected of SFN ($\beta = -0.16$), and

cognitive failure ($\beta = -0.16$) compared to males. Time since diagnosis was not predictive for any of the variables in the model. Trait anxiety predicted more cognitive failure ($\beta = 0.48$), more depressive symptoms ($\beta = 0.81$), less social support, ($\beta = -0.34$) and more symptoms suspected of SFN ($\beta = 0.32$), but not dyspnea.

When repeating the path analyses with fatigue at 6 months, similar results were obtained. The fit indices at 6 months were good: CMIN = 36.75, $df = 25$, $p = 0.06$, TLI = 0.96, CFI = 0.98, and RMSEA = 0.04 (CI 0.00-0.07). This model explained 36% of the variance in fatigue at 6 months.

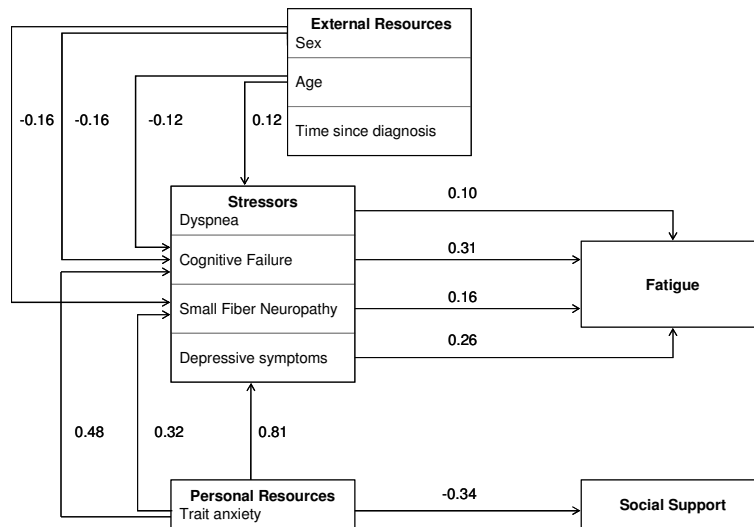


Figure 6.2 Model that was tested for understanding the associations among, sex, age, time since diagnosis, social support, trait anxiety, cognitive failure, depressive symptoms, dyspnea, small fiber neuropathy and fatigue in sarcoidosis.^a

^a Error terms are omitted in this Figure. Significant path coefficients are presented as standardized estimates. Sex is a categorical variable (0 = female, 1 = male). All predictors were measured at baseline and fatigue at 12 months follow-up

Discussion

To our knowledge, this is the first study that developed and tested a conceptual model of fatigue in sarcoidosis in a longitudinal design. This model appeared to be valid for explaining variation in fatigue. All tested baseline stressors (cognitive failure, symptoms suspected of SFN, depressive symptoms, and dyspnea) appeared to be significant predictors of fatigue 12 months after the evaluation of fatigue. The same model was valid for the prediction of fatigue at 6 months follow-up. This indicates that the tested model remained stable across time. Cognitive failure and depressive symptoms were the most important predictors of high levels of fatigue. Background

variables (time since diagnosis, sex and age), social support and trait anxiety appeared to be no predictors of fatigue.

The relationship between cognitive failure and fatigue is in line with a previous study, showing that patients with high levels of cognitive failure also reported higher levels of fatigue, compared to patients with lower levels of cognitive failure⁴. Elfferich et al.⁴ suggested that the relationship between cognitive failure and fatigue can be explained by a common underlying mechanism. In the literature, fatigue as well as cognitive failure has been associated with the over-expression and absence of cytokines. Imbalances in cytokines have been shown to directly influence synaptic plasticity and forms of memory associated with the hippocampus. These changes in the central nervous system may influence learning and memory functions³¹. An alternative explanation is that patients, who experience more cognitive failures, are continuously putting more cognitive effort in daily tasks (compensation) and subsequently will become more tired. This will be most strongly expressed in mental fatigue and to a lesser extent in physical fatigue, as we found in our correlational data.

It is important to note that anxiety predicted cognitive failure in the present study. This is in line with other studies in other populations^{32,33} that showed that anxiety appeared to be an important correlate of cognitive complaints. Possibly, patients with high trait anxiety are more sensitive to minor failures, similar to patients predisposed with high neuroticism,³⁴ and may therefore over-report subjective cognitive failure.

The negative associations between depressive symptoms and fatigue, symptoms suspected of SFN and fatigue, and dyspnea and fatigue, are in accordance with earlier findings in sarcoidosis that also examined fatigue in sarcoidosis, although none of these studies had a longitudinal design^{5,6,9}. In addition, the relationship between fatigue and depressive symptoms is in line with the results of studies in other chronic medical illness, such as diabetes, chronic obstructive lung disease, cardiac disease and rheumatoid arthritis³⁵. Research evidence suggests that the relationship between depressive symptoms and severity of medical illness is bidirectional. Depressive symptoms may indirectly lead to increased symptoms, because depressive symptoms are associated with poor self care (diet, exercise, cessation of smoking, medication regimens) in patients with chronic diseases. However, physical symptoms and resulting functional impairment caused by complications of medical illness also are likely to pose a burden on the patient's life and provoke depression³⁵. In the current study most patients are chronically ill, i.e., the mean time since diagnosis was 8 years. Possibly, the functional impairment associated with chronic sarcoidosis increases depressive symptoms. The relationship between depressive symptoms and fatigue may also be explained by a cytokine imbalance, initiated by an inflammatory immune response in sarcoidosis³⁶. Sarcoidosis patients treated with immunomodulating drugs exhibited a relation between fatigue and plasma IL-1 β concentrations³⁷. In addition, Heessen et al. showed that fatigue in MS patients is associated with activation of proinflammatory cytokines³⁸. The cytokine imbalance of patients suffering from depression also appeared to be disturbed³⁹. In addition, the finding that older patients reported more often dyspnea than younger patients confirms previous research⁴⁰. Also, the finding that females reported higher levels of symptoms associated with SFN

is in line with earlier research. Hoitsma et al.⁴¹ showed that gender was associated with pain, which is one of the core symptoms of SFN⁴².

Neither trait anxiety, social support, time since diagnosis, sex nor age predicted fatigue. A previous cross-sectional study reported an association between trait anxiety and fatigue in sarcoidosis⁴³. However, instead of a cross-sectional design, the current study has a longitudinal design which may explain the different results regarding trait anxiety. Also, the strong association between depressive symptoms and trait anxiety found in this study may explain the absence of a significant direct association between trait anxiety and fatigue. Possibly, the presence of depressive symptoms mediate the relationship between trait anxiety and fatigue. Regarding the relationship between sex and fatigue and age and fatigue, different results have been reported in the literature^{44,45}. The results of the current study suggest that dyspnea may mediate an indirect relationship between age and fatigue. In addition, symptoms suspected of SFN may be a mediator of relationships between fatigue and sex and fatigue and trait anxiety. Furthermore, the absence of an association between time since diagnosis and fatigue is in accordance with a previous study⁴⁵, indicating that fatigue does not resolve spontaneously across time⁴⁶.

This is the first study examining a conceptual model of fatigue in sarcoidosis. Previously, models of fatigue have been examined in cancer⁴⁷ and a healthy working population. Regarding social support, Michielsen et al.⁴⁸ also failed to demonstrate an association between fatigue and social relationships in a healthy working population. Stephanski et al.⁴⁷ examined fatigue in patients with cancer, also by means of path analysis. Their model differed from the model in this study, but the variables depressive symptoms, age and sex were also incorporated in the model to predict fatigue. In accordance with our results, they showed that depressive symptoms were related to fatigue.

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, because the symptomatology of these patients may be worse, compared to other sarcoidosis patients. However, this model may also be valid for patients who present with less severe symptoms, though with less strong associations between the variables. Future research is needed to examine this model in other sarcoidosis patients to confirm this assumption. Strengths of the study are the use of the method Structural Equation Modeling and the longitudinal design.

Future studies are warranted to replicate the findings of our study. Further research involving more comprehensive neuropsychological batteries are needed to achieve more details of cognitive functioning in sarcoidosis. In addition, possible moderating or confounding pathways between sex, age, trait anxiety, cognition and fatigue require more attention in further research. Also, further research is needed to assess the association between trait anxiety, cognition and depressive symptoms in relation to fatigue in sarcoidosis.

In conclusion, cognitive failure, depressive symptoms, symptoms suspected of small fiber neuropathy, and to a lesser extent dyspnea appeared to be significant predictors of fatigue 12 months after baseline. Therefore, in the management of

sarcoidosis patients with low energy levels it is recommended to emphasize these symptoms.

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