

Chapter 8

General discussion and summary

Introduction

Fatigue is a common complaint in sarcoidosis¹, and has been associated with an impaired quality of life². So far, the cause of fatigue remains unknown. In the literature, only a few studies have explored the role of psychological variables in fatigue. However, these studies are all cross-sectional, which prevents inferences regarding causality³⁻⁵. Moreover, fatigue is suggested to differ between individual patients⁶, though this is not empirically defined.

The aim of the studies presented in this thesis was to evaluate the problem definition and classification of fatigue in sarcoidosis. In addition, concepts related to fatigue were examined across time. Sarcoidosis outpatients of the department of Respiratory Medicine of the Maastricht University Medical Centre participated in this study. During a period of 18 months, patients completed questionnaires regarding fatigue, quality of life, depressive symptoms, small fiber neuropathy, cognitive failure, dyspnea, social support, and personality. In addition, they completed questions concerning restless legs, sleep, and activities. Clinical information was retrieved from the medical records. Additionally, data from two cross-sectional patient cohorts (Dutch and American sarcoidosis patients) were used.

In this chapter a general overview of the findings from the dissertation is presented. These findings are linked to implications for clinical practice, and the strengths and limitations of the results of this study are discussed. In addition, recommendations for futures studies are given.

Main findings and conclusions

In **Chapter 1**, a summary of the role of fatigue in sarcoidosis and an outline of the thesis was presented.

Problem definition and classification of fatigue

In **Chapter 2**, a systematic review of the literature regarding fatigue in sarcoidosis was presented. This review stressed the importance of fatigue and emphasized the need for longitudinal prospective studies to better define fatigue. Standardization of the assessment of fatigue, identification of prognostic factors for the development of fatigue, and exploration of treatment strategies aimed to reduce fatigue are needed.

In **Chapter 3**, the prevalence and the severity of fatigue between US and Dutch sarcoidosis patients were compared. In addition, potential relationships between fatigue and demographic and clinical parameters were examined. No relationships between fatigue, and clinical or demographical parameters were found in the total group. However, when examining the US and Dutch patients separately, fatigue was associated with age, extra-pulmonary involvement and drug-use in the US patients. Furthermore, although fatigue was equally prevalent, it was more severe in Dutch as compared to US patients with sarcoidosis. The high prevalence of extremely tired

Dutch patients, confirms that fatigue is an important and prevalent problem among patients, which requires more attention in the management of sarcoidosis. In addition, the substantial number of patients who reported no fatigue, fatigue, or extreme fatigue raised the question whether fatigue in sarcoidosis may be subdivided in different types of fatigue.

In **Chapter 4**, it was evaluated whether fatigue can be subdivided in types of fatigue as according to Sharma⁶: Early morning fatigue, Intermittent fatigue, and Afternoon fatigue by means of latent cluster analysis. The Intermittent Fatigue (IF) type was confirmed in the current study. In addition, two new types of fatigue were defined: All Day Fatigue (ADF) and Mild Fatigue (MF). MF patients reported mild or no complaints of fatigue. IF patients presented with complaints of fatigue, that varied during the day. ADF patients felt tired the whole day, and they reported more psychological problems and physical symptoms, in comparison to the other groups. In addition, they were most frequently unable to work. In order to improve the wellbeing of patients with ADF, the effectiveness of psychological counseling should be evaluated in future research. The categorization of patients in these three types of fatigue may help healthcare providers to tailor interventions to patients' individual needs and may also help to optimize treatment in sarcoidosis patients.

In **Chapter 5**, the minimal clinically important difference (MCID) of the Fatigue Assessment Scale (FAS) was assessed. Using anchor-based and distribution-based methods, the MCID in the FAS was examined and estimated on a change of 4 points for sarcoidosis patients. The MCID reflects a clinically relevant change score and may be useful in clinical and research trials, because it indicates a likelihood of treatment success in the management of fatigue. In addition, the MCID may be helpful for clinicians to interpret the clinical meaning of changes on fatigue scores of individual patients

Fatigue in sarcoidosis and related concepts: theoretical model

In addition to the problem definition and classification of fatigue, concepts related to fatigue were discussed. The absence of associations between fatigue and clinical and demographical parameters (Chapter 3) was an indication to examine other factors which are potentially related to fatigue.

In **Chapter 6**, a conceptual model of fatigue was developed and tested in order to examine the variables which potentially predict fatigue in sarcoidosis. The model in Figure 8.1 appeared to be valid for explaining variation in fatigue. Cognitive failure and depressive symptoms were the most important predictors of fatigue, followed by symptoms suspected of small fiber neuropathy, and dyspnea. Moreover, the model showed a strong association between depressive symptoms and anxiety. These results suggested an indirect relationship between personality (trait anxiety) and fatigue. Furthermore, the relationship between fatigue and cognitive failure and fatigue and symptoms associated with small fiber neuropathy may be mediated by trait anxiety as well. These symptoms should be critically evaluated and included in the management of sarcoidosis patients.

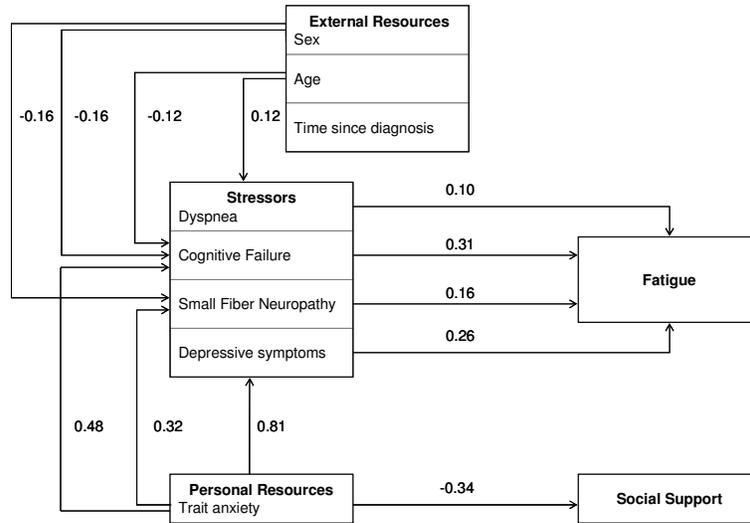


Figure 8.1 Model that was tested for understanding the associations among, sex, age, time since diagnosis, social support, trait anxiety, cognitive failure, depressive symptoms, dyspnea, small fiber neuropathy and fatigue in sarcoidosis^a
^a Error terms are omitted in this Figure. Significant path coefficients 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.

In **Chapter 7**, the triad of fatigue, depressive symptoms and anxiety was examined to untwine the complex relationship between psychological distress and fatigue. It appeared that fatigue was related, but not fully overlapping with trait anxiety and depressive symptoms. Moreover, type of fatigue mediated these relationships. Patients with ADF reported high levels of trait anxiety and depressive symptoms, more often than patients in the other two types of fatigue. Therefore, depressive symptoms and trait anxiety require special attention in the management of fatigue in sarcoidosis, especially for patients with ADF.

Clinical practice

Fatigue is a common and very important problem in sarcoidosis. In line with earlier studies, it was found that fatigue is frequently reported among patients^{1,3,6-9}. Furthermore, according to other studies, anxiety and depressive symptoms are prevalent^{1,7,10-15} and related to fatigue^{3,4}. Hence, fatigue has a great impact on patients' lives. Therefore, in the management of sarcoidosis patients treatment for fatigue is mandatory. However, currently, no standard treatment for fatigue is available in the management of sarcoidosis. The search for effective treatment may be hampered because the etiology of fatigue in sarcoidosis remains complex.

However, recent findings suggest that inflammation may play a pivotal role in the cause of fatigue¹⁶. Possibly, treatment focused on the disease activity may improve fatigue levels in a subgroup of patients.

Pharmacological interventions

The anti-tumor necrosis factor (TNF)- α antibody inhibits the activity of TNF- α ¹⁷. TNF- α , along with other cytokines, is critical in the development of the noncaseating granulomas that are the hallmark of sarcoidosis¹⁸. The efficacy of anti-TNF- α to treat fatigue has been demonstrated previously in small studies¹⁹⁻²¹. In addition, Wagner et al.²² reported that methylphenidate could treat sarcoidosis-associated fatigue. Subsequently, in a double-blind, placebo-controlled crossover trial with 10 patients, Lower et al.²³ showed that the stimulant d-methylphenidate was associated with a reduction in fatigue. Further research in larger samples is required to examine the effectiveness of treatment with anti-TNF- α or methylphenidate on fatigue.

In Chapter 7 it was shown that anxiety and depressive symptoms were highly prevalent in sarcoidosis and predictive for fatigue across time. Depressive symptoms might be important therapeutic targets as well, because patients with a major depressive disorder are likely to benefit from therapy with antidepressant medication²⁴. For instance, Häuser et al.²⁵ showed that treatment with antidepressants was associated with reduction of pain, depression, fatigue, sleep disturbances, and improvement of health-related quality of life in patients with fibromyalgia syndrome.

Psychological interventions

Psychological interventions are considered to be useful for patients with chronic conditions, because these patients often present with psychological distress associated with their disease²⁶. However, until now psychological interventions in sarcoidosis have not been studied. In other chronic disorders where fatigue plays an important role, such as chronic fatigue syndrome and cancer, psychological interventions appeared to be effective in reducing fatigue²⁷. White et al.²⁷ showed that cognitive behavioral therapy is an effective therapy in addition to specialist medical care to improve outcomes for chronic fatigue syndrome.

Cognitive behavioral therapy is a treatment based on the modification of behavior and cognitions. The following categories are described for cognitive behavioral therapy: coping skill methods, problem-solving methods, and cognitive restructuring methods. This therapy underlies the assumption that systematic errors and unrealistic cognitive appraisals of events can lead to negative emotions and maladaptive behaviors. Empirical evidence supports the effectiveness of cognitive behavioral therapy²⁸. Cognitive behavioral therapy may also be beneficial for the fatigued sarcoidosis patients. Especially for patients with ADF it is important to evaluate the usefulness of psychological counseling, since these patients experience the most psychological distress, i.e., depressive symptoms and anxiety, compared to the other patients (Chapter 4 and 7). According to the guidelines for treatment of anxiety

disorders and depression in the Netherlands^{29,30} cognitive behavioral therapy might be helpful in these patients to reduce levels of depressive symptoms and anxiety. Cognitive behavioral therapy is recommended as the treatment of choice^{29,30}. For instance, counseling regarding activity levels during the day may be useful for patients who have a maladaptive coping style. Possibly, patients' patterns of physical activity are characterized by alternating periods of extreme rest and periods of extreme levels of activity during the day. This pattern of physical activity may indicate maladaptive coping³¹. These patients ignore their fatigue and overexert themselves. Keeping a diary to describe their fatigue on a daily basis should be an additional part in future study designs, because the activity level may fluctuate between the measurement points. In addition, an actometer may be useful to measure physical activity objectively³². Psychological counseling is needed to teach patients more effective coping strategies, for instance, an intervention by learning patients to stay within their energy boundaries. This strategy appeared to be beneficial for patients with chronic fatigue syndrome in terms of fatigue reduction³³.

Evaluating interventions

For researchers it is recommended to consider the patients' perspective of clinical significance besides the statistical significant results. The MCID is the smallest change score of interest that patients perceive as relevant³⁴. The MCID may be relevant for researchers and clinicians who want to assess changes in fatigue, for instance, when evaluating treatment effects in future clinical trials. In addition, the MCID also provides more insight into the impact of fatigue on patients' lives. Previous studies³⁵⁻³⁸ in diseases comparable to sarcoidosis have also estimated the MCID in order to evaluate changes in health status, the 6 minute-walk distance and a respiratory scale, though a MCID for fatigue was still lacking. The MCID for the FAS, i.e., 4 points change (Chapter 5), may improve the clinical interpretation of changes in sarcoidosis-associated fatigue. Therefore, in the management of sarcoidosis it is recommended to use the MCID of the FAS.

Methodological considerations

Limitations

It is important to acknowledge the limitations of the studies in this thesis. First, all patients were recruited in a tertiary referral centre, which may diminish the generalizability of the results of this study. Second, a limitation of the study in Chapter 3 was that the recruitment of patients differed between the two studied sarcoidosis populations. Before they participated in the current study, the American patients participated in a study examining exercise capacity in an unselected sarcoidosis group. The most common reason for not participating in that exercise study was insufficient time to perform the study which reflects a selection bias. This may have

underestimated the incidence of fatigue in US patients. Third, because of the cross-sectional design of Chapters 3 and 4 it is not possible to comment on the causality of fatigue and the stability of the types of fatigue. Fourth, self-reported measures were used to assess fatigue and psychological symptoms. Gold standards to measure fatigue and psychological symptoms objectively are currently lacking³⁹. Therefore self-reported measures remain a highly valuable method to assess the symptoms, especially from the patient's perspective. Fifth, only a minority of the patients was included at disease onset. Consequently, time since diagnosis varied between the patients at inclusion. It is possible that patients who were diagnosed two years ago experienced other biological or psychological processes compared with patients who were diagnosed, for instance, six years ago. These processes may result in a bias when grouping these patients. However, it is difficult to include a sarcoidosis patient at the exact moment of disease onset, because the disease is waxing and waning. Moreover, often there is a delay between the onset of sarcoidosis and the diagnosis⁴⁰.

Strengths

Important strengths of the studies are the longitudinal design (Chapter 5, 6 and 7), the sample size, and the use of advanced methods. The longitudinal design provides a better framework to comment on causality and effect of fatigue in comparison with a cross-sectional design. Compared to other fatigue studies, the sample size of the current study ($n = 443$) is large. Except for the sample sizes of studies based on patient surveys^{1,5,9,41-43}, all other studies had a smaller sample size^{2-4,7,8,10,13,21,23,44-53}. In addition, in Chapter 3, a multicentre cross-sectional comparison of fatigue was performed on a number of factors, such as presentation, extra pulmonary involvement and treatment. Moreover, the use of advanced methods, such as structural equation modeling (Chapter 6) and latent clustering (Chapter 5) have a number of advantages. One advantage of latent clustering is that the identification of the number of latent classes is based on a statistical model that can be empirically tested. Thus, the classification of latent clustering is less arbitrary compared to other cluster methods, such as K-means clustering⁵⁴. A benefit of structural equation modeling is the availability of fit indices that evaluate the global fit of even complex models that entail several linear equations. Furthermore, structural equation modeling provides directly testing of a specified theoretical model of interest rather than testing an alternative hypothesis, which is commonly used in behavioral research⁵⁵.

Directions for future research

The findings presented in the current dissertation illustrated that fatigue is an important problem in sarcoidosis and appeared to be unrelated to the used clinical and demographical parameters. It was shown that symptoms, such as cognitive failure, depressive symptoms, symptoms suspected of small fiber neuropathy, and

dyspnea were predictive of fatigue across time. For the patients it is of utmost importance that these symptoms are taken seriously and should be an integral part in the management of sarcoidosis patients. Regarding cognitive failure, neuropsychological assessment is needed to measure objective cognitive functioning. In addition, the relationship with inflammation, sleeping problems, small fiber neuropathy and autonomic dysfunction is still unclear and requires further research.

Future studies should also focus on patients with acute sarcoidosis (time since diagnosis less than 2 years) in order to examine the relationships in patients with shorter disease duration. Obviously, there is still a need for well designed prospective clinical trials investigating the effectiveness of pharmacological and psychological treatment of fatigue, depressive symptoms and anxiety in patients with sarcoidosis. It is important to address these issues in further research in order to expand the knowledge on fatigue management, thereby, improving the quality of life of the patients.

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