Fatigue in Sarcoidosis

Layout: Tiny Wouters

Cover:

Production: Ridderprint

ISBN:

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PROEFSCHRIFT

Proefschrift ter verkrijging van de graad van doctor aan Tilburg University, op gezag van de rector magnificus, prof. dr. Ph. Eijlander, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in DZ1 van de Universiteit op woensdag 16 mei 2012 om 14:15 uur door Wilhelmina Petronella Elisabeth de Kleijn, geboren op 17 februari 1984 te Heumen.

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Chapter 1

General introduction

Sarcoidosis

Sarcoidosis is a systemic disorder of unknown cause, characterized by the spontaneous formation of granuloma[1-3]. Sarcoidosis may affect several organs, such as the lungs, lymphoid system, skin, eyes, heart, nervous system, and liver[4]. However, involvement of the lungs is most common in approximately 90% of the patients[5]. These patients present with respiratory symptoms such as cough and dyspnea. Furthermore, patients frequently report non-specific constitutional symptoms related to small fiber neuropathy, such as pain, general muscle weakness[6], exercise impairment[7], cognitive failure[8], depressive symptoms[9], and fatigue[10,11]. Sarcoidosis affects men and women of all ethnic groups and ages with an incidence peaking at 20 to 40 years of age. The disease occurs throughout the world, with an incidence varying from 1 to 2 cases per 100,000 people in Asiatic people to 35.5 per 100,000 in Americans[12]. The prevalence in the Netherlands is thought to be about 30-40 per 100,000[13]. However, incidence and prevalence rates may be confounded by the highly variable clinical presentation and a lacking registration system[14].

Sarcoidosis is diagnosed by excluding other diseases and is confirmed by biopsies and chest X-rays (CXR)[15]. The following radiographic stages (See Figure 1.1) were described by deRemee[16]: stage 0 (normal CXR), stage I (bilateral hilar lymphadenopathy), stage II (bilateral hilar lymphadenopathy and parenchymal abnormalities), stage III (parenchymal abnormalities without bilateral hilar lymphadenopathy), and stage IV (end stage lung fibrosis).

Clinical presentation

Depending on the duration of illness, organ involvement, and the fluctuating granulomatous activity, the course of sarcoidosis is highly variable. The clinical presentation varies from asymptomatic, to an ‘acute onset’, and to a chronic course. The acute form, i.e., Löfgren’s syndrome, presents with distinct skin presentation, fever, arthralgia and enlarged lymph nodes at the chest radiograph. The prognosis of acute onset sarcoidosis is good in general and spontaneous resolution frequently occurs within two years. In 10-30% of the cases the disease has an insidious onset and in these patients sarcoidosis becomes chronic. In chronic sarcoidosis, the course is often relapsing with spontaneous remission being less likely[17]. A worse prognosis is associated with respiratory functional impairment causing lung fibrosis, cardiac sarcoidosis, hypercalcemia and neurosarcoidosis[18]. The mortality rate of sarcoidosis is approximately 5%[19].

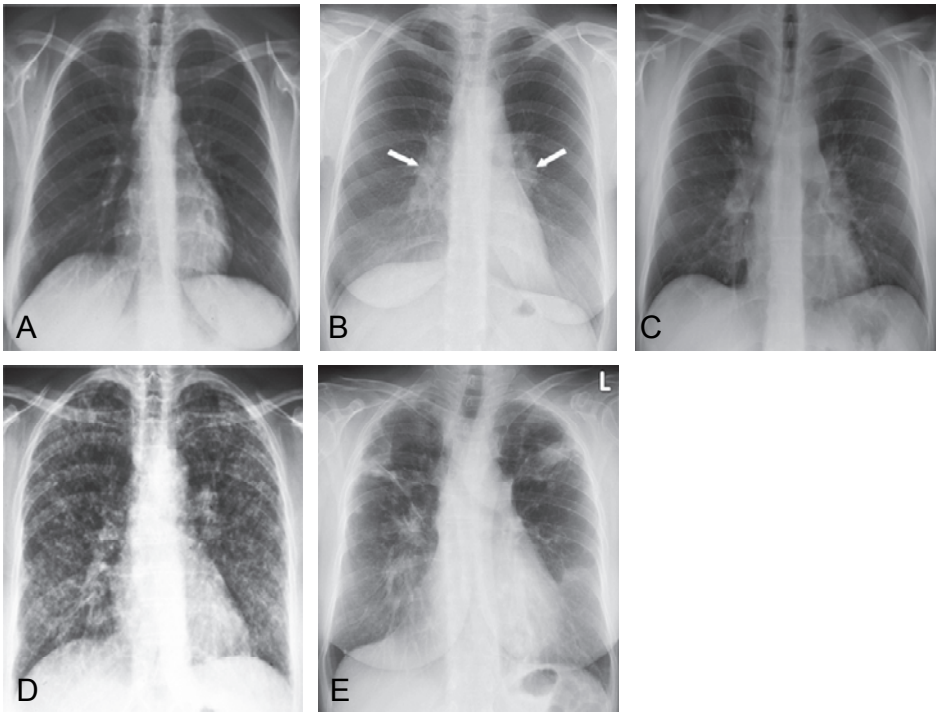

Figure 1.1 Chest X-ray stages 0-IV: radiographic appearances of sarcoidosis.
A) Stage 0: normal chest radiograph;
B) Stage I: bilateral hilar lymphadenopathy (arrows), without evidence of interstitial lung disease;
C) Stage II: both lymphadenopathy and parenchymal abnormalities (nodular and reticulonodular opacities);
D) Stage III: parenchymal infiltration without hilar lymph node enlargement (reticulonodular infiltrates);
E) Stage IV: obvious interstitial abnormalities with fibrotic lesions.

Fatigue

Since fatigue is a consistent complaint in sarcoidosis, several investigators have attempted to elucidate the potential causes of fatigue in sarcoidosis. So far, no organic substrate has been found for symptoms of fatigue. This means that even patients without respiratory functional impairment, no chest radiograph abnormalities and markers of disease activity having returned to normal, may experience substantial fatigue[20].

The combination of a high prevalence of fatigue and the uncertainty about the cause of fatigue may have a major impact on the patient's live. It appeared that fatigue is associated with a worse quality of life[21]. Various aspects of sarcoidosis, such as the relatively young age at disease onset, the chronic nature of the disease, the

unpredictable course of the disease, and the broad range of frequently persistent symptoms may account for the aggravating influence on the patient's quality of life.

The impact of persisting fatigue on sarcoidosis patients is frequently underestimated by physicians, health care workers, family and colleagues. Denial of symptoms of fatigue may possibly lead to the development of psychosocial problems. In addition, accommodation to fatigue by extreme resting may have unfavorable effects: the condition of the patients deteriorates and patients remain tired[22]. Psychosocial problems may also stimulate that high levels of fatigue sustain in chronic diseases[23]. Although the influence of psychological factors on fatigue is a very important issue, it still is an underestimated problem in sarcoidosis. Furthermore, all previous studies had a cross-sectional design, which makes inferences regarding causality impossible. An overview about the current literature regarding fatigue is provided in the next chapter.

Aim and design present study

This dissertation describes a prospective longitudinal follow-up study in patients with sarcoidosis. The results of this study are likely to point to sub-groups of sarcoidosis patients, who may warrant some form of behavioral intervention in addition to the medical management of the disease. In addition, knowledge concerning the prognostic variables of fatigue may be relevant in the clinical practice. These variables may be potential targets for therapy. Taking into account individual differences and tailoring interventions to patients' individual needs may also lead to more successful interventions and help optimize treatment in sarcoidosis patients.

Sarcoidosis outpatients (n = 443) of the ild care center of the department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC+), a tertiary referral center in the Netherlands, were asked to participate. These 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[24]. Patients were excluded in case of poor expression in the Dutch language, and/or relevant co-morbidity such as cancer, dementia, or a history of psychiatric illness. Eligible patients completed the first set of questionnaires in May 2007. Patients completed subsequent sets of questionnaires 6, 12, and 18-months after this baseline measurement. The Medical Ethical Committee of the MUMC+ (MEC 07-4-015) approved the study protocol and written informed consent was obtained from all patients.

Because currently no objective measure is available to examine fatigue in sarcoidosis, self-report questionnaires are used. Table 1.1 summarizes the variables used in the various studies. The Fatigue Assessment Scale (FAS) is a short self-report questionnaire for measuring fatigue. This questionnaire is the only fatigue questionnaire that has been validated in sarcoidosis patients till now. All patients completed the FAS[25,26], the Center for Epidemiological Studies-Depression Scale (CES-D)[27,28], the State and Trait Anxiety Inventory (STAI)[29], the Perceived Social

Support Scale (PSSS)[30,31], The World Health Organization Quality of Life Bref (WHOQOL-Bref)[32], the Small Fiber Neuropathy Screenings List (SFNSL)[33], the Single-Item Measures of Personality (SIMP)[34], the Cognitive Failure Questionnaire (CFQ)[35], and the Borg dyspnea index (BDI)[36]. In addition, patients completed questions regarding restless legs, sleep, activity, and fatigue. Details of these questionnaires will be provided in the following chapters.

Table 1.1 Time frame of the gathered demographical clinical and psychological information

	Baseline	6 months follow-up	12 months follow-up	18 months follow-up
Demographic information	X			
Clinical variables	X			
Medication	X	X	X	X
Fatigue	X	X	X	X
Quality of Life	X	X	X	X
Depressive symptoms	X			
Trait anxiety	X			
Small Fiber Neuropathy	X		X	
Cognitive failure		X	X	X
Dyspnea	X			
Social Support	X			
Personality	X			
Restless legs	X	X	X	
Fatigue and sleep questions	X	X	X	
Activities questions		X	X	

Clinical data, such as lung function measurements and chest radiographs, were derived from the patients' medical files. Lung function measurements, including forced expiratory volume in one second (FEV1) 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 (See Figure 1.1).

In addition to this prospective longitudinal follow-up study, cross-sectional data from two patient cohorts were used. A cohort of Dutch patients was matched for age, gender and radiographic stage with a cohort of US patients.

Outline of thesis

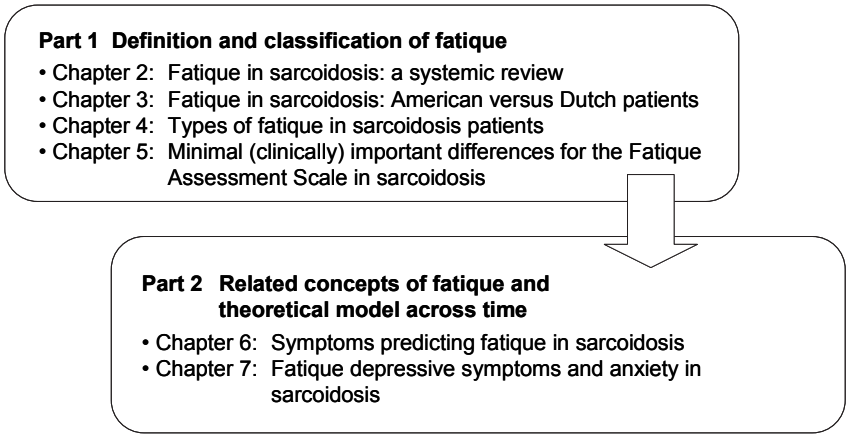

Figure 1.2 Outline of the thesis.

Part 1: Fatigue in sarcoidosis: problem definition and classification

The first part of the thesis addresses the problem definition and classification of fatigue in sarcoidosis. These issues are described in Chapter 2 to 5. **Chapter 2** provides an overview of the current literature regarding fatigue in sarcoidosis. This review focuses on published studies that are designed to assess the subjective aspects of fatigue experienced by sarcoidosis patients. Furthermore, the data on prevalence, etiology, and treatment of sarcoidosis-associated fatigue are summarized. The aim of **Chapter 3** is to compare the prevalence and the severity of fatigue between US and Dutch sarcoidosis patients, and to determine whether fatigue is related to demographic and clinical parameters. The next two chapters elaborate on the classification of fatigue in sarcoidosis. In **Chapter 4** it is examined whether fatigue in sarcoidosis can be subdivided in types of fatigue: Early-morning fatigue, Intermittent fatigue, and Afternoon fatigue, as previously described by Sharma[11]. Furthermore, the demographic, psychological, and clinical characteristics of the derived clusters are described. In **Chapter 5**, the Minimal Clinically Important Difference (MCID) for the FAS is estimated. 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. Both anchor-based and distribution-based methods are employed to establish the MCID of the FAS.

Part 2: Fatigue in sarcoidosis and related concepts: theoretical model across time

Subsequently, the role of psychological factors in relationship to fatigue across time is discussed in Chapters 6 and 7. In **Chapter 6**, the development and validation of a conceptual model of fatigue in sarcoidosis is addressed. This model is based on the model of Taylor and Aspinwall[37]. Data concerning demographic variables, trait anxiety, social support and stressors, all measured at baseline, are included. Fatigue at 12 months follow-up is the dependent variable in the model. In **Chapter 7** a prospective 18-months follow-up study is reported. The purpose of this study is to examine the prevalence of depressive symptoms and anxiety in relationship to fatigue in sarcoidosis, stratified for the types of fatigue. Furthermore, it is evaluated whether anxiety and depressive symptoms predict fatigue across time.

Finally, **Chapter 8** provides a summary and general discussion. Additionally, the present outcomes are related to implications for clinical practice, and recommendations for future studies are given.

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Chapter 2

Fatigue in sarcoidosis: a systematic review

De Kleijn WPE, De Vries J, Lower EE, Elfferich MDP, Baughman RP, Drent M

Curr Opin Pulm Med 2009; 15: 499-506.

Abstract

Purpose of review
Several studies have investigated fatigue among sarcoidosis patients. The purpose of this review is to analyze published data on the assessment, prevalence, etiology, and treatment of sarcoidosis-associated fatigue.

Recent findings
Fatigue was identified as a prominent problem in sarcoidosis, and its presence was frequently associated with impaired quality of life, compared with patients without fatigue. Although the studies with good methodological fatigue assessment found no relationship between clinical parameters and fatigue in sarcoidosis patients, the remaining studies reported associations between fatigue and clinical and psychological parameters. No studies were designed to analyze the etiology of fatigue, but some studies showed that prednisone-treated patients reported more fatigue compared with untreated patients. In addition, only one study focused on a treatment for fatigue, dexmethylphenidate hydrochloride. Several instruments to measure fatigue were used, with the Fatigue Assessment Scale most frequently utilized.

Summary
This review illustrates the importance of fatigue as an under-recognized complication of sarcoidosis. It further emphasizes the need for longitudinal prospective studies to better define sarcoidosis-associated fatigue, explore its impact on quality of life, define aggravating or alleviating factors and evaluate new potential treatment strategies.

Introduction

Fatigue remains an underestimated and difficult problem in the management of sarcoidosis patients[1,2]. A study among Dutch sarcoidosis patients showed that fatigue was the most often reported symptom[3]. The etiology for this complaint remains unclear, as it is usually multifactorial. Although the granulomas and their released cytokines may be involved in the etiology of fatigue, the disease treatment along with comorbidities, including depression[4], weight gain, exercise intolerance, or altered sleep patterns[5], may be culprits too. Frequently, the disease itself is a direct cause of this troublesome symptom; however, in some patients the successful treatment of sarcoidosis with corticosteroids can worsen fatigue. Regardless of the etiology, fatigue was negatively related to the patients' quality of life[3].

Currently, no general agreement exists on the definition of fatigue. According to a number of researchers, fatigue can be divided into at least two categories: physical and mental[6], or passive and active fatigue[7]. However, a recent study claims that fatigue should be treated as a unidimensional concept[8].

As in other chronic diseases, fatigue needs to be objectively measured in sarcoidosis. Although various fatigue questionnaires exist, the Fatigue Assessment Scale (FAS) is the only one that has been validated for use in sarcoidosis patients[9]. Unfortunately, physical measurements of fatigue, such as exercise testing, fail to correlate with the patients' complaints of fatigue. This review focuses on published studies that are designed to assess the subjective aspects of fatigue experienced by sarcoidosis patients. Furthermore, the data on prevalence, etiology, and treatment of sarcoidosis-associated fatigue are analyzed.

Methods

A computerized search of the literature from 1997 until October 2008 was performed using the search terms 'sarcoidosis' and 'fatigue'. Hits were identified in PubMed (113 hits), PsycINFO (3 hits), the Cochrane Library (3 hits), and Web of Science (78 hits). Reference lists of relevant studies were checked to identify any additional published research not identified by computerized database searches.

Selection criteria

Studies included for evaluation met the following criteria: the study objective was to describe fatigue in sarcoidosis; the study population consisted of only sarcoidosis patients or included an identifiable and separately analyzed subgroup of patients with sarcoidosis; the article was a full report (no case report, editorial, poster text, letter, or review); the study was published in English; and published in a peer reviewed journal.

The described inclusion criteria[10,11] were applied to the initial 197 hits, with 55 identified as duplicate. On the basis of titles, abstracts, and references, 23 articles met

the inclusion criteria. After full article inspection, 20 articles met our selection criteria and were included in this review[3,5,9,12–26,27••,28••]. Figure 2.1 reveals the flow chart of the study selection.

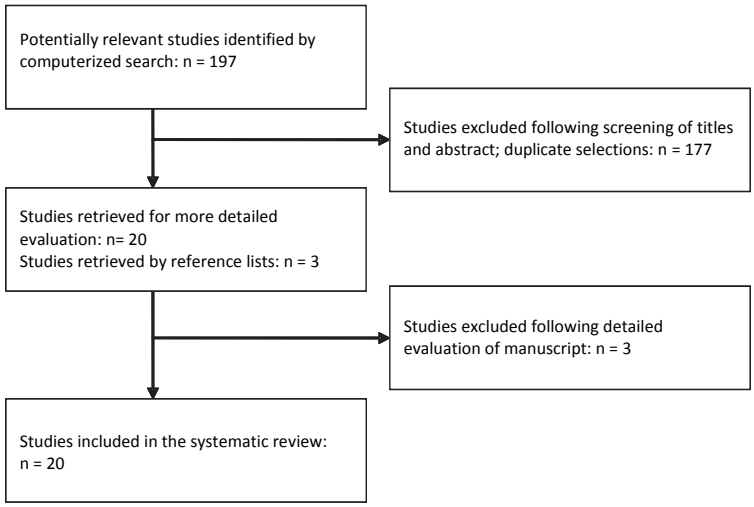

Figure 2.1 Study selection process

Assessment of methodological rank

The procedure of a systematic review was chosen, because we wanted to include as many studies into fatigue as possible. In order to conduct a meta-analysis it is necessary that studies employ the same questionnaire. As most studies used different questionnaires or methods to assess fatigue only a few studies would remain.

Using a standardized systematic review checklist of 17 predefined criteria, the methodological rank of the studies was independently assessed by three reviewers (DK, DO, and DV). The checklist was a modified version of an established criteria list for systematic reviews on quality of life[11,29]. Table 2.1 lists the criteria analyzed. One point was assigned to each item that met a criterion. If an item did not meet a particular criterion, it was described insufficiently, or not at all, no point was assigned. With the highest possible score 17, studies scoring 70% or more of the maximum attainable score (i.e., ≥12 points) were considered to be of 'high rank'. Studies scoring between 50% and 70% (9 or 10 points) were rated as 'moderate rank', whereas, studies scoring lower than 50% (≤8 points) were considered 'low rank'[11].

Table 2.1 Methodological rank of studies on fatigue among sarcoidosis patients[a]

Study	Criteria																	Points
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	
[21]	1	1	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	12
[3]	1	1	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	12
[23]	0	1	1	1	1	1	1	1	0	1	1	0	1	0	0	1	1	12
[9]	1	1	0	1	1	1	0	0	0	1	1	0	1	0	0	1	1	10
[25]	0	0	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	10
[15]	0	0	1	1	1	1	1	1	0	1	1	0	1	0	0	1	0	10
[14]	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	1	1	10
[28••]	0	0	1	1	1	1	1	0	0	0	1	0	1	0	1	1	1	10
[27••]	0	0	1	1	1	1	0	0	0	1	1	0	1	0	0	1	1	9
[19]	0	0	0	1	1	1	0	1	0	1	1	0	1	0	0	1	1	9
[17]	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	1	0	9
[26]	0	0	1	1	1	1	0	1	0	1	1	0	1	0	0	1	0	9
[5]	1	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	1	9
[22]	0	0	0	1	1	0	0	1	0	1	1	0	1	0	0	1	1	8
[18]	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	0	0	8
[24]	0	0	1	1	1	1	1	0	0	0	1	0	1	0	0	1	0	8
[20]	0	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	0	7
[12]	0	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	0	7
[16]	0	0	0	1	1	0	0	0	0	1	1	0	1	0	0	1	0	6
[13]	0	0	0	1	1	0	0	0	0	1	1	0	1	0	0	1	0	6
All	4	4	15	20	20	17	7	8	0	15	20	0	20	0	1	19	11	

A. A description is given of fatigue by describing the subjective experience of the patient;
B. A reason is given for choosing a certain questionnaire;
C. The diagnosis of sarcoidosis is according to the World Association of Sarcoidosis and Other Granulomatous Disorders criteria;
D. A description is included of at least two socio-demographic variables (e.g., age, sex, employment status, educational status);
E. A description is present of at least two clinical variables (e.g., duration of symptoms, use of medication, lung function tests);
F. Inclusion and/or exclusion criteria are provided;
G. Participation rates for patient groups are described and these rates are exceeding 75%;
H. The study describes potential prognostic factors by using multivariate analyses or structural equation modelling;
I. Characteristics of responders were compared with non-responders in order to give information about the representativeness of the responders (A patient who participates in a study is defined as a responder and a patient who refused to participate is defined as a non-responder);
J. The study size is consisting of at least 50 patients (arbitrarily chosen);
K. The collection of data is prospectively gathered;
L. The design is longitudinal (more than 1 year);
M. The process of data collection is described (e.g., interview or self-report);
N. The follow-up period is at least 6 months;
O. The loss to follow-up is no more than 20%;
P. The results are compared between two groups or more (e.g., healthy population, groups with different severity of sarcoidosis or age) and / or results are compared with at least two time points (e.g., longitudinally or pre- versus post-treatment);
Q. A psychometrically sound fatigue questionnaire is used.

[a] Studies scoring ≥12 points were considered to be of 'high rank' studies scoring 9 or 10 points were rated as 'moderate rank', and studies scoring 8 points or less were considered 'low rank' studies.

Results

Table 2.2 provides all study characteristics. Fatigue was the major study outcome in eight of the identified studies; whereas, it was a minor outcome in twelve studies. In six of these twelve studies, quality of life and/or health status were the main objectives, and three studies analyzed muscle function in relation to sarcoidosis fatigue. The remaining three studies described fatigue in relationship to stress, pain, and the 6-minute walk distance (6MWD) during an exercise test. Sample sizes ranged from 10 to 1046, and patients mostly were treated with systemic corticosteroids medication for treatment of sarcoidosis.

Methodological rank

Table 2.1 summarizes the assessment of the methodological rank of the 20 studies. Initially an eight-percent discrepancy was reported among the three reviewers; however, these differences were resolved at a consensus meeting. The rank scores ranged from 6 (low rank) to 12 points (high rank) with the mean rank score 9. Three, ten, and seven studies were considered as high, medium, and low rank, respectively. All studies prospectively collected data (item K), described the data collection (item M), and included at least two socio-demographic (item D) and at least two clinical (item E) variables. Most studies provided inclusion and exclusion criteria (item F), evaluated more than 50 patients (item J), or compared their results between two or more groups (item P). Fifteen of the 20 studies defined patients with sarcoidosis using American Thoracic Society (ATS)/ World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) criteria[30]. As patients in the remaining five studies were self-reported members of the Dutch Sarcoidosis Society (DSS), no data from medical records were available for disease confirmation. Half of the studies used a psychometrically valid fatigue questionnaire (item Q). Eight studies used multivariate analyses or structural equation modeling to describe potential prognostic factors (item H), and seven trials reported a participation rate of more than 75% (item G). Only a few studies described the subjective experience of fatigue by the patient (item A) or provided a reason for choosing a certain questionnaire (item B). Only one double blinded trial[28••] compared two instruments of fatigue, and reported no patients lost after 8 weeks follow-up (item O). In addition, this study[28••] used a crossover design, which has a higher level of internal validity, compared with the cross-sectional designs in the remaining studies. However, none of the studies provided a longitudinal design (item L, N). This is a major shortcoming, because no conclusion can be drawn with respect to the causality of fatigue. Moreover, none of the studies described whether the nonresponders were comparable to the responders (item I).

Table 2.2 Characteristics of studies on fatigue among sarcoidosis patients[a]

Study	Major outcomes	Sample size (n)	Male/female (n)	Age mean	Medication (n)
[21]	Fatigue	60	31/29	41	Corticosteroids 26
[3]	Fatigue	145	52/93	44	Corticosteroids 73
[23]	Fatigue, psychometric qualities	150	54/96	44	
[9]	Fatigue	1046[d]	390/617	45-49[b]	Corticosteroids 282
		80[d]	36/44	41	Corticosteroids 21
[25]	Exercise, 6MWD	142	41/101	51	Corticosteroids 124
[15]	QOL, depression	64	37/27	43	Corticosteroids 21
[14]	QOL	64	37/27	43	
[28••]	Fatigue	10	2/8	52	Corticosteroids 9; hydroxylchloroquine 7; methotrexate 6; azathioprine 1; eflunomide 1.
[27••]	Fatigue	81	20/61	48	
[19]	Pain	821	305/508	46	Corticosteroids 469; NSAIDS: 259; analgesics: 268; psychological /neurological drugs 100
[17]	QOL	37	21/16	45	Corticosteroids 14
[26]	QOL, symptoms	150	54/96	44	Corticosteroids 74
[5]	Fatigue	38	22/16	40	
[22]	Stress	1046	390/617	45-49[b]	Corticosteroids 282
[18]	Development of HS	149[c]	48/101	44	Current therapy for sarcoidosis 105; corticosteroids 94
	questionnaire	111[c]	24/87	45	Current therapy for sarcoidosis 62; corticosteroids 55
[24]	Muscle weakness	22	14/8	42	Corticosteroids 11
[20]	Muscle weakness	34	18/16	45	Corticosteroids 9
[12]	Muscle weakness	18	11/7	43	Corticosteroids 7
[16]	QOL	975	358/617	47	Corticosteroids 559; heart medication 89; pain killers 328; psychological/neurological medication 119; NSAIDS 322; bronchodilators 291; eye drops 235.
[13]	Fatigue	1026	380/646	47	Corticosteroids 565

6MWD = 6-meter walking distance; HS = Health Status; NSAIDS = Non-steroidal Anti-Inflammatory Drugs; QOL = Quality of Life.

[a] Information about sarcoidosis patients is presented, no information about controls or other than patient groups is included; [b] Median age; [c] 149 patients of development study and 111 patients of validation study; [d] 1046 members of Dutch Sarcoidosis Society and 80 outpatients

Fatigue

International studies recognize that fatigue is a common problem for sarcoidosis patients[2,3]. Despite adequate treatment for other manifestations of sarcoidosis, a substantial number of sarcoidosis patients suffer from persistent fatigue[13,14]. According to initial Dutch studies, fatigue was the most frequently reported symptom in sarcoidosis patients[13–15]. Fatigue afflicted 80% of the members of the DSS, which consist mainly of chronic sarcoidosis patients[9]. Furthermore, in a study of sarcoidosis patients from Dutch hospitals[15], 73% of the symptomatic sarcoidosis patients reported fatigue. This self-reported fatigue approximates the incidence of fatigue reported by another group of chronic inflammatory disease patients, rheumatoid arthritis patients[17]. In addition, the sarcoidosis patients reported a lower level of energy compared with healthy controls[17]. Table 2.3 summarizes the incidence, assessment, and conclusion about fatigue reported in the selected studies.

Sex differences in fatigue are inconsistent. Although compared with male Sarcoidosis patients, females from both the DSS[16], and Croatia[23] reported more symptoms of fatigue, a Dutch study of chronic outpatients showed higher scores for fatigue in men[9]. Furthermore, an additional Dutch study failed to reveal sex differences for fatigue[21].

Assessment of fatigue

The 20 analyzed studies utilized a variety of objective instruments to measure fatigue. As noted in Table 2.3, fatigue was usually measured with questionnaires, whereas other subjective tests, including interview and symptom inventories, were infrequently used.

The three high rank studies[3,21,23], three medium rank studies[9,25,28••] and one low rank study[22] employed the 10-item FAS to measure fatigue in sarcoidosis. The FAS is a well validated and reliable fatigue measure among sarcoidosis patients. Two studies reported that the content validity, construct validity and internal consistency of the FAS were good. The test–retest reliability was 0.89[9,23].

Five additional medium rank studies[5,9,14,19,26] measured fatigue using the facet Energy and Fatigue of the World Health Organization Quality of Life Assessment Instrument-100 (WHOQOL-100). This facet consists of four questions: ‘How easily do you get tired?’, ‘How much are you bothered by fatigue?’, ‘Do you have enough energy for everyday life?’, and ‘How satisfied are you with the energy you have?’ This tool appeared to be a sensitive instrument to measure fatigue[14]. In two medium rank studies, fatigue was measured with fatigue questionnaires that are not validated in sarcoidosis, that is, the Fatigue Scale[27••] and the Functional Assessment of the Chronic Illness Therapy–Fatigue (FACIT-F)[28••].

Table 2.3 Incidence, assessment, and conclusions about fatigue of studies among sarcoidosis patients[a]

Study	Incidence of fatigue n (%)	Assessment of fatigue	Conclusions about fatigue
[21]	44 (73%)	FAS	Clinical or serological parameters, except D_LCO, did not predict fatigue.
[3]	83 (57%)	FAS, symptom inventory	Tired patients reported a worse QOL, and clinical parameters were unrelated to fatigue.
[23]	83 (55%)	FAS	The Croatian translation of the FAS is reliable and valid.
[9]	837 (80%)[b] 68 (85%)[b]	FAS, WHOQOL-100 facet Energy & Fatigue	The FAS is a promising measure to assess fatigue.
[25]	98 (69%)	FAS	Fatigue was related with 6MWD and with dyspnea.
[15]	27 (73%)[c]	Interview	Fatigue was a major complaint, and QOL was related to the perception of complaints.
[14]	28 (76%)[c]	WHOQOL-100, interview	WHOQOL-100 is a sensitive instrument to measure fatigue. The facet Energy & Fatigue was related to depression, but unrelated to the domain Psychological Health and lung function.
[28••]	10 (100%)[d]	FAS, FACIT-F	Treatment with d-MPH was associated with a significant improvement in fatigue
[27••]		Fatigue Scale	Patients with extrapulmonary involvement are more fatigued than patients with pulmonary involvement.
[19]	599 (73%)	WHOQOL-100, symptom inventory	Fatigue was related to pain.
[17]	28 (76%)	Interview	Sarcoidosis patients reported as much fatigue as patients with RA, and more than controls.
[26]	88 (60%)	WHOQOL-100, symptom inventory	Fatigue predicted QOL after controlling for demographics and clinical parameters.
[5]	25 (66%)	WHOQOL-100 facet Energy & Fatigue, symptom inventory	Fatigue was related to an acute phase response, but not to markers of disease activity. Tired patients suffered more frequently from dyspnea, exercise intolerance, muscle pain, eye problems and needed more sleep.
[22]		FAS	Fatigue was related to perceived stress, when the role of depression was partialed out.
[18]		SHQ	SHQ is appropriated to measure fatigue in sarcoidosis, including fatigue.
[24]	22 (100%)[d]	Domain fatigue of CRDQ, Borg score fatigue, 6MWD	Quadriceps peak torque was negatively associated with fatigue. Patients reported more fatigue than healthy controls.
[20]		Vitality subscale SF-36	Vitality was related to inspiratory muscle endurance.
[12]	6 (33%)[c]	Interview	Fatigued patients had lower maximum expiratory muscle pressures than those without fatigue.
[16]	720 (74%)	Symptom inventory	Women reported more fatigue, and women who used oral steroids reported more fatigue.
[13]	728 (71%)	Symptom inventory	The most frequently reported symptom was fatigue. Symptoms and corticosteroids were not related. Women suffered more frequently from fatigue.

6MWD = 6-meter walking distance; CRDQ = Chronic Respiratory Disease Questionnaire; D_LCO = Diffusing Capacity of the lung for Carbon monoxide; d-MPH = dexmethylphenidatehydrochloride; FACIT-F = Functional Assessment of the Chronic Illness Therapy-Fatigue; FAS = Fatigue Assessment Scale; QOL = Quality of Life; RA = Rheumatoid Arthritis; SF-36 = Short Form 36; SHQ = Sarcoidosis Health Questionnaire; WHOQOL-100 = World Health Organization questionnaire of Quality of Life.

[a] Information about sarcoidosis patients is presented; no information about controls or other patient groups is included.

[b] 837 members of Dutch Sarcoidosis Society and 68 outpatients .

[c] Percentage among patients with current symptoms.

[d] Fatigue was an inclusion criterion

The 14 questions in the Fatigue Scale are designed to distinguish mental from physical fatigue. It is both reliable and valid in 100 consecutive patients in general medicine practice[27••]. The FACIT-F, which examines 41 items, is considered a reliable and valid measure of fatigue in cancer patients[31]. No difference was noted in the assessment of fatigue by the FAS or FACIT-F in one study[28••]. In three medium rank studies[14,15,17] and one low rank study[12], patients were interviewed about fatigue. Furthermore, patients completed a symptom questionnaire or inventory in three medium rank studies[5,19,26], in two low rank studies[13,16], and in one high rank study[3].

In the remaining low rank studies fatigue was measured using health status instruments, such as the Sarcoidosis Health Questionnaire (SHQ)[18], the subscale Vitality of the Short Form 36 (SF-36)[20], and the fatigue domain of the Chronic Respiratory Disease Questionnaire (CRDQ)[24]. Although the SHQ[18] is a reliable and validated instrument for assessing health status in sarcoidosis, the domain fatigue was queried in the SHQ with only one item: 'Daily Functioning-Felt you were full of energy'. Spruit et al.[24] also assessed fatigue utilizing a Borg fatigue score[32] after an incremental cycle exercise test. Regarding the SHQ, Vitality of the SF-36, CRDQ, and the Borg fatigue scale, no information is available of the validity and reliability of the fatigue measurement in sarcoidosis.

Causes of fatigue

Despite the complex and multifaceted etiology of fatigue, several investigators have attempted to elucidate the potential causes of fatigue in sarcoidosis. Most studies have evaluated clinical parameters with few studies postulating psychological factors as underlying mechanisms of fatigue.

Two high rank studies found no relationship between fatigue in sarcoidosis patients and clinical variables tested, including pulmonary function, metabolic measures, laboratory parameters of inflammation, or T-cell activation and granuloma formation[3,21]. Likewise, one medium rank study found no correlation between fatigue and lung function[14].

However, other medium rank studies reported associations between fatigue and acute phase response, 6MWD, dyspnea, pain, and extrapulmonary involvement. In a recent study[27••] sarcoidosis patients with pulmonary plus extrapulmonary involvement reported more fatigue than patients with pulmonary involvement only. In addition, Drent et al.[5] found that fatigue was related to an acute phase response, but unrelated to markers of disease activity. Moreover, fatigue was related to dyspnea, as measured with the Medical Research Council, and to the 6MWD during an exercise test[25]. Furthermore, a large study of sarcoidosis patients without comorbid conditions showed that fatigue was associated with specific types of pain, such as muscle pain, chest pain, arthralgia, abdominal pain, and headache[19].

With regard to the psychological factors stress and depression, fatigue was found to be related to depression[14]. Moreover, a Dutch study correlated high scores on perceived stress with more fatigue, even after depressive symptoms were excluded[22].

Some low rank studies have also sought to correlate fatigue with muscle weakness as quantified by expiratory muscle pressure, inspiratory muscle endurance, and quadriceps peak torque. Patients with fatigue experienced significantly lower maximum expiratory muscle pressures[12], a lower inspiratory muscle endurance than those without symptoms[20], a lower fat free mass over body weight ratio, and a lower quadriceps peak torque after an incremental exercise test[24]. Moreover, fatigued sarcoidosis patients compared with non-fatigued patients also reported more exercise intolerance and muscle pain[24]. These studies were limited by the small sample size.

Treatment and fatigue

Interestingly, treatment for symptomatic sarcoidosis may improve or worsen the fatigue experienced by sarcoidosis patients. Most of the twenty analyzed studies reported some treatment for their fatigued sarcoidosis patients. Although corticosteroids remain the mainstay of sarcoidosis treatment, some chronic patients also received a variety of steroid-sparing regimens. In a medium rank study[9], that examined fatigue in two groups of sarcoidosis patients, it appeared that DSS patients who used prednisone exhibited higher fatigue scores than patients not using prednisone. However, fatigue was unrelated to prednisone use in the outpatient group. One low rank study found that women who used oral steroids reported lower scores in the facet Energy and Fatigue[16].

Thus far, few data are available regarding specific treatment for fatigue-associated sarcoidosis. Only one treatment study was included in this 20-study analysis. In a recent small double-blinded, placebo-controlled cross over medium rank study, the stimulant dexmethylphenidate hydrochloride (d-MPH) was associated with a significant reduction in sarcoidosis-associated fatigue[28••].

Fatigue and quality of life

Fatigue is not synonymous with impaired quality of life (QOL). In a high rank study fatigued sarcoidosis patients reported a worse QOL in all domains[3]. In an additional medium rank study fatigue remained an important negative predictor for the QOL domains of physical and psychological health and level of independence, after controlling for demographics, disease stage and clinical parameters[26]. However, in another study, no correlation was found between the facet Energy and Fatigue and the domain Psychological Health of the WHOQOL-100[14].

Discussion

The purpose of this review was to focus on subjective fatigue among sarcoidosis patients in published studies. In addition to the methodological rank of the selected studies, we reviewed the assessment, potential causes, treatment, and QOL in sarcoidosis-associated fatigue. The mean methodological rank score is moderate, and

one major shortcoming of the current fatigue studies is the lack of longitudinal follow-up.

Regardless of the rank of study, all 20 published reports confirm that fatigue is a prominent symptom in sarcoidosis, because of the high prevalence, the aggravating influence on patients' life, and a lack of convincing evidence for the cause of fatigue. Despite no consistent definition, this symptom is reported in up to 85% of symptomatic sarcoidosis patients in multinational studies, and it frequently is associated with an impaired QOL. Furthermore, high rank studies found no potential causes for sarcoidosis-associated fatigue. Possibly, the inflammation and granuloma burden in sarcoidosis may be responsible for fatigue; however, little is known about phenotypic prognostic factors for fatigue such as specific organ involvement or disease chronicity. Likewise no data are available regarding genotypes and sarcoidosis-associated fatigue. Hence, the etiology of fatigue remains enigmatic and complex, which might reflect the interrelationships between mental and physical domains.

Although the definition of fatigue is not standardized and its etiology remains complex, validated questionnaire instruments help to measure fatigue. The FAS is the most widely used objective measurement for sarcoidosis-associated fatigue and available in several languages (http://www.ildcare.eu/pages/artsen_informatie_fasen.html, please contact the authors for further information). This reliable and validated instrument is short and lends itself to usage for both inpatients and outpatients. All three high rank studies and three of the medium rank studies utilized this tool. It is important to assess fatigue by means of a questionnaire validated in sarcoidosis patients, because fatigue might be expressed differently in sarcoidosis compared with a healthy controls or another disease population.

Regarding treatment strategies, only one recent medium rank study showed that treatment with d-MPH improved sarcoidosis-associated fatigue[28••]. Other studies suggest that prednisone usage can even be associated with more severe fatigue[9,16], although corticosteroids can successfully treat the symptoms of sarcoidosis. Unfortunately, these studies were not designed to ascertain if steroids represent cause or effect for fatigue. It is possible that corticosteroids represent a surrogate marker for more severe or chronic disease or the development of comorbid conditions of weight gain, diabetes, depression, inactivity, or altered mood states including sleep. In addition to medication, cognitive behavioral therapy should also be considered as treatment strategy, because cognitive behavioral therapy and graded exercise programs have been shown effective in treating fatigue in patients with chronic fatigue syndrome[33].

For future research we recommend improved study designs, that is, studies with longitudinal design and more patients, and to explore relationships between fatigue and associated factors such as sleeping disorders, cognitive problems, small fiber neuropathy (SFN), and treatment with anti-tumor necrosis factor-alpha (anti- TNF-α) drugs. Although the included studies that found relationships between fatigue and clinical or psychological variables were considered of medium to low rank, they often focused on aspects not examined in higher rank studies. In addition, many high rank

studies were conducted in referral centers whereas, for example the Dutch survey[9,13,16,22] involved unselected patients.

Although the high rank studies are methodologically more sound because they can provide much information about their participants, participants in studies such as the Dutch survey may be more representative of patients not seen in referral centers. The study on d-MPH[28••] was not an incidence study, because fatigue was an entry criterion for all patients. However, it provides information regarding reproducibility and placebo effect. Therefore, we recommend duplicating existing low and medium rank studies but this time using a more rigid methodological design, for example, regarding found relationships between fatigue and acute phase response, 6MWD, dyspnea, pain, organ involvement, muscle weakness, stress and depression.

Sleeping disorders[34] and cognitive problems (Elfferich M, De Vries J, Wijnen P et al., unpublished data) are factors that may interact with fatigue in sarcoidosis. Therefore, questions regarding sleeping disorders and neuropsychological assessment should be assessed in addition to the FAS.

SFN is frequently reported among patients with sarcoidosis and is associated with autonomic dysfunction[35]. Moreover, it has been found that autonomic dysfunction is frequently accompanied by chronic fatigue[36]. Therefore, it is interesting to explore the relation between SFN and fatigue in sarcoidosis.

Treatment with anti-TNF-α improves lung function[37] in sarcoidosis and appeared to be useful in treating chronic sarcoidosis[38]. Also, in Crohn's disease[39] and in rheumatoid arthritis[40] a positive effect on fatigue was demonstrated. Two case reports described a reduction in fatigue due to anti-TNF-α medication in sarcoidosis[41,42]. In addition, an observational study[43•] showed a reduction of fatigue and other symptoms after treatment with anti-TNF-α in 12 sarcoidosis patients. Moreover, changes depicted by the positron emission tomographic scan were correlated with these clinical improvements. Future studies should incorporate untreated as well as treated multinational sarcoidosis patients and they should be randomized and blinded in order to improve the evaluation of treatment in general, especially with biologicals, including anti-TNF-α drugs.

Conclusion

More research is needed to standardize the assessment of fatigue, identify prognostic factors for the development of fatigue, and explore treatment strategies to reduce fatigue and thereby improving patients' quality of life. Longitudinal studies will provide follow-up needed to better identify predictors of fatigue and new potential targets for therapy.

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Changes imaged by the positron emission tomographic scan were correlated with a decrease in complaints of fatigue.

Chapter 3

Fatigue in sarcoidosis: American versus Dutch patients

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Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 92-97

Abstract

Background
Fatigue is a major problem in sarcoidosis. Fatigue has mainly been examined in patients from the Netherlands.

Objective
The aims of the study were to establish the prevalence of fatigue in US and Dutch patients and to determine whether fatigue was related to the common demographic and clinical parameters.

Design
Two patients groups were studied: Dutch outpatients at Maastricht University Medical Center in the Netherlands (n = 121) and US patients at the University of Cincinnati Medical Center in the USA (n = 126). Both groups completed the Fatigue Assessment Scale. Clinical data were gathered from the patients' medical files.

Results
The prevalence of fatigue was similar in the US and Dutch patients, but more severe in the latter group. Fatigue was unrelated to demographic and clinical parameters in the total group. However, when examining the US and Dutch patients separately, fatigue was associated with age, extrapulmonary involvement and drug use in the US group.

Conclusions
Dutch patients report more severe fatigue compared with US patients. Interestingly, fatigue was related to clinical and demographical parameters in the US patients, although no such relationships were found in the Dutch patients.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin[1]. It is characterized by the formation of noncaseating granulomas[2]. The disease can involve any organ of the body, but sarcoidosis is most commonly found in the lungs. Depending on the organs involved and the severity of granulomatous inflammation, patients suffer from a broad range of symptoms. The clinical manifestations may be variable and are often non-specific, such as fatigue, fever, pain, and a general feeling of malaise[3].

Fatigue is the most frequently reported symptom, and it has a strong relationship with the patients' quality of life[3-5]. However, fatigue remains an under recognized and poorly managed problem in clinical practice.

Our ability to understand fatigue has been hampered by several methodological issues. First, quantification of fatigue is difficult and several instruments have been used in an attempt to quantify the perception of fatigue[6,7]. The Fatigue Assessment Scale (FAS) is an easy, useful, reliable and valid scale for assessing fatigue in sarcoidosis patients[6]. In addition, efforts to examine the pathogenesis of fatigue in sarcoidosis have been unsuccessful. It has been suggested that fatigue in sarcoidosis is associated with an acute phase response. However, no single clinical variable, including lung function tests, and laboratory parameters for inflammation, T-cell activation, and granuloma formation has been proven useful in predicting the presence or severity of fatigue[8].

The aim of the present study was to compare the prevalence and the severity of fatigue between US and Dutch sarcoidosis patients, and to determine whether fatigue is related to the common demographic and clinical parameters.

Methods

Patients

Two patient cohorts from tertiary sarcoidosis referral clinics were studied (n = 247). The first group consisted of 121 Dutch outpatients from the Sarcoidosis Management Team of the department of Respiratory Medicine of the Maastricht University Medical Centre (the Netherlands). The second group consisted of 126 US patients from the University of Cincinnati Medical Center (United States). The US patients consisted of consecutive sarcoidosis patients seen over a six week period in one clinic, who participated in another study examining fatigue[9] as well. Of these patients, 126 had completed information required for inclusion into the current study. The Dutch patients were selected from outpatients followed at the Sarcoidosis Management Center and were matched for age, gender and radiographic stage with the US patients. This study is retrospective, since the data of both populations are merged afterwards. In all cases, patients had a clinical presentation compatible with sarcoidosis. The diagnosis was confirmed, according to the international guidelines

combined with biopsyproven noncaseating epitheloid cell granulomas in most cases[10]. In case of patients with Löfgrens syndrome no biopsy was obtained.

The procedures followed were in accordance with the Helsinki declaration of 1975, as revised in 1983. The institutional internal review board approved the study protocol and written informed consent was obtained from all patients.

Measures

Clinical data

Relevant clinical data, such as treatment of sarcoidosis, 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. Values were expressed as a percentage of those predicted. 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 Assessment Scale (FAS)

All respondents completed the Fatigue Assessment Scale (FAS)[6]. The FAS is a general fatigue questionnaire consisting of 10 items and the scores range from 10 to 50. Besides using the total score, we divided the total FAS score into two groups: FAS scores 10-21 (not tired) and FAS scores 22–50 (tired). In line with De Vries et al.[6], we further divided the FAS tired group into two subgroups: tired (scores 22-34) and extremely tired (scores 35 and higher). The psychometric properties of the FAS are good in sarcoidosis patients[6].

Statistical procedure

Within each group mean differences on fatigue between men and women were examined using t-tests. Pearson correlations were calculated to measure whether age was related with fatigue. To examine the relationship between fatigue and clinical parameters, Pearson correlations (time since diagnosis, FVC, FEV_1), and t-tests (radiographic stages, prednisone, cytotoxic medication, hydroxylchloroquine) were performed. Each type of medication was examined separately in relation to fatigue whenever the number of patients was sufficient to analyze. It was not possible to examine the use of antidepressants or TNF-α.

Stepwise multiple regression analyses were performed to examine the predictive value of clinical (FEV1, FVC, radiographic staging, pulmonary-extra pulmonary, current prednisone use, current medication), and demographic factors (country, sex, age) for fatigue scores for the total group and the Dutch and US group separately.

In addition, a chi-square analysis was performed to examine the relationship between these patient groups and categories of fatigue, including not tired, tired, and

extremely tired. To explore differences in fatigue between Dutch and US patients an analysis of covariance was performed with age as covariate.

In order to explore differences in lung function a one–way ANOVA was performed between Dutch and US patients. Additionally, this analysis was repeated when patients with extrapulmonary involvement and pulmonary involvement were separated. Furthermore, US patients using hydroxylchloroquine were compared with patients not using this drug on radiographic stage, (extra) pulmonary involvement, FVC, and FEV_1, by means of t-tests and chi-square tests.

Absolute correlations from 0.10 to 0.29 are considered small, from 0.30 to 0.49 medium, and from 0.50 and higher as large[11]. All p-values were two-tailed, and SPSS 14.0 was used to perform the statistical analyses.

Results

Clinical features in fatigued patients

The demographic, medical, and psychological characteristics of the US and Dutch patients are summarized in Table 3.1.

For the total group and for both group separately, the relationship between fatigue and clinical and demographic data was examined. Fatigue was unrelated to lung function test results (FEV1, FVC), radiographic stages and sex in the total group. In addition, the multiple regression analysis on the total group showed that fatigue was not predicted by country (beta = 0.25), or prednisone use (beta = 0.18), $F(2, 240) = 9.27$, $p < 0.001$).

When examining the separate groups, the fatigue scores in Dutch patients were not predicted by clinical or demographic factors, such as age, time since diagnosis, and prednisone use. In the US patients, younger patients (beta = 0.21) with extra pulmonary involvement (beta = 0.17), and currently using prednisone (beta = 0.31) reported higher fatigue scores, $F(3, 122) = 8.39$, $p < 0.001$. These independent variables explained 15% of the variance of fatigue in US patients. US patients using hydroxylchloroquine had lower fatigue scores ($t = 3.50$, $p = 0.003$). In addition, fatigue was unrelated to use of cytotoxic medication in the US patients. The difference in fatigue between patients who used prednisone and those who did not use prednisone remained significant ($p = 0.002$) after excluding the patients who received hydroxylchloroquine, besides prednisone. The mean prednisone dose in the treated group was 9.1 ± 7.5 mg daily (range 1 - 60 mg). No dose effect was found. Furthermore, it appeared that US patients using hydroxylchloroquine did not differ with respect to radiographic staging, lung function test results, and (extra)pulmonary involvement.

Table 3.1 Demographical, medical, and psychological characteristics of the sarcoidosis patients

	Dutch patients n = 121	US patients n = 126
Gender: female/male	41 / 80	41 / 85
Age	50.1 ± 9.1 (26-78)	50.5 ± 9.4 (26-81)
Caucasian / African American	114 / 3	50 / 76
Time since diagnosis	10.9 ± 8.5 (2-44)	9.3 ± 7.0 (1-43)
Extra pulmonary / pulmonary	22 / 99	33 / 93
Radiographic stages: 0 / I / II / III / IV	40 / 24 / 30 / 19 / 8	30 / 37 / 19 / 32 / 8
FEV_1	90.6 ± 21.6	75.1 ± 22.0
FVC	98.8 ± 20.9	81.3 ± 20.4
Current therapy: yes / no	65 / 56	112 / 14
Prednisone: yes / no	41 / 80	77 / 49
Cytotoxic agents: yes / no [a]	36 / 85	61 / 65
Anti TNF-α: yes / no [b]	1 / 120	5 / 121
Hydroxylchloroquine: yes / no	2 / 119	22 / 104
Antidepressants: yes / no	5 / 116	26 / 100
Fatigue Assessment Scale score	30.3 ± 8.1	27.1 ± 7.4

Data are expressed as absolute number or mean ± SD with range in parentheses, if appropriate. FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; TNF-α = Tumor Necrosis Factor-alpha.

[a] Cytotoxic agents: Methothrexate, Azathioprine, Cyclophosphamide, and Leflunomide (US patients), Methothrexate and Azathioprine (Dutch patients).

[b] Anti TNF-α: Infliximab and Adalimumab (US patients), Infliximab (Dutch patients).

The percentage of tired Dutch patients (83.2%) was not significantly higher compared with that of the US patients (74.6%). However, the percentage of extremely tired Dutch patients (37.8%) was significantly higher compared with that of the US patients (19.0%), χ^2 (2, n = 245) = 11.03, p = 0.004). After adjusting for age, Dutch patients reported more fatigue than the US patients (F(1, 236) = 9.95, p = 0.002). As presented in Figure 3.1, the majority of patients reported fatigue (FAS score ≥ 22), and at least one in every six patients was extremely tired (FAS score ≥ 35).

US patients had a lower FVC, F(1, 243) = 44.09, p < 0.0001, and a lower FEV_1, F(1, 243) = 31.15, p < 0.0001, compared with the Dutch patients.

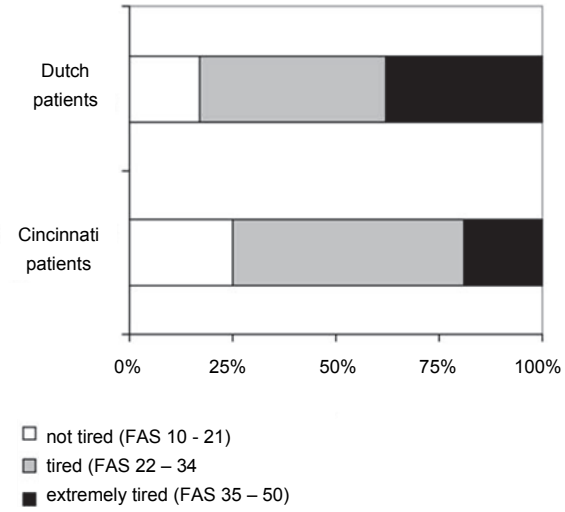

Figure 3.1 Percentages of patients who are not tired, tired, and extremely tired. The percentage of extremely tired Dutch patients (37.8%) was significantly higher compared with that of the US patients (19.0%), χ^2 (2, n = 245) = 11.03, p = 0.004)

Discussion

The present study examined the frequency of fatigue in a group of sarcoidosis patients seen over a six week period in an American clinic. This group was matched to a group of Dutch sarcoidosis patients. Although fatigue was equally prevalent, it was more severe in Dutch as compared to US patients with sarcoidosis. In line with the results of previous studies[8], we found no relations between fatigue, and clinical or demographical parameters in the total group. However, when examining the US and Dutch patients separately, fatigue was associated with age, extrapulmonary involvement and drug-use in the US patients. In this group, younger patients, patients using prednisone and having extrapulmonary involvement showed higher fatigue scores.

Depression and fatigue

Antidepressant use may reduce fatigue, and may therefore explain the difference in the severity of fatigue between the Dutch and US patients. US patients used antidepressants more frequently, compared with Dutch patients. This difference is also reflected in multinational research that shows that antidepressants medication use in the US exceeds that of three European countries by at least 3-fold[12]. Depression

is common in patients with sarcoidosis[13], for example the prevalence of depressive symptoms in American sarcoidosis patients was found to be 60%[14]. Also, Dutch studies examining depressive symptoms in sarcoidosis patients emphasize its important role in sarcoidosis[15,16]. Depressive symptoms include complaints of fatigue, and as a consequence, it is tempting to speculate that US patients complain less of extreme fatigue compared with the Dutch patients, because the US patients used antidepressants more frequently. However, not every case of fatigue is well controlled by antidepressants; it also is reported as a side effect of antidepressant medication in a minority of patients[17]. Longitudinal research is needed to explore the possible bidirectional relationship between fatigue and depressive symptoms.

Therapeutic options for fatigue

Interestingly, US patients using hydroxylchloroquine reported a lower fatigue score in this study. Baltzan et al. concluded that maintenance therapy with another anti-malarial, chloroquine, is useful in decreasing disease activity, and delaying relapse in pulmonary patients[18]. However, it is not clear that treatment of disease will reduce fatigue. Moreover, hydroxylchloroquine is most often subscribed in sarcoidosis patients with mild symptoms, such as skin and hypercalcemia, and occasionally for neurological involvement[19,20]. Yet it is not used for symptoms such as fatigue, which might bias our results. In the present study, the effect of treatment was not studied, only the differences between treated and untreated patients. Moreover, baseline data before this drug was administered, are lacking. Therefore, a prospective study is required to establish the positive and negative effects of certain drugs. Recently, other therapeutic options to treat fatigue such as anti-TNF-α[21-23] and (d-isomer) methylphenidate[24,25] are examined in small studies. The treatment of fatigue with these drugs should be evaluated in future multicentre studies.

The relationship between fatigue and prednisone use together with extrapulmonary involvement, which was only found in the US patients, might be explained by the high number of African Americans in this group. In the United States, African Americans are more likely to have extrapulmonary disease[26]. Several of these areas of extrapulmonary involvement such as lupus pernio, bone and muscle involvement, have a more refractory character[27].

A limitation of the study was that the recruitment of patients differed between the two studied sarcoidosis populations, probably resulting in a selection bias for the US group. Before they participated in the current study, the US patients participated in a study examining exercise capacity in an unselected sarcoidosis group. The most common reason for not participating in that study was insufficient time to perform the study. Consequently, this may have underestimated the incidence of fatigue. However, the interesting feature is that both groups had a high rate of fatigue. In the present study, the percentage of tired Dutch patients was 83.2% and that of the US patients 74.6%. The percentages found in the present study are within the range found in prior studies[4,6,8]. However, the Dutch group is in the high end of the range. Future studies are needed to explore these findings in a prospective study.

Additionally, fatigue can not be distinguished from dyspnea and muscle weakness, these symptoms may also be associated with fatigue. This might result in a selection bias in this population, because patients may complain of dyspnea and direct (sarcoidosis related) or indirect (steroids associated) muscle weakness. Another limitation of the current study is its cross sectional nature. We cannot draw causal relationships between fatigue and clinical and demographic parameters; a longitudinal design is needed for a better understanding of these relationships.

Notwithstanding the above mentioned limitations, this study offers a multicentre comparison of fatigue in sarcoidosis on a number of interesting factors, such as presentation, extra pulmonary involvement and treatment.

In conclusion, fatigue is a major problem in sarcoidosis patients. It was not related to clinical, radiologic or physiologic parameters, in the total group. However, when analyzing the US and Dutch patients separately, fatigue was found to be associated with age, extrapulmonary involvement and prednisone use in the US group. More study is warranted to better clarify the etiology, possible relationships with various disease manifestations, and appropriate treatment.

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Chapter 4

Types of fatigue in sarcoidosis patients

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J Psychosom Res 2011;71:416-422

Abstract

Objective

Fatigue is frequently reported in sarcoidosis and appears to differ between patients. Three types of fatigue (Early Morning Fatigue, Intermittent Fatigue, and Afternoon Fatigue) are described in the literature for sarcoidosis, but have not been validated. Therefore, the aim of this study was to examine whether these types of fatigue can be identified in sarcoidosis.

Methods

Outpatients (n = 434) from Maastricht University Medical Centre participated in this study. Data were obtained from medical records. Patients also completed questionnaires regarding depressive symptoms, fatigue, quality of life, restless legs, dyspnea, personality, anxiety, sleeping problems, symptoms indicative for small fiber neuropathy, and employment.

Results

Latent Cluster Analysis revealed three clusters: 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 tired the whole day. The three patient clusters differed regarding clinical, psychological, and demographical characteristics, with All Day Fatigue patients reporting the most complaints.

Conclusion

Intermittent fatigue was validated and two other types were found. Careful consideration to categorize patients with sarcoidosis in the three types of fatigue will help healthcare providers to understand the challenges these patients encounter. The usefulness of psychological counseling should be evaluated in future research in order to improve the wellbeing of the patients, especially for those with All Day Fatigue.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin in which practically every organ can be involved. Lungs are the most commonly affected organ, however involvement of other organ systems such as lymph nodes, skin, eyes, muscles, heart, and joints are frequently observed. Symptoms can vary considerably depending on the specific organs involved and the severity of the granulomatous inflammation[1]. In addition to various symptoms related with the affected organs, patients often suffer from fatigue[2].

The etiology of fatigue associated with sarcoidosis is usually multifaceted. These include the release of cytokines from the granulomas[3-5] as a function of the disease itself and/or depression[6], weight gain, exercise intolerance, or altered sleep patterns as a result of disease related problems. Although to date no accepted definition of fatigue exists, several researchers have proposed to divide fatigue into at least two categories: physical and mental fatigue[7], or passive and active fatigue[8]. However, another study considers fatigue as a one-dimensional concept[9]. In this latter study, fatigue is regarded as a subjective experience, as measured by the Fatigue Assessment Scale (FAS).

Fatigue is the most frequently (71%) reported symptom in the sarcoidosis population in the Netherlands[2]. Moreover, fatigue appeared to be related with worse Quality of Life (QOL)[10], cognitive failure[11], and depressive symptoms[12]. Since there are no medications available for patients with fatigue, it is important to educate these patients to successfully cope with their fatigue. However, patients appear to experience variations in the type of fatigue[13], making it difficult to apply one universal coping strategy to all patients. Therefore, it is important in clinical practice to identify the possible types of fatigue which will ultimately enable healthcare providers to tailor the intervention appropriately to individual patients.

Sharma[13] described four types of fatigue in sarcoidosis: 1) Early-morning fatigue, where the patient arises with feelings of inadequate sleep; 2) Intermittent fatigue, where the patient wakes up normally but feels tired after a few hours of activity. After a short rest, the patient is able to resume activity, succeeded by another period of fatigue; 3) Afternoon fatigue, where the patient arises in the morning with adequate energy but feels exhausted in the early afternoon. As a result, the patient goes to bed early and stays in bed until the next morning; 4) Post-sarcoidosis chronic fatigue syndrome. This was recently identified[14] and occurs in about 5% of patients who seemingly have recovered from active sarcoidosis. In this condition, the patients complain of fatigue despite the absence of physical signs of sarcoidosis[13]. In our study, it was not possible to examine the post-sarcoidosis fatigue, because most of the participating patients had chronic sarcoidosis. Studies examining empirical evidence for the remaining three types of fatigue in sarcoidosis patients are needed to understand the challenges these patients encounter. However, this evidence is currently lacking in sarcoidosis.

Types of fatigue have been described in patients other than sarcoidosis such as with chronic heart failure[15], and were provided with empirical evidence by means of

Latent Cluster Analysis (LCA)[16]. The purpose of LCA is to find the minimal number of clusters that best describe the associations between the observed indicators, such that individuals belonging to the same cluster are similar to one another, but differ from individuals in other clusters[17]. However, the classifications in fatigue found for chronic heart failure cannot be applied to sarcoidosis as the disease process is different from chronic heart failure which may influence the results.

The aims of this study were 1) to examine whether fatigue in sarcoidosis can be subdivided in types of fatigue: Early-morning fatigue, Intermittent fatigue, and Afternoon fatigue as previously described by Sharma[13] by means of LCA and 2) to describe the demographic, psychological, and clinical characteristics of the resulting clusters.

Methods

Study subjects

All sarcoidosis patients (n = 588) known at the outpatient clinic of ild care center of the Department of Respiratory Medicine of the Maastricht University Medical Centre, a referral centre for sarcoidosis in the Netherlands, were asked to participate in this study. Of these patients, 434 (74%) participated in this study (see Figure 4.1 for the patients selection). Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchial alveolar lavage fluid analysis results. The diagnosis was based on a positive biopsy in 71% of the cases. In patients with typical features of Löfgren's syndrome and characteristic features of bronchoalveolar lavage (BAL) fluid analysis results, no biopsy was obtained. This policy is consistent with the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines[18]. Comorbidity was defined as any medical problem not related to sarcoidosis. Disorders or conditions considered as comorbidity included cardiovascular disease, thyroid disease, diabetes, anemia, cancer, muscle weakness and immobility due to musculo-skeletal disorders. Extrapulmonary localizations of sarcoidosis were not considered as comorbidity but as sarcoidosis-related. The exclusion criteria were poor expression in the Dutch language (n = 3), relevant comorbidity, such as malignancy (n = 7), dementia (n = 1), and a history of psychiatric illness (n = 2). The institutional internal review board approved the study protocol, and written informed consent was obtained from all participants.

Methods

The following questions were used as indicators to identify the types of fatigue: 1) ‘Do you have difficulties when waking up in the morning?’ (1 *no difficulties at all* to 5 *very much*), 2) ‘Do you feel tired a few hours after waking up?’ (*no*; *yes*), 3) ‘How do you feel in the early afternoon ?’ (1 *not tired at all* to 5 *exhausted*), 4) ‘Do you need more

sleep?' (*no* ; *yes*), 5) 'Do you feel tired the whole day?' (*no*; *yes*), 6) 'Do you take a nap during the daytime?'(*no*; *yes*).

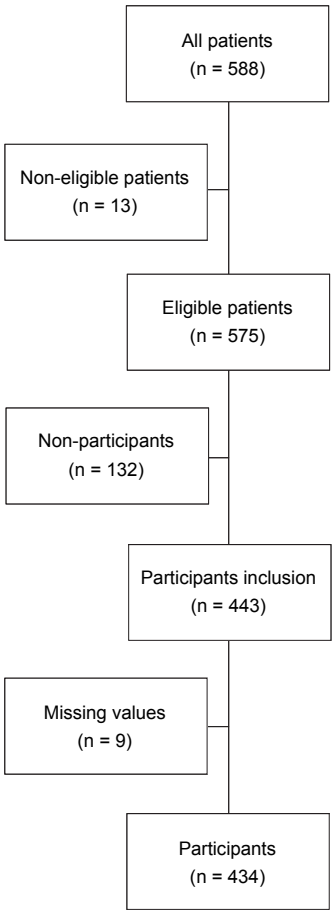

Figure 4.1 Flow chart of the patient selection.

The patients completed the Fatigue Assessment Scale (FAS)[19], the Center for Epidemiological Studies-Depression Scale (CES-D)[20], the State and Trait Anxiety Inventory (STAI)[21], the Small Fiber Neuropathy Screenings List (SFNSL)[22], the World Health Organization Quality of Life assessment instrument Bref (WHOQOL-BREF)[23], and the Single-Item Measures of Personality (SIMP)[24]. In addition, patients were asked to rate the Borg dyspnea index[25] and whether they suffered from restless legs (*yes* or *no*), pain (1 *no* to 5 *very*), woke up more often during the night (*yes* or *no*), or had difficulties fallen asleep (*yes* or *no*). Moreover, patients were asked whether they

were employed (*yes* or *no*), declared to be unfit to work (*yes* or *no*), and whether they worked on irregular hours (*yes* or *no*).

The FAS is a 10-item questionnaire to assess self-reported fatigue. Besides a total fatigue score, the FAS can be divided into a mental fatigue score as well as a physical fatigue score. The reliability and validity of the FAS appeared to be good in sarcoidosis patients[19,26]. Cronbach's alpha in this sample was 0.90. The CES-D is a 20-item scale that measures the presence and degree of depressive symptoms. Reliability and criterion validity appear to be good[27]. Cronbach's alpha in the current sample was 0.89. The STAI measures trait and state anxiety, and only trait anxiety was incorporated in this study. 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. Cronbach's alpha in the current sample was 0.93. High trait anxiety was defined as a score of 40 or above, based on Dutch norm scores[21]. The SFNSL is a 21-item self-administered measure of symptomatology related to Small Fiber Neuropathy. The reliability and the validity of the SFNSL are good[22]. Cronbach's alpha in the current sample was 0.91. A higher score on the FAS, CES-D, STAI and SFNSL indicates more complaints. The WHOQOL-Bref instrument was derived from the WHOQOL-100 to measure QOL. QOL has been defined by the World Health Organization Quality of Life group as 'an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to their goals, expectations, standards, and concerns'. The WHOQOL-Bref consists of the following broad dimensions: Physical Health (7 items), Psychological Health (6 items), Social Relationships (3 items), Environment (8 items) and the Overall Facet (2 items). Scoring of each domain ranges from 4 to 20, and scoring of the Overall Facet ranges between 2 and 10[23]. It is concluded that the content validity, construct validity, and the reliability of the WHOQOL-Bref are good[28]. Cronbach's alpha in the current sample was 0.92. A higher score indicates a better QOL. The Borg Dyspnea Index is a self-rated scale for dyspnea and scored from 0 (no impairment) to 10 (severe impairment). Test re-test reliability of this instrument was found to be good[25]. The SIMP measures personality by means of five descriptions representing the poles of each of the Big Five factors: Extraversion, Agreeableness, Conscientiousness, Emotional Stability and Openness[24]. The items are self-rated from 1 to 9 and a higher score indicates a higher Emotional Stability, more Agreeableness, more Openness, less Conscientiousness, or less Extraversion. The SIMP is a short valid and reliable measure[24].

Demographics and relevant clinical data, such as time since diagnosis, lung function measurements, Body Mass Index (kg/m^2), multisystemic involvement, treatment with corticosteroids, and chest radiographs were derived from the patients' medical files. Lung function measurements, including forced expiratory volume in one second (FEV1) 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. Values were expressed as a percentage of

those predicted. Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV: the end stage of lung fibrosis.

Analysis

Types of fatigue were identified by means of latent class analysis (LCA), based on six indicators. Patients with missing values in all six indicators (n = 9) were excluded from the analyses, though patients with partially missing information were retained in the analyses. The two indicators with five ordered categories—'Do you have difficulties when waking up in the morning?' (1 *no difficulties at all* to 5 *very much*), and 'How do you feel in the early afternoon?' (1 *not tired at all* to 5 *exhausted*)—were treated as ordinal. Treating them as nominal did not result in a better fit.

Latent class modeling aims to obtain the smallest number of clusters that accounts for all the associations[17]. Initially, we fitted 1- to 5-class models and compared their Bayesian Information Criteria (BIC)[29]. Because the two ordinal indicators turned out to be more strongly related than could be explained by standard latent class models, we allowed these variables to be associated within classes (to be locally dependent). The preferred model is the one with the lowest BIC and a non-significant (bootstrap) p-value, for the goodness-of-fit chi-square test. The latter indicates that there is no need to reject the model concerned in favor of a more complex model[17]. Using the latent class model, each respondent was assigned to the most likely cluster (i.e., the one with highest posterior class membership probability).

For comparison of psychological, demographical and clinical characteristics between the encountered latent classes we used the chi-square tests for categorical and F tests for continuous variables. In line with De Vries et al.[19] we also divided the FAS into two groups: FAS scores 10 to 21 (not tired) and FAS scores 22 to 50 (tired). Percentages of tired patients were computed for each defined cluster.

The LCA was performed with Latent GOLD 4.5[30,31], and for the other data analyses we used Statistical Package Social Science 17.0[32]. A p-value < 0.05 was considered statistically significant.

Results

Table 4.1 provides the information for model selection. As shown, a solution with three clusters resulted in the lowest BIC value. Moreover, its p-value for the goodness-of-fit test indicated that there was no need to reject this model in favor of a more complex model.

The Wald tests reported in Table 4.2 show that all indicators were significantly related to the three clusters ($p < 0.01$ for all six indicators).

Table 4.1 Diagnostic criteria for the estimated Latent class models.

	Log-likelihood value (LL)	BIC (LL)	Number of parameters	df	Bootstrap p-value
1-Cluster	-2175	4429	13	421	<0.01
2-Clusters	-2101	4324	20	414	<0.01
3-Clusters	**-2051**	**4267**	**27**	**407**	**0.05**
4-Clusters	-2038	4283	34	400	0.14
5-Clusters	-2033	4314	41	393	0.23

BIC(LL) = Bayesian Information Criterion, computed using the log-likelihood value; the preferred model (in bold) is the one with the lowest BIC value.

Table 4.2 Significance tests for indicators in 3-class model.

Indicators	*Wald*	*p*	R^2
1. Do you have difficulties when waking up in the morning?	23.1	<0.01	0.27
2. Do you feel tired a few hours after waking up?	35.2	<0.01	0.33
3. How do you feel in the early afternoon?	11.1	<0.01	0.14
4. Do you need more sleep?	16.3	<0.01	0.32
5. Do you feel tired the whole day?	12.3	<0.01	0.88
6. Do you take a nap during the daytime?	27.7	<0.01	0.24

The cluster-specific means and percentages on the six indicators are enumerated in Table 4.3a. The first group, called Mild Fatigue (MF); n = 130, contained patients who scored relatively low on all six indicators. Cluster two contained patients who were likely to need more sleep (indicator 4), who most often took a nap (indicator 6), and did not feel tired all day (indicator 5), but a few hours after waking up (indicator 2). This group (n = 220) was called Intermittent Fatigue (IF). The third group (n = 84), called All Day Fatigue (ADF), consisted of patients who indicated that they felt very tired the whole day and also during the early afternoon (indicator 3). These patients needed slightly less sleep and naps and had more difficulties with waking up (indicator 1) compared to the patients with IF.

Table 4.3a Class proportion and class-specific means and percentages for the six indicators in the 3-class model.

Indicators	MF (n = 130, 0.31)	IF (n = 220, 0.49)	ADF (n = 84, 0.19)
1. Do you have difficulties when waking up in the morning? (1 *no difficulties at all* to 5 *very much*)	1.7	2.6	3.4
3. How do you feel in the early afternoon? (1 *not tired at all* to 5 *exhausted*)	2.0	3.0	3.7
2. Do you feel tired a few hours after waking up?[a]	4%	31%	0%
4. Do you need more sleep?[a]	6%	70%	50%
5. Do you feel tired the whole day?[a]	4%	0%	97%
6. Do you take a nap during the daytime?[a]	13%	67%	60%

[a] Percentage of patients who answered 'yes' to the question. ADF = All Day Fatigue; IF = Intermittent Fatigue; MF = Mild Fatigue

Because the BIC value of the fourth-cluster solution came close to the BIC value of the three-cluster solution, both solutions are shown in Tables 4.3a and 4.3b. The fourth cluster displays a similar pattern to IF patients, except that patients in this fourth cluster often needed more sleep and less often took a nap, compared to the IF patients (see Table 4.3b).

Table 4.3b Class proportion and class-specific means and percentages for the six indicators in the 4-class model.

Indicators	MF (n = 130, 0.31)	IF (n = 110, 0.23)	4th cluster (n = 110, 0.23)	ADF (n = 84, 0.19)
1. Do you have difficulties when waking up in the morning? (1 *no difficulties at all* to 5 *very much*)	1.8	2.6	2.7	3.4
3. How do you feel in the early afternoon? (1 *not tired at all* to 5 *exhausted*)	2.1	3.5	2.5	3.7
2. Do you feel tired a few hours after waking up?[a]	7%	41%	22%	0%
4. Do you need more sleep?[a]	0%	60%	98%	52%
5. Do you feel tired the whole day?[a]	1%	0%	0%	95%
6. Do you take a nap during the daytime?[a]	17%	87%	49%	60%

[a] Percentage of patients who answered 'yes' to the question. ADF = All Day Fatigue; IF = Intermittent Fatigue; MF = Mild Fatigue

According to the FAS score, 52% of the MF patients were tired, and 48% were not tired. In the IF group 91% of the patients were tired, and 9% were not tired. Approximately every ADF patient (99%) was tired and 1% of the patients were not tired.

Demographical and clinical characteristics for all patients, and stratified according to the three clusters, are summarized in Table 4.4. All groups differed regarding fatigue ($F(2, 427) = 121.1$, $p < 0.01$), mental fatigue, ($F(2, 427) = 76.9$, $p < 0.01$), physical fatigue, ($F(2, 427) = 120.8$, $p < 0.01$), depressive symptoms ($F(2, 421) = 35.1$, $p < 0.01$), trait anxiety ($F(2, 422) = 29.4$, $p < 0.01$, the QOL domains Psychological Health ($F(2, 426) = 28.6$, $p < 0.01$), Physical Health ($F(2, 425) = 84.4$, $p < 0.01$), and the Overall Facet ($F(2, 428) = 60.2$, $p < 0.01$, employment ($\chi^2(2, 428) = 30.1$, $p < 0.01$) and being unfit to work ($\chi^2(2, 409) = 39.0$, $p < 0.01$). ADF patients were more often declared to be unfit to work and unemployed, compared to the IF and MF patients (p's < 0.01). Likewise, IF patients were more often declared to be unfit to work and unemployed than the MF patients (p's < 0.01). The ADF patients also scored higher on fatigue, mental fatigue, physical fatigue, depressive symptoms, trait anxiety, and lower on the Overall Facet of Quality of Life and the QOL domains Physical and Psychological Health, compared with the other groups (p's < 0.05). Similarly, the IF patients reported more depressive symptoms, fatigue, mental fatigue, physical fatigue, trait anxiety, and scored lower on the Overall Facet and Physical and Psychological Health in comparison with the MF patients (p's < 0.05).

Table 4.4 Symptoms, demographical, clinical, and sleep related characteristics, stratified by type of fatigue in sarcoidosis.

		MF (n = 130)	IF (n = 220)	ADF (n = 84)	All patients (n = 434)
Demographics	Age in years	48.0 ± 11.2 (n =130)	47.7 ± 10.9 (n =220)	48.2 ± 11.1 (n = 84)	47.9 ± 11.0 (n = 434)
	Female [d]	35% (n = 130)	50% (n = 220)	52% (n = 84)	46% (n = 434)
Clinical	Radiographic stage: 0 / I / II / III / IV	35/7/25/15/18% (n = 129)	42/11/25/11/11% (n = 219)	40/7/23/13/17% (n = 84)	35/7/25/15/18% (n = 432)
	Use of corticosteroids	35% (n = 130)	34% (n = 216)	41% (n = 84)	35% (n = 430)
	Multisystemic involvement	45% (n = 130)	48% (n = 217)	48% (n = 83)	47% (n = 430)
	BMI (kg/m^2)	26.6 ± 4.6 (n = 124)	27.7 ± 5.4 (n = 198)	27.8 ± 6.8 (n = 82)	27.4 ± 5.5 (n = 404)
	Time since diagnosis in years	8.3 ± 9.6 (n = 130)	7.2 ± 6.5 (n = 219)	8.0 ± 8.0 (n = 84)	7.7 ± 7.8 (n = 433)
	FEV_1 [b]	87.6 ± 23.5 (n = 129)	91.9 ± 21.0 (n = 212)	84.4 ± 22.8 (n = 83)	89.1 ± 22.3 (n = 424)
	FVC [b]	97.5 ± 21.3 (n = 129)	101.1 ± 18.7 (n = 212)	93.4 ± 18.9 (n = 83)	98.5 ± 19.7 (n = 422)
	DLCO [b]	80.4 ± 19.6 (n = 129)	83.9 ± 15.3 (n = 212)	76.7 ± 17.8 (n = 83)	81.4 ± 17.5 (n = 424)
Symptoms	SFN-associated symptoms [d]	14.8 ± 12.8 (n = 120)	26.7 ± 13.8 (n = 191)	31.0 ± 17.5 (n = 79)	23.9 ± 15.6 (n = 390)
	Dyspnea [c]	2.0 ± 1.7 (n = 120)	2.6 ± 1.8 (n = 204)	3.8 ± 2.5 (n = 80)	2.6 ± 2.0 (n = 404)
	Depressive symptoms [a]	9.3 ± 8.0 (n = 125)	15.4 ± 8.9 (n = 215)	19.6 ± 10.6 (n = 84)	14.4 ± 9.7 (n = 424)
	Pain [d]	1.8 ± 0.9 (n = 128)	2.7 ± 1.1 (n = 217)	2.9 ± 1.2 (n = 83)	2.4 ± 1.2 (n = 428)
	Fatigue [a]	22.2 ± 6.8 (n = 128)	31.0 ± 6.9 (n = 218)	36.2 ± 6.3 (n = 84)	29.4 ± 8.5 (n = 430)
	Mental Fatigue [a]	9.4 ± 3.4 (n = 127)	13.4 ± 3.8 (n = 218)	15.7 ± 4.5 (n = 83)	12.7 ± 4.5 (n = 428)
	Physical Fatigue [a]	12.8 ± 4.0 (n = 127)	17.6 ± 3.8 (n = 218)	20.5 ± 2.7 (n = 83)	16.7 ± 4.6 (n = 428)
Sleep	Fallen asleep is difficult [c]	1.8 ± 1.1 (n = 130)	1.9 ± 1.0 (n = 219)	2.6 ± 1.4 (n = 84)	2.0 ± 1.2 (n = 433)
	Restless legs [d]	22% (n = 126)	44% (n = 218)	45% (n = 84)	38% (n = 428)
	Wakes up more often during night	44% (n = 126)	50% (n = 218)	55% (n = 84)	49% (n = 428)
	Sleep quality [a]	3.3 ± 1.1 (n = 127)	2.9 ± 1.0 (n = 219)	2.5 ± 1.1 (n = 84)	2.9 ± 1.1 (n = 430)
Psychological	Trait anxiety [a]	34.9 ± 10.1 (n = 125)	41.5 ± 9.7 (n = 216)	45.0 ± 10.0 (n = 84)	40.3 ± 10.5 (n = 425)
	Openness	5.9 ± 1.9 (n = 124)	6.0 ± 1.9 (n = 208)	6.2 ± 1.9 (n = 82)	6.0 ± 1.9 (n = 414)
	Conscientiousness	4.9 ± 2.1 (n = 124)	4.9 ± 2.1 (n = 207)	5.0 ± 2.1 (n = 82)	4.8 ± 2.0 (n = 413)
	Extraversion	5.0 ± 2.1 (n = 124)	5.2 ± 2.1 (n = 210)	5.6 ± 2.4 (n = 83)	5.2 ± 2.2 (n = 417)
	Agreeableness	5.2 ± 2.2 (n = 124)	5.7 ± 2.3 (n = 208)	5.8 ± 2.2 (n = 82)	5.5 ± 2.3 (n = 414)
	Emotional stability [d]	4.8 ± 2.2 (n = 124)	4.0 ± 2.0 (n = 208)	3.8 ± 2.2 (n = 83)	4.2 ± 2.1 (n = 415)
	Overall Facet [a]	6.9 ± 1.4 (n = 129)	5.8 ± 1.4 (n = 218)	4.8 ± 1.3 (n = 84)	6.0 ± 1.6 (n = 431)
	Physical Health [a]	14.9 ± 2.9 (n = 128)	12.0 ± 2.6 (n = 216)	10.3 ± 2.4 (n = 84)	12.5 ± 3.1 (n = 428)
	Psychological Health [a]	15.0 ± 2.5 (n = 128)	13.6 ± 2.2 (n = 218)	12.7 ± 2.4 (n = 83)	13.8 ± 2.5 (n = 429)
	Social Relationships [d]	15.3 ± 2.7 (n = 128)	14.3 ± 3.0 (n = 216)	13.9 ± 3.0 (n = 84)	14.5 ± 2.9 (n = 428)
	Environment [d]	16.3 ± 2.5 (n = 128)	15.1 ± 2.3 (n = 218)	14.5 ± 2.7 (n = 84)	15.4 ± 2.5 (n = 430)
Employment	Employment [a]	73% (n = 125)	56% (n = 219)	35% (n = 84)	54% (n = 428)
	Working on irregular hours	30% (n = 90)	31% (n = 119)	15% (n = 26)	29% (n = 235)
	Unfit to work [a]	12% (n = 121)	30% (n = 207)	53% (n = 81)	29% (n = 409)

Data are expressed as means ± standard deviation or in percentages. Comparisons between ADF, IF and MF: [a] Significant difference between the three types of fatigue; [b] Significant difference between ADF versus IF; [c] Significant difference between ADF versus IF and MF; [d] Significant difference between MF versus IF and ADF. *ADF* All Day Fatigue; *BMI* Body Mass Index; *DLCO* Diffuse capacity of the lung for carbon monoxide; *FEV_1* Forced Expiratory Volume in one second; *FVC* Forced Vital Capacity *IF* Intermittent Fatigue; *MF* Mild Fatigue; *SFN* Small Fiber Neuropathy.

The following question of the WHOQOL-Bref 'How satisfied are you with your sleep?' was examined separately. All groups differed regarding sleep quality ($F(2,427) = 13.0$, $p < 0.01$). ADF patients were less satisfied with their sleep quality, compared to IF patients and MF patients ($p < 0.05$), and IF patients were less satisfied, compared to MF patients ($p < 0.01$).

Significant differences were found between ADF and IF regarding lung function tests: DLCO: $F(2, 421) = 5.6$, $p < 0.01$; FEV1: $F(2, 421) = 3.9$, $p = 0.02$; and FVC: $F(2, 419) = 5.0$, $p < 0.01$. ADF patients had lower scores on lung function tests (DLCO: $p < 0.01$; FEV1, $p = 0.03$; FVC: $p < 0.01$), compared with the IF patients. MF patients did not differ with respect to clinical characteristics in comparison to the other groups. ADF patients had more difficulties with falling asleep, compared with the other patients ($F(2, 430) = 13.9$, p's < 0.01), and complained more of dyspnea $F(2, 401) = 20.6$, p's < 0.01).

Finally, significant differences were found between MF patients and the other groups, regarding restless legs (χ^2 $(2, 428) = 18.1$, $p < 0.01$), pain ($F(2, 425) = 35.9$, $p < 0.01$), Emotional Stability ($F(2, 412) = 7.3$, $p < 0.01$), sex (χ^2 $(2, 434) = 9.6$, $p < 0.01$), the QOL domains Social Relationships ($F(2, 425) = 8.0$, $p < 0.01$) and Environment ($F(2, 427)=15.4$, $p < 0.01$), and SFN-associated symptoms ($F(2, 387) = 37.7$, $p < 0.01$). The MF patients less often reported restless legs, and scored lower on trait anxiety, pain, and SFN-associated symptoms, compared with both fatigued groups (p's < 0.01). MF patients had a higher mean score on Emotional Stability, compared to ADF patients and IF patients (p's < 0.01). Furthermore, they were more often male, and scored higher on the QOL domains Social Relationships and Environment (p's < 0.05), compared with the other groups. No significant differences were found between the groups in the other characteristics.

Discussion

The aims of this study were 1) to examine whether fatigue in sarcoidosis can be subdivided in types of fatigue: Early-morning fatigue, Intermittent fatigue, and Afternoon fatigue as previously described by Sharma[13] by means of LCA and 2) to describe the demographic, psychological, and clinical characteristics of the resulting clusters.

LCA revealed three clusters: a subgroup with mild or no complaints of fatigue (MF patients), a subgroup with complaints of fatigue that varied during the day (IF patients), and a subgroup of patients who felt tired the whole day (ADF patients). Importantly, the ADF patients reported more psychological problems and clinical symptoms, in comparison to the other groups. In addition, they were most frequently unable to work.

It should be noted that the BIC value for the four-cluster solution was only slightly higher than the value for the three-cluster solution, indicating that the two models are equally good according to this criterion. The four-cluster solution is, however, clearly less preferred when looking at other criteria. First, the p-values for the

goodness-of-fit test indicated that there was no need to retain the more complex four-cluster model in favor of the simpler three-cluster model. Second, the proportion of classification errors was higher in the four-cluster model compared to the three-cluster solution, indicating stronger overlap between clusters. Third, the interpretation of the four-cluster solution had no substantial contribution from a theoretical perspective: the fourth cluster turned out to be very similar to the IF type. Therefore, we decided to keep the three-cluster solution as our final model.

In keeping with the findings described by Sharma[13], three types of fatigue were identified in this study when leaving the Post-sarcoidosis chronic fatigue syndrome aside. However, not every type of fatigue as described by Sharma has been validated in this study. For example, the Intermittent Fatigue type as described by Sharma was confirmed in our study. However, we did not identify an Afternoon Fatigue type, because we were not able to find a group of patients who specifically complained of fatigue in the afternoon. Instead, a group of patients was found whose complaints of fatigue were mild and not associated with a specific moment of the day. Based on these findings, Sharma's Early Morning Fatigue (EMF) type should be relabeled to ADF. Both EMF and ADF share the common feature that the patients have difficulties with starting up, but the present results showed a prolonged fatigue which lasted all day, instead of only fatigue in the morning.

Although the three groups appeared to differ in symptom severity, It is unlikely that the three types of fatigue can be explained in the context of the clinical stages that evolve chronically. Neither the chest X-ray stage nor the time since diagnosis had an impact on the extent of fatigue. This was in line with the results of a study by Marcellis et al.[33] who found no relationship between fatigue and the chest X-ray stage or time since diagnosis. In addition, the patients with ADF had lower lung function test scores than the patients with IF, but not significant differently from the MF group. It was expected that the MF patients would score significantly higher on the lung function tests, compared to the other groups. This was expected because lung function is a measure of disease severity in sarcoidosis and MF patients reported only mild symptoms. The disassociation between lung function and symptoms of fatigue confirms the results of previous research[34]. Thus it is plausible that regularly used clinical measurements such as lung function tests, are not appropriate to measure fatigue.

An alternative explanation is that an unknown underlying physical mechanism decreased the lung function test results of the MF patients. Also, the MF group may be better able to cope with their fatigue and other disease-related symptoms, compared to the other patients. Half of the MF patients had complaints of fatigue, as measured with the FAS, but they scored relatively low on all indicators used to define the types of fatigue (See Tables 4.3a and 4.3b). Possible explanations to why MF patients did not experience their fatigue as problematic may include: 1) They may have psychologically adapted to their fatigue; and/or: 2) they may have a more emotionally stable personality, compared to the other patients. We found that MF patients had a higher score on Emotional Stability, as measured with the SIMP[24], compared to ADF patients, and IF patients. In addition, MF patients had the lowest scores on trait anxiety, in comparison to the other groups. Studies in other chronic

diseases, such as breast cancer, show that trait anxiety is an important predictor of fatigue[35]. Which of the before mentioned explanations for the decreased lung function in MF patients are most important in sarcoidosis, needs to be explored in future research.

Regarding the psychological variables, the comparison between the groups showed a consistent pattern. ADF patients had the worst scores, followed by the IF and MF patients. Similar patterns were found in the frequencies of patients having an employment and in the number of patients who have been declared to be unfit to work. The clear relationship between psychological distress and type of fatigue indicates that psychological counseling is important in patient care. Vercoulen et al.[36] described that psychological factors could be involved in the development, but particularly in the maintainability of chronic fatigue. The nature of patients' attributions, avoidance of physical activity, and depressive symptoms also play a role. Given the high rate of depressive symptoms found in patients with chronic fatigue, it is likely that depressive symptoms are involved in the development and/or maintainability of fatigue. This relationship between depressive symptoms and chronic fatigue is complex, because both somatic and psychological factors are involved. In addition, avoidance of physical activity may lead to maintainability of fatigue. Recently, Esteban et al.[37] showed that low physical activity was significantly related to high levels of fatigue in chronic obstructive pulmonary disease patients. These results may be explained by avoidance of physical activity. It is assumed that patients "learn" that physical exertion increases fatigue and muscle aches, therefore patients try to evade these problems by avoiding physical activity. The physical condition of these inactive patients will deteriorate further and a vicious cycle between inactivity and fatigue arises. Finally, attributions of the symptoms of physical factors can also lead to maintainability of fatigue. For instance, denial of the influence of psychological factors coincides with difficulties coping with fatigue. The results of this study showed that ADF patients less often indicated that they needed more sleep, while they reported more symptoms of fatigue, in comparison to the IF patients. Therefore, it is possible that they have difficulties coping with fatigue and demand too much from themselves.

Treatment of depressive symptoms and anxiety may lead to an improvement in energy level. Especially ADF patients may benefit from psychological treatment, because these patients suffer the most from psychological problems. In fact, 69% of ADF patients had an anxiety score indicative of high trait anxiety and 57% had a score indicative for depression.

It is important to keep the causality problem in mind as to which came first: fatigue or disease-related symptoms? Sleeping problems and depressive symptoms can cause and maintain fatigue, but fatigue may also cause these symptoms[38]. Our results suggest that in ADF patients sleep disorders may be at least partly responsible for the fatigue complaints.

Several limitations of our study are noteworthy of mention. Firstly, because of the cross-sectional design of our study, it is not possible to comment on 1) cause and effect of fatigue and 2) the stability of the types of fatigue. Future research in a longitudinal prospective manner to elucidate the development of fatigue symptoms in

patients diagnosed with sarcoidosis is needed. Moreover, it will be important to identify clinical predictors correlative with the development of the various types of fatigue. In addition, it is important to acknowledge that all patients were recruited in a tertiary referral centre, which may diminish the generalizability of the results of this study. Secondly, our study used self-reported measures to assess fatigue and psychological symptoms. Gold standards to measure fatigue and psychological symptoms objectively are currently lacking[34], therefore subjective assessment remains a highly valuable method to understand the symptoms especially from the patient's perspective. Thirdly, the restricted number of questions regarding sleep may not have allowed a clear distinction between symptoms related to sleep disorders. There may be great clinical implications to differentiate sleep disorders from fatigue symptoms especially with regard to treatment options. However, the aim of this study was to examine the different presentations of fatigue and the focus was not on treatment options; sleep disorders were not specifically excluded. Follow-up study aimed to identify the most appropriate treatment option(s) will require more careful evaluation of sleeping disorders that may include sleep questionnaires as fatigue appeared to be related with sleep disturbances. Recently, Fortier-Brochu et al.[39] showed that severe fatigue was found in individuals with both severe and mild sleep disturbances. In addition, Bailes et al.[40] showed that fatigue was associated with obstructive sleep apnea. The relationship between fatigue and sleep in sarcoidosis has been studied previously and sleep disorders appeared to be a frequent phenomenon in sarcoidosis[41–43]. Turner et al.[41] found a higher prevalence of sleep apnea in patients with sarcoidosis, compared to control patients. In addition, in a study of Verbraecken et al.[42] obstructive sleep apnea, periodic leg movement or restless legs were found in more than half of the sarcoidosis patients. Drent[43] demonstrated that symptoms of fatigue disappeared after treating sleep apnea and sarcoidosis. Moreover, sleep disturbances are often related to small fiber neuropathy and autonomic dysfunction[41] which may in part explain the fatigue. However, sleep problems may be caused by anatomical dysfunction as well. For instance, involvement of the tongue, tonsils, infiltration of the upper airway, and larynx can provoke sleep apnea[44]. Because fatigue and sleep disorders frequently occur in patients with sarcoidosis, future studies should focus on the relationship between autonomic dysfunction, sleep disorders and fatigue in sarcoidosis to include in the management of sarcoidosis appropriate treatment strategies.

Strengths of this study are the large number of participants and the clustering method used[45].

In conclusion, three types of fatigue were found in this study. ADF patients reported the most clinical and psychological symptoms, followed by IF and MF patients. Appropriate classification of patients with sarcoidosis in the three types of fatigue identified in this study will further our understanding of the challenges these patients encounter. Furthermore, this classification may provide potential targets for the management of sarcoidosis. Especially patients who are suffering from ADF may benefit from the usefulness of psychological interventions. These interventions may be considered in the multidisciplinary management of sarcoidosis to improve the well-being of the patients.

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Chapter 5

Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis

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Respir Med 2011; 105: 1388-1395

Abstract

Objective
The usefulness of any questionnaire in clinical management and research trials depends on its ability to indicate a likelihood of treatment success during follow-up. The Minimal Clinically Important Difference (MCID) reflects a clinically relevant change score. The aim of this study was to estimate the MCID for the Fatigue Assessment Scale (FAS) in patients with sarcoidosis.

Methods
Outpatients (n = 321) of the ild care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre, The Netherlands, participated in this prospective follow-up study. Anchor-based and distribution-based methods were used to estimate the MCID. Based on the anchor Physical Quality of Life, a Receiver Operating Characteristic (ROC) was obtained. The distribution-based methods consisted of the Effect Size and Standard Error Measurement (SEM).

Results
The anchor-based MCID found with ROC was 3.5. The distribution-based methods showed that the corresponding change scores in the FAS for a small effect was 4.2. The SEM criterion was 3.6 points change in the FAS.

Conclusions
Based on the anchor-based and distribution-based methods, the MCID is a 4-point difference on the FAS. This MCID can be used in the follow-up of fatigue (FAS) in clinical trials and in the management of individual sarcoidosis cases.

Introduction

Fatigue is the most common symptom in sarcoidosis that often leads to a decreased quality of life (QOL)[1-3]. Furthermore, fatigue is associated with symptoms of depression[4], cognitive impairment[5], exercise intolerance[6], and stress[7]. Because of this substantial influence on the patient's life, it is important to appropriately assess fatigue with a valid and reliable measure in clinical practice as well as in clinical trials.

Combined with clinical outcomes assessment, measurement of fatigue provides greater insight into suitable clinical interventions and patients' response to treatment. In the absence of an objective measure for fatigue, it is usually measured by means of self-reported questionnaires. The Fatigue Assessment Scale (FAS) is a short self-report questionnaire for measuring fatigue. This instrument has shown to be a valid and reliable fatigue measure among sarcoidosis patients[8,9]. Several studies found significant differences in the score of the FAS between subgroups of sarcoidosis patients[2,5,7,10-12]. Although these differences were statistically significant, they may be irrelevant from the patients' point of view.

A limitation of questionnaires in general is that their statistical scores do not provide directly a clinical interpretation. The minimal clinically important difference (MCID) has been developed as a measure for the smallest change score of interest which patients perceive as relevant[13]. Treatment effects that exceed the MCID denote clinical significance and support implementation into clinical practice. Thus, the MCID indicates that the minimal change in fatigue scores across time of individual patients represents a clinically relevant difference, thereby helping clinicians to interpret the clinical meaning of changes on fatigue scores of individual patients. In addition, the MCID is relevant in both the planning of clinical trials and interpretation of the results when evaluating outcomes of intervention studies using the FAS. Till now, no MCID has been established for this fatigue questionnaire in sarcoidosis. Moreover, the MCID criteria that are already established for fatigue questionnaires in other populations[14-17] cannot be applied to a sarcoidosis population, because the MCID criteria vary by population[18].

Therefore, the aim of this study was to estimate the MCID for the FAS in patients with sarcoidosis in order to evaluate clinical outcome of interventions.

As recommended by Revicki et al.[19] we have employed both anchor-based and distribution-based methods to establish the MCID of the FAS. Distribution-based and anchor-based methods have been used to determine a MCID in fatigue[14-17]. The anchor-based method compares measures of fatigue to other measures or phenomena that have clinical relevance. The distribution-based method is based on the characteristics of the particular patient population, such as sample variability and precision of the questionnaire[20]. An anchor-based approach was chosen for this study in order to link the change in fatigue with a meaningful external anchor. In addition, two distribution-based methods were used to evaluate the responsiveness of the MCID found with the anchor-based approach.

Methods

Patients

All sarcoidosis outpatients (n = 588) of the ild care team of the Department of Respiratory Medicine of the Maastricht University Medical Centre (MUMC+) a tertiary referral center in The Netherlands, were asked to participate. The flowchart of the patient participation is shown in Figure 5.1. Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchoalveolar lavage (BAL) fluid analysis results according to the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines[21]. 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).

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. In May 2008 the same patients received a second set of questionnaires with an envelope. The most common reason for not completing the second set of questionnaires was 'insufficient time'. The data were collected by the ild care team. The Medical Ethical Committee of the MUMC+ approved the study protocol and written informed consent was obtained from all patients.

Measures

The patients were sent questionnaires at baseline and after 12 months. The patients completed the Fatigue Assessment Scale (FAS)[8] to assess the change in fatigue during the one-year follow-up. For the anchor-based method, the change in physical quality of life (Physical QOL) across time was assessed with the World Health Organization Quality of Life BREF (WHOQOL-BREF)[22]. This anchor was chosen because previous research found strong associations between the FAS and this instrument in sarcoidosis[3].

The FAS is a 10-item self-report fatigue questionnaire. The reliability and validity of the FAS are good, also in sarcoidosis patients[8,9]. The response scale is a 5-point Likert scale (1 *never* to 5 *always*). Total scores on the FAS can range from 10 to 50, with high scores indicating more fatigue. Consequently, possible changes in FAS scores of patients could range from -40 to 40 between baseline and follow-up.

The domain 'Physical Health' of the WHOQOL-BREF was used for the anchor Physical QOL. This anchor was based on the change score in the domain Physical Health during the one-year follow-up period. The WHOQOL-BREF is a 26-item instrument to assess quality of life from the patients' perspective[22]. The content validity, construct validity, and the reliability of the WHOQOL-BREF are good[23,24].

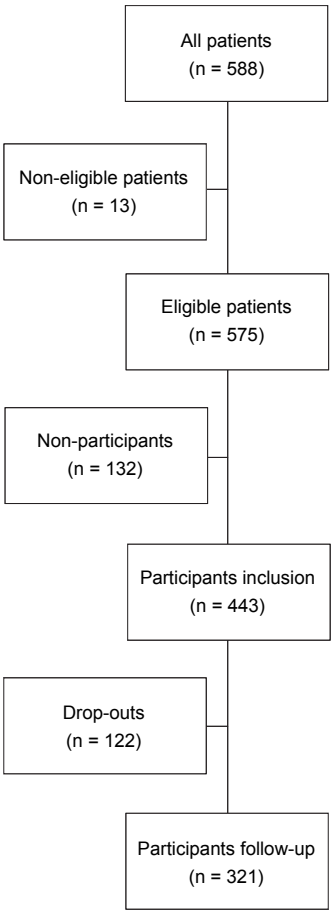

Figure 5.1 Flowchart of patient selection

The domain Physical Health consists of the following questions: '*To what extent do you feel that physical pain prevents you from doing what you need to do?', 'How much do you need any medical treatment to function in your daily life?', 'Do you have enough energy for everyday life?', 'How well are you able to get around?', 'How satisfied are you with your sleep?', 'How satisfied are you with your ability to perform your daily living activities?', and 'How satisfied are you with your capacity for work?*'. The response scale of the domain Physical Health is a 5-point Likert scale (1 to 5) and scores can range from 4 to 20, with high scores indicating a better Physical QOL[22]. Consequently, change scores on the anchor Physical QOL between baseline and follow-up could range from -16 to 16.

Statistical Procedures

Patients who dropped-out after the baseline measurement and patients who remained in the study were compared on demographical (sex, age, ethnicity), clinical (lung function tests, radiographic staging, (extra) pulmonary involvement, time since diagnosis), and psychological variables (FAS total score, WHOQOL-BREF domain scores) by means of t-tests and chi-square tests.

Change scores for the FAS and the anchor were calculated by subtracting the baseline score from the 12-month score. A positive change on the anchor describes an improvement whereas a positive change on the FAS indicates an increase in fatigue. Because the different meaning of a positive change may complicate the interpretation of the results, the sign of the FAS change score was reversed, so that a positive change score represents an improvement (decline in fatigue).

As recommended by Revicki et al.[19] both distribution-based and anchor-based methods were used to estimate the minimal clinically important difference.

Distribution-based method

Two distribution-based methods were used to estimate the MCID for the FAS. According to Norman et al.[25], an effect size (*ES*) of 0.5 approximates the threshold of discrimination for changes in health-related quality of life for chronic diseases. Therefore, the expected change scores in the FAS were calculated for an effect size of 0.5 to estimate the minimal change[26]. The corresponding change scores on the FAS ($\Delta x12$) were the product of these indices and the standard deviation (*SD*) at baseline, i.e., $\Delta x12 = ES \cdot SDx1$.

In addition, the Standard Error Measurement (SEM)[27,28] was used to identify the minimal clinically important change in the FAS. The SEM was calculated to identify the minimal clinical important change using the revised Jacobson formula[29,30]. An observed change that exceeded the standard measurement error was considered to reflect a change. Patients with a score that did not exceed the measurement error were considered to be stable. In addition, patients were considered to have a minimally improved or minimally worsened fatigue, if their score increased or decreased one-SEM, respectively.

Anchor- based method

Concerning the anchor-based method, Pearson's correlations were calculated to measure whether the change score of the anchor Physical QOL was associated with the change score of the FAS. Revicki et al.[19] recommended a correlation threshold of 0.30 between an anchor and patient-reported outcome measure such as QOL, to establish a MCID.

Subsequently, patients were divided into one of three groups: improved, stable, or worsened Physical QOL. Patients were considered to be either improved or worsened in Physical QOL if the change score (between baseline and follow-up) exceeded the measurement error of the WHOQOL-BREF domain Physical Health[27-30]. In addition, patients with a score that did not exceed the measurement error were considered to

be stable in Physical QOL. Frequencies and means were calculated for each group of the anchor Physical QOL.

The receiver operating characteristic (ROC)[31] method is another anchor-based method that was used to estimate the MCID[32]. For this method, the FAS was considered as the diagnostic test and the anchor Physical QOL functioned as the golden standard. The anchor Physical QOL distinguished persons who improved or worsened from persons who remained stable on Physical QOL. Additional ROC curves were obtained for the anchor change score with a $CI_{95\%}$. This change score is the smallest change that can be considered above the measurement error with a 95% level of confidence[33]. These change scores were calculated by multiplying the change scores of the anchor by 1.96. The ROC was obtained by plotting the sensitivity against 1-specificity for each possible FAS change score. The area under the ROC curve represents the probability that FAS scores will correctly discriminate between patients who improved and worsened on Physical QOL. Probabilities range from 0.5 to 1, with 0.5 representing the ability to discriminate on chance and 1 representing the ability to correctly discriminate all the patients. An area under the curve of 0.7 to 0.8 is considered acceptable and an area of 0.8 to 0.9 is considered excellent[34]. The ROC cut-off point is the value for which the sum of percentages of true positive and true negative classifications is largest (sensitivity + specificity). Because we are interested in the minimal change, the smallest value was chosen as the cut-off point when several options were found for the largest sum (rounded to two decimals). This optimal cut-off point is the estimation of the anchor-based MCID for the FAS.

Results

Demographical, clinical, and psychological characteristics at baseline are presented in Table 5.1. No differences were found in these variables between the patients who dropped-out of the study and the patients remaining in the study.

Anchor-based method

The anchor Physical QOL was found to be eligible for estimating a MCID for the FAS, because the correlation between the change scores of the FAS and the anchor ($r = 0.47$ ($p < 0.001$, $CI_{95\%}$ 0.38 - 0.55)) exceeded the threshold of $r = 0.30$[19,24]. The measurement error of Physical Health was |1.63|. Based on this value, the three groups of the anchor Physical QOL (worsened, stable, and improved) were distinguished: a change score of -1.63 or lower for patients who had worsened (n = 62), a change score between -1.63 and 1.63 for patients who remained stable (n = 186), and a change score of 1.63 or higher for patients who had improved (n = 67). The corresponding mean change scores on the FAS were -3.8, 0.3, and 3.0 for each anchor group, respectively.

The ROC was obtained to estimate the anchor-based MCID for the FAS for both improved patients and worsened patients. The area under the ROC curve for the

improved patients was 0.6, this means that the ability of the FAS to discriminate patients who improved in Physical QOL was just above chance level. Thus, the cut-off value for a MCID in the FAS was 3.5 points, which corresponded to an optimal balance between a sensitivity of 45% and a specificity of 81%, e.g., 45% of the patients were correctly identified as improved and 81% of the patients were correctly identified as *not* improved.

Table 5.1 Descriptive statistics of the participants and dropouts[a]

	Participants n = 321	Dropouts n = 122	Statistics[b]
Demographics			
Male%	55.8	48.4	$\chi^2(1, n = 443)= 1.7$
Caucasian/African/Asian/other%	95.6/3.1/0.3/0.9	93.4/3.3/0.8/2.5	$\chi^2 (4, n = 442)= 2.1$
Age (range in years)	48.5 ± 10.8 (28-79)	46.8 ± 12.1 (19-80)	*t* (441)= -1.2
Medical variables			
Time since diagnosis (years)	7.8 ± 7.7 (0-65)	7.2 ± 7.9 (0-42)	*t* (439)= -0.8
Multisystemic involvement%	48.0	48.3	χ^2 (1, n = 439)= 0
Radiographic stage:	42.6/8.2/23.5/	34.4/ 9.8/27.0/	χ^2 (4, n = 441)= 2.9
0/I/II/III/IV%	11.6/14.1	14.8 /13.9	
FVC	99.4 ± 19.4	96.8 ± 20.6	*t* (429)= -1.2
FEV_1	90.2 ± 22.4	87.1 ± 21.9	*t* (431)= -1.2
DLCO	82.2 ± 17.8	79.6 ± 16.7	*t* (431)= -1.4
Psychological variables			
Fatigue Assessment Scale score	29.5 ± 8.4	28.8 ± 8.4	*t* (433)= -0.8
Quality of life:			
Overall Facet	5.9 ± 1.6	6.2 ± 1.6	*t* (443)= 1.6
Physical Health	12.5 ± 3.1	12.8 ± 3.1	*t* (430)= 1.0
Psychological Health	13.8 ± 2.5	13.8 ± 2.6	*t* (431)= 0.1
Social Relationships	15.4 ± 2.9	14.5 ± 3.0	*t* (430)= -0.1
Environment	15.4 ± 2.5	15.2 ± 2.6	*t* (432)= -0.7

[a]Data are expressed in mean ± standard deviation or in percentages. [b] All statistical values are not significant. DLCO = Diffuse capacity of the lung for carbon monoxide; FEV_1 = Forced Expiratory Volume in 1 s; FVC = Forced Vital Capacity.

When the analysis was repeated with patients who were worsened versus patients who remained stable in Physical QOL, the area under the curve was 0.7. This means that the FAS fairly discriminated patients who worsened in Physical QOL. The cut-off value of the FAS is -3.5, which corresponded to a sensitivity of 82% and a specificity of 51%.

When selecting the patients with an anchor change score in Physical QOL with a 95% interval, the same cut-off of 3.5 points change on the FAS was found for both the improved and the worsened patients. The area under the curve was 0.8 for the improved patients, and 0.9 for the worsened patients. This means that the ability of the FAS to discriminate patients who changed in Physical QOL was good. In addition,

the sensitivity and specificity increased to 79% and 84% for the worsened patients and 71% and 78% for the improved patients, respectively.

Distribution-based methods

The corresponding minimal change on the FAS for an effect size of 0.5 was 4.2.

The reliability coefficient Cronbach's alpha of the FAS was 0.9, resulting in a one-SEM of 3.6. This reflects the cut-off point of a statistical minimal change in the FAS.

Minimal clinically important change

In sum, for the anchor-based method, mean scores of -3.8 for the worsened patients and 3.0 for the improved patients were found, and the ROC cut-off was |3.5|. For the distribution-based method, the ES was |4.2| and the SEM was |3.6|. These estimates for the minimal clinically important changes found with both methods are rounded to 4 points change on the FAS, because the FAS is measured in whole points. This cut-off of the minimal clinically important change is represented in Figure 5.2 with two dashed lines. Patients who scored above or below these lines were considered to be either minimally improved or minimally worsened in fatigue, respectively.

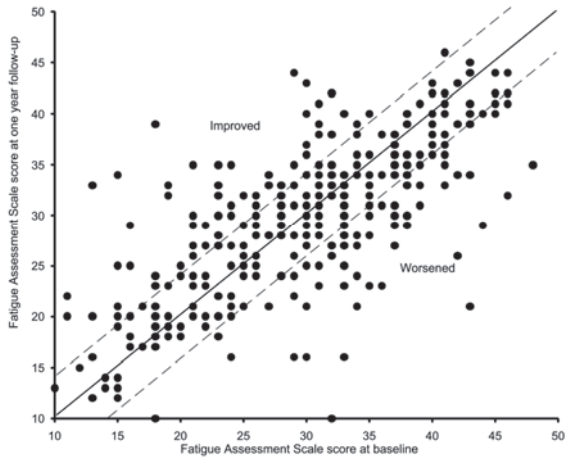

Figure 5.2 Minimal Clinically Important difference of the Fatigue Assessment Scale.

Discussion

The FAS is a validated fatigue questionnaire used in the management and follow-up of sarcoidosis patients as well as an outcome measure in clinical trials. However, until now a minimal clinically important difference (MCID) was lacking. Therefore, the aim of this study was to determine the MCID of the FAS in sarcoidosis patients. To estimate the MCID both anchor-based and distribution-based methods were used in this study because they are complementary, i.e. each has different advantages[20]. Both methods revealed similar results. The MCID was estimated on a change of 4 points indicating that when the FAS scores of a patient changes between two time points with at least 4 points, this change in fatigue is clinically meaningful.

Anchor-based method

The anchor Physical QOL takes into account Physical health from the patients' perspective. Based on the anchor Physical QOL, the minimal change was estimated at 3.5 points change on the FAS by means of a ROC curve. The same threshold for a minimal clinically important change in fatigue was found for patients with a large and a small change in Physical QOL, which strengthens the criterion for change. The high percentages provided by the ROC curve for the anchor with a 95% confidence interval indicate that the chance to incorrectly define a patient as changed or unchanged is low when using a threshold of 4 points on the FAS (rounded). This may be important when the negative effects of group assignment are large, e.g., when treatment has side-effects or is expensive.

Other studies applied anchor-based methods, based on non-clinical anchors to determine a MCID for fatigue instruments[13,14]. Pouchot et al.[15] matched the scores of the fatigue measures with the self-reported ratings of fatigue on a global scale. A limitation of this method is that the differences between patients may be incomparable to longitudinal changes within patients. Moreover, a global rating is frequently used in anchor-based methods, but coincides with several difficulties: patients have to rate the change in fatigue in an extended period of time in the past, these retrospective ratings are susceptible for recall bias and current mood states. In addition, little information is available about the validity and reliability of these global ratings. Furthermore, depending on the magnitude of the correlation with fatigue, the global ratings do not explain the total variance in fatigue[20]. Purcell et al.[14] determined in a follow-up study MCID scores for the Multidimensional Fatigue Inventory using the anchors Health-related Quality of Life, performance status, and productive hours. No associations between performance status or productive hours and fatigue have been reported in sarcoidosis. Therefore, in the current study, we chose to select an anchor from the WHOQOL-BREF, which is a validated and reliable instrument[23,24] and associated with fatigue in sarcoidosis[2]. Clinical anchors were not selected, because previous studies showed no significant relationships between the FAS and widely used medical data in sarcoidosis[2]. In addition, in this study longitudinal changes within patients were examined to evaluate the development of fatigue.

Distribution-based methods

An advantage of the distribution-based methods is that they provide a MCID which exceeds random variation[20]. Wyrwich et al.[27,28] and Rejas et al.[35] showed that the SEM criterion is a promising measure to estimate the MCID, because the SEM relies on the precision of the instrument, is independent of sample size, and takes spurious change due to measurement error into account. Moreover, the SEM criterion is a frequently used measure in studies which determined a minimal change in diseases similar to sarcoidosis[36-40]. In addition, the effect size represents the individual change, also is independent of sample size[20], and also is commonly used to determine a change[41,42]. In this study, it appeared that the MCID based on the anchor approximated the MCID found with the distribution-based methods. The similar result from both the anchor-based and distribution-based method might suggest that the estimation for the MCID is robust.

Systemic manifestations are considered important in sarcoidosis. The extent of physiological impairment or organ system loss of function is still applied to classify the severity of sarcoidosis: most often still based on stratification of respiratory functional impairment[21,43]. It has been widely accepted now that an integral assessment frame work of health status, incorporating physiological functioning, complaints like fatigue, exercise impairment and quality of life, improves conceptual insight in the impact of sarcoidosis on patients' lives and offers the clinician avenues in individual management[6]. Therefore, in the management of sarcoidosis it is mandatory to have insight in the MCID of the validated fatigue questionnaire in sarcoidosis: the FAS.

The results of this study are relevant for researchers and clinicians who want to assess clinically important changes in fatigue in sarcoidosis patients. Researchers should consider clinical significance from the patients' perspective, as well as statistical significant results. The MCID also improves conceptual insight in the impact of sarcoidosis on patients' lives. Moreover, the MCID is a clinically important concept, as it may assist clinicians with the interpretation of observed changes in the FAS and may influence the perceived success of an intervention. In addition, the MCID could have implications for the design of clinical trials in terms of the selection of a useful clinical outcome measure. Therefore, in the management of sarcoidosis it is recommended to have insight in the MCID of the validated fatigue questionnaire in sarcoidosis, i.e., the FAS. The MCID identified in this study is aimed to improve the clinical interpretation of changes in sarcoidosis-associated fatigue as measured by the FAS.

One limitation of this study may be that the patients were recruited in a tertiary referral centre, which may have caused selection bias and, therefore, the results may be not representative for every sarcoidosis patient. Consequently, we recommend using the MCID found in this study as a guideline. A limitation of the Standard Error Measurement is that this approach relies on the assumption that measurement error is constant across the range of possible scores[20]. For future studies it is important to take into account that a change of one point may be different for a patient who shows an impaired energy level at baseline in contrast to a patient who shows little or no impairment.

In conclusion, using various methods the present study showed that a change in a patient's FAS score across time of at least 4 represents a clinically important difference, i.e. the fatigue of the patient has increased or decreased.

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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 activity[1]. Besides the symptoms related to specific organs, patients also often report fatigue[2].

Fatigue is the most frequently reported symptom in the sarcoidosis population in the Netherlands[2]. 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 failure[4], depressive symptoms[5], dyspnea[6], 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 Fatigue[9].

The primary limitations of previous research were the cross-sectional design[10] 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 Aspinwall[11], 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 sarcoidosis[10]. 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 cancer[12]. 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.

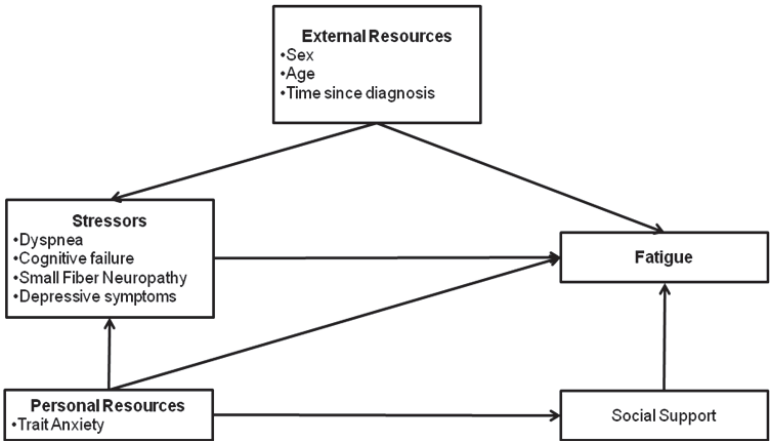

Figure 6.1 Initial conceptual model of fatigue in sarcoidosis[a].
[a] Error terms are omitted in this Figure. All predictors were measured at baseline and fatigue at 12 months follow-up

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 guidelines[15]. 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 scores[16].

Stressors

At baseline the patients completed the Center for Epidemiological Studies-Depression Scale (CES-D)[17] and 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-D[17] 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[21]. 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 SFN[18]. The CFQ is a self-report questionnaire consisting of 25 items assessing impairment in attention, perception, memory and motor functioning in everyday life[19]. 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 angiography[23] and was translated in Dutch[22].

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 variables stressors (depressive symptoms, symptoms suspected of SFN, dyspnea) 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 (χ^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 18.0[26], 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 fit[30].

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
FEV1	89.9 ± 22.4
DLCO	81.8 ± 17.9
Medication	
Prednisone [a]	95 (32.5%)
Immunosupressants [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; FEV_1 = 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 (β = 0.31), depressive symptoms (β = 0.26), symptoms suspected of SFN (β = 0.16), and dyspnea (β = 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 (β = 0.12) more often than younger ones, and younger patients reported cognitive failure (β = -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 (β = -0.16), and

cognitive failure (β = -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 (β = 0.48), more depressive symptoms (β = 0.81), less social support, (β = -0.34) and more symptoms suspected of SFN (β = 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.

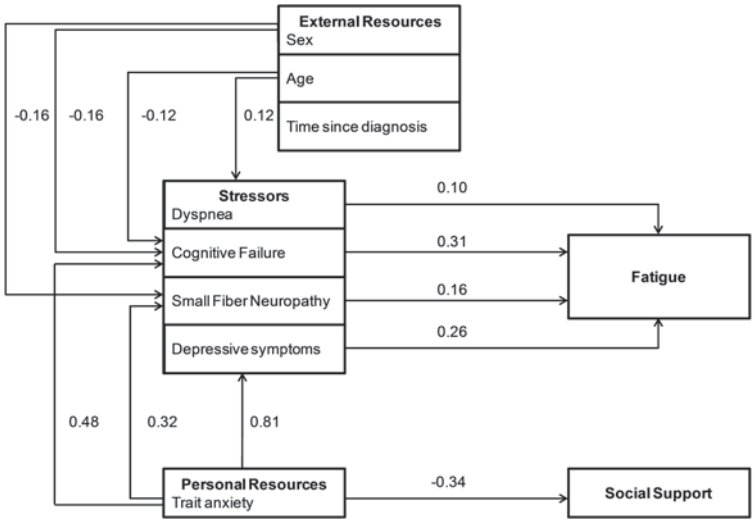

Figure 6.2 Model that was tested for understanding the associations among, sex, age, time since diagnosis, social support, cognitive failure, depressive symptoms, dyspnea, small fiber neuropathy and fatigue in sarcoidosis.[a]

[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 failure[4]. 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 functions[31]. 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 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 line with the results of studies in other chronic medical illness, such as diabetes, chronic obstructive lung disease, cardiac disease and rheumatoid arthritis[35]. 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 depression[35]. 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 sarcoidosis[36]. Sarcoidosis patients treated with immunomodulating drugs exhibited a relation between fatigue and plasma IL-1β concentrations[37]. In addition, Heessen et al. showed that fatigue in MS patients is associated with activation of proinflammatory cytokines[38]. The cytokine imbalance of patients suffering from depression also appeared to be disturbed[39]. In addition, the finding that older patients reported more often dyspnea than younger patients confirms previous research[40]. 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 SFN[42].

Neither trait anxiety, social support, time since diagnosis, sex nor age predicted fatigue. A previous study reported an association between trait anxiety and fatigue in sarcoidosis[43]. However, instead of a cross-sectional design, this study has a longitudinally 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 study[45], indicating that fatigue does not resolve spontaneously across time[46].

This is the first study examining a conceptual model of fatigue in sarcoidosis. Previously, models of fatigue have been examined in cancer[47] 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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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 (FEV1) 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 9-13% (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 range of concomitance of high levels of depressive symptoms and were 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 later 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 at 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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Chapter 8

General discussion and summary

Introduction

Fatigue is a common complaint in sarcoidosis[1], and has been associated with an impaired quality of life [2]. 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 causality[3-5]. Moreover, fatigue is suggested to differ between individual patients[6], though this is not empirically defined.

The aim of the studies presented in this thesis was to evaluate the prevalence, and classification of fatigue. In addition, the role of psychological factors in fatigue in sarcoidosis was examined. 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.

Prevalence and classification of fatigue in sarcoidosis

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 Sharma[6]: 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

Psychological factors and fatigue in sarcoidosis

In addition to the definition and classification of fatigue, the role of psychological factors in relationship to fatigue across time was 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.

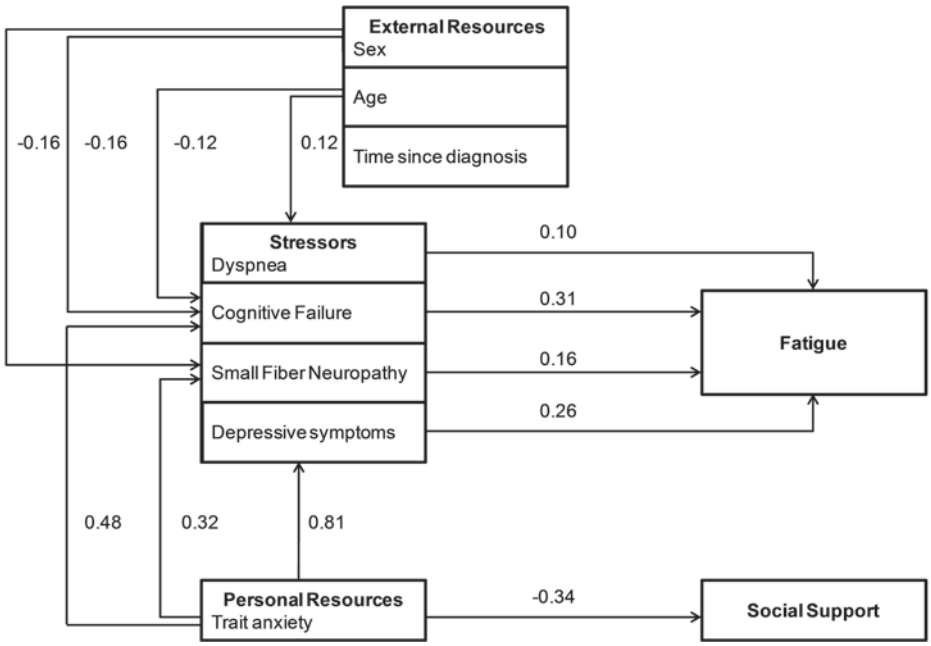

Figure 8.1 Model that was tested for understanding the associations among, sex, age, time since diagnosis, social support, cognitive failure, depressive symptoms, dyspnea, small fiber neuropathy and fatigue in sarcoidosis [a]

[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 fatigue[16]. 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 sarcoidosis[18]. The efficacy of anti-TNF-α to treat fatigue has been demonstrated previously in small studies[19-21]. 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 medication[24]. For instance, Haüser 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 disease[26]. 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 fatigue[27]. 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 therapy[28]. 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 coping[31]. 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 objectively[32]. 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 reduction[33].

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 relevant[34]. 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 studies[35-38] 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 lacking[39]. 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 diagnosis[40].

Strengths

Important strengths of the studies are the longitudinal design (Chapter 5, 6 and 7), and the sample size. 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 clustering[54]. 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 research[55].

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, neuro-psychological 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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Nederlandse samenvatting

Inleiding

Vermoeidheid is een veel voorkomende klacht bij de ziekte sarcoïdose en is geassocieerd met een verminderde kwaliteit van leven. In de literatuur bestaan slechts enkele studies over de rol die psychologische factoren spelen bij vermoeidheid van sarcoïdosepatiënten. Deze studies zijn echter allemaal cross-sectioneel, waardoor geen conclusies kunnen worden getrokken over causaliteit. Daarnaast komt vermoeidheid niet bij iedere patiënt voor en zijn er aanwijzingen dat vermoeidheid op verschillende manieren door patiënten wordt ervaren. Deze individuele verschillen zijn echter niet empirisch gedefinieerd.

Het doel van dit proefschrift is een beter beeld te krijgen van vermoeidheid bij sarcoïdose. Hiervoor zijn bij sarcoïdosepatiënten de prevalentie en classificatie van vermoeidheid onderzocht. Daarnaast is de rol van psychologische factoren bij vermoeidheid in kaart gebracht.

Sarcoïdosepatiënten van het ild care team van de polikliniek Longziekten van het Maastricht Universitair Medisch Centrum (MUMC+) hebben deelgenomen aan deze studie. De deelnemende patiënten hebben hiervoor gedurende een periode van 18 maanden vragenlijsten ingevuld. Deze vragenlijsten hadden betrekking op vermoeidheid, kwaliteit van leven, depressieve symptomen, klachten passend bij dunne vezel neuropathie, cognitieve klachten, kortademigheid, sociale steun en persoonlijkheid. Ook hebben zij vragen beantwoord over rusteloze benen, slaap en dagelijkse activiteiten. Relevante klinische informatie is uit de medische dossiers van de patiënten verkregen. Tevens zijn de gegevens van twee cross-sectionele patiëntencohorten (Nederlandse en Amerikaanse sarcoïdosepatiënten) geanalyseerd.

Belangrijkste bevindingen en conclusies

In **hoofdstuk 1** wordt vermoeidheid bij sarcoïdose beschreven en een overzicht van het proefschrift gepresenteerd.

Prevalentie en classificatie van vermoeidheid bij sarcoïdose

In **hoofdstuk 2** wordt een literatuuroverzicht over vermoeidheid bij sarcoïdose gepresenteerd. Uit dit literatuuroverzicht blijkt het belang van longitudinale prospectieve studies om vermoeidheid beter te kunnen definiëren. Ook is het gebruik van gestandaardiseerde vermoeidheidsvragenlijsten, identificatie van prognostische factoren voor de ontwikkeling van vermoeidheid en onderzoek naar therapeutische strategieën die vermoeidheid verminderen noodzakelijk.

In **hoofdstuk 3** wordt de prevalentie en de ernst van vermoeidheid tussen Amerikaanse en Nederlandse sarcoïdosepatiënten vergeleken. Tevens worden potentiële verbanden onderzocht tussen vermoeidheid en demografische en klinische parameters. In de totale patiëntengroep wordt geen relatie tussen vermoeidheid en klinische of demografische parameters gevonden. Bij de Amerikaanse patiënten is

vermoeidheid echter wel gerelateerd aan leeftijd, extrathoracale lokalisatie van sarcoïdose en medicatiegebruik. Hoewel vermoeidheid even frequent voorkomt bij Nederlandse als Amerikaanse patiënten blijken de vermoeidheidsklachten ernstiger te zijn bij Nederlandse patiënten. De hoge prevalentie van zeer vermoeide Nederlandse patiënten bevestigt dat vermoeidheid een belangrijk en veelvoorkomend probleem is bij patiënten en nadrukkelijk aandacht bij de behandeling van sarcoïdose vereist. Vanwege het substantiële aantal patiënten dat geen vermoeidheid, vermoeidheid of extreme vermoeidheid rapporteerde, ontstond de vraag of vermoeidheid kon worden onderverdeeld in verschillende typen.

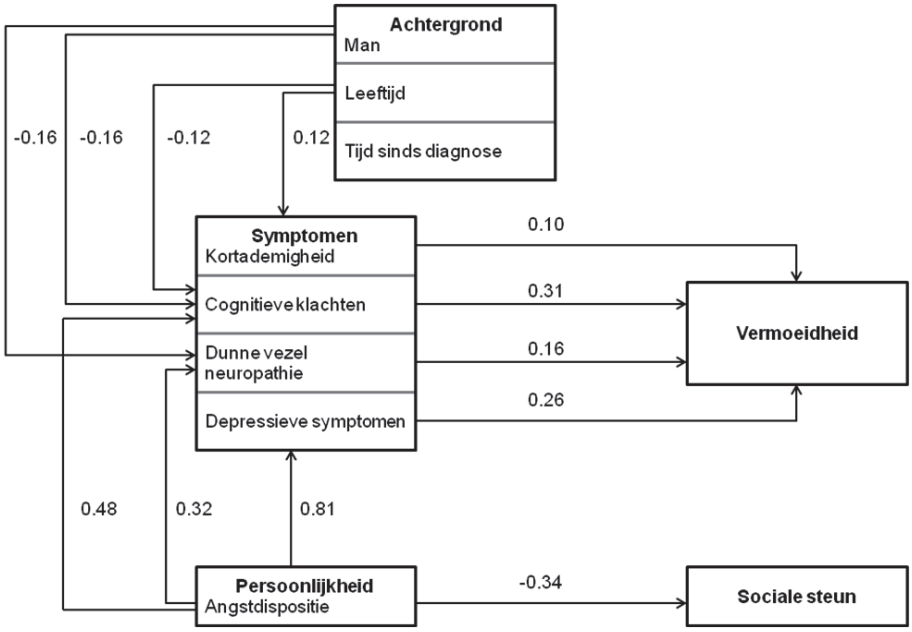
In **hoofdstuk 4** wordt door middel van latente cluster analyses onderzocht of vermoeidheid kan worden onderverdeeld in de volgende typen: vermoeidheid vroeg in de ochtend, wisselende vermoeidheid en vermoeidheid in de middag. Het wisselende type (Intermittent Fatigue) wordt bevestigd in de huidige studie. Daarnaast worden twee nieuwe soorten van vermoeidheid gedefinieerd: vermoeidheid gedurende de hele dag (All Day Fatigue) en een milde vermoeidheid (Mild Fatigue). De laatste groep patiënten rapporteert geen tot milde klachten van vermoeidheid. Intermittent Fatigue patiënten beschrijven klachten van vermoeidheid die variëren gedurende de dag. All Day Fatigue patiënten voelen zich de hele dag moe en ze rapporteren meer psychologische problemen en lichamelijke klachten in vergelijking met de andere groepen. Daarnaast zijn ze meestal niet in staat om te werken. Het is belangrijk deze patiënten te identificeren en te screenen. De indeling van het vermoeidheidspatroon van patiënten in deze drie typen van vermoeidheid kan ertoe leiden dat zorgverleners interventies op maat kunnen aanbieden aan patiënten. Deze indeling kan ook helpen om de behandeling te optimaliseren bij sarcoïdosepatiënten. Dit zou kunnen worden bereikt door het aanbieden van psycho-educatie en het leren van effectieve copingstrategieën om het welzijn van patiënten die de hele dag moe zijn te verbeteren. Het wordt aanbevolen om de effectiviteit van deze psychologische begeleiding te evalueren in toekomstig onderzoek.

In **hoofdstuk 5** is het minimale klinisch relevante verschil (Minimal Clinical Important Difference: MCID) van de Fatigue Assement Scale (FAS) onderzocht. De MCID in de FAS score is geschat op een verandering van 4 punten. De MCID kan nuttig zijn in de klinische praktijk en voor onderzoek omdat het de kans op succes weergeeft van een behandeling. Daarnaast kan de MCID van belang zijn voor artsen om de klinische betekenis van veranderingen in vermoeidheid bij individuele patiënten te interpreteren.

Psychologische factoren en vermoeidheid bij sarcoïdose

Naast de prevalentie en classificatie van vermoeidheid is de rol van psychologische factoren in relatie tot vermoeidheid onderzocht. De afwezigheid van verbanden tussen vermoeidheid en klinische en demografische parameters (hoofdstuk 3) geeft namelijk aan dat andere factoren gerelateerd zijn aan vermoeidheid bij sarcoïdose.

In **hoofdstuk 6** wordt een conceptueel model van vermoeidheid ontwikkeld en getest om de variabelen die mogelijk vermoeidheid voorspellen te onderzoeken. Het model in Figuur 9.1 blijkt geschikt voor het verklaren van variatie in vermoeidheid. Cognitieve klachten en depressieve symptomen zijn de belangrijkste voorspellers van vermoeidheid, gevolgd door symptomen gerelateerd aan dunne vezel neuropathie en kortademigheid. Bovendien zijn sterke relaties gevonden tussen depressieve symptomen en angst. Deze resultaten suggereren een indirecte relatie tussen persoonlijkheid (angstdispositie) en vermoeidheid. De verbanden tussen vermoeidheid en cognitieve klachten en vermoeidheid en symptomen die geassocieerd worden met de dunne vezel neuropathie zijn waarschijnlijk sterker bij patiënten met een angstige persoonlijkheid. Deze symptomen moeten kritisch worden geëvalueerd en worden opgenomen in de behandeling van sarcoïdose-patiënten.



Figuur 9.1 Model voor vermoeidheid bij sarcoïdose
Error termen zijn weggelaten in dit figuur. Significante coëfficiënten zijn gepresenteerd als gestandaardiseerde bètagewichten. Alle voorspellers zijn gemeten bij aanvang van de studie en vermoeidheid is gemeten na 12 maanden.

In **hoofdstuk 7** wordt de triade van vermoeidheid, depressieve symptomen en angst onderzocht om de complexe relaties tussen psychische klachten en vermoeidheid te verklaren. Het blijkt dat vermoeidheid gerelateerd is aan angst en depressieve symptomen, maar dat er geen sprake is van een volledig overlap tussen deze drie variabelen. Bovendien rapporteren patiënten die de hele dag moe zijn vaker angst en depressieve symptomen, dan patiënten in de andere twee typen van vermoeidheid. Daarom vereisen patiënten die de hele dag moe zijn speciale aandacht bij de behandeling van vermoeidheid bij sarcoïdose, waarbij geadviseerd wordt actief te screenen op depressieve klachten en angst.

De bevindingen die zijn gepresenteerd in dit proefschrift tonen aan dat vermoeidheid een belangrijk probleem is bij sarcoïdose en niet gerelateerd is aan klinische en demografische parameters. Symptomen zoals cognitieve klachten, depressieve symptomen, symptomen gerelateerd aan dunne vezel neuropathie en kortademigheid voorspellen vermoeidheid. Voor de patiënten is het essentieel dat deze symptomen worden gescreend en indien nodig worden behandeld. Daarnaast is neuropsychologisch onderzoek nodig om cognitief functioneren objectief in kaart te brengen. Dit dient bij voorkeur te geschieden door een multidisciplinair behandelteam, waarvan ook een psycholoog deel uitmaakt.

De relaties tussen vermoeidheid, inflammatie, slaapproblemen, dunne vezel neuropathie en autonome disfunctie zijn nog onduidelijk. Toekomstige studies dienen zich te richten op deze vraagstukken om meer inzicht te krijgen in vermoeidheid bij sarcoïdose. Daarnaast is het nodig om de gevonden resultaten te repliceren bij patiënten met acute sarcoïdose (tijd sinds de diagnose minder dan 2 jaar) om de bevindingen ook bij patiënten met een kortere duur van de ziekte te onderzoeken. Ook is er nog steeds behoefte aan goed opgezette prospectieve klinische studies, waarin de effectiviteit van farmacologische en psychologische behandeling van vermoeidheid wordt onderzocht. Het is belangrijk de kennis en erkenning van vermoeidheid bij patiënten met sarcoïdose en de behandeling uit te breiden met als doel de kwaliteit van leven van de patiënten te verbeteren.

List of publications

Publications

1. **De Kleijn WPE,** Elfferich MDP, De Vries J, Jonker GJ, Lower EE, Baughman RP, King Jr. TE, Drent M. Fatigue in Sarcoidosis: American versus Dutch patients. Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 92-97.
2. **De Kleijn WPE**, De Vries J, Lower EE, Elfferich MDP, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review. Curr Opin Pulm Med 2009; 15: 499-506.
3. **De Kleijn WPE**, De Vries J, Wijnen PAHM, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. Respir Med 2011; 105: 1388-1395.
4. **De Kleijn WPE,** Drent M, Shigemitsu H, Vermunt JK, De Vries J. Types of fatigue in sarcoidosis patients. J Psychosom Res 2011; 71: 416-422.
5. **De Kleijn WPE,** Drent M, M, Ponds RW, Elfferich MDP, De Vries J. Symptoms predicting fatigue in sarcoidosis. *Submitted*
6. **De Kleijn WPE,** Drent M, De Vries J. Nature of fatigue moderates depressive symptoms and anxiety in sarcoidosis. *Submitted*

Dankwoord

In dit dankwoord maak ik graag gebruik van de gelegenheid om een aantal mensen hartelijk te bedanken voor hun bijdrage aan de totstandkoming van dit proefschrift.

Allereerst wil ik de Sarcoïdose Belangenvereniging Nederland bedanken die dit onderzoek in belangrijke mate financieel mogelijk heeft gemaakt.

Tevens wil ik alle patiënten bedanken die hebben meegewerkt aan de studies in dit proefschrift. Bedankt voor jullie openheid en inzet bij het invullen van de vragenlijsten. Door jullie bijdrage is het mogelijk een steeds beter beeld te krijgen van vermoeidheidsklachten bij sarcoïdose.

In het bijzonder gaat mijn dank uit naar mijn promotoren: prof. dr. Jolanda de Vries van Tilburg University en prof. dr. Marjolein Drent van Maastricht University. Jullie begeleiding vanuit verschillende invalshoeken heb ik zeer gewaardeerd.

Jolanda, bedankt dat je me de kans hebt gegeven om te promoveren op het onderwerp sarcoïdose bij de afdeling medische psychologie van Tilburg University. Ik heb van jou veel geleerd over het verrichten van wetenschappelijk onderzoek. Jouw visie, enthousiasme en heldere kijk op onderzoek heeft mij vaak een positieve 'energy boost' gegeven. Ik waardeer dat je, ondanks je drukke bestaan, altijd tijd voor me vrij hebt gemaakt. Bedankt hiervoor. Ik heb er veel bewondering voor hoe je al je taken als psycholoog, professor, manager en moeder weet te combineren.

Marjolein, ook jou wil ik graag bedanken voor de mogelijkheid die je me hebt geboden om psychologisch onderzoek uit te voeren binnen jouw departement. Je medische kennis, bevlogenheid en affiniteit met de sarcoïdosepatiënten waren inspirerend en zinvol.

Mijn co-auteurs wil ik bedanken voor hun kritische en waardevolle feedback op mijn manuscripten en voor de prettige en leerzame samenwerking. I would also like to thank my foreign co-authors for their critical and valuable feedback on my manuscripts and for the pleasant and helpful cooperation.

De leden van de promotiecommissie, prof dr. Guus van Heck, prof. dr. Johan Polder, prof. dr. Jan Anne Roukema, dr. Ruth Wirnsberger en dr. Rudolf Ponds bedank ik van harte voor hun waardevolle tijd om mijn proefschrift te lezen en beoordelen. Ook wil ik prof. dr. Ad Appels en prof. dr. Ien van de Goor bedanken voor de vervanging van dr. Rudolf Ponds en prof. dr. Johan Polder als opponenten bij de verdediging van mijn proefschrift.

Alle dames van het secretariaat van het ild care team van de afdeling Longziekten van het MUMC+ wil ik bedanken voor de praktische hulp en ondersteuning de afgelopen jaren. Met name jullie goede ondersteuning bij het versturen van de vragenlijsten heeft mij veel werk uit handen genomen.

Tevens gaat mijn dank uit naar Tiny en de ild care foundation voor de bijdrage aan de mooie layout van mijn proefschrift.

Mijn oud-collega's van Tilburg University wil ik bedanken voor zowel de praktische als wetenschappelijke ondersteuning en natuurlijk voor de gezellige tijd. In het bijzonder wil ik Henneke, Mariska, Marleen en Annelieke bedanken voor de gezellige en openhartige gesprekken tijdens onze etentjes of wandelingen tijdens de lunch. Ik hoop dat we elkaar nog regelmatig zullen zien nadat we gepromoveerd zijn. Henneke

en Mariska, fijn dat jullie mijn paranimfen willen zijn en 16 mei voor mij klaar staan. Mijn dank gaat ook uit naar Lotje voor het wegwijs maken en vriendelijke welkom toen ik startte als nieuwe aio en naar Hester voor je humor en relativeringsvermogen. Jenny, mijn verjaardag- en kamergenootje, ik heb met jou de afgelopen jaren met veel plezier kamer P610 gedeeld. Bedankt voor je tips, directe opvang in 'crisismomenten' en het delen van alle grappige momenten met 'Flip'. Ook hartelijk dank voor het beschikbaar stellen van je thermoskan voor oneindig theedrinken en voor je gastvrijheid tijdens de aio-sinterklaasavonden.

Mijn huidige collega's, met name Elkie, Inge en Ben van de Radboud Universiteit Nijmegen, wil ik bedanken voor hun flexibiliteit waardoor het mogelijk was al tijdens de afrondende fase van mijn aio-traject met een nieuwe baan te starten. Ook wil ik jullie en Lieke, Sven, Marloes, Nick, Heleen, Daphne, Renske en Camille bedanken voor de leerzame, gezellige en ontspannende momenten tijdens de drukke en soms spannende periode in de laatste fase van de afronding van mijn proefschrift.

Beste vrienden Wies, Suzan, Jannes, Loes, Janette, Arjen, Jeroen en Marloes bedankt voor de gezellige stapavonden, romantische filmuurtjes, theeleuten, borrels en muzikale momenten. Vooral aan onze 'Florida-avonturen' heb ik goede herinneringen en ik hoop dit in de toekomst met jullie voort te zetten.

Anneke, Hennie en Jessica wil ik bedanken voor jullie ondersteuning. Hennie en Jessica, medepsychologen, ik waardeer jullie interesse vanuit het vakgebied.

Oma, bedankt voor alles. Ik hoop dat je met veel trots het boekje van je kleinkind op de boekenplank zet.

Johan, Lauco, Semir en Petrina, lieve (schoon)broer(tje)s en zusje, bedankt voor jullie afleiding van het werk. We vormen een hechte groep en ik waardeer jullie humoristische en relativerende inbreng.

Lieve papa en mama, bedankt voor alle onvoorwaardelijk steun en vertrouwen in mij. Zonder jullie geloof in mij en de door jullie gegeven kansen zou ik nooit zover gekomen zijn. Het voelt goed om te weten dat er altijd een veilige haven voor mij is.

Lieve Sebastiaan, de laatste bijzondere woorden van dit dankwoord zijn voor jou. Bedankt voor je liefde, vertrouwen en steun. Ik vind het fijn dat ik altijd op jouw hulp kan rekenen en om samen met jou van het leven te genieten.

Met de voltooiing van dit proefschrift is een belangrijke stap gezet. Op weg naar een nieuwe uitdaging!

Willemien de Kleijn
Maart 2012

Curriculum vitae

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Willemien de Kleijn was born on February 17, 1984 in Overasselt, the Netherlands. She completed her pre-university education at the Merlet College, Cuijk, in 2002. From 2002 to 2007 she studied at Radboud University where she obtained the degrees Bachelor of Science (BSc) and Master of Science (MSc) in Neuropsychology and Rehabilitation Psychology. She completed her clinical internship and research internship at the Medical Psychology department of Radboud University Nijmegen Medical Centre. Thereafter, she started in 2008 her PhD research at Tilburg University, supervised by Prof. dr. J. De Vries and Prof. dr. M. Drent. This research, focused on the psychological role of fatigue in sarcoidosis, is presented in this thesis. Currently, she is working as a teacher at Radboud University, Nijmegen, the Netherlands.