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].

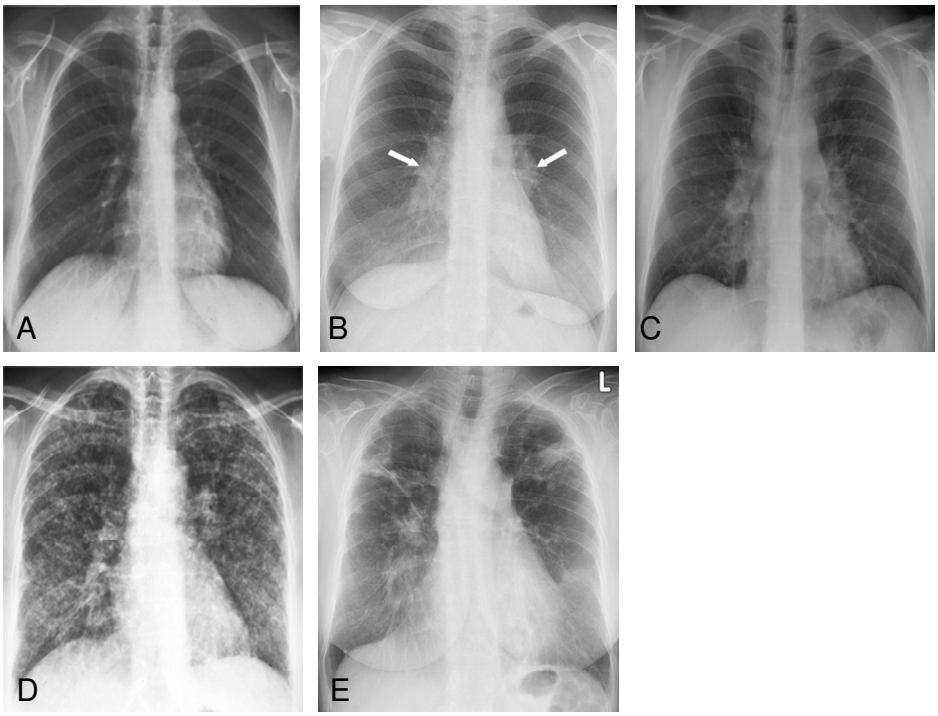

Figure 1.1 Chest X-ray stages 0-IV: radiographic appearances of sarcoidosis.
A) Stage 0: normal chest radiograph;
B) Stage I: bilateral hilar lymphadenopathy (arrows), without evidence of interstitial lung disease;
C) Stage II: both lymphadenopathy and parenchymal abnormalities (nodular and reticulonodular 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 (FEV_1) and forced vital capacity (FVC), were measured with a pneumotachograph. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single breathe method. Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV: with signs of pulmonary fibrosis, loss of volume, hilar retraction and bullae (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

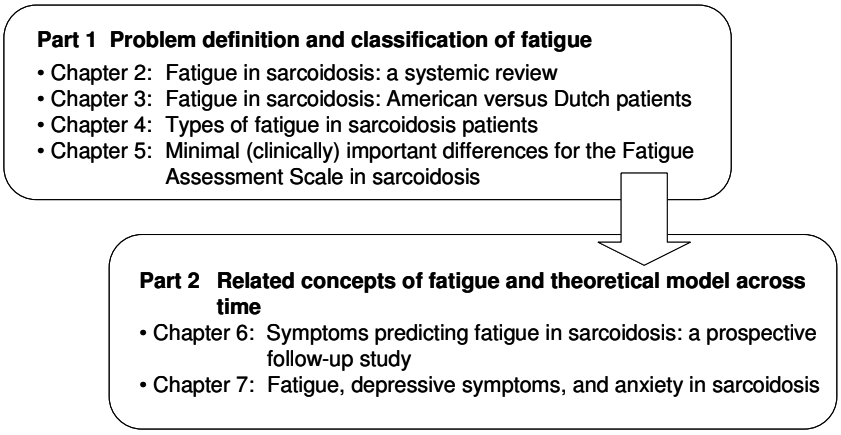

Figure 1.2 Outline of the thesis.

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.

References

1. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet. 2003;361:1111-8.
2. Kataria Y, Holter J. Sarcoidosis: a model of granulomatous inflammation of unknown etiology associated with a hyperactive immune system. Methods. 1996;9:268-94.
3. Morgenthau AS, Iannuzzi MC. Recent advances in sarcoidosis. Chest. 2011;139:174-82.
4. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizzato G, Rose C, Selroos O, Semenzato G, Sharma OP. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16:149-73.
5. Baughman RP, Teirstein AS, Judson M, Rossman MD, Yeager H Jr, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, McLennan G, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki B, Weinberger SE, Terrin ML, Knatterud GL, Cherniak R, and a case control etiologic study of sarcoidosis (ACCESS) Research group. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164:1885-9.
6. Hoitsma E, Marziniak M, Faber CG, Reulen JP, Sommer C, De Baets M, Drent M. Small fibre neuropathy in sarcoidosis. Lancet. 2002;359:2085-6.
7. Marcellis RGJ, Lenssen AF, Elfferich MDP, De Vries J, Kassim S, Foerster K, Drent M. Exercise capacity, muscle strenght and fatigue in sarcoidosis. Eur Resp J. 2011;38:628-34.
8. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-α treatment. Respiration. 2010;80:212-9.
9. Elfferich MD, De Vries J, Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28:65-71.
10. Wirnsberger R, De Vries J, Wouters E, Drent M. Clinical presentation of sarcoidosis in the Netherlands an epidemiological study. Neth J Med. 1998;53:53-60.
11. Sharma OP. Fatigue and sarcoidosis. Eur Respir J. 1999;13:713-4.
12. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007;357:2153-65.
13. Longziekten Feiten en Cijfers. Nederlandse Longstichting, Interstitiële longaandoeningen, 2008.
14. Judson MA, Baughman RP, Thompson BW, Teirstein AS, Terrin ML, Rossman MD, Yeager H, McLennan G, Bresnitz EA, DePalo L, Hunninghake G, Iannuzzi MC, Johns CJ, Moller DR, Newman LS, Rabin DL, Rose C, Rybicki BA, Weinberger SE, Knatterud GL, Cherniak R, Group AR. Two year prognosis of sarcoidosis: the ACCESS experience. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20:204-11.
15. Newman LS, Rose CS, Maier LA. Sarcoidosis. N Engl J Med. 1997;336:1224-34.
16. DeRemee RA. The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. Chest. 1983;83:128-33.
17. Agostini C, Maffessanti M, Semenzato G. Systemic disease / Sarcoidosis. In: Geoffrey J. Laurent and Steven D. Shapiro, editor. Encyclopedia of Respiratory Medicine: Academic Press, Oxford; 2006. p. 196-202.
18. Hoitsma E, Faber CG, Drent M, Sharma OP. Neurosarcoidosis: a clinical dilemma. Lancet Neurol. 2004;3:397-407.
19. Reich JM. Mortality of intrathoracic sarcoidosis in referral vs population-based settings: influence of stage, ethnicity, and corticosteroid therapy. Chest. 2002;121:32-9.
20. James DG. Complications of sarcoidosis. Chronic fatigue syndrome. Sarcoidosis. 1993;10:1-3.
21. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest. 2006;130:989-94.
22. Ax S, Gregg VH, Jones D. Coping and illness cognitions chronic fatigue syndrome. Clin Psychol Rev. 2001;21:161-82.
23. Van Hoogmoed D, Fransen J, Bleijenbrg G, Van Riel P. Physical and psychosocial correlates of severe fatigue in rheumatoid arthritis. Rheumatology. 2010;49:1294-302.
24. Statement on sarcoidosis. Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med. 1999;160:736-55.

25. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol. 2004;9:279-91.
26. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res. 2003;54:345-52.
27. Beekman ATF, Deeg DJH, Van Limbeek J, Braam AW, De Vries MZ, Van Tilburg W. Criterion validity of the Center for Epidemiologic Studies Depression Scale (CES-D): results from a community-based sample of older subjects in the Netherlands. Psychol Med. 1997;27:231-5.
28. Radloff LS. The CESD-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas. 1977;1:385-401.
29. Van der Ploeg HM, Defares PB, Spielberger CD. ZBV: a Dutch-language adaptation of the Spielberger State-trait anxiety Inventory. Lisse, the Netherlands: Swets & Zeitlinger; 1980.
30. Blumenthal JA, Burg MM, Barefoot J, Williams RB, Haney T, Zimet G. Social support, type A behavior, and coronary artery disease. Psychosom Med. 1987;49:331-40.
31. De Vries J. The perceived social support scale, Dutch version. Tilburg: Tilburg University; 1998.
32. Trompenaars FJ, Masthoff ED, Van Heck GL, Hodiamont PP, De Vries J. Content validity, construct validity, and reliability of the WHOQOL-Bref in a population of Dutch adult psychiatric outpatients. Qual Life Res. 2005;14:151-60.
33. Hoitsma E, De Vries J, Drent M. The small fiber neuropathy screening list: construction and cross-validation in sarcoidosis. Respir Med. 2011;105:95-100.
34. Woods SA, Hampson SE. Measuring the Big Five with single Items using a bipolar response scale. Eur J Pers. 2005;19:373-90.
35. Broadbent DE, Cooper PF, FitzGerald P, Parker KR. The Cognitive Failure Questionnaire (CFQ) and its correlates. Br J Clin Psychol. 1982;21:1-16.
36. Borg G. Psychophysical bases of perceived exertion. Med Sci Sports. 1982;14:377-81.
37. Taylor SE, Aspinwall LG. Mediating and moderating processes in psychosocial stress. In: Kaplan HB, editor. Psychosocial stress perspectives on structures, theory, life-course and methods. San Diego, CA: Academic Press; 1996. p. 71-110.