SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2009; 26; 92-97

Fatigue in sarcoidosis: American versus Dutch patients

W.P.E. de Kleijn[1, 2], M.D.P. Elfferich[2, 3], J. De Vries[1, 2, 4], G.J. Jonker[2, 5], E.E. Lower[6], R.P. Baughman[6], T.E. King Jr.[7], M. Drent[2, 8]

[1] C*o*RPS, Department of Medical Psychology, Tilburg University, the Netherlands; [2] ild care team; Maastricht University Medical Centre, the Netherlands; [3] Department of Physical Therapy, Maastricht University Medical Centre, the Netherlands; [4] Department of Medical Psychology, St. Elisabeth Hospital, Tilburg, the Netherlands; [5] Department of Pulmonology, Maxima Medical Center, Eindhoven, the Netherlands; [6] Department of Internal Medicine, University of Cincinnati Medical Center, US; [7] Department of Medicine, University of California San Francisco, USA; [8] Departments of Respiratory Medicine, Maastricht University Medical Centre, the Netherlands

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 was found in the Dutch patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2009; 26: 92-97)*

Key words: sarcoidosis, fatigue; race, multinational

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, quan-

Received: 15 October 2008
Accepted after Revision: 09 March 2009
Correspondence: Prof. dr. M. Drent
Department of Respiratory Medicine,
Maastricht University Medical Centre (MUMC)
PO Box 5800
6202 AZ Maastricht
The Netherlands
Tel. 0031 43 3876497
Fax 0031 43 3874718
E-mail: m.drent@mumc.nl; www.ildcare.eu

tification 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 complete 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 biopsy-proven noncaseating epitheloid cell granulomas in most cases (10). In case of patients with Lofgrens 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 (FEV_1, FEV, 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 an 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 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 (FEV_1, 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

Table 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
FEV1	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 *	36 / 85	61 / 65
Anti TNF-α: yes / no †	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 if appropriate with range in parentheses.
FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TNF-α: Tumor Necrosis Factor-alpha.
* Cytotoxic agents: Methothrexate, Azathioprine, Cyclophosphamide, and Leflunomide (US patients), Methothrexate and Azathioprine (Dutch patients).
‡ Anti TNF-α: Infliximab and Adalimumab (US patients), Infliximab (Dutch patients).

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

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 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.

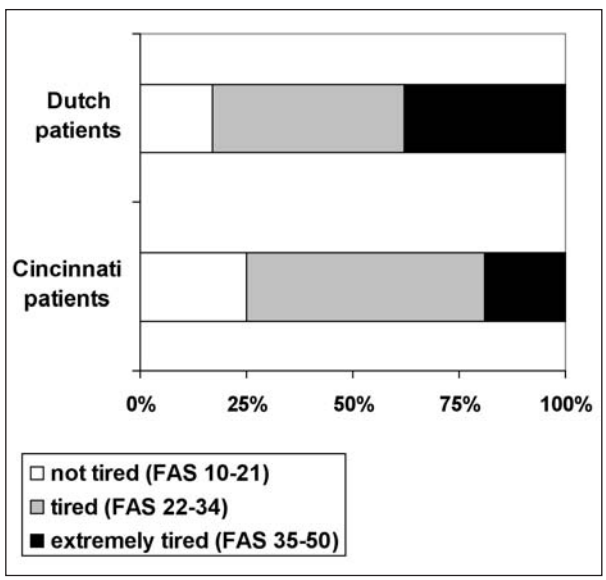

Fig. 1. Percentages of patients who are not tired, tired, and extremely tired. The percentage of extremely tired Dutch patients (37.8 %) was significantly higher compared with that of the US patients (19.0%), χ^2 (2, n = 245) = 11.03, p = 0.004)

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 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 dyspnoea 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 dyspnoea 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 analysing 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 relation with various disease manifestations and appropriate treatment.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357: 2153-65.
2. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. Lancet 2003; 361: 1111-8.
3. Wirnsberger RM, De Vries J, Wouters EF, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. Neth J Med 1998; 53: 53-60.
4. 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.
5. Sharma OP. Fatigue and sarcoidosis. Eur Respir J 1999; 13: 713-4.
6. 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.
7. Wirnsberger RM, De Vries J, Breteler MH, et al. Evaluation of quality of life in sarcoidosis patients. Respir Med 1998; 92: 750-6.
8. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21:127-36.
9. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. Chest 2007; 132: 207-13.
10. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granu-

lomatous Disorders. Sarcoidosis Vasc Diffuse Lung Dis 1999; 16: 149-73.
11. Cohen JW. Statistical power analysis for the behavioral sciences. 2 ed; 1988.
12. Zito JM, Tobi H, de Jong-van den Berg LT, et al. Antidepressant prevalence for youths: a multi-national comparison. Pharmacoepidemiol Drug Saf 2006; 15: 793-8.
13. Goracci A, Fagiolini A, Martinucci M, Calossi S et al. Quality of life, anxiety and depression in sarcoidosis. Gen Hosp Psychiatry 2008; 5: 441-5.
14. Chang B, Steimel J, Moller DR, et al. Depression in sarcoidosis. Am J Respir Crit Care Med 2001; 163: 329-34.
15. Drent M, Wirnsberger RM, Breteler MH, et al. Quality of life and depressive symptoms in patients suffering from sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 1998; 15: 59-66.
16. De Vries J, Drent M. Relationship between perceived stress and sarcoidosis in a Dutch patient population. Sarcoidosis Vasc Diffuse Lung Dis 2004; 21: 57-63.
17. Kelly K, Posternak M, Alpert JE. Toward achieving optimal response: understanding and managing antidepressant side effects. Dialogues Clin Neurosci 2008; 10: 409-18.
18. Baltzan M, Mehta S, Kirkham TH, Cosio MG. Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. Am J Respir Crit Care Med 1999; 160: 192-7.
19. Baughman RP, Lower EE. Evidence-based therapy for cutaneous sarcoidosis. Clin Dermatol 2007; 25: 334-40.
20. Fazzi P. Pharmacotherapeutic management of pulmonary sarcoidosis. Am J Respir Med 2003; 2: 311-20.
21. Fouchier SM, Moller GM, Van Santen-Hoeufft M, et al. Successful treatment with infliximab of a patient with refractory sarcoidosis. Ned Tijdschr Geneeskd 2004; 148: 2446-50.
22. Hoitsma E, Faber CG, van Santen-Hoeufft M, De Vries J, Reulen JP, Drent M. Improvement of small fiber neuropathy in a sarcoidosis patient after treatment with infliximab. Sarcoidosis Vasc Diffuse Lung Dis 2006; 23: 73-7.
23. Ten Hoor E, van Kan GJH, de Vries J, Jonker G, Drent M. Infliximab reduces fatigue in chronic sarcoidosis patients. Sarcoidosis Vasc Diffuse Lung Dis 2006; 23: 156-7.
24. Wagner MT, Marion SD, Judson MA. The effects of fatigue and treatment with methylphenidate on sustained attention in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2005; 22: 235.
25. Lower EE, Harman S, Baughman RP. Double-blind, randomized trial of dexmethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue. Chest 2008; 133: 1189-95.
26. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885-9.
27. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. Q J Med 1983; 208: 525-33.