Chapter 6

The relationship between fatigue and clinical parameters in acute pulmonary sarcoidosis

Jolanda De Vries, Snježana Rothkrantz-Kos,
Marja P. van Dieijen-Visser, Marjolein Drent

Sarcoidosis Vasc Diffuse Lung Dis 2004; in press

Abstract

Background

Studies on the relationship between fatigue and clinical parameters are sparse. In the present study this relationship was examined in a systematic way.

Methods

Patients with time since diagnosis ≤ 2 years, visiting the outpatient clinic of the University Hospital Maastricht (n = 60; 34 untreated, 26 treated) were clinically evaluated and completed the Fatigue Assessment Scale (FAS). A representative sample of the Dutch population (n = 1893) also completed the FAS. Pulmonary disease severity was estimated from lung function test results and measures of metabolic derangement. Acute phase response markers high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA) and sarcoidosis activity parameters, soluble interleukin-2-receptor (sIL-2R), and angiotensin-converting enzyme (ACE) were also measured.

Results

Only 27% of the sarcoidosis patients were diagnosed as non-fatigued (FAS score < 22), compared to 80% in the control population (n = 1893). In the sarcoidosis patients no sex differences and no differences in fatigue scores between the treated and the untreated groups were found. Patients with fatigue (FAS-score ≥ 22) had lower DLCO values ($p < 0.05$). However, none of the tested clinical or serological parameters appeared to be a significant predictor of fatigue.

Conclusion

In the present study, it was confirmed that fatigue is a major problem in sarcoidosis. The extent of fatigue could not be explained by clinical parameters. Thus, up to now, no clinical or physiological variable seems useful in predicting which patients are fatigued. In this light, the Fatigue Assessment Scale might be considered as a supplementary tool in sarcoidosis.

Introduction

Sarcoidosis is a disorder of unknown origin most frequently occurring in the lung. Although sarcoidosis occurs worldwide, the prevalence and the course of the disease vary across countries and ethnic group[1]. In the Netherlands the prevalence is estimated to be 40 – 50/100000[2].
Clinical manifestations of sarcoidosis depend on the intensity of the inflammation and organ systems affected. Pulmonary sarcoidosis may present itself in a variety of ways with symptoms related directly to the chest such as coughing, dyspnea on exertion, retro-sternal chest pain, chest discomfort, and wheezing[3,4]. Furthermore, fatigue, arthralgia, and erythema nodosum are common features of sarcoidosis, which vary however, across countries[4-7]. Fatigue appeared to be a major problem in 30 to 90 per cent of the patients[3,3,8-15]. This fatigue can be substantial and persistent[3-5,9,10,12,14,15].
Fatigue is disabling for the patient, causes an impaired quality of life (QOL), and may become chronic[16]. In a study among 64 sarcoidosis patients, even patients who did not suffer from fatigue had an impaired QOL compared to healthy persons. However, patients who reported fatigue had the most impaired quality of life[15]. In addition, fatigue is a predictor of depressive symptoms[17,18] as well as of pain[7]. Because of the capacity of fatigue to cause impaired QOL, it is important to measure and study fatigue.
An acute phase response evidenced by moderate increase of the C-reactive protein (CRP) level was found in sarcoidosis patients who suffered from fatigue and other related symptoms[12]. Besides, in the same study, a presence of metabolic derangement was shown to be related to fatigue and to the CRP concentrations. In line with this, a relation between elevated CRP concentrations and fatigue was demonstrated in rheumatoid arthritis, Crohn's disease, and ulcerative colitis patients[19].
Nowadays more sensitive parameters have been introduced to monitor inflammation such as high-sensitivity C-reactive protein (hs-CRP) and serum amyloid A (SAA). Besides, a new questionnaire has been developed, allowing to measure fatigue in sarcoidosis patients more in-depth[20,21], as compared to the single item fatigue question and the facet Energy and Fatigue of the WHOQOL-100 questionnaire, used previously[15]. Therefore, the aim of this study is to examine whether the more sensitive measures used to monitor inflammation can be used to explain fatigue in patients with acute manifestations of pulmonary sarcoidosis.

Materials and Methods

Participants

From January 2000 to October 2002, 60 (34 untreated and 26 treated) patients who visited the outpatient clinic of the University Hospital Maastricht, a referral center for sarcoidosis, with a time since diagnosis of ≤ two years ("acute" sarcoidosis patients) were included in this study. Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchoalveolar lavage (BAL) fluid analysis results, according to the WASOG guidelines. 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 localisations of sarcoidosis were not considered as comorbidity but as sarcoidosis related. None of the patients had any significant medical history or co-morbidity.
Informed consent was obtained from all participating patients. A control group of persons also completed the fatigue questionnaire. This group, comprising of 1893 persons, was a representative sample of the Dutch population[20]. They completed a computer-administered questionnaire. The respondents of the latter sample were all involved in an internet-based panel. Every week this panel received a questionnaire directly on their personal computer. With regard to the demographics of the reference sample, there were 1128 males and 765 females and the mean age of the reference sample was 44.7 (SD = 15.3; range 16 – 87). This sample was not analyzed as part of this study but was used as a reference group.

Lung function testing

Lung function measurements, including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), were measured with a pneumotachograph. The diffusing capacity for carbon monoxide (DLCO) was measured by the single-breath method (both Masterlab, Jaeger, Würzburg, Germany). Values were expressed as a percentage of those predicted[22].

Chest radiographs

Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV, the end stage of lung fibrosis[3,23]. A radiologist, blinded to the patient's history, performed all interpretations.

Serum markers

Simultaneously with lung function tests and fatigue assessment, blood samples were taken and serum was stored at -20^{o}C until actual measurement of inflammatory markers. Serum IL2 receptor (sIL-2R) was determined on the IMMULITE Automated Analyser, by means of a two-site chemiluminescent enzyme immunometric assay, with a detection limit of 50 kU/L, and a measuring range 50 – 7500 kU/L (Diagnostic Product Corporation, Los Angeles, CA, cat no LKIP1). The imprecision of the assay (both within- and between run) appeared to be below 7.20%. The reference range for sIL-2R was 241 – 846 kU/L.
Hs-CRP and SAA were determined by particle-enhanced immunonephelometry, on the BN Prospec from Dade Behring. The detection limit for hs-CRP was 0.175 mg/L and the measuring range was 0.175 – 1100 mg/L, depending on the dilution (Dade Behring, Liederbach Germany, N Hs CRP, cat no OQIY 13; supplement reagent OUMU).
The detection limit of SAA was 3 mg/L, with a measuring range of 3 – 1000 mg/L, depending on the dilution (Dade Behring, Liederbach Germany, N SAA reagent, cat no OQMP 11).

The imprecision of the SAA BN ProSpec method appeared to be below 10.7%. The reference values were 0.90 – 10.22 mg/L.
Evaluation of the hs-CRP assay on the BN ProSpec was reported previously. Reference values were 0.26 – 7.24 mg/L[24].
Serum ACE (ACE) was measured by a colorimetric method (Fujirebio Inc., Tokyo, Japan, cat. nr. FU 116). ACE acts on a substrate p-hydroxybenzoyl-glycyl-L-hystidyl-L-leucine and separates p-hydroxybenzoyl-glycine, which is converted in two subsequent reactions in quinoneimine dye. To evaluate the ACE activity, the absorbance of quinoneimine dye is measured at 505 nm. The imprecision of the ACE assay appeared to be below 5.6%. Reference values of ACE were 9 – 25 U/L.

Metabolic measures

Body composition was measured by single frequency bioelectrical impedance analysis (RJL systems, Detroit, USA) in the supine position on the right side. Fat-free mass (FFM) was calculated from [(height)^2/resistance] and body weight using the Lukaski formula. Resting energy expenditure (REE) was measured after an overnight fast under standardized conditions[25] by indirect calorimetry using a ventilated hood (Oxycon beta, Mijnhardt, Bunnik, The Nederlands). REE was adjusted for FFM and gender, by analysis of covariance[26].

Questionnaire

The Fatigue Assessment Scale (FAS)[20,21] was used to measure fatigue (Appendix). This questionnaire consists of ten questions. The response scale is a 5-point scale (1 never to 5 always). Scores on the FAS can range from 10 to 50. The psychometric properties are good also in sarcoidosis. Moreover, the FAS appeared to be unidimensional in a large sarcoidosis population [20,21].

Table 6.1. Demographics data of the evaluated sarcoidosis patients.

Variables	Total group	Untreated patients	Treated patients
Number of cases	60	34	26
Sex: male/female	31 / 29	15 / 19	16 / 10
Age[a], years	40.8 ± 10.4 (19 – 66)	40.3 ± 10.5 (23 – 66)	41.5 ± 10.5 (19 – 58)
Time since diagnosis[a], months	10.2 ± 9.6 (0 – 24)	8.9 ± 9.0 (0 – 24)	12.0 ± 10.2 (0 – 24)
Smoking: no/yes[b]	53 / 7	27 / 7	26 / 0

[a] The data are presented as mean ± standard deviation with range in parentheses.
[b] Significant difference ($p < 0.01$) between the treated and untreated patients.

The cut-off score of the FAS (22) was derived from two large representative samples of 1) the Dutch working population and 2) the general population. In both samples, 80% of the participants had a FAS score below 22[27]. In addition, this result was compared with other fatigue measures such as the emotional exhaustion subscale of the Dutch Maslach Burnout Inventory (UBOS)[28] to verify the appropriateness of the found FAS cut-off score.

In a large study among 1046 sarcoidosis patients, the FAS appeared to be a unidimensional scale. The content validity (factor analysis and mokken scale analysis), construct validity (factor analysis comparing with the Beck Depression Inventory), and internal consistency (Cronbach's alpha) of the FAS were good. The test-retest reliability was 0.89[20,21]. A change in score of 5 or more is considered clinically significant (minimal clinical difference for score to be significant).
Patients also completed the Bath Breathlessness Scale (BBS)[29]. This is a 35-item adjective subjective breathlessness (dyspnea) scale measuring four aspects of breathlessness. In addition, patients can be asked to indicate on an 8-point response scale (range 0 to 7) how breathless they felt during the last two weeks. In the present study, only the question about perceived severity of breathlessness was used.

Statistical Analysis

For all of the selected patients non-missing and interpretable results were obtained for the laboratory tests, lung function tests, metabolic derangement measures and the FAS. The comparison between the sarcoidosis group and the reference sample, was performed by means of one sample t-tests. The distributions of the explanatory variables CRP, SAA, ACE and sIL-2R were positively skewed. Therefore, the data are presented as median with interquartile range. Patients were divided into two groups: non-fatigued (FAS score < 22) and fatigued (FAS score ≥ 22). Differences between the fatigued and non-fatigued groups were tested by means of Student t-tests or Mann-Whitney U test, depending on the distribution (normal or skewed) of the tested (explanatory) variables, *i.e.* serum markers, metabolic derangement measures and lung function test results.
A log transformation (ln) was applied to normalize the data prior to further analyses. First, the relationship between fatigue (as continuous variable) and the laboratory parameters was examined by means of Pearson correlations. Second, univariate logistic regression was used to test the discriminatory effect of each explanatory variable with regard to being fatigued or non-fatigued. Finally, multivariate logistic regression was used to assess simultaneously the effect of the three clinical parameters with the lowest p-values from the univariate analyses. The lung function test results were firstly treated as continuous variables and thereafter the values were dichotomized (the abnormal values were considered those with the %predicted of $< 80\%$). The metabolic derangement measures were treated as continuous variables. The hs-CRP, CRP, SAA, sIL-2R and ACE levels were not treated as continuous variables in the logistic regression analyses, but were dichotomized. The reason was that the distribution of the data was highly skewed and all levels below the lower detection limit of these assays were recorded as the lower detection limit value. As the upper reference limit can be influenced by the presence of some subclinical inflammation and, therefore gives outliers, the values of the 90^{th} percentile of the reference values were used to dichotomize the laboratory parameters. The likelihood ratio tests (-2 LL) were used. All p-values were two-tailed and $p < 0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS10.0 for Windows (SPSS, Chicago, IL, USA).

Results

General and clinical characteristics of sarcoidosis patients

General characteristics of sarcoidosis patients (n = 60) are presented in Table 6.1. In the group of untreated patients (n = 34) there were 7 smokers (20.6%), while all patients of the treated group (n = 26) were non-smokers.

Clinical characteristics of the patients are presented in Table 6.2. With respect to lung function data, the FEV1 ($p < 0.01$) and FVC ($p < 0.05$) values appeared lower in the treated group as compared to the untreated group. No differences in radiographic staging or the DLCO between the two groups were found. Also, with regard to serological data and the metabolic derangement measures, no differences were observed between the treated and untreated group.

The perceived severity of dyspnea was also assessed. During the previous two weeks prior to the study, the sarcoidosis patients had a mean score of 3.28 (SD = 1.71) on a possible range of 0 to 7. This score represents a moderate level of dyspnea. Compared with a group of idiopathic pulmonary fibrosis patients from a previous study (mean = 3.80, SD = 2.0)[30] the sarcoidosis group scored significantly but not extremely lower.

Table 6.2. Clinical characteristics of the sarcoidosis patients.

Variables	Total group (n = 60)	Untreated patients (n = 34)	Treated patients (n = 26)
Lung function tests[c]			
DLCO	87.6 ± 17.3	90.1 ± 13.4	84.2 ± 21.4
FEV1[b]	90.1 ± 22.6	94.2 ± 18.4	84.8 ± 26.5
FVC[a]	99.0 ± 20.2	102.3 ± 16.14	94.6 ± 24.3
Radiographic stages			
0/I/II/III/IV	14 / 15 / 11 / 18 / 2	6 / 11 / 8 / 9 / 0	8 / 4 / 3 / 9 / 2
Serological parameters[d]			
ACE (U/L)	21.0 (17.0 – 30.0)	21.0 (17.0 – 31.0)	22.0 (18.0 – 31.0)
CRP (mg/L)	9.0 (5.0 – 15.0)	3.7 (1.4 – 12.7)	3.8 (1.3 – 8.5)
hs-CRP (mg/L)	3.5 (1.3 – 10.5)	7.0 (2.0 – 15.3)	10 (6.0 – 15.5)
SAA (mg/L)	6.3 (3.3 – 11.7)	5.9 (2.6 – 11.1)	6.9 (4.0 – 11.8)
sIL-2R (kU/L)	711 (405 – 1066)	737 (427 – 1269)	697 (454 – 865)
Metabolic derangement measures			
REE (kcal/24h)	95.9 ± 10.1	94.7 ± 11.7	97.5 ± 7.5
REE/FFM (kcal/kg FFM)	31.0 ± 4.5	30.8 ± 4.9	31.3 ± 4.1
Fatigue measure			
FAS score[c]	27.5 ± 8.6	25.7 ± 9.0	29.7 ± 7.7
	(10 – 48)	(10 – 45)	(13 – 48)

[a] Significant difference ($p < 0.05$) between the treated and untreated patients.

[b] Significant difference ($p < 0.01$) between the treated and untreated patients.

[c] The data are presented as mean ± standard deviation.

[d] Because of the non-gaussian distribution of the data, the values are presented as median with range (25th – 75th percentiles).

Evaluation of the FAS (fatigue) score

The whole patient group (n = 60) had a mean FAS score of 27.5 (SD = 8.6), whereas the reference group (n = 1893) had a mean score of 18.0 (SD = 5.7) ($t = -8.51$, $p < 0.001$). Only 27% of sarcoidosis patients had a FAS score < 22 (mean ± SD: 17.1 ± 3.6), compared to 80% in the control population.
Table 6.3. shows that the difference between both groups on the total FAS score reflects substantial differences for each individual item. In each instance, the sarcoidosis patients are more fatigued than the reference group. The only exception is question 10 ('When I am doing something I can concentrate quite well'). As this question is not recoded, a high score on this question indicates a low score for fatigue. In other words the reference group has more problems with staying concentrated.
In sarcoidosis patients, no sex differences were found with respect to the FAS score. In contrast, in the control group females had higher fatigue scores as compared to males ($t = -6.1$, $p < 0.001$). No differences in fatigue scores between the treated and the untreated groups were found (Table 6.2).

Table 6.3. A comparison between the sarcoidosis group and the reference group at the FAS item level.

Question/Item	Sarcoidosis patients[a]	Reference group[a]	t-value[b]
1	3.53 ± 1.19	2.13 ± 0.88	9.17
2	3.47 ± 1.21	1.90 ± 0.94	10.0
3	2.75 ± 1.20	1.78 ± 0.87	6.25
4[c]	2.62 ± 1.19	3.74 ± 1.14	-7.28
5	2.92 ± 1.12	1.72 ± 0.79	8.24
6	2.43 ± 1.13	1.79 ± 0.81	4.43
7	2.10 ± 1.07	1.47 ± 0.67	4.57
8	2.40 ± 1.11	1.77 ± 0.72	4.41
9	2.15 ± 0.99	1.48 ± 0.71	5.25
10[c]	3.67 ± 1.13	1.72 ± 0.79	13.34

[a] The data are presented as mean ± standard deviation.
[b] $p < 0.001$ for each of the ten items, between the sarcodosis group and reference group.
[c] These questions are not recoded, meaning that a high score reflects low score for fatigue.

FAS score in relation to clinical data

Since with regard to the laboratory parameters, metabolic derangement measures, radiographic staging and lung function data (except for FVC and FEV1) no differences were observed between the treated and untreated groups (Table 6.2), grouping of the data was allowed. Figure 6.1 shows the distribution of the clinical data in fatigued and non-fatigued groups in respectively untreated and treated groups of patients.

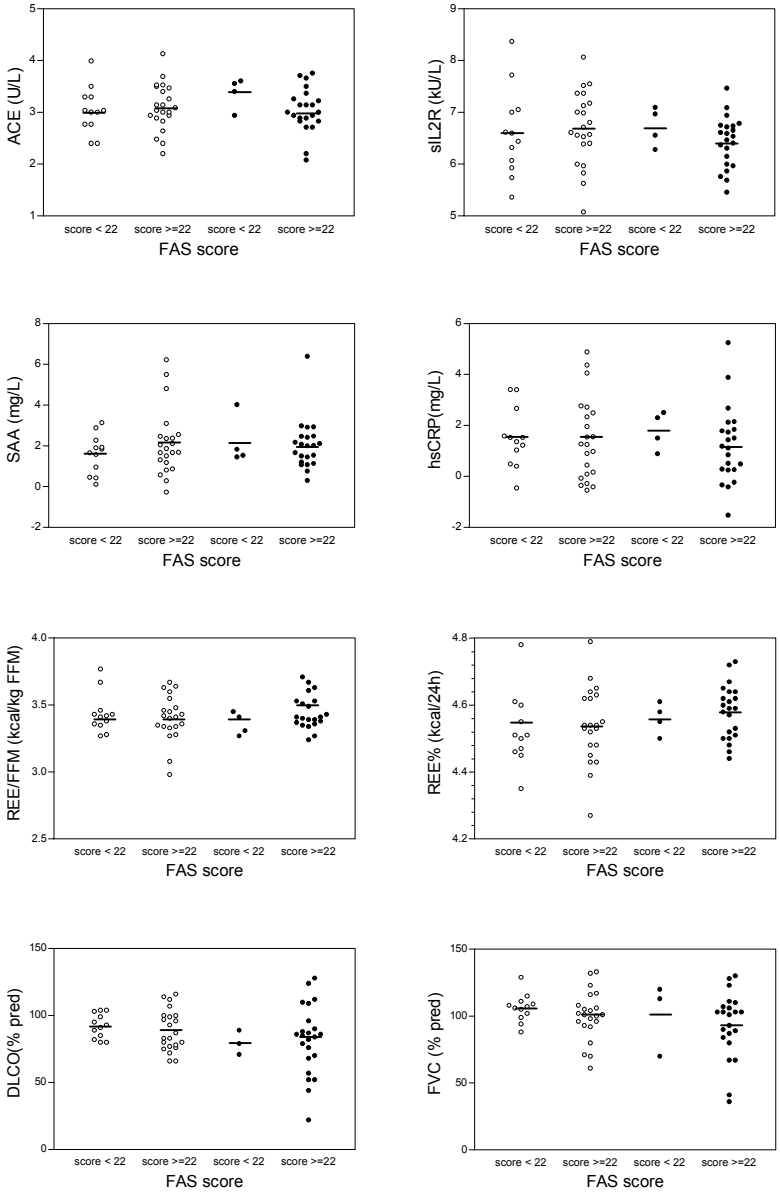

Figure 6.1. Scatter of serological parameters and metabolic derangement measures.
Patients were divided into two groups with respect to their FAS score. The group with fatigue had a FAS score ≥ 22, whereas group without fatigue had a FAS score < 22. The horizontal line represents the mean values of the (logarithmic transformed, except for the DLCO, FEV1 and FVC) data, divided according to treatment.
Open circles indicate untreated patients, whereas closed circles indicate with prednison treated patients. For the DLCO and FVC there was one missing case in treated non-fatigued group.

These results further suggest that prednisone treatment at the moment of 'sampling' probably had no influence on the results of clinical or serological tests (Figure 6.1). Therefore, for the further evaluation of the FAS score with respect to clinical data, patients were divided into two groups: the group without fatigue (total FAS-score < 22) and the group with fatigue (total FAS score ≥ 22).
Patients with fatigue (FAS-score ≥ 22) had lower DLCO values ($p < 0.05$). However, with regard to FEV1, FVC and the radiographic staging no differences between the fatigued and non-fatigued groups were observed. Also regarding laboratory parameters and metabolic derangement measures no significant differences between fatigued and non-fatigued groups were present.
Among the laboratory markers, only sIL-2R and SAA correlated with the metabolic derangement measures ($p < 0.05$). The sIL-2R correlated with REE% ($r = 0.30$, $p = 0.023$), whereas SAA correlated with REE/VVM ($r = 0.31$, $p < 0.02$). sIL-2R and SAA correlated also with each other ($r = 0.39$, $p < 0.01$). sIL-2R appeared to correlate with ACE to a large extent ($r = 0.60$, $p < 0.0001$).

Prediction of fatigue (FAS-score ≥ 22) using clinical data

First, a serie of univariate logistic regression analyses was completed. Table 6.4. shows the odds ratios with their corresponding confidence intervals. As can be seen from the Table 6.4, no statistically significant predictors were found. For each single variable the analyses were repeated correcting for prednisone use (*data not shown*).

Table 6.4. Prediction of fatigue assessed by Fatigue Assessment Scale (FAS) by clinical data in patients with acute pulmonary sarcoidosis.

Variables	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value[c]
Prednison use				
Yes	3.0 (0.8 – 10.8)	0.078	2.7 (0.7 – 10.0)	
Severity of disease[a]				
RFI Present	2.1 (0.6 – 7.5)	0.249	1.3 (0.3 – 5.4)	
Presence of hypermetabolism				
REE	1.0 (1.0 – 1.1)	0.852		
REE/FFM	1.0 (0.9 – 1.2)	0.827		
Serum markers[b]				
ACE > 24.4 U/L	0.7 (0.2 – 2.1)	0.495		
sIL-2R > 685 kU/L	1.0 (0.3 – 3.2)	0.969		
SAA > 6.9 mg/L	3.0 (0.8 – 10.8)	0.078	2.6(0.6 – 10.0)	
hs-CRP > 5 mg/L	0.9 (0.2 – 3.3)	0.860		
CRP > 5 mg/L	1.3 (0.4 – 4.3)	0.712		
				0.1633

[a] Severity of disease. RFI Present, if DLCO< 80% or FEV1< 80% or FVC< 80%. RFI absent if all of these parameters ≥ 80.
[b] The serum markers were dichotomised according to the 90th percentile of the reference values.
[c] The p-value in the multivariate analysis is for the prediction of fatigue by the SAA, corrected for prednisone use and the presence of respiratory functional impairment.
The p-values correspond to the -2LL test in the respectively univariate or multivariate analysis.

However, no significant results were obtained. The three variables with the lowest p-values from the univariate analysis: prednisone use ($p = 0.078$), presence of respiratory functional impairment ($p = 0.249$) and the SAA values ($p = 0.078$) were used in the multivariate logistic regression analysis. However, no significant model could be obtained ($p = 0.163$).

Discussion

The present study clearly showed that fatigue is a major problem in sarcoidosis. Seventy-three percent of the sarcoidosis patients were fatigued, compared with 20% in the control population. No differences were found in fatigue scores between the treated and the untreated group and between male and female patients. The prednisone treatment at the moment of 'sampling' appeared not to have influence on the results of clinical or serological tests, which allowed for the grouping of the patients. Subsequently, patients were divided with respect to the FAS score in the fatigued and non-fatigued groups. The fatigued patients tended to have decreased lung function test results, although only the DLCO ($p < 0.05$) appeared to be significantly decreased. With regard to radiographic staging no differences between the groups concerning fatigue were observed. With respect to serological data and metabolic derangement measures patients with fatigue tended to have increased values, albeit not significantly. The serological parameters SAA and sIL-2R correlated well with metabolic derangement measures, whereas ACE, CRP, and hs-CRP showed no relationship with metabolic derangement measures. Among the clinical parameters, none of the explanatory variables were able to predict whether patients were fatigued or not and no combined model could be found.

Fatigue

Compared with a representative sample, the sarcoidosis patients had much higher fatigue scores. The finding that fatigue is a major problem in sarcoidosis is in accordance with previous studies[3-5,8-15]. However, besides the fact that the fatigue was assessed by means of a more appropriate questionnaire, this was the first time that fatigue scores in sarcoidosis patients were compared with a healthy population. Another study that used the FAS, examined a large group of Dutch persons working at least 20 hours per week ($n = 765$)[21]. In the latter study about 80% of the persons from the working population sample had a FAS score of < 22, comparable to the control sample used in the present study. This emphasizes the large difference with the sarcoidosis population and provides a further underpinning of the severity of fatigue in sarcoidosis.
The present study differs from the previous studies in the way the fatigue was assessed. In this study, a fatigue questionnaire (FAS) was used. In the other studies, fatigue was measured with a single dichotomous (yes/no response) fatigue question. The FAS provides information on the severity of fatigue instead of merely presence or absence of fatigue. Furthermore, it is known that single items as used in previous studies are less reliable[31].

Fatigue in relation to clinical data

In disorders like COPD it was appreciated that, at least in part, in hypermetabolic patients the resting energy expenditure (REE) was attributed to the level of the systemic inflammation[25,32]. The study of Drent *et al*. indicated that an acute phase response (reflected through increased CRP values), in combination with metabolic derangement (reflected through increased REE) might provide some insight into fatigue in sarcoidosis[12]. Even those cases without signs of pulmonary involvement appeared to have increased REE values[12]. Therefore, assessment and inclusion of REE (corrected or not for the fat-free mass, FFM) was considered to have an additional value in the management and follow-up of sarcoidosis patients. For that reason, clinical data indicating lung function and metabolic derangement together with serological data were used to see whether a combined model could be found that was able to predict fatigue.

Among all the tested markers, SAA was the strongest ($p = 0.078$ (Table 6.4.), if corrected for prednison use, $p = 0.108$) but non-significant positive univariate predictor of fatigue. The lack of significance at 0.05 level might be due to the fact that the present sample size was too small. Therefore, a careful interpretation of this result is needed. In fatigue, the concentration of brain 5-hydroxytyptamine (5-HT or serotonine) was shown to be increased[33,34]. Interestingly, in a murine model it was shown that an increase of 5-HT upon stimulation of interleukin-6 was accompanied by the increase of SAA[34]. Nevertheless, larger studies are needed to validate the results of this study and confirm whether the SAA can indeed be used to monitor fatigue.

With respect to corticosteroid treatment, some trend between corticosteroid use and fatigue appeared to exist, although the result of logistic regression analysis seemed not significant. As the sample size is rather small, careful interpretation of this result is needed. In a logistic regression analysis we corrected for the effect of prednisone, as we indeed considered the OR for prednisone of 3, with a p-value of 0.078 rather high. In a larger sample, this p value might become significant (the same holds for the SAA). However, no differences in fatigue scores and most of the clinical parameters (Table 6.2) between the treated and the untreated groups were found. Therefore, it might be assumed that in our sample the influence of corticosteroid therapy is limited.

Neither the CRP nor hs-CRP were able to predict fatigue. Overall, the CRP values were higher as compared to hs-CRP values. This only emphasizes the discrepancies between the two methods as shown earlier[24]. Moreover, activity markers such as ACE and sIL2R also showed no relation to fatigue. Besides, in contrast with previous findings[12], in the present study no relationship with the measures of metabolic derangement and the CRP or hs-CRP could be found. Despite the discrepancies between the methods (CRP and hs-CRP), the lack of relationship of the CRP or hs-CRP with the measures of metabolic derangement is difficult to explain. It is probably population related. Moreover, the SAA and sIL-2R appeared to correlate with metabolic derangement measures, nevertheless confirming the relationship of the acute phase response with metabolic derangement in sarcoidosis, at least partly, in agreement with a previous study[12].

As mentioned before, one of the limitations of this study is the small sample size. Since we expected low correlations, a large sample size would be needed to make firm statements. However, large populations of sarcoidosis patients are difficult to recruit for any study since the disease is not extremely common. In comparison to our previous

study[12], a different type of statistical analysis was now used with the aim to predict fatigue (logistic regression analysis). Although both, the previous as the present study show some overlap in clinical parameters (REE, CRP), in the present study we added additional clinical (presence of respiratory functional impairment) and laboratory parameters (sIL-2R, SAA and ACE). In the multivariate analysis we combine all these parameters. Furthermore, the CRP concentrations reported in the previous study were measured with a less sensitive CRP method, which appeared to be very sensitive to sample turbidity and might give unreliable results[24]. It was to be expected that the CRP concentrations would only slightly be increased in sarcoidosis patients[12,35]. To measure these minor increases from the upper reference level, the more sensitive CRP method is needed. Therefore, in this study we used the so-called high-sensitivity CRP method to accurately measure the CRP concentrations.

Although it was beyond the scope of this study, it might have been important to compare the exercise test and its relationship with the FAS. Changes in gas-exchange with exercise were previously demonstrated to be the most sensitive physiologic measurement to assess the extent of pulmonary disease in early radiographic stages of sarcoidosis[32,33]. Accordingly, a significant maximal exercise limitation in sarcoidosis patients without significant pulmonary impairment was shown by Delobbe *et al.*[34]. In line with this, a recent study, further confirmed the value of exercise testing. Namely, HRCT findings appeared to be much more sensitive in depicting respiratory disability, especially abnormal gas exchange, as compared to radiographic staging[35]. Currently, a prospective study is conducted to evaluate the possible relationship of impaired gas exchange with fatigue and dyspnoea more carefully. Preliminary results showed only a moderate relationship with the FAS score between the subscore mental fatigue and desaturation during exercise ($r=-0.23$, $p<0.05$)[33].

The results of this study emphasize the difficulties that clinicians face when trying to objectify fatigue. Fatigue, as an integral part of the clinical picture of sarcoidosis, is disabling for the patient and causes an impaired quality of life[3,4,12]. The course of the disease is mainly monitored by assessing clinical features and using auxiliary diagnostic procedures. However, an objective system for the assessment of disease activity and fatigue is still lacking. Moreover, the non-specific symptoms including fatigue are often hard to objectify, as confirmed by this study. Up to now, no clinical or physiological variable seems useful in predicting which patients are fatigued. The feeling of fatigue is a subjective experience that is associated with many diseases and states. However, the large ostensibly healthy population was screened by means of the FAS for the presence of fatigue and the cut-off of 22 was carefully chosen[21]. Besides, the FAS was constructed in a way to minimize the intersubjective agreement, the well-known source of error and bias in human judgement[36].

Conclusion

The present study confirmed that fatigue is a major problem in sarcoidosis. None of the tested variables such as lung function data, metabolic derangement measures and laboratory parameters of inflammation, T cell activation or granuloma formation seemed useful in predicting which patients are fatigued. In this light, the Fatigue Assessment Scale can be considered as a supplementary tool in sarcoidosis to assess fatigue.

Appendix

The Fatigue Assessment Scale (FAS)[a] [b]

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	1	2	3	4	5

[a] The following ten statements refer to how well the person usually feels. Per statement one out of five answer categories can be chosen, varying from Never to Always. 1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often; 5 = Always.

[b] Based on large representative samples of the Dutch population, the cut-off score of the FAS is 21, *i.e.*, scores of ≥ 22 are considered to represent substantial fatigue. A change in the FAS score of 5 points is considered to be clinically relevant.

References

1 Thomas PD, Hunninghake GW: Current concepts of the pathogenesis of sarcoidosis. *Am Rev Respir Dis* 1987;135:747-60.
2 James DG: Epidemiology of sarcoidosis. *Sarcoidosis* 1992;9:79-87.
3 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.
4 Wirnsberger RM, De Vries J, Wouters EFM, Drent M: Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med* 1998;53:53-60.
5 Pietinalho A, Ohmichi M, Hiraga Y, Lofroos AB, Selroos O: The mode of presentation of sarcoidosis in Finland and Hokkaido, Japan. A comparative analysis of 571 Finnish and 686 Japanese patients. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;13:159-66.
6 Fite E, Alsina JM, Mana J, Pujol R, Ruiz J, Morera J: Epidemiology of sarcoidosis in Catalonia: 1979-1989. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;13:153-8.
7 Hoitsma E, DeVries J, van Santen-Hoeufft M, Faber CG, Drent M: Impact of pain in a Dutch sarcoidosis patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2003;20:33-39.
8 De Vries J, Drent M, Van Heck GL, Wouters EFM: Quality of life in sarcoidosis: a comparison between members of a patient organisation and a random sample. *Sarcoidosis Vasc Diffuse Lung Dis* 1998;15:183-8.
9 Thomeer MJ, Costabel U, Rizzato G, Poletti V, Demedts M: Disease perception in members of a sarcoidosis patient association: a survey.? *Sarcoidosis Vasc Diffuse Lung Dis* 2001;18 (Suppl. 1):60-61.
10 Demedts M, Wells AU, Anto JM, Costabel U, Hubbard R, Cullinan P, Slabbynck H, Rizzato G, Poletti V, Verbeken EK, Thomeer MJ, Kokkarinen J, Dalphin JC, Taylor AN: Interstitial lung diseases: an epidemiological overview. *Eur Respir J Suppl* 2001;32:2s-16s.
11 Drent M, Bomans PH, Van Suylen RJ, Lamers RJS, Bast A, Wouters EFM: Association of man-made mineral fibre exposure and sarcoidlike granulomas. *Respir Med* 2000;94:815-20.
12 Drent M, Wirnsberger RM, De Vries J, van Dieijen-Visser MP, Wouters EFM, Schols AMWJ: Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999;13:718-22.
13 James DG: Complications of sarcoidosis. Chronic fatigue syndrome. *Sarcoidosis* 1993;10:1-3.
14 Sharma OP: Fatigue and sarcoidosis. *Eur Respir J* 1999;13:713-4.
15 Wirnsberger RM, De Vries J, Breteler MHM, van Heck GL, Wouters EFM, Drent M: Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998;92:750-6.
16 De Vries J, Michielsen H, Van Heck GL, Drent M: Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol, in press* 2004.
17 Drent M, Wirnsberger RM, Breteler MHM, Kock LM, De Vries J, Wouters EFM: Quality of life and depressive symptoms in patients suffering from sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998;15:59-66.
18 DeRemee RA: Dysphoria and sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998;15:21.
19 Fagan EA, Dyck RF, Maton PN, Hodgson HJ, Chadwick VS, Petrie A, Pepys MB: Serum levels of C-reactive protein in Crohn's disease and ulcerative colitis. *Eur J Clin Invest* 1982;12:351-9.
20 Michielsen HJ, De Vries J, Van Heck GL, Van de Vijver FJR, Sijtsma K: Examination of the dimensionality of fatigue: The construction of the Fatigue Assessment Scale (FAS). *Eur J Psychol Ass, in press.* 2003.
21 Michielsen HJ, De Vries J, Van Heck GL: Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale (FAS). *J Psychosom Res* 2003;54:345-52.
22 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC: Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5-40.
23 DeRemee RA: The roentgenographic staging of sarcoidosis. Historic and contemporary perspectives. *Chest* 1983;83:128-33.

24 Rothkrantz-Kos S, Bekers O, Gubbels A, Drent M, Schmitz MPJ, van Dieijen-Visser MP: Evaluation of two new high-sensitivity CRP methods. *Ann Clin Biochem* 2003;40:398-405.
25 Schols AMWJ, Buurman WA, Staal van den Brekel AJ, Dentener MA, Wouters EFM: Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996;51:819-24.
26 Ravussin E, Bogardus C: Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. *Am J Clin Nutr* 1989;49:968-75.
27 Michielsen HJ: Working out fatigue: Conceptualization, assessment and theory. *Doctoral thesis* 2002; Tilburg University.
28 Maslach C, Jackson SE: The Maslach burnout Inventory manual (2nd edition). 1986; Sage, Paolo Alto, California.
29 Skevington SM, Pilaar M, Routh D, Macleod RD: On the language of breathlessness. *Psychol Health* 1997;12:677-89.
30 De Vries J, Kessels BLJ, Drent M: Quality of life of idiopathic pulmonary fibrosis patients. *Eur Respir J* 2001;17:954-61.
31 Sadler IJ, Jacobsen PB, Booth-Jones M, Belanger H, Weitzner MA, Fields KK: Preliminary evaluation of a clinical syndrome approach to assessing cancer-related fatigue. *J Pain Symptom Manage* 2002;23:406-16.
32 Medinger AE, Khouri S, Rohatgi PK: Sarcoidosis: the value of exercise testing. *Chest* 2001;120:93-101.
33 Lenters M, Maassen van den Brink KI, Rothkrantz-Kos S, Wouters EFM, van Dieijen-Visser MP, Drent M: Abnormal gas exchange in chronic sarcoidosis. *Sarcoidosis* 2001;18 (Suppl.1):49.
34 Delobbe A, Perrault H, Maitre J, Robin S, Hossein-Foucher C, Wallaert B, Aguilaniu B: Impaired exercise response in sarcoid patients with normal pulmonary functio. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;19:148-53.
35 Drent M, De Vries J, Lenters M, Lamers RJ, Rothkranz-Kos S, Wouters EFM, Van Dieijen-Visser MP, Verschakelen JA: Sarcoidosis: assessment of disease severity using HRCT. *Eur Radiol* 2003;13:2462-71.
36 Schols AMWJ, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EFM: Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147:1151-6.
37 Newsholme EA, Blomstrand E: Tryptophan, 5-hydroxytryptamine and a possible explanation for central fatigue. *Adv Exp Med Biol* 1995;384:315-20.
38 Wang J, Dunn AJ: Mouse interleukin-6 stimulates the HPA axis and increases brain tryptophan and serotonin metabolism. *Neurochem Int* 1998;33:143-54.
39 Peros-Golubicic T: Serum C-reactive protein measurement in the detection of intercurrent infection in patients with sarcoidosis. *Acta Med Croatica* 1995;49:1-3.
40 Annett J: Subjective rating scales: science or art? *Ergonomics* 2002;45:966-87.