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A M E R I C A N C O L L E G E O F  
 C H E S T  
P H Y S I C I A N S

## Fatigue Is Associated With Quality of Life in Sarcoidosis Patients\*

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**Background:** Fatigue is one of the core symptoms of sarcoidosis patients. Although it is known that fatigue affects quality of life (QOL) in other patient groups, this relationship has never been studied in sarcoidosis patients using a reliable and valid fatigue scale and a multidimensional QOL instrument. The present cross-sectional study among sarcoidosis patients attempts to gain more insight into this relationship.

**Methods:** One hundred forty-five sarcoidosis patients of an outpatient pulmonary clinic in Zagreb, Croatia, completed the Fatigue Assessment Scale (FAS) and QOL scale (World Health Organization Quality of Life Assessment Instrument-100) between January 2002 and May 2004. Clinical parameters were derived from the patients' medical files.

**Results:** Tired patients reported a worse QOL in all domains and fatigue negatively predicted all QOL domains by means of multivariate regression analyses ( $\beta$  values ranging from  $-0.31$  to  $-0.64$ , all  $p < 0.001$ ). Corticosteroid use was not a predictor of QOL. Diffusion capacity of the lung for carbon monoxide was the only clinical parameter associated with a QOL domain, namely level of independence.

**Conclusions:** Fatigue was related to all QOL domains. Furthermore, standard clinical parameters were not associated with fatigue or QOL, except for level of independence. If these results were to be replicated in a prospective study, fatigue as measured by the FAS could be a good indicator of QOL in sarcoidosis patients. (CHEST 2006; 130:989-994)

**Key words:** fatigue; quality of life; sarcoidosis

**Abbreviations:** DLCO = diffusing capacity of the lung for carbon monoxide; FAS = Fatigue Assessment Scale; QOL = quality of life; WHOQOL-100 = World Health Organization Quality of Life Assessment Instrument-100

Sarcoidosis is a multiorgan disorder of unknown origin. In young adults, pulmonary sarcoidosis is the second-most-common respiratory disease after asthma. Its clinical manifestations are largely non-

specific, depending on the intensity of the inflammation and organ system.<sup>1</sup> The disease is most frequently situated in the lungs, but practically any organ can be involved. Constitutional symptoms, such as fever and weight loss, as well as chest-related symptoms, such as coughing, dyspnea, and chest discomfort, may be present. Fatigue is one of the core symptoms in sarcoidosis patients.<sup>2-4</sup> James<sup>5</sup> described the "post-sarcoidosis chronic fatigue syndrome," which entails the presence of fatigue in patients with a history of sarcoidosis, even when the chest radiograph and markers of disease activity have returned to normal.

Besides fatigue, sarcoidosis patients had a worse QOL, as measured by the World Health Organization Quality of Life Assessment Instrument-100 (WHOQOL-100), on the domains physical health, level of independence, and overall QOL in compar-

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ison with healthy control subjects.<sup>6</sup> Medical factors, such as pulmonary function<sup>3,7,8</sup> or time since diagnosis,<sup>9</sup> could not account for the suboptimal QOL. Previous studies among patients with other diseases, *eg*, multiple sclerosis,<sup>10</sup> breast cancer,<sup>11</sup> and the chronic fatigue syndrome,<sup>12</sup> found that subjectively experienced fatigue affected health status. Till now, the relationship between fatigue and QOL has never been the object of study in sarcoidosis. An attempt using a facet of the WHOQOL-100, energy and fatigue, and the domain of psychological health was performed by Wirmsberger et al,<sup>7</sup> who reported a nonsignificant relationship between these scales. The aim of this study was to evaluate the relationship between fatigue and QOL in sarcoidosis with appropriate validated questionnaires.

## MATERIALS AND METHODS

### Patients

The sample consisted of consecutive patients from Jordanovic Hospital in Zagreb, Croatia, who were asked by their pulmonary physician to complete a questionnaire. One hundred fifty patients participated in this study. Complete spirometry and diffusion capacity of the lung for carbon monoxide (DLCO) data were available from 145 patients. Therefore, these 145 patients were selected for all analyses. Fifty-two men (36%) and 93 women (64%) had a mean age of 44.3 years (SD, 9.1; range, 21 to 75 years). Mean time since diagnosis was 4.0 years (SD, 7.8; range, 0 to 49 years). Diagnosis of sarcoidosis was based on consistent clinical features, together with biopsy-proven noncaseating epithelioid cell granulomas according to the international guidelines.<sup>1</sup> The clinical symptoms of the patients varied from none (sarcoidosis detected on routine chest radiography) to more or less severe respiratory symptoms or symptoms related to other organ involvement. Of all patients, 84.8% were living with a partner. Furthermore, 19.3% had a low education level (primary school), and 20.7% had a college education level. 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

All respondents completed the Fatigue Assessment Scale (FAS)<sup>13</sup> and the WHOQOL-100,<sup>14</sup> Croatian version.<sup>15</sup> Data concerning clinical parameters were derived from medical files.

**Lung Function Testing:** Lung function measurements, including FEV<sub>1</sub> and FVC, were measured with a pneumotachograph. DLCO was measured by the single-breath method (both Masterlab; Jaeger; Wurzburg, Germany). Values were expressed as a percentage of those predicted.

**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. Two groups were distinguished: one group included stages 0 and I, and the second group stages II to IV.

**Symptoms:** A symptom inventory questionnaire consisted of 43 items including dichotomous questions concerning current symp-

toms, such as breathlessness, reduced exercise capacity, arthralgia, and fatigue. The questionnaire was used in several previous studies.<sup>2,9</sup>

The FAS is a fatigue questionnaire consisting of 10 items: 5 questions reflecting physical fatigue, and 5 questions assessing mental fatigue. Although these two aspects of fatigue are represented in the questionnaire, the FAS was unidimensional when completed by a Dutch working population and a representative group of the general population,<sup>13,16</sup> as well as by two groups of Dutch sarcoidosis patients<sup>8</sup> and the present Croatian sample.<sup>17</sup> The unidimensional structure points out that the proper score to use here is the FAS total score. The response scale is a 5-point scale (1 = never, 5 = always). Scores on the FAS range from 10 to 50. The psychometric properties are good in healthy<sup>13,16</sup> and sarcoidosis patients.<sup>8</sup> The translation procedure of the FAS in the Croatian language followed the translation-backtranslation procedure.<sup>15</sup> The Croatian FAS has also shown good psychometric properties in the Croatian sarcoidosis sample of the present study.<sup>17</sup>

The WHOQOL-100 is a cross-culturally developed, generic, multidimensional QOL that measures 100 items.<sup>14</sup> The general evaluative facet consists of 4 questions, and the other 96 questions assess 24 facets of QOL within six domains: physical health, psychological health, level of independence, social relationships, environment, and spirituality. Each facet is represented by four items with a 5-point Likert-type response scale. Scores on each facet and domain can range from 4 to 20. The reliability and validity of this instrument, which have also been tested in groups of Dutch individuals with sarcoidosis, are good.<sup>19,20</sup> The psychometric qualities of the WHOQOL-100 in a Croatian diabetic group are adequate.<sup>15</sup>

### Statistical Procedure

Frequencies were used to present the available demographic, medical, and psychological data. Pearson correlations were calculated between the FAS and the WHOQOL-100 domains and facets. When fatigue was examined in relation to the QOL facet energy and fatigue and the QOL domain physical health, the two overlapping items ("Do you have enough energy for everyday life" and "Are you bothered by fatigue") were removed from the FAS total score to avoid overlap. We also computed a correlation between the FAS and the QOL domain physical health without the QOL facet energy and fatigue, thereby removing four QOL items. Following Cohen,<sup>21</sup> absolute correlations between 0.10 and 0.29 are considered small, between 0.30 and 0.49 are considered medium, and  $\geq 0.50$  as large. In addition, we divided the total FAS score into two groups: FAS scores 10 to 21 (not tired) and FAS scores 22 to 50 (tired). In line with De Vries et al,<sup>22</sup> we also divided the FAS into three groups, 10 to 21, 22 to 34, and 35 to 50. The last group consists of individuals who are extremely fatigued. We compared both FAS score divisions on QOL domains and facets using multivariate analysis of variance. When the results for the domains and facets were considered separately, we used a Bonferroni-adjusted  $\alpha$  level. Finally, seven hierarchical regression analyses were performed with the six WHOQOL domains and overall QOL as dependent variable. In block 1, gender and age were included. Block 2 consisted of the clinical parameters time since diagnosis, smoking behavior, DLCO, FEV<sub>1</sub>, FVC, disease stage, and corticosteroid use. Block 3 contained the FAS. All *p* values were two tailed, and SPSS 11.5 (SPSS; Chicago, IL) was used to perform all statistical analysis.

## RESULTS

The demographic, medical, and psychological characteristics are summarized in Table 1. The population

**Table 1—Demographic and Medical Characteristics of the Croatian Sarcoidosis Patients\***

Demographics	Total Sample	Men	Women	Using Corticosteroids	Not Using Corticosteroids
Male/female gender, No.	52/93	52	93	28/45	24/48
Age, yr	44.3 ± 9.9	42.4 ± 9.0	45.4 ± 10.3†	46.0 ± 9.8	42.6 ± 9.8
With partner, No.					
Yes	123	44	79	64	59
No	21	8	13	9	12
Missing	1	0	1	0	1
Education, No.					
Low	28	3	25‡	18	10
Middle	82	33	49‡	43	39
High	30	14	16‡	9	21
Missing	5	2	3‡	3	2
Medical data					
Time since diagnosis	4.0 ± 7.8 (median, 1)	3.7 ± 8.6	4.2 ± 7.4	5.5 ± 8.6	2.5 ± 6.6†
Smoking status					
Never	113	38	75	58	55
Stopped	21	8	12	10	10
> 1 yr	12	6	6	5	7
Corticosteroid use					
Yes	73	28	45	73	72
No	72	24	48		
Lung function results, % predicted					
DLCO	85.7 ± 15.5	85.4 ± 14.9	85.9 ± 15.9	83.6 ± 16.9	87.7 ± 13.7
FEV <sub>1</sub>	96.7 ± 20.6	93.0 ± 21.5	98.8 ± 19.9	93.2 ± 21.5	100.3 ± 19.1†
FVC	98.0 ± 16.8	92.6 ± 14.6	101.0 ± 17.2‡	95.6 ± 18.6	100.4 ± 14.4
Radiographic stage					
0	23	6	17†	14	9†
I	47	12	35†	11	36†
II	46	26	20†	23	23†
III	28	8	20†	24	4†
IV	1	0	1†	1	0†

\*Data are expressed as mean ± SD unless otherwise indicated.

†p < 0.05.

‡p < 0.01.

consisted of a vast majority of women, and the mean age was 44.33 ± 9.91 years. Women had more fatigue than men ( $t[1,133] = -3.18$ ,  $p < 0.01$ ; Table 2). Mean time since diagnosis was 4.04 ± 7.80 years, and nearly half of the sample used corticosteroids. The patients using corticosteroids were more tired than the patients who did not ( $t[1,133] = -3.50$ ,  $p < 0.01$ ). Of the

patients who did not use corticosteroids at the time of the study, two reported taking corticosteroids < 1 month ago, one < 6 months ago, and two from 6 to 12 months ago. Fatigue was the most common complaint ( $n = 85$ , 59.4%), followed by breathlessness ( $n = 67$ , 46.2%), reduced exercise capacity ( $n = 65$ , 44.8%), and arthralgia ( $n = 54$ , 37.2%). Tired individuals

**Table 2—Fatigue and QOL in Croatian Sarcoidosis Patients\***

Variables	Total	Men	Women	Using Corticosteroids	Not Using Corticosteroids
FAS	24.2 ± 8.1	21.3 ± 8.3	25.8 ± 7.5	26.5 ± 8.3	21.8 ± 7.2
Overall QOL	13.7 ± 2.6	14.4 ± 2.6	13.3 ± 2.6†	13.2 ± 2.8	14.2 ± 2.3
Domain 1, physical health	13.3 ± 3.1	14.7 ± 3.1	12.5 ± 2.9†	12.6 ± 3.1	14.0 ± 3.0†
Domain 2, psychological health	14.6 ± 2.3	15.8 ± 2.0	13.9 ± 2.1†	13.9 ± 2.5	15.2 ± 1.9†
Domain 3, level of independence	14.1 ± 3.4	14.9 ± 3.5	13.6 ± 3.3†	13.0 ± 3.2	15.2 ± 3.3†
Domain 4, social relationships	15.7 ± 2.3	16.4 ± 2.0	15.3 ± 2.4†	15.3 ± 2.5	16.0 ± 2.1
Domain 5, environment	14.7 ± 2.2	15.4 ± 2.1	14.3 ± 2.2†	14.3 ± 2.4	15.1 ± 2.0
Domain 6, spirituality	15.9 ± 2.9	16.4 ± 2.3	15.6 ± 3.2†	15.2 ± 2.8	16.6 ± 2.8†

\*Data are expressed as mean ± SD.

†Significant at the Bonferroni-adjusted  $\alpha$  level.

reported less exercise capacity, more breathlessness, and more arthralgia:  $t(1,131) = -3.96$ ,  $p < 0.001$ ;  $t(1,129) = -4.47$ ,  $p < 0.001$ ; and  $t(1,131) = -2.15$ ,  $p < 0.05$ , respectively. Fatigue did not correlate  $> 0.3$  with DLCO, FEV<sub>1</sub>, or FVC (Table 3). Patients with different radiographic stages did not differ according to fatigue:  $t(1,133) = -1.05$  ( $p > 0.05$ ).

The WHOQOL facet energy and fatigue was strongly related to fatigue after controlling for overlap in similar items of both scales ( $r = -0.76$ ,  $p < 0.001$ ). High correlations ( $r > 0.50$ ) were found between fatigue and the QOL domains physical ( $r = -0.73$ ) and psychological health ( $r = -0.72$ ,  $r = -0.56$ , with physical health after controlling for four-item overlap), level of independence ( $r = -0.71$ ), and environment ( $r = -0.51$ ). At facet level, fatigue was strongly associated with overall QOL ( $r = -0.58$ ); pain and discomfort ( $r = 0.52$ ); positive feelings ( $r = -0.57$ ); cognitive functions ( $r = -0.67$ ); self-esteem ( $r = -0.58$ ); negative feelings ( $r = 0.60$ ); mobility ( $r = -0.59$ ); activities of daily living ( $r = -0.77$ ); working capacity ( $r = -0.65$ ); personal relationships ( $r = -0.50$ ); and physical safety and security ( $r = -0.52$ ). Fatigue correlated  $-0.45$  (all  $p < 0.001$ ) with the facet sleep and rest.

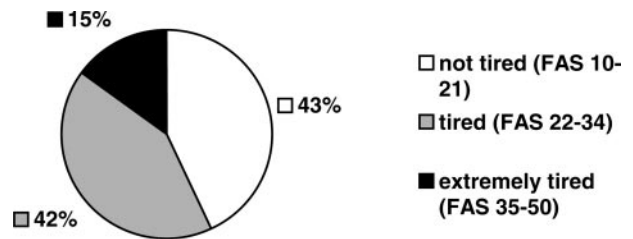
A majority of 83 patients (57.3%) had a FAS score  $\geq 22$  (tired). Twenty-one patients (14.5%) reported a FAS score  $\geq 35$  (extremely tired). When the high-fatigue and low-fatigue groups were compared on QOL, tired patients had a worse QOL:  $F(7,125) = 13.72$ ,  $p = 0.000$ ; and  $F(14,250) = 6.85$ ,  $p = 0.000$  (Fig 1). For both FAS score group divisions, tired patients differed from their energetic counterparts in all domains. Tired patients also reported a lower QOL on all facets compared with the nonfatigued patients, with one exception. The patients did not differ on the facet transport.

Finally, regression analyses showed that fatigue ( $\beta$  values ranging from  $-0.31$  to  $-0.64$ , all  $p < 0.001$ ) was the most important negative predictor of each QOL domain after controlling for demographic and clinical parameters (Table 4). Gender, age, time since diagnosis, and DLCO in various combinations

**Table 3—Correlations Among Fatigue, QOL, and Clinical Parameters**

Variables	DLCO	FEV <sub>1</sub>	FVC
FAS	-0.18*	-0.19*	-0.18*
Overall QOL	0.02	0.04	-0.01
Domain 1, physical health	0.25*	0.14	0.11
Domain 2, psychological health	0.16*	0.11	0.06
Domain 3, level of independence	0.26*	0.19*	0.15
Domain 4, social relationships	0.05	0.02	-0.03
Domain 5, environment	-0.05	-0.01	-0.08
Domain 6, spirituality	0.23*	0.12	0.13

\* $p < 0.05$ .



**FIGURE 1.** Distribution of low, middle, and high scores on the FAS.

were also predictors of QOL (total  $R^2$ , 22 to 58%). Corticosteroid use was not associated with QOL.

## DISCUSSION

Although fatigue is one of the major symptoms in sarcoidosis and is known to affect different aspects of QOL, the association between these two important concepts has never been the main object of study in sarcoidosis patients. Using psychometrically sound questionnaires, the current cross-sectional study was the first to scrutinize this relationship thoroughly. Fatigue appeared to be strongly related to all aspects of QOL, independently of other frequently reported symptoms, clinical parameters, and demographics. Standard clinical parameters of respiratory capacity were only associated with level of independence. In line with other studies,<sup>3,7,8</sup> fatigue was not related to respiratory functional impairment. Therefore, other factors should be considered to account for this devastating problem in sarcoidosis.

The association between fatigue and the QOL domains physical and psychological health as well as level of independence was very strong. Regarding the physical health facets, the rather low association between fatigue and the WHOQOL facet sleep and rest points out that sleeping problems certainly are not the only determinant of the subjective feeling of fatigue. The high correlation between fatigue and the level of independence domain supports the idea that fatigue affects daily life. Fatigue seems to be a debilitating symptom, affecting one's possibilities to live a self-governed life. In accordance with Schweitzer et al,<sup>12</sup> fatigue was a predictor of less satisfaction with social relationships, although the amount of variance was not high. The study of Schweitzer did not concern patients with chronic fatigue syndrome. Similar to sarcoidosis patients, their main complaint is fatigue. Chronic fatigue syndrome patients reported a reduced social support network and less participation in social activities. Surprisingly, items concerning physical safety influ-

**Table 4—Demographic, Medical Factors, and Fatigue Predictors of QOL\***

Variables	B	SE B	$\beta$	$R^2$	$\Delta R^2$
Overall QOL					
Time since diagnosis	− 0.05	0.03	− 0.16†		
Fatigue	− 0.19	0.03	− 0.59§	0.39	0.26
Physical health revised					
Being female	− 1.35	0.54	− 0.20†		
Age	− 0.07	0.03	− 0.20†		
Time since diagnosis	0.08	0.03	0.19†		
Fatigue	− 0.20	0.03	− 0.49§	0.43	0.19
Psychological health					
Being female	− 0.96	0.34	− 0.20‡		
Fatigue	− 0.18	0.02	− 0.64§	0.58	0.31
Level of independence					
DLCO	0.04	0.02	0.16†		
Fatigue	− 0.27	0.03	− 0.64§	0.58	0.31
Social relationships, fatigue	− 0.12	0.03	− 0.43§	0.25	0.14
Environment, fatigue	− 0.14	0.02	− 0.50§	0.31	0.19
Spirituality, fatigue	− 0.10	0.03	− 0.31‡	0.22	0.07

\*B = regression coefficient;  $\beta$  = standardized regression coefficient;  $R^2$  = proportion explained variance.

†p < 0.05.

‡p < 0.01.

§p < 0.001.

enced the relationship between the environment domain and fatigue. The war in Croatia did not influence the prevalence of sarcoidosis<sup>23</sup> or the level of psychosomatic complaints among civilians.<sup>24</sup> Speculatively, it might be that these somatic patients pay more attention to or are more sensitive to environmental hazards because their health already is affected. Finally, in line with a study using the Sickness Impact Profile,<sup>3</sup> fatigue was also strongly related to overall QOL.

An obvious limitation of this study is its cross-sectional nature. We cannot draw causal relationships between fatigue and QOL.<sup>25</sup> Secondly, although the Croatian version of the WHOQOL-100 has not been validated in a sarcoidosis sample, this language version was developed as part of the original World Health Organization QOL project, together with versions developed in 14 other cultural settings.<sup>26</sup> Because overall psychometric properties of the WHOQOL-100 were good and the psychometric properties of the WHOQOL-100 in a Croatian diabetic group were adequate,<sup>15</sup> we believe we have reliable QOL data. In addition, because we merely used questionnaires, this could have biased our results.<sup>27</sup>

However, until there is a “gold standard” for measuring fatigue objectively, we can only measure fatigue on a subjective level. It is well known that a complex construct such as fatigue can be measured more reliably when it is measured by more than one item. Because fatigue is one symptom, if not the core symptom, in sarcoidosis patients, its assessment should be done thoroughly. The FAS has proven good reliability and validity in sarcoidosis patients<sup>8,17</sup>;

therefore, the FAS can measure fatigue more adequately than a fatigue item or a fatigue subscale of a more global scale. Furthermore, the FAS is translated into several languages and is available from the first author. It is a short, easy-to-administer scale; because of this, we advise using the FAS in the follow-up and management of sarcoidosis patients. Besides the fact that fatigue is a major clinically relevant problem in sarcoidosis, the present study showed that it is strongly associated with various domains of QOL. Moreover, in line with others,<sup>3,7,8</sup> this study underlines the fact that regularly used measurements such as spirometry are not appropriate to depict the real impact of the disease on the patients' lives. Even if other measures of disease are normal, fatigue might be a major problem for the patient. Hence, treatment of sarcoidosis patients should not only concentrate on improving clinical parameters, but also pay attention to the subjective experience of fatigue because of its debilitating effect. Intervention studies, for instance cognitive behavior therapy,<sup>28,29</sup> are needed to investigate the possibilities for improving energy levels and thereby QOL. Future prospective studies could also focus on the specific types of fatigue in sarcoidosis patients<sup>30</sup> and their relationship with general QOL instruments and sarcoidosis-specific scales.<sup>31</sup> We would like to stress the importance of including fatigue measurement in the clinical follow-up of sarcoidosis patients. Searching for the antecedents of fatigue in this patient population in order to reduce fatigue and to improve their QOL is mandatory.

## APPENDIX

### FAS

The following 10 statements refer to how you usually feel. For each statement, you can choose one of five answer categories varying from never to always (1 = never; 2 = sometimes; 3 = regularly; 4 = often, and 5 = always):

1. I am bothered by fatigue.
2. I get tired very quickly.
3. I don't do much during the day.
4. I have enough energy for everyday life.
5. Physically, I feel exhausted.
6. I have problems getting started.
7. I have problems thinking clearly.
8. I feel no desire to do anything.
9. Mentally, I feel exhausted.
10. When I am doing something, I can concentrate quite well.

Items 4 and 10 require reversed scoring. The scale score is calculated by summing all items.

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