SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2004; 21; 57-63

Relationship between perceived stress and sarcoidosis in a Dutch patient population

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Abstract. *Background and aim:* A relationship between stress and sarcoidosis has been considered. However, studies concerning perceived stress, appraisal of life events, are scarce in sarcoidosis patients. Therefore, the aim of the present study was to further examine the role of perceived stress in sarcoidosis. *Methods:* Members of the Dutch Sarcoidosis Society (n = 1046; 59.0% females; the age range 40-49 contained the most persons) completed the Perceived Stress Scale (PSS), a symptom inventory, the Beck Depression Inventory (BDI), and the Fatigue Assessment Scale (FAS). *Results:* The PSS score of sarcoidosis patients was high ($p < 0.001$), especially those of females ($p < 0.001$). Moreover, patients with psychological problems had higher PSS scores ($p < 0.001$). Notably, the presence of psychological problems and gender appeared to be unrelated. Furthermore, perceived stress was related to the BDI ($r = 0.67$, $p < 0.001$), especially to the cognitive subscale ($r = 0.67$, $p < 0.001$) and, to a lesser extent, to the physical depression subscale ($r = 0.42$, $p < 0.001$). *Conclusions:* Perceived stress was found to be high and related to symptoms in sarcoidosis. Moreover, depressive symptoms appeared to be related to perceived stress. Therefore, the management of sarcoidosis should include coping and appraisal therapy aiming to reduce stress and depressive symptoms. ***(Sarcoidosis Vasc Diffuse Lung Dis 2004; 21; 57-63).***

Key Words. Immunity. Stress. Sarcoidosis.

Introduction

In sarcoidosis, a disseminated granulomatous disease of unknown origin, practically every organ can be involved. Depending on the organs involved and the severity of granulomatous inflammation, patients suffer from a broad range of persistent physical problems. Besides respiratory symptoms such as coughing and dyspnea on exertion, patients often suffer from systemic symptoms such as fever, weight loss, and fatigue [1]. The question arises whether these dysphoric symptoms are functional, *i.e.* based on psychogenic influences, or are real manifestations of the underlying organic disease [2].

Stress is frequently defined as a relationship between the person and the environment in which the individual perceives that something of personal value is at stake and judges that his or her resources are taxed or overwhelmed by the situation [3-7]. It is well known that stress influences immunologic function. A few studies have shown that physical (bicycle ergometry test) and psychological stress (acoustic stress test) can lead to characteristic alterations of plasma hormone concentrations and the lymphocyte subset distribution in both healthy subjects and sarcoidosis patients [8,9]. Klonoff and Kleinhenz [10] evaluated whether patients perceived events as stressful. They reported that their studied sarcoidosis patients (n = 17)

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did not perceive more stress than a group of persons in a community who were trying to quit smoking. Moreover, a higher score on daily hassles predicted more impaired lung function [10,11]. Recently, a Japanese study [12] found that in a group of 55 sarcoidoisis patients the magnitude of stressful life events in the year prior to the diagnosis of sarcoidosis was higher compared to a healthy control group. In addition, the patients scored higher on alexithymia, *i.e.*, non-expression of emotions. Moreover, most patients suffered from lack of sleep and psychosocial stress. The existing studies indicate that there might be a relationship between stress and sarcoidosis. However, these studies are rather small. Moreover, whether stress is related to reported symptoms and problems, and patient characteristics has hardly been studied in sarcoidosis. Previous studies in other diseases such as angina pectoris, musculoskeletal disease, inflammatory bowel disease, and asthma have shown that psychosocial aspects like stress may play a role in disease severity and problems with disease [13-16]. Studies in sarcoidosis relating stress to other problems that patients experience are scarse. In addition, the self-perception of stress may be one of the predisposing factors in the onset of sarcoidosis [12]. However, previous studies have mostly focussed on life events and lifestyle, *i.e.*, rather objective measures of stress, and not on perceived stress, *i.e.*, the evaluation of events. This self-perception is another way of examining stress. Therefore, the aim of the present study was to examine perceived stress and its relationship with reported problems in a large group of sarcoidosis patients.

Material and methods

Study population

All members of the Dutch Sarcoidosis Society (DSS), a patient organisation, suffering from sarcoidosis (N = 2352) were sent a test-booklet together with a covering letter in which they were asked to participate in a study on fatigue. More than 1000 patients (1046; 44.5%) completed the questionnaires. Demographic characteristics of the studied sample are presented in *Table I*.

Questionnaires

All respondents completed the following questionnaires: the Perceived Stress Scale (PSS) [17], the Fatigue Assessment Scale (FAS) [18], the Beck Depression Inventory (BDI) [19], and a Symptom Inventory Questionnaire (SIQ).

Table I
Demographic, medical, and psychological data of the sarcoidosis patients

	FREQUENCIES, N (%)	
Demographic data	*Study group*	
Gender: male/female/missing	390/617/39	
Age: 15-19	2 (0.2)	
20-29	46 (4.4)	
30-39	216 (20.9)	
40-49	297 (28.4)	
50-59	267 (25.5)	
60-69	143 (13.7)	
≥70	67 (6.4)	
missing	5 (0.5)	
Medical data		
Smoking: yes/no/missing	82/951/13	
Time since diagnosis[1]:	4.6 ± 1.4	
Prednisone use: yes/no/missing	282/609/155	
Family member with sarcoidosis: yes/no/missing	104/903/39	
Psychological data		
FAS score[1]	29.3 ± 7.6 (10-50)	cut-off score: 21
BDI score[1]	10.2 ± 6.4 (0-41)	cut-off score: 21
PSS score[1]	30.1 ± 6.7 (14-52)	compare value: 25

[1]Data are expressed as mean ± SD with range in parentheses.

The PSS consists of 14 questions that assess the degree to which situations within a person's life are appraised as stressful. Responses are given on a 4-point scale ranging from 1 = never, to 4 = always. This instrument has been used intensively in studies on stress and illness. The PSS has good reliability and validity [17].

The FAS is a fatigue questionnaire consisting of 10 items: five questions reflecting physical fatigue and five questions for mental fatigue. Although these two aspects of fatigue are represented in the questionnaire, the FAS appeared to be unidimensional in a Dutch working population as well as a representative sample of the general population [18,20]. 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 [18,20] also in sarcoidosis patients [21].

The BDI consists of statements that are arranged in 21 groups of four possible responses. Patients have to select the statement from each group that best describes their feelings in the past week. Each answer is scored on a four-point Likert-type scale ranging from 0 to 3. A summation of the ratings in the 21 groups indicates the severity of depression (possible range 0-63). The items can be divided into the Cognitive Depression Inventory (CDI) containing 15 items and the Physical Depression Inventory (PDI) that has 6 items. The psychometric properties of the BDI are good [19]. Depression scale scores for clinically diagnosed patients correlated highly with clinicians' ratings of depth of depression and the scale significantly differentiated between groups of non-depressed, mildly depressed, and severely depressed patients [19]. Moreover, the internal consistency of the BDI is mostly higher than 0.85 [22].

The SIQ consisted of 43 items including questions concerning socio-demographic and medical data such as medical history, family history, illness duration, diagnostic procedures, treatment, and current symptoms. This questionnaire also included questions focussing on the presence of

various categories of pain, including muscle pain, chest pain, abdominal pain, arthralgia, impaired mobility and/or headache. Most of the questions were multiple choice, sometimes giving the possibility to tick more than one answer. A number of questions were open-ended, allowing patients to give information concerning their personal situation. The SIQ was pre-tested in a population of 10 sarcoidosis patients and was also used in previous studies [23].

Statistical procedure

Frequencies were used for the characteristics of the patient group. One sample t-test for comparing the mean PSS score of the patients with the mean PSS score from a study among a representative sample of 765 Dutch persons working at least 20 hours each week (53.5% male; mean age 40.3 years) who had been recruited through random digit dialling [24]. Whether age and perception of future symptom development were related to the PSS scores was examined with Kruskal-Wallis tests. Kruskal-Wallis tests were also performed to examine the relationship between perception of future symptom development and depression (CDI, PDI, BDI). For the association between perception of future symptom development and having psychological problems, a Chi-square test was conducted. The relationships between sex, present prednisone use, having a partner and having a family member with sarcoidosis and PSS, psychological problems and PSS, and additional medical problems and PSS were examined with Mann-Whitney U tests. Mann-Whitney U tests were also performed to disentangle the relation between symptoms and perceived stress. A Pearson correlation was used to establish a relationship between illness duration and the PSS. Pearson correlations and partial correlations were calculated between depression and fatigue, on the one hand, and perceived stress, on the other hand. Because of the large sample size, a p-value below 0.01 was considered statistically significant. Finally, two stepwise multiple regression analyses were performed with PSS as dependent variable. In the first regression analysis sex, age, number of symptoms, types of symptoms, having additional medical problems, having psychological problems, and future symptom development were included as independent variables. In the second analysis, the scores on the BDI, CDI, and PDI were added as independent variables. Before the stepwise multiple linear regression analysis was performed, the linear assumptions were tested. First, normality was examined using histograms with kurtosis and skewness. All variables should be normality distributed. Second, linearity and homoscedasticity were tested using (partial) plots with standardised residuals and standardised predictor values. Linear regression analysis is allowed if the points on the plots are randomly distributed. In the present study, the linear assumptions were not violated and hence a linear regression analysis was allowed.

Results

The patient group comprised 390 (37.3%) male and 617 (59.0%) female patients. Gender was unknown for 39 (3.7%) patients. The participants' median age range was 45-49 years. A minority of the patients smoked. The mean illness duration was more than four years (see *Table I*).

Female patients (mean = 30.7) scored higher on the PSS than males (mean = 28.9; U = 88371.0, $p < 0.001$). There was also an age difference with regard to the PSS scores (χ^2 (6) = 13.58, $p < 0.05$; mean PSS scores per age range are 15-19 years = 22.0, 20-29 years = 32.1, 30-39 years = 29.7, 40-49 years = 30.7, 50-59 years = 30.0, 60-69 years = 28.7, older than 69 mean = 30.4). Having a family member that also has sarcoidosis (n = 104) and the presence (n = 808) or absence (n = 184) of a partner were both unrelated to perceived stress. However, compared with females, male patients more often had a partner (χ^2 (1) = 9.93, $p < 0.01$). Furthermore, illness duration (no gender differences) and prednisone use during the study (more males; χ^2 (1) = 4.33, $p < 0.05$) were also not associated with the PSS scores.

Compared with the representative sample of 765 Dutch persons working at least 20 hours each week [24], sarcoidosis patients scored higher on the PSS (t = 12.6, $p < 0.001$). Patients who reported psychological problems also scored higher on the PSS (U = 50619.5, $p < 0.001$), while gender and having psychological problems were unrelated to each other. Compared with patients without additional medical problems (n = 839), patients with additional medical diseases (n = 126) experienced more stress (U = 38473.5, $p < 0.01$). There were no gender differences.

Only 2.3% of the patients did not report any as symptom, whereas 96.2% indicated as suffering from at least one symptom (1.5% missing). With the exception of skin problems, heart complaints, cough during the two weeks prior to the study, and eye problems, all symptoms were related to patients' PSS scores. The number of symptoms that a patient reported was significantly correlated with perceived stress ($r = 0.24$, $p < 0.001$). More females than males reported muscle pain, chest pain, arthralgia, eye problems, dry mouth, an increase in sleep, increase in temperature during the previous two weeks, and shortness of breath (see *Table II*). Moreover, females reported more symptoms ($t(990) = -5.59$, $p < 0.001$).

There appeared to be a difference in PSS score between patients with different opinions about their symptoms in the future (χ^2 (3) = 30.7, $p < 0.001$). Compared with patients who thought that their symptoms would reduce (n = 122), stay the same

Table II
Reported symptoms, depression, and fatigue of the studied sarcoidosis patient population females (n = 617) compared to males (n = 390)

	PERCENTAGE SAYING 'YES'			
	FEMALES	MALES	STATISTICAL TEST VALUE	P-VALUE
Muscle pain	45.9	33.8	$\chi^2(1) = 13.14$	< 0.001
Chest pain	38.9	30.0	$\chi^2(1) = 7.48$	< 0.01
Arthralgia	68.7	54.4	$\chi^2(1) = 19.29$	< 0.001
Eye problems	42.3	30.3	$\chi^2(1) = 13.71$	< 0.001
Dry mouth	31.1	16.9	$\chi^2(1) = 24.04$	< 0.001
Sleep increase	72.9	64.6	$\chi^2(1) = 8.36$	< 0.001
Temperature increase	18.0	9.7	$\chi^2(2) = 15.53$	< 0.001
Breathlessness	91.4	84.1	$\chi^2(1) = 12.61$	< 0.001

(n = 497) or deteriorate (n = 249), patients who thought that their symptoms would disappear (n = 83) had lower PSS scores. Moreover, patients who thought their symptoms would remain the same scored lower on the PSS than patients who thought that their symptoms would deteriorate. Having psychological problems was also related to patients' perception of future symptom development (χ^2 (3) = 19.5, p < 0.001). More patients who thought that their symptoms would deteriorate also reported having psychological problems. Scores on the BDI, PDI, and CDI were higher for patients who believed that their symptoms would deteriorate than for the other patients. In addition, patients who thought that their symptoms would stay the same had higher PDI scores than patients who thought that their symptoms would go away. Gender was not related to patients' perception of symptom development.

Perceived stress was correlated with the BDI (r = 0.67). When looking at the two subscales of depression, it appeared that perceived stress was more related to the cognitive subscale (r = 0.67) than to the physical depression subscale (r = 0.42; all p's < 0.001). The relationship between perceived stress and fatigue (FAS) was 0.54 (p < 0.001) and remained significant after correction for the BDI (r = 0.24, p < 0.001). These relationships between perceived stress and depression and fatigue were all stronger for male than female patients (see *Table III*).

When the BDI, CDI, and PDI were not included in the regression analysis the following results emerged. Perceived stress was predicted by having psychological problems (Beta = 0.438), being female (Beta = 0.104), having an additional medical problem (Beta = 0.078), being younger (Beta = –0.091), the number of symptoms reported (Beta = 0.154), and no eye problems (Beta = –0.111). These independent variables explained 27.6% of the variance of perceived stress (F(6,806) = 51.2, p < 0.001). However, when the depression scores were included as independent variables in a stepwise multiple regression analysis, perceived stress was predicted by the CDI (Beta = 0.552), having psychological problems (Beta = 0.204), having additional medical problems (Beta = 0.063), being younger (Beta = –0.076), and the PDI (Beta = 0.077). In this analysis, 52.1% of the variance in perceived stress was explained by these predictors (F(5,728) = 158.6, p < 0.001). Thus, physical symptoms disappeared as predictors in favour of depressive symptoms.

Discussion

Compared with persons working at least 20 hours per week, sarcoidosis patients reported higher

Table III
Pearson correlations between perceived stress (PSS) and depressive symptoms and fatigue according to gender in the studied sarcoidosis patients

	PSS		
	FEMALES	MALES	P-VALUE
BDI	0.63	0.73	< 0.001
CDI	0.64	0.74	< 0.001
PDI	0.35	0.48	< 0.001
FAS	0.50	0.58	< 0.001
FAS corrected for BDI	0.24	0.22	< 0.001

BDI = Beck Depression Inventory, CDI = Cognitive Depression Inventory, PDI = Physical Depression Inventory, FAS = Fatigue Assessment Scale

perceived stress scores. In addition, female patients, older patients, and patients with psychological or additional medical problems had higher perceived stress scores. Moreover, a number of symptoms as well as the cumulation of symptoms was related to perceived stress. Finally, patients who indicated that they thought that their symptoms would disappear in the future reported less perceived stress. Thinking that one's symptoms will get worse coincided with reporting psychological problems and higher scores on depression. Finally, regression analyses showed that depression, especially the cognitive component, was a major predictor of perceived stress. Furthermore, having additional medical problems and being younger were persistent predictors of perceived stress.

Compared with a random sample of 765 Dutch people working at least 20 hours each week [24], sarcoidosis patients reported more perceived stress. This is in accordance with results from studies with other diseases such as angina pectoris, musculoskeletal disease, and inflammatory bowel disease [13-15]. Moreover, as in the present study others have found a positive relation between symptoms and perceived stress [14]. It is known from experimental studies that (perceived) stress predicts getting the common cold [25-28]. Stressful lifestyles, e.g., working night shifts or other events may trigger sarcoidosis. Yamada and colleagues [12] found that nearly all of the sarcoidosis patients in their study were probably in stressful situations at the time of diagnosis. The patients reported more stress compared with a healthy control group. However, in another sarcoidosis study where perceived stress was examined [10], the patients did not report more perceived stress. The mean perceived stress score of both sarcoidosis samples differed significantly (data not shown), with our sample having the higher score. This inconsistency might have been caused by the recruitment procedure, differences in sample size, or differences in the percentage of chronic patients in the sample. Future studies are needed to find the reason(s) for the inconsistency.

Stress is known to affect factors such as immunity [29], natural killer (NK) cell activity [30], production of antibodies to latent viruses [31], plasma nerve growth factor levels [32], and the production of helper T-cells and interferon [33]. Recently, Stowell and colleagues [34] found that the relationship between (active and avoidance) coping and proliferation to mitogen depended on the perceived stress level. Moreover, the two coping styles were only strongly associated with proliferation of peripheral blood leukocytes to phytohemagluttinin (PHA) and concanavalin A (Con A) in participants reporting high levels of perceived stress. Thus, stress can alter the cellular immune processes that underlie the signs and symptoms of sarcoidosis. Furthermore, relaxation training and self-hypnosis training, two brief, low-cost psychological interventions to decrease stress, have shown to increase levels of T-lymphocytes, B-lymphocytes, NK cells, CD8+ and CD4+ cell counts [33,35]. Therefore, relaxation treatment, self-hypnosis training, and/or coping therapy might be an alternative way to treat sarcoidosis patients, especially the chronic patients.

In the present study, no relationship was found between corticosteroid use and perceived stress. Previously only two studies have been conducted in which the effect of corticosteroids on perceived stress was examined. Koh *et al* [36] reported information about an asthmatic man who became acutely delirious after receiving a dose of steroids that was higher than previously prescribed doses, under a condition of emotional stress. In the other study, more in-vitro fertilisation pregnancies occurred among women who received prednisone. The authors argued that corticosteroids might counteract the detrimental effect of a stress-related androgen excess by depressing adrenal and ovarian androgens [37].

In accordance with a previous study [38], female sarcoidosis patients reported more symptoms and perceived more stress than males. These results are consistent with trends in the general population that women report more symptoms [39] and are more emotionally expressive [40]. In line with this, it is tempting to speculate that there is a gender difference in thresholds for perceiving and reporting symptoms.

Younger age and having additional medical problems were persistent predictors of perceived stress. The peak incidence of sarcoidosis occurs between 20 and 40 years of age. This is a time when being ill creates considerable distress, especially with regard to psychosocial and economic problems [10]. The fact that co-morbidity is related to perceived stress is also not surprising. Illness takes much of a patient's time and energy. Having additional disease and probably more symptoms might increase stress due to additional limitations and possibly increased psychosocial and economic problems.

A study among stressed and healthy persons showed that acute psychological stress simultaneously alters hormone levels, recruitment of lymphocyte subsets, and production of reactive oxygen species [41]. Another study revealed that perceived stress was related to cortisol levels during the first hour after awakening following dexamethasone pretreatment. In addition, scoring high on burnout was associated with lower overall cortisol secretion on all days, and a higher suppression of cortisol secretion after dexamethasone administration. In the subgroup of teachers with both high levels of perceived stress and high levels of burnout, a lower overall cortisol secretion was observed on the first 2 days, with stronger increases during the first hour after awakening after dexamethasone suppression. This subgroup also showed the highest number of somatic symptoms [42].

Perceived stress appeared to be related to fatigue, even when the role of depression was partialed out. A longitudinal study among 765 Dutch individuals working at least 20 hours per week showed that perceived stress predicted fatigue [24]. Therefore, it is likely that perceived stress is also a predictor of fatigue in sarcoidosis. Future research is needed to elucidate the causal relationship between perceived stress and fatigue in sarcoidosis. One possible research line might be the unconscious amygdalar fear conditioning as the link between psychological stress and fatigue. Gupta [43] has postulated that a conditioned network in the cell assembly of the amygdala may cause the Chronic Fatigue Syndrome (CFS). In this hypothesis the combination of psychological stress and a virus infection as the input factors may become a conditioned stimulus that results in a conditioned response, *i.e.*, immune reactivity (stress signature) as output. A chronic activation of the immune system leads to chronic sympathetic outpouring from the amygdala, a part of the limbic brain structure.

The large correlation between the concepts depression and perceived stress was consistent with other studies [10,44-46]. Perceived stress and depression are positively related to each other. Persons who score high on perceived stress also score on depression, especially on cognitive depression. However, whether perceived stress precedes depressive symptoms or is a consequence of these symptoms is not established.

The present study has some limitations. First, the patient group consisted of members of the patient organisation, which may be a selected group. That is, particular persons will become a member of a patient organisation. The patients in the present study appeared to have a chronic course of sarcoidosis. An extremely large percentage indicated having one or more physical symptoms. Patients suffering from symptoms are constantly confronted with their disease. Therefore, they may need more information concerning all kinds of aspects of sarcoidosis. Presumably, sarcoidosis patients decide to become a member of the patient organisation only if they suffer from more or less 'chronic' symptoms. Another issue might be that patients who feel isolated look for contact with fellow-sufferers through the organisation. Finally, the members who did not participate in the present study (55.5%) are likely to be a group of patients who did not suffer from symptoms anymore. Unfortunately, this assumption could not be checked within the present study because there was no information available about the occurrence of symptoms in the non-response group. Results from the present study are probably more applicable to chronic sarcoidosis patients. Given these two limitations of the study the outcomes of the present study must be interpreted with care.

The present study does not provide information on causality. It is unknown whether stress caused sarcoidosis or that the illness itself is the source of stress. However, it is known that common infections may be caused by psychological stress [47]. In addition, the results found by Staton and colleagues [48] suggest that stress proteins are expressed constitutively at high levels in alveolar macrophages retrieved by bronchoalveolar lavage, regardless of health. It is also possible that perceived stress plays a role in the outcome of sarcoidosis, since a previous study has shown that psychological factors significantly affect outcomes of physical illness [49]. This underlines the importance of a multidisciplinary approach in the management and care of sarcoidosis patients [50].

In conclusion, patients with sarcoidosis reported perceived stress. Females reported more stress and symptoms. Perceived stress appeared to be related to symptoms, sex, age, having additional medical problems, having psychological problems, depression, and fatigue. Considering the relationship between stress and the immune function, relaxation therapy and coping strategies might offer an alternative in the management of sarcoidosis.

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