Chapter 9

Quality of life of couples living with sarcoidosis

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Abstract

Background

Consequences of sarcoidosis are wide-ranging and the symptom burden has a great impact on patients' quality of life (QoL). However, the QoL of couples living with sarcoidosis has not yet been studied. Our aim was to assess the QoL of couples living with sarcoidosis and to evaluate whether living with a partner with sarcoidosis influences the partner's QoL. Furthermore, we aimed to assess whether non-specific symptoms (fatigue, cognitive failure, small fiber neuropathy (SFN) related symptoms, depressive symptoms, and state/trait anxiety) predict QoL of partners as well as sarcoidosis patients.

Methods

Sarcoidosis outpatients, recruited at Maastricht University Medical Centre (n=443), and their partners (n=208), completed several questionnaires, including the World Health Organization Quality of Life – BREF (WHOQoL–BREF), Fatigue Assessment Scale (FAS), SFN screening list (SFNSL), and Cognitive Failure Questionnaire (CFQ).

Results

QoL of the partners as well as the sarcoidosis patients was reduced compared with healthy controls, especially regarding the physical health domain. All non-specific symptoms studied, as well as perceived social support, predicted one or more QoL domains in the sarcoidosis patients, but these factors did not predict the QoL of their partners.

Conclusions

The QoL of partners of sarcoidosis patients was reduced, although to a lesser extent than that of the patients. Although the non-specific symptoms and perceived social support were related to the patients' QoL, this was not the case for the partners. In the management of sarcoidosis is it important to focus not only on the patients, but also on their partners.

Introduction

Sarcoidosis is a multisystem inflammatory disorder of unknown cause(s) that imposes a burden on patients' lives.[1] It affects men and women all over the world, at a relatively young age.[2] In addition to the specific organ-related symptoms, less specific disabling symptoms, including fatigue, cognitive failure, symptoms associated with small fiber neuropathy (SFN), and physical impairments, may have a major influence on the daily activities and the social and professional lives of the patients. These symptoms can lead to stress, anxiety, depression, and social and physical limitations.[3-8] Moreover, sarcoidosis patients experience reduced work ability.[9-11]

The impact of any disease depends on the patient's disease perception and coping strategies. Various aspects of sarcoidosis, such as the often unpredictable and chronic nature of the disease,[2] the uncertainty about the cause, and the broad range of frequently persistent symptoms may result in an aggravating influence on patients' lives. Hence, living with a long-term disease like sarcoidosis significantly affects patients' quality of life (QoL), with negative consequences for general health and social and psychosocial well-being. QoL is a concept that concerns someone's evaluation of their functioning in a wide range of domains, but always includes the physical, psychological, and social domains. Anxiety and depressive symptoms are also common in patients with sarcoidosis and are associated with disease severity.[6,7] Previous QoL studies showed that the QoL of patients with sarcoidosis is predicted by fatigue, depressive symptoms, reduced exercise capacity, dyspnea, and arthralgia.[1,4,8,12-16] Recently, Moor et al. demonstrated that sarcoidosis not only leads to anxiety, psychological distress and impaired well-being in the patients, but also in their partners.[17] Studies on the influence of other non-specific symptoms and studies examining the impact of living with a partner with sarcoidosis are scarce.

Therefore, the aim of our study was to evaluate whether living with a partner suffering from sarcoidosis influences the QoL of that partner, as well as to evaluate the QoL of the patients themselves. Moreover, we aimed to assess whether non-specific symptoms, including fatigue, cognitive failure, SFN-related symptoms, and psychological factors including depressive symptoms and anxiety in sarcoidosis patients predict the QoL of partners and patients.

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Materials and methods

Study design and subjects

We conducted a cross-sectional, prospective cohort study evaluating fatigue and QoL in sarcoidosis patients and their partners between 2007 and 2009. Data regarding fatigue in sarcoidosis patients were previously used in Willemien de Kleijn's PhD project.[18] Data from the current study regarding the QoL of sarcoidosis patients and their partners were analyzed in 2018, and not reported previously. Patients (n=588) evaluated and/or treated at the ILD Center of the Department of Pulmonology of Maastricht University Medical Center, a tertiary referral center in the Netherlands were asked to participate between September 2007 and July 2008. After inclusion of the patients, their partners (if they had a partner) were also asked to participate. Patients were all diagnosed with sarcoidosis based on the guidelines of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG).[2] The Medical Ethics Committee of MUMC+ (MEC 07-4-015) approved the study protocol, and written informed consent was obtained from all patients.

Procedure

Information about the study was sent by e-mail (which every patient and/or partner asked to participate had access to), and patients as well as their partners were asked to complete and return an informed consent form if they were willing to participate. After having agreed to participate, they received the set of questionnaires and were asked to return the completed set to the hospital in an enclosed envelope.

The following characteristics were collected: gender and age (patients and partners), and time since diagnosis of sarcoidosis and sarcoidosis treatment (patients). Patients completed several questionnaires: World Health Organization Quality of Life-BREF (WHOQoL-Bref), Fatigue Assessment Scale (FAS), Small Fiber Neuropathy Screening List (SFNSL), Cognitive Failure Questionnaire (CFQ), State and Trait Anxiety Inventory (STAI), Center for Epidemiological Studies Depression Scale (CES-D) and Perceived Social Support Scale (PSSS). The partners were asked to complete the WHOQoL-BREF, FAS, and CFQ.

Questionnaires

Questionnaire scores of patients and partners in the present study were compared with corresponding questionnaire scores of a healthy control sample (n=62) recruited for a

study by Marcellis et al..[19] These healthy controls were recruited in the same geographical area/institution and timeframe as our study sample. We used the raw data of this healthy control population.

Detailed descriptions of the questionnaires (WHOQoL-BREF, FAS, SFNSL, CFQ, STAI, CES-D, PSSS) can be found in the online supplement.[20-26]

Statistical analysis

All statistical analyses were performed using SPSS version 24 for Mac. The chi-square test, the independent samples t-test (partners vs controls and patients vs controls) and paired t-tests (patients vs partners) were used to test for statistically significant differences between patients, their partners and controls. Hierarchical linear regression analyses were used to assess the associations between the scores for the various domains of the sarcoidosis patients' and partners' WHOQoL-BREF and the sarcoidosis patients' fatigue (FAS), SFN-associated symptoms (SFNSL), cognitive failure (CFQ), depression (CESD), anxiety (STAI) and perceived social support (PSSS). Adjustments were made for age, sex, treatment and time since diagnosis in the analysis regarding patients, and for age and sex in the analysis regarding partners. Since each WHOQoL-BREF domain was analyzed by means of a separate regression model, a Bonferroni correction was used to reduce the risk of false positive findings, by adjusting the significance level in these 5 regression analyses from 0.05 to 0.01. Hence, within each of the ten WHOQoL-BREF regression models (five for patients and five for partners) p-values of less than 0.01 were considered to indicate statistical significance. In view of this correction, we also reported 99% confidence intervals (instead of the conventional 95% confidence intervals) around the estimated regression coefficients.

In a posthoc analysis we have performed a mediation analysis using the Baron & Kenny method.[27] A moderation analysis was performed by including the product of two mean-centered predictors in a regression analysis, on top of the main effects of these two predictors.

Results

Three quarters of the approached sarcoidosis patient sample (443/588) agreed to participate, of whom 10 were excluded from further analyses because they did not complete the main outcome measure QoL. Two-hundred and eight partners decided to participate and completed the questionnaires. The sarcoidosis patients whose partners

participated in the study (n=208) did not differ from those without a partner or whose partners did not participate (n=225), except for age (see Table 9.1).

Table 9.1 summarizes the demographic and clinical data and the questionnaire scores of the 433 included patients are summarized. The prevalence of the various non-specific symptoms among the sarcoidosis patients and their partners is shown in Figure 9.1.

Table 9.1 Summary of the demographic and clinical characteristics of the sarcoidosis patient sample studied.

	Total sarcoidosis sample (n=433)	Sarcoidosis patients included in partner analysis (n=208)	Sarcoidosis patients excluded from partner analysis (n=225)
male: n (%)	233 (53.8)	108 (51.9)	126 (55.5)
age, years (range)	48 ± 11.1 (19-79)	46.5 ± 10.2 (27-79)	49.3 ± 11.7 (19-78)*
time since diagnosis, years (range)	7.7 ± 7.8 (0-65)	7.2 ± 6.4 (0-44)	8.1 ± 8.9 (0-65)
medication			
none (%)	157 (36.3)	71 (34.1)	86 (37.9)
prednisone (%)	219 (50.6)	105 (50.5)	116 (51.1)
methotrexate (%)	74 (17.1)	38 (18.3)	36 (15.9)
TNF-α antagonists (%)	38 (8.8)	21 (10.1)	17 (7.5)
FAS score	29.3 ± 8.4	30.1 ± 8.5	28.7 ± 8.3
SFNSL score	29.9 ± 15.6	24.8 ± 15.8	23.1 ± 15.4
CFQ score	36.6 ± 16.1	43 ± 17.1	34.8 ± 16.1
STAI			
state	11.6 ± 3.7	11.5 ± 3.5	11.6 ± 3.8
trait	40.6 ± 7.7	40.6 ± 7.7	40.6 ± 7.7
CESD	14.2 ± 9.7	14 ± 9.5	14.5 ± 9.9
PSSS	62.5 ± 13.4	63.3 ± 13.4	61.8 ± 13.4
WHOQoL–BREF			
1. physical health	12.2 ± 3.1	12.2 ± 3	12.3 ± 3.1
2. psychological health	14.2 ± 2.3	14.3 ± 2.3	14.1 ± 2.4
3. social relationships	14.2 ± 2.8	14.4 ± 2.8	14.0 ± 2.9
4. environment	15.5 ± 2.5	15.8 ± 2.4	15.2 ± 2.6
5. overall QoL	6 ± 1.6	6 ± 1.6	6 ± 1.6

Data are expressed as mean ± SD or range in parentheses if appropriate. CESD=Center for Epidemiological Studies-Depression Scale; CFQ=Cognitive Failure Questionnaire; FAS=Fatigue Assessment Scale; PSSS=Perceived Social Support Scale; SFNSL=Small Fiber Neuropathy Screening List; STAI=State and Trait Anxiety Inventory; TNF=tumour necrosis factor; WHOQoL–BREF=World Health Organization Quality of Life–BREF. *statistically significant: p=0.01.
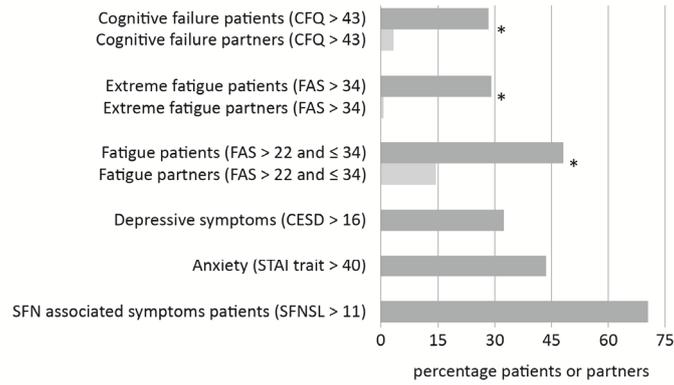
Figure 9.1   Non-specific symptoms in the sarcoidosis patients and their partners.
CESD=Center for Epidemiological Studies-Depression Scale; CFQ=Cognitive Failure Questionnaire; FAS=Fatigue Assessment Scale; SFNSL=Small Fiber Neuropathy Screening List; STAI=State and Trait Anxiety Inventory;. *=p<0.001

Quality of life partners and patients

Table 9.2 summarizes the characteristics and outcomes of the partners of the sarcoidosis patients and the sarcoidosis patients themselves, and the comparison with healthy control subjects.

The overall QoL scores of the partners were lower than those of the healthy controls (p<0.001). The QoL domain scores (Physical, Psychological, Social, Environment) were also lower for partners than for healthy controls.

The QoL of the sarcoidosis patients was significantly more impaired than that of their partners, overall as well as in the different domains (all p-values <0.001, except social relationships p=0.002).

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Table 9.2 Characteristics of partners of sarcoidosis patients compared to those of sarcoidosis patients (n=208) and healthy controls.

	Partners	Patients	Healthy Controls	Δ Partners - patients	Partners vs Controls*	Partners vs Patients*	Patients vs Controls*
subjects, number	208	208	62				
male: n (%)	96 (46.2)	108 (51.9)	40 (64.5)		0.023	0.239	0.138
age, years (range)	46.2 ± 11.3 (16-80)	46.5 ± 10.2 (27-79)	46.4 ± 9.9 (30-65)		0.622	0.900	0.763
time since diagnosis, years (range)	NA	7.2 ± 6.4 (0-44)	NA				
WHOQoL-BREF domains							
1. physical	16.6 ± 2.1	12.2 ± 3.0	18.0 ± 1.5	4.47 ± 3.5	<0.001	<0.001	<0.001
2. psychological	15.7 ± 2.0	14.3 ± 2.3	17.0 ± 1.9	1.29 ± 2.7	<0.001	<0.001	<0.001
3. social	15.2 ± 2.6	14.4 ± 2.8	17.3 ± 2.4	0.73 ± 3.2	<0.001	0.002	<0.001
4. environment	16.7 ± 2.0	15.8 ± 2.4	17.7 ± 1.6	0.95 ± 2.7	<0.001	<0.001	<0.001
5. overall	8.2 ± 1.2	6.0 ± 1.6	8.7 ± 1.0	2.28 ± 1.9	<0.001	<0.001	<0.001
FAS score	17.5 ± 4.9	30.1 ± 8.5	15.6 ± 4.0	12.6 ± 9.9	<0.001	<0.001	<0.001
CFQ total score	24.9 ± 11.2	43.0 ± 17.1	31.3 ± 10.1	18.2 ± 20.1	<0.001	<0.001	<0.001

Data are expressed as mean ± SD if appropriate. CFQ=Cognitive Failure Questionnaire; FAS =Fatigue Assessment Scale; WHOQoL-BREF= World Health Organization Quality of Life–BREF. *p-values resulting from a paired t-test testing for differences between the two groups.

Associations of QoL of partners and sarcoidosis patients

Hierarchical multiple linear regression analyses demonstrated that, after adjustment for the covariates age and gender of the partner, none of the non-specific symptoms (fatigue, SFN-associated symptoms, cognitive failure, state/trait anxiety, depressive symptoms and perceived social support) of the patients, including their QoL, were associated with the overall QoL score and those for the four QoL domains of their partners.

Hierarchical multiple linear regression analyses demonstrated that, after adjustment for the covariates age, gender, time since diagnosis and treatment, all non-specific symptoms we studied, except momentary anxiety, were associated with the overall QoL score and those for the four QoL domains of the sarcoidosis patients, predicting 32% to 63% of the variance (Table 9.3).

Depressive symptoms were negatively associated with the overall QoL score and those for all domains, except social relationships. Perceived social support was positively associated with all QoL domains, except physical health. Fatigue was negatively associated with the overall QoL score and those for the physical and psychological QoL domains. SFN-associated symptoms were negatively associated with the physical and

environmental QoL domains. Trait anxiety was negatively associated with the psychological and social QoL domains. Finally, cognitive problems were only negatively associated with the QoL domain of physical health, but this association was subject to a mediation effect (see below).

To simplify, overall QoL is predicted by fatigue and depressive symptoms. The QoL domain physical health is predicted by fatigue, SFN-associated symptoms, depressive symptoms and cognitive failure. The QoL domain psychological health is predicted by fatigue, trait anxiety, depressive symptoms and perceived social support. The QoL domain social relationships is predicted by trait anxiety and perceived social support. And last, the QoL domain environment is predicted by SFN-associated symptoms, depressive symptoms and perceived social support (see Figure 9.2).

Table 9.3 Predictors of the WHOQoL-BREF.

	WHOQoL–BREF				
	Overall QoL score	1. Physical health	2. Psychological health	3. Social relationships	4. Environment
FAS	-0.10* (-0.13, -0.08) β=-0.55	-0.21* (-0.26, -0.17) β=-0.59	-0.06* (-0.09, -0.02) β=-0.20	-0.03 (-0.08, 0.03)	-0.03 (-0.10, 0.05)
SFNSL	-0.01(-0.02, 0.01)	-0.04* (-0.06, -0.02) β=-0.20	0.02 (0.00, 0.03)	-0.01 (-0.04, 0.02)	-0.03* (-0.06, -0.01) β=-0.18
CFQ	0.01 (0.00, 0.03)	0.02* (0.00, 0.05) β=0.12	0.00 (-0.02, 0.01)	0.02 (-0.01, 0.05)	0.01 (-0.02, 0.03)
STAI Trait	0.00 (-0.04, 0.04)	0.02 (-0.05, 0.08)	-0.10* (-0.15, -0.05) β=-0.32	-0.10* (-0.17, -0.02) β=-0.26	-0.03 (-0.10, 0.05)
STAI State	-0.03 (-0.10, 0.04)	-0.11 (-0.22, 0.01)	-0.06 (-0.15, 0.03)	0.02 (-0.12, 0.16)	-0.02 (-0,16, 0.12)
CESD	-0.04* (-0.07, -0.01) β=-0.24	-0.06* (-0.11, -0.01) β=-0.17	-0.08* (-0.12, -0.03) β=-0.31	-0.06 (-0.13, 0.00)	-0.07* (-0.13, -0.01) β=-0.27
PSSS	0.00 (-0.01, 0.01)	0.00 (-0.02, 0.02)	0.02* (0.01, 0.04) β=0.11	0.07* (0.05, 0.10) β=0.34	0.03* (0.01, 0.06) β=0.17
R^2	51%	63%	62%	42%	32%

CESD=Center for Epidemiological Studies-Depression Scale; CFQ=Cognitive Failure Questionnaire; FAS=Fatigue Assessment Scale; PSSS=Perceived Social Support Scale; SFNSL=Small Fiber Neuropathy Screening List; STAI=State and Trait Anxiety Inventory, WHOQoL–BREF=World Health Organization Quality of Life–BREF. Unstandardized regression coefficients and their 99% confidence intervals are shown. For significant effects, standardized regression coefficients are reported in bold face. R^2 = Percentage of additionally explained variance of the model including predictors above and beyond the model with theoretically important covariates only. * p<0.01.
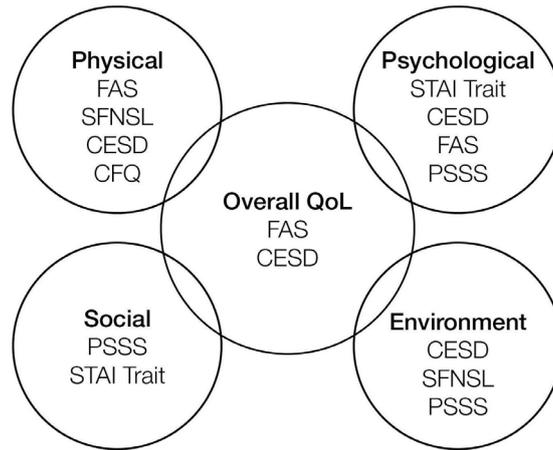
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Figure 9.2   Simplification of the effect of predictors on overall quality of life (QoL) and the four domains as presented in Table 9.3.
CESD=Center for Epidemiological Studies-Depression Scale; CFQ=Cognitive Failure Questionnaire; FAS=Fatigue Assessment Scale; PSSS=Perceived Social Support Scale; SFNSL=Small Fiber Neuropathy Screening List; STAI=State and Trait Anxiety Inventory, WHOQoL–BREF=World Health Organization Quality of Life–BREF.

Relative importance of the QoL predictors in partners and sarcoidosis patients

The QoL predictors for partners were not significant, and are therefore not described any further here.

As regards the patients, the predictors explained 62.9% of the variance in the physical health domain scores. This domain was best predicted by fatigue, followed by SFN-associated symptoms, depressive symptoms, and cognitive failure.

The predictors explained 61.9% of the variance in the psychological health domain. This domain was best predicted by trait anxiety, depressive symptoms, fatigue, and perceived social support. Perceived social support had a positive effect on the psychological QoL, while the other variables had negative effects.

The predictors explained 41.7% of the variance in the social relationships domain. This domain was best predicted by trait anxiety and perceived social support. Perceived social support had a positive effect on QoL while trait anxiety had a negative effect.

The predictors explained 31.8% of the variance in the environment domain. This domain was best predicted by the depressive symptoms, SFN-associated symptoms, and perceived social support. Again, perceived social support had a positive effect on QoL, while depressive symptoms and SFN-associated symptoms had a negative effect.

The predictors explained 50.7% of the variance in the overall QoL score, and this was best predicted by fatigue and depressive symptoms.

Mediation analysis

The results in Table 9.3 suggest that cognitive failure had a positive effect on QoL (unstandardized B 0.024), indicating that patients with more cognitive failure had a higher physical QoL. Since cognitive failure has a great impact on the lives of sarcoidosis patients, and given that the present sample included mostly young patients with a busy social and working life, this finding was against our expectations. In regression models, a significant association between a predictor and outcome may in fact be explained by a third variable, such as a confounder, mediator or moderator. Therefore, we inspected the partial and zero-order correlations between the physical domain of QoL and the predictors. The zero-order correlations showed that there was, as expected, a negative association between CFQ and physical QoL. However, after adjusting for the influence of other predictors (primarily fatigue and depressive symptoms), this negative association disappeared through collinearity. Figure 9.3 shows two mediation models where fatigue and depressive symptoms, respectively, mediate the association between cognitive failure and physical QoL. Indeed, the significant zero-order correlation between these two measures disappeared when the mediating effects of fatigue and depressive symptoms were included in the model (see Figures 9.3A and 9.3B). Furthermore, a moderation analysis showed a significant interaction effect between the CFQ and FAS as well as CESD on physical QoL (CFQ-FAS: $\beta=0.078$, SE=0.001, t=2.182, p=0.03 respectively CFQ-CESD: $\beta=0.176$, SE=0.001, t=3.795, p<0.001). These results suggest that there may be multiple mechanisms underlying the relations between these variables.
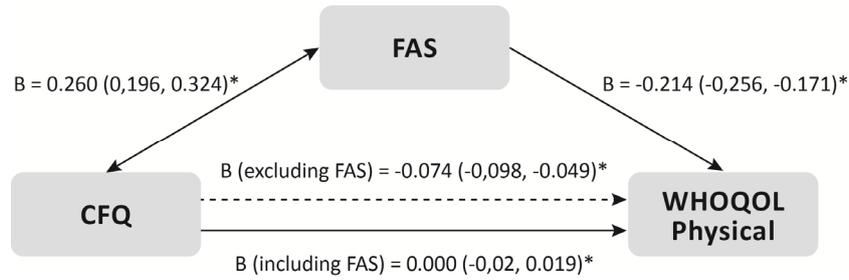
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Figure 9.2A Impact of the Fatigue Assessment Scale (FAS) score on the Cognitive Failure Questionnaire (CFQ) regression coefficient in predicting the quality of Life (WHOQoL=World Health Organization Quality of Life). B=standardized regression coefficient, * = statistically significant
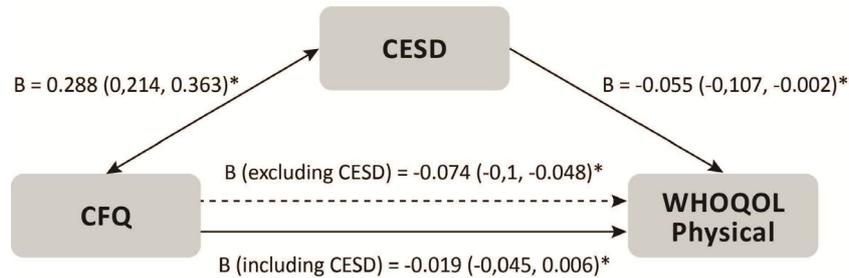

Figure 9.2B Impact of depressive symptoms score (CES-D=Center for Epidemiological Studies-Depression Scale) on Cognitive Failure Questionnaire (CFQ) regression coefficient in predicting the quality of life (WHOQoL=World Health Organization Quality of Life). B=standardized regression coefficient, * = statistically significant.

Discussion

This is the first study to show that the QoL of couples where one of the partners suffers from sarcoidosis is reduced compared to that of healthy controls. Neither the QoL nor non-specific symptoms of the sarcoidosis patients predicted the QoL of the partners of the sarcoidosis patients we studied. Predictors of the QoL of the sarcoidosis patients themselves were fatigue, depressive symptoms, SFN-associated symptoms, cognitive failure, anxiety, and perceived social support. All of these non-specific symptoms, except perceived social support, had a negative impact on various aspects of the QoL of the sarcoidosis patients. This underlines the importance of determining all these non-specific symptoms in sarcoidosis patients.

The importance of patient-centeredness in healthcare has grown over the years. So far, family involvement and perspectives have infrequently been studied in sarcoidosis. A novel finding from our study is that partners of sarcoidosis patients also had a lower QoL than healthy persons, but to a lesser extent than that of the sarcoidosis patients we studied. The QoL of the partners living with a sarcoidosis patient was mainly lower in the psychological and social domains. We did not study the perceived social support for partners, but one could speculate that partners have less perceived social support and often feel misunderstood by people in their environment because of the lack of awareness of sarcoidosis as a disease. Previous studies have shown a relationship between social support and the QoL of partners of patients.[28,29] This needs to be examined in future studies. They may also experience psychological distress, leading to anxiety,[17] as sarcoidosis can be unpredictable and they worry about the consequences regarding the future of the patient as well as their own future. There is a need for further studies into dyadic coping in sarcoidosis.

In line with other studies, we found a lower QoL for our sarcoidosis patient sample than for healthy controls, especially in the physical health domain, meaning that they feel less physically healthy than the healthy population.[13,14,16,30] Apart from major organ involvement, sarcoidosis patients can be bothered with reduced muscle strength, loss of physical condition, pain, extreme fatigue, and SFN-associated symptoms.[1,31] Psychological factors are pervasive, and include anxiety, depressive symptoms and mental fatigue, including memory problems, lack of mental clarity, poor concentration and inability to focus. These factors may not correspond with inflammatory disease activity nor respond to sarcoidosis treatment.[1,5] The symptoms are disabling, persist after other signs of sarcoidosis activity have resolved, and adversely impact on major life areas, including QoL and work ability.[32,33] Tan et al. did find that the more symptoms affecting the patient, the more it affected the partner's QoL.[34]

Depressive symptoms, anxiety, and cognitive failure have increasingly been reported in clinical practice as well as in studies.[4,6,7,35-38] Depressive symptoms are a known predictor of QoL in sarcoidosis.[4,38] A novel finding is that not only depressive symptoms, but also trait anxiety and subjective cognitive failure predicted QoL in our sarcoidosis sample. The association between cognitive failure and QoL disappeared when we included fatigue and depressive symptoms as mediators (see Figure 9.3A and 9.3B). This may imply multiple competing interpretations. First, cognitive failure presumably results in more depressive symptoms or fatigue, which in turn results in a lower physical QoL. This is in line with a previous study by Hendriks et al. who found that cognitive failure predicted fatigue.[5] Alternatively, it could indicate that depressive

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symptoms or fatigue causally affect both cognitive failure and physical QoL. Since we also found significant moderating effects between cognitive failure and depressive symptoms as well as fatigue on physical QoL there may also be a moderating mechanism underlying the associations between these variables. This hypothesis was also supported by a previous study by our group in neurosarcoidosis patients, showing fatigue to be a strong predictor of cognitive impairment.[39] Studies in dialysis patients also found that depressive symptoms predicted cognitive impairment.[40,41] As follow-up data were lacking in our study and cross-sectional studies generally have limitations with regard to establishing causality, the results have to be interpreted with some caution, and future follow-up studies are warranted to distinguish between these two interpretations for sarcoidosis patients.

To date, studies have shown a high prevalence of fatigue[8,12,42-45] and SFN-associated symptoms[46,47] in sarcoidosis patients. In line with previous studies,[13-15] our study found that sarcoidosis-associated fatigue was negatively associated with overall QoL, as well as the physical and psychological QoL domains, indicating that these QoL domains tend to decrease as patient fatigue increases. Of the partners, only 15% experienced fatigue (mainly moderate; 30/31 partners) in comparison with 78% of the sarcoidosis patients. Whether the moderate fatigue in a small proportion of partners might be caused by their own disabilities and/or health problems needs to be explored in future studies. In agreement with earlier studies, a substantial number of our sarcoidosis sample were suffering from SFN-associated symptoms.[31,46,47] SFN is a very difficult disease to diagnose and to treat.[48] This causes a lot of uncertainty and frustration for those having to deal with these problems. The presence of SFN-associated symptoms was found to be negatively associated with the physical and environmental QoL domains, indicating that physical and environmental QoL tends to decrease when patients experience more SFN-associated complaints. This could, at least partly, be explained by the fact that patients feel they are not being taken seriously by relatives and friends, and experience misunderstanding because of lack of awareness of sarcoidosis and SFN.

The clinical course of sarcoidosis is highly variable, ranging from spontaneous resolution to disabling chronic disease with various manifestations.[49] In our cohort, no relation was found between the various manifestations and QoL (data not shown), stressing the importance of assessing not only the organs affected by sarcoidosis but also the non-specific symptoms.[5,31]

All of the above-mentioned non-specific symptoms are not visible in sarcoidosis patients, making it difficult for them to get acknowledged, leading to feelings of

misunderstanding in many patients and even their partners.[17] Sarcoidosis patients have reported that QoL is the most important outcome of their treatment and of care, more important than radiographs, pulmonary function tests and blood tests.[32] Most patients would like to see more attention and support for their psychological problems.[17] We also found that patients with better support show a better QoL in all domains, except for physical health. Moreover, although it was beyond the scoop of this study, it would be interesting to evaluate how not living with a partner might influence the QoL of sarcoidosis patients.

Sarcoidosis clinicians usually work in a multidisciplinary team. Our results underline the importance of a multidisciplinary approach assessing not only organ involvement, but any symptoms (organ-related or non-organ-related) and of using a holistic approach with attention to psychological support, for both patients and their partners. One of the possible interventions could be mindfulness-based exercise interventions, which have been found to reduce psychological symptoms and fatigue.[50]

A limitation of the present study was that all patients were recruited in a tertiary referral center. This could have led to selection bias, since it is the more complex patients (in terms of affected organs and symptoms) who are often referred to tertiary referral centers. Hence, our results may not be generalizable to all sarcoidosis patients. However, our results are comparable with those of other QoL studies in sarcoidosis patient samples. Another limitation is that not all partners of the patients with sarcoidosis seen at the outpatient clinic participated in this study, and some patients did not have a partner. However, the sample of sarcoidosis patients whose partners participated did not differ from those without a partner or with a partner who did not participate in our study (except for age). Unfortunately, information on the medical health status of the partners was not collected in this study. It is tempting to speculate that this explains for the lower QoL of the partners compared to healthy controls. Though, the QoL of partners was higher than the QoL of the sarcoidosis patients. Strikingly, however, no relation was found between the QoL of the partners and the burden of the sarcoidosis experienced by the patients themselves indicating that this does not have an impact on the QoL of their partners. One final limitation was the fact that we did not have a matched control group, and that the sample of healthy controls used in our study was rather small, which might increase the influence of sampling error on the estimated statistics in the control sample. Our control group did consist of persons living in the same geographical area/institution and timeframe, and was previously used by our group for similar comparisons in previous studies.[13,19,44]

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Conclusion

Couples living with sarcoidosis have a lower QoL than healthy controls. Sarcoidosis patients often struggle with fatigue, SFN-associated symptoms, anxiety, depressive symptoms, and memory and concentration problems. All these symptoms have a negative impact on the QoL of patients, but not on that of their partners. Although these factors pose challenges for objective assessment, they are recognized illness-related symptoms meriting formal consideration with validated instruments. Perceived social support positively impacts on the QoL. Further studies are needed to investigate whether offering psychosocial support at the outpatient clinic for sarcoidosis patients as well as their partners would lead to better coping strategies and improve QoL for both of them.

References

1   Drent M, Strookappe B, Hoitsma E and De Vries J. Consequences of sarcoidosis. Clin Chest Med 2015;36:727-37.

2   Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 1999;160:736-55.

3   de Kleijn WP, Drent M and De Vries J. Nature of fatigue moderates depressive symptoms and anxiety in sarcoidosis. Br J Health Psychol 2013;18:439-52.

4   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.

5   Hendriks C, Drent M, De Kleijn W, et al. Everyday cognitive failure and depressive symptoms predict fatigue in sarcoidosis: a prospective follow-up study. Respir Med 2018;138S:S24-S30.

6   Hinz A, Brahler E, Mode R, et al. Anxiety and depression in sarcoidosis: the influence of age, gender, affected organs, concomitant diseases and dyspnea. Sarcoidosis Vasc Diffuse Lung Dis 2012;29:139-46.

7   Holas P, Krejtz I, Urbankowski T, et al. Anxiety, its relation to symptoms severity and anxiety sensitivity in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2013;30:282-8.

8   Jastrzebski D, Ziora D, Lubecki M, et al. Fatigue in sarcoidosis and exercise tolerance, dyspnea, and quality of life. Adv Exp Med Biol 2015;833:31-6.

9   Arkema EV, Eklund A, Grunewald J and Bruze G. Work ability before and after sarcoidosis diagnosis in Sweden. Respir Med 2018; 144S:S7-S12.

10   Rice JB, White A, Lopez A, et al. Economic burden of sarcoidosis in a commercially-insured population in the United States. J Med Econ 2017;20:1048-55.

11   Hendriks CMR, Saketkoo LA, Elfferich MDP, et al. Sarcoidosis and work participation: the need to develop a disease-specific core set for assessment of work ability. Lung 2019.

12   Aggarwal AN, Sahu KK and Gupta D. Fatigue and health-related quality of life in patients with pulmonary sarcoidosis treated by oral corticosteroids. Sarcoidosis Vasc Diffuse Lung Dis 2016;33:124-9.

13   Drent M, Marcellis R, Lenssen A and De Vries J. Association between physical functions and quality of life in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:117-28.

14   Michielsen HJ, Drent M, Peros-Golubicic T and De Vries J. Fatigue is associated with quality of life in sarcoidosis patients. Chest 2006;130:989-94.

15   Michielsen HJ, Peros-Golubicic T, Drent M and De Vries J. Relationship between symptoms and quality of life in a sarcoidosis population. Respiration 2007;74:401-5.

16   Wirnsberger RM, de Vries J, Breteler MH, et al. Evaluation of quality of life in sarcoidosis patients. Respir Med 1998;92:750-6.

17   Moor CC, van Manen MJG, van Hagen PM, et al. Needs, perceptions and education in sarcoidosis: a live interactive survey of patients and partners. Lung 2018;196:569-75.

18   De Kleijn W. Fatigue in sarcoidosis. Edited by. Tilburg: Tilburg University; 2012.

19   Marcellis RG, Lenssen AF, Kleynen S, et al. Exercise capacity, muscle strength, and fatigue in sarcoidosis: a follow-up study. Lung 2013;191:247-56.

20   Development of the world health organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. Psychol Med 1998;28:551-8.

21   De Vries J, Michielsen H, Van Heck GL and Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol 2004;9:279-91.

22   Hoitsma E, De Vries J and Drent M. The small fiber neuropathy screening list: construction and cross-validation in sarcoidosis. Respir Med 2011;105:95-100.

23   Broadbent DE, Cooper PF, FitzGerald P and Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol 1982;21 (Pt 1):1-16.

24   Van der Ploeg HM, Defares PB, Spielberger CD. A Dutch-Language adaptation of the Spielberger State-Trait Anxiety Inventory. Lisse, The Netherlands: Swets & Zeitlinger; 1980.

9

25   Radloff L. The CESD-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1977;1:385-401.

26   De Vries J. The Perceived Social Support Scale, Dutch version. Tilburg, The Netherlands: Tilburg University; 1998.

27   Baron RM and Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-82.

28   Brand C, Barry L and Gallagher S. Social support mediates the association between benefit finding and quality of life in caregivers. J Health Psychol 2016;21:1126-36.

29   Nightingale CL, Curbow BA, Wingard JR, et al. Burden, quality of life, and social support in caregivers of patients undergoing radiotherapy for head and neck cancer: a pilot study. Chronic Illn 2016;12:236-45.

30   Antoniou KM, Tzanakis N, Tzouvelekis A, et al. Quality of life in patients with active sarcoidosis in Greece. Eur J Intern Med 2006;17:421-6.

31   Voortman M, Hendriks CMR, Elfferich MDP, et al. The burden of sarcoidosis symptoms from a patient perspective. Lung 2019;197:155-161.

32   Baughman RP, Barriuso R, Beyer K, et al. Sarcoidosis: patient treatment priorities. ERJ Open Res 2018; 4.

33   Gerke AK, Judson MA, Cozier YC, et al. Disease burden and variability in sarcoidosis. Ann Am Thorac Soc 2017;14:S421-8.

34   Tan JY, Molassiotis A, Lloyd-Williams M and Yorke J. Burden, emotional distress and quality of life among informal caregivers of lung cancer patients: an exploratory study. Eur J Cancer Care (Engl) 2018; 27.

35   Chang B, Steimel J, Moller DR, et al. Depression in sarcoidosis. Am J Respir Crit Care Med 2001;163:329-34.

36   Elfferich MD, De Vries J and Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2011;28:65-71.

37   Elfferich MD, Nelemans PJ, Ponds RW, et al. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. Respiration 2010;80:212-9.

38   Goracci A, Fagiolini A, Martinucci M, et al. Quality of life, anxiety and depression in sarcoidosis. Gen Hosp Psychiatry 2008;30:441-5.

39   Voortman M, De Vries J, Hendriks CMR, et al. Everyday cognitive failure in patients suffering from neurosarcoidosis. Sarcoidosis Vasculitis and Diffuse Lung Diseases 2019;36: 2-10.

40   Zhang YH, Yang ZK, Wang JW, et al. Cognitive changes in peritoneal dialysis patients: a multicenter prospective cohort study. Am J Kidney Dis 2018;72:691-700.

41   Jung S, Lee YK, Choi SR, et al. Relationship between cognitive impairment and depression in dialysis patients. Yonsei Med J 2013;54:1447-53.

42   Bosse-Henck A, Koch R, Wirtz H and Hinz A. Fatigue and excessive daytime sleepiness in sarcoidosis: prevalence, predictors, and relationships between the two symptoms. Respiration 2017;94:186-97.

43   Drent M, Lower EE and De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012;40:255-63.

44   Marcellis RG, Lenssen AF, Elfferich MD, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J 2011;38:628-34.

45   Strookappe B, De Vries J, Elfferich M, et al. Predictors of fatigue in sarcoidosis: the value of exercise testing. Respir Med 2016;116:49-54.

46   Bakkers M, Merkies IS, Lauria G, et al. Intraepidermal nerve fiber density and its application in sarcoidosis. Neurology 2009;73:1142-8.

47   Hoitsma E, Drent M, Verstraete E, et al. Abnormal warm and cold sensation thresholds suggestive of small-fibre neuropathy in sarcoidosis. Clin Neurophysiol 2003;114:2326-33.

48   Voortman M, Fritz D, Vogels OJM, et al. Small fiber neuropathy: a disabling and underrecognized syndrome. Curr Opin Pulm Med 2017;23:447-57.

49   Schupp JC, Freitag-Wolf S, Bargagli E, et al. Phenotypes of organ involvement in sarcoidosis. Eur Respir J 2018;51.

50   Saketkoo LA, Karpinski A, Young J, et al. Feasibility, utility and symptom impact of modified mindfulness training in sarcoidosis. ERJ Open Res 2018;4.

Online supplement questionnaires

1. The WHOQoL-Bref is a generic, cross-culturally developed comprehensive measure of QoL. It consists of 24 questions in four domains (physical health, psychological health, social relationships and environment) related to QoL and two questions that assess overall QoL and general health.[18] The response scale is a five-point scale (1=very poor/not at all/very dissatisfied/ never, to 5=very good/extreme amount/extremely/completely/very satisfied/always). Higher score indicates a better Qol.

2. The FAS is a 10-item self-report fatigue questionnaire. In addition to the total fatigue score, the FAS yields a mental fatigue score and a physical fatigue score. The response scale is a five-point scale (1=never, to 5=always; range 10-50). A score >22 indicates fatigue and a score >34 indicates extreme fatigue. The FAS shows good reliability and validity in measuring the fatigue of sarcoidosis patients.[19]

3. The SFNSL is a 21-item self-administered questionnaire to screen for symptoms related to SFN. The response scale is a five-point scale (0=never/not, to 4=always/severe; range 0 to 84). The cut-off score for the SFNSL is 11: a score below 11 indicates few or no SFN-related symptoms (normal temperature threshold testing [TTT]), while a score of 11-48 indicates probable or highly likely SFN, and a score above 48 is indicative of SFN (abnormal TTT).[20]

4. The CFQ is a self-report questionnaire consisting of 25 items assessing deficits regarding attention, perception, memory and motor functioning in everyday life. The response scale is a five-point scale (0=never, to 4=very often; range 0-100). A higher total score indicates more subjective cognitive failure. A high CFQ score is defined as a score ≥43.[21]

5. The STAI concerns differences between individuals in their disposition to respond to stressful situations with varying amounts of stress. This scale consists of 20 statements, asking patients to describe how they generally feel. The response scale is a four-point scale (1=not at all, to 4=very much so; range 20-80). A higher score indicates more anxiety. The psychometric characteristics of the Dutch version of this questionnaire are well established and considered good.[22] High trait anxiety was defined as a score above 40, based on Dutch norm scores.[22]

6. The CES-D[23] is a 20-item scale designed to measure the presence and degree of depressive symptoms. Scores on the CESD can range from 0-60, in which a higher score indicates more depressive symptoms. The response scale is a four-point scale (0=rarely/never, to 3=mostly/always; range 0-60). Scores ≥16 are indicative of a depressive disorder. Reliability and criterion validity appear to be good.[50]

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7. The PSSS12 was used, concerning 12 items. The total score of the 12-item version of the PSSS was used to assess general perception of social support. The response scale is a seven-point scale (1=very strongly disagree, to 7=very strongly agree; range 12-84). The PSSS has good reliability and validity in patients undergoing coronary angiography,[51] and has been translated into Dutch.[24]