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Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis

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Summary
Background: Although sarcoidosis most commonly affects the lungs, it is a multisystemic disease that often involves other organs. In this study, we compared fatigue, dyspnea, and the impact upon the activities of daily living and health status scores between patients with isolated pulmonary and pulmonary plus extrapulmonary sarcoidosis.
Methods: In this cross-sectional study, we investigated 81 biopsy proven sarcoidosis patients. Fatigue was assessed by the standardized Fatigue Scale (FS). Dyspnea was determined by the Baseline Dyspnea Index (BDI) and the Modified Medical Research Council (MRC) Dyspnea Scale. Activities of daily living were assessed with the List of Daily Activities (DAL). Health status was measured by two standardized questionnaires: a generic measure — fifteen-dimensional measure of health-related quality of life (15D), and a respiratory-specific measure — St George's Respiratory Questionnaire (SGRQ). Patients were excluded if they had an associated illness that could influence their health status.
Results: Statistically significant differences were demonstrated between the isolated pulmonary group and the pulmonary plus extrapulmonary group for fatigue (FS—total score: 2.4 ± 0.64 vs. 2.8 ± 0.62, $p = 0.007$), dyspnea (BDI: 8.45 ± 2.44 vs. 5.92 ± 1.84, $p < 0.001$; there was no statistically significant difference in MRC), activities of daily living

Abbreviations: ACCESS, a case control etiology of sarcoidosis study; BDI, Baseline Dyspnea Index; DAL, List of Daily Activities; FS, Fatigue Scale; MRC, Modified Medical Research Council Dyspnea Scale; SGRQ, The St George's respiratory questionnaire; 15D, Fifteen-dimensional measure of health-related quality of life.

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(DAL: 4.33 ± 2.93 vs. 5.87 ± 2.40, $p = 0.014$), and health status (SGRQ—total score: 33.07 ± 22.81 vs. 43.69 ± 21.55, $p = 0.04$).
Conclusion: There are significant and clinically relevant differences in the severity of symptoms, restrictions of activities of daily living and impairment of health status between the patients with isolated pulmonary and pulmonary plus extrapulmonary sarcoidosis. Patients with pulmonary plus extrapulmonary sarcoidosis are more impaired in all these categories.
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Introduction

Sarcoidosis is a chronic multisystemic disease that is most commonly present in the lungs but may involve any organ.[1,2]

Patients with pulmonary sarcoidosis may have symptoms related directly to the chest such as cough, dyspnea on exertion, chest pain, chest discomfort, and wheeze. Patients may also develop symptoms related to extrapulmonary organ involvement. In addition, sarcoidosis may cause constitutional symptoms such as fever, anorexia, weight loss, generalized weakness, fatigue, and pain that are not attributable to involvement of any specific organ. Fatigue is a major concern of sarcoidosis patients that influences their health status and the quality of life.[3,4]

Health status is a subjective parameter that is being used more frequently to assess health interventions. Questionnaires have been developed, both generic and disease-specific, to assess health status.

Differences in patients reported outcomes between sarcoidosis patients with isolated pulmonary involvement and those with extrapulmonary manifestations have not been well described. We hypothesized that sarcoidosis patients with pulmonary plus extrapulmonary involvement would have more severe fatigue, be more limited in activities of daily living and have a more severe impairment in health status. However, we expected dyspnea to be similar in those with isolated pulmonary involvement and those with pulmonary plus extrapulmonary involvement.

The aim of this study was to assess the differences of the severity of fatigue and dyspnea symptoms, activities of daily living and health status between the patients with isolated pulmonary and those with pulmonary plus extrapulmonary sarcoidosis.

Methods

This cross-sectional study was conducted at the Institute for Lung Diseases and Tuberculosis of the Clinical Center of Serbia in Belgrade over the period from October 2006 to March 2007. We examined 81 consecutive patients with biopsy proven pulmonary sarcoidosis. They all had noncaseating epithelioid cell granulomas on their lung biopsy specimens without a known cause being identified. All subjects were ≥18 years old, and did not have any associated illnesses that could influence their health status (those with significant comorbidity, like cardiac or respiratory disorders, were excluded from analysis). Subjects who did not understand the questions from any of the symptoms or health status administered questionnaires were also excluded.

We classified patients into two groups according to the organs affected by sarcoidosis. The first group consisted of patients with isolated pulmonary involvement. The second group consisted of patients who in addition to pulmonary involvement had extrapulmonary sarcoidosis in one or more additional organs on the basis of clinical, radiographic or pathologic criteria. The investigators who classified the patients as having isolated pulmonary or pulmonary plus extrapulmonary sarcoidosis had extensive clinical experience with the diagnosis and clinical management of sarcoidosis patients.

Study subjects underwent a physical examination, pulmonary function testing, and completed questionnaires for fatigue, dyspnea, activities of daily living, and health status measurement. This study was approved by the institution's institutional review board and patients' consent obtained.

Fatigue measurement

Fatigue was assessed by the standardized *Fatigue Scale*.[5] This scale contains 14 questions and distinguishes mental fatigue (with six items) that describes cognitive difficulties, and physical fatigue (eight items). A total fatigue score is also calculated. Each fatigue score ranges from 1 to 4. Higher scores correspond with more severe fatigue. The scale was found to be both reliable and valid[5] and has shown sensitivity to treatment changes.[6]

Dyspnea questionnaires

Dyspnea was measured by two standardized questionnaires: the Baseline Dyspnea Index (BDI)[7] and the Modified Medical Research Council (MRC) Dyspnea Scale.[8]

The BDI partitions dyspnea into three components: degree of the functional impairment, level of the activity, and the level of effort required to develop dyspnea. Each component is graded on a five-point rating scale from 0 ('extreme impairment') to 4 ('without impairment'); therefore the total BDI score can range from 0 to 12.

The MRC scale classifies subjects into one of five categories according to their degree of dyspnea when performing certain activities.[8] Scores range from 0 to 4, with the higher scores indicating more severe dyspnea.

Activities of daily living

The degree of limitation in activities of daily living was evaluated with the List of Daily Activities (DAL), a scale that was originally designed by Stewart and coworkers.[9] It has 11 items that are related to the usual activities that

persons with good health can perform without particular effort. The number of positive responses comprises the DAL score and indicates the degree of impairment. The scale has been used in several studies in patients with chronic pulmonary diseases.[10]

Patient health status

We used two standardized questionnaires for the measuring of health status: a generic measure — the fifteen-dimensional measure of health-related quality of life (15D)[11] and a respiratory-specific measure — the St George's Respiratory Questionnaire (SGRQ).[12]

15D is a multiattributive instrument for measurement of health-related quality of life.[11] It was developed and validated in a large Finnish population. It consists of 15 different and mutually exclusive health dimensions, each represented by one item.[13,14] The total questionnaire score ranges between 0 and 1, where 1 signifies the highest level of health status. 15D was used in different diseases in many different countries. The Serbian version of 15D was previously used in patients with asthma where it demonstrated good psychometric measurement properties.[15]

SGRQ is an instrument that was originally designed to measure the health status of COPD patients.[12] Its validity, reliability, and responsiveness were also shown in other pulmonary diseases. The questionnaire consists of 50 items with 76 responses, and encompasses three domains of health status: (1) *symptoms*, focusing on distress because of respiratory symptoms, (2) *activities*, measuring decreased mobility or physical activity and (3) *impacts*, measuring the psychosocial influence of disease on the everyday life and patients' well being. Scores of these domains, as well as the total score, are scaled from 0 to 100, where higher scores represent poorer health status.

Pulmonary function

Pulmonary function measurements included forced expiratory vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), peak expiratory flow (PEF) measured with a pneumotachograph (Masterlab, Jaeger, Wurzburg, Germany), and total lung capacity (TLC) measured using the helium dilution technique (Masterlab, Jaeger, Wurzburg, Germany). The transfer factor of the lung for carbon monoxide (T_{LCO}) was measured using the single-breath method (Masterlab, Jaeger, Wurzburg, Germany).

Statistical analysis

Statistical analysis was performed using the standard computer statistical package (''SPSS 10.0 for Windows'', 1999). Values were expressed as mean $\pm$ 1 standard deviation (SD). Differences of mean values of clinical variables (symptoms, activities of daily living and health status scores) between patients groups were measured by means of *t*-Test for independent samples. A probability value of $p < 0.05$ was considered to be statistically significant, and $p < 0.01$ highly statistically significant.

Results

The demographic characteristics, forced expiratory volume in 1 s (FEV_1) predicted, symptoms, activities of daily living and health status scores of the study patients are presented in Table 1. The average disease duration was 14.8 years, and mean value of FEV_1 was 106.9 $\pm$ 18.6% predicted.

The total time required to complete the fatigue and dyspnea questionnaires, DAL and health status questionnaires ranged from 30 to 45 min. Patients' positive responses on the DAL are presented in Table 2. More than half patients gave affirmative answers to 7 out of 11 items on DAL scale. These results show that most sarcoidosis patients had significant impairment in their activities of daily living despite the fact that most had normal spirometry (Table 1).

There were 49 patients with isolated pulmonary involvement and 32 patients with pulmonary plus extrapulmonary sarcoidosis (Table 3). There was no significant difference in age or gender frequency between the pulmonary and pulmonary plus extrapulmonary groups (Table 3). The frequencies of the extrapulmonary organ involvement with sarcoidosis are presented in Fig. 1. The skin and neurologic system were the most frequent locations of extrapulmonary disease.

A statistically significant difference was found between the average of all fatigue scores, BDI scores, DAL scores, and total and activity domain SGRQ scores with regard to

Table 1 Characteristics of patients ($N = 81$), symptoms and health status scores

	$X \pm$ SD	Range
Sex, m/f	20/61	
Age, years	48.15 $\pm$ 11.25	18—70
Disease duration, years	14.81 $\pm$ 8.08	1—40
FEV_1 (% predicted)	106.88 $\pm$ 18.58	71—153
Fatigue scores		
FS—TS	2.56 $\pm$ 0.66	1.07—4
FS—PS	2.65 $\pm$ 0.73	1—4
FS—MS	2.43 $\pm$ 0.72	1—4
Dyspnea scores		
BDI	7.39 $\pm$ 2.53	2—12
MRC	1.35 $\pm$ 1.10	0—4
DAL	4.92 $\pm$ 2.82	0—9
SGRQ		
Total score	37.43 $\pm$ 22.77	0—90.51
Symptoms	39.32 $\pm$ 24.03	0—90.40
Activities	46.37 $\pm$ 26.32	0—100
Impacts	31.73 $\pm$ 24.40	0—93.02
15D	0.76 $\pm$ 0.16	0.31—1.00

N = number of patients; X = mean; SD = standard deviation; FS—TS = Fatigue Scale—total score; FS—PS = Fatigue Scale—physical component score; FS—TS = Fatigue Scale—mental component score; BDI = Baseline Dyspnea Index; MRC = Modified Medical Research Council Dyspnea Scale; DAL = List of Daily Activities; and SGRQ = The St George's Respiratory Questionnaire.

Table 2 Percentage of patient positive responses on the List of Daily Activities Questions ($N = 78$)

	Questions	Affirmative responses, %
1	Do you need help with eating, dressing, bathing, or using the lavatory because of your health?	3.8
2	Are you in bed or a chair for most or all of the day because of your health?	1.3
3	When you travel around in our community, does someone have to assist you because of your health?	15.4
4	Do you have to stay indoors most or all of the day because of your health?	25.6
5	Does your health keep you from working at a job or doing work around the house?	53.8
6	Are you unable to do certain kinds or amounts of work or housework or do you have to work part-time because of your health?	64.1
7	Do you have any trouble either walking one block or climbing one flight of stairs (without shopping bags) because of your health?	50
8	Do you have troubles bending, lifting, or stooping because of your health?	62.8
9	Does your health limit you in any way from doing anything you want to do?	71.8
10	Does your health limit the kind of vigorous activities you can do, such as running or lifting heavy objects?	82.1
11	Do you have any trouble either walking several blocks or climbing a few flights of stairs (without shopping bags), because of your health?	61.5

the patient groups such that the pulmonary plus extrapulmonary group was more impaired than the isolated pulmonary group (Table 4). Differences between symptoms and impacts domain SGRQ scores, MRC dyspnea scores and 15D scores did not reach the statistical significance.

We did not find a significant difference of any pulmonary function parameter between the patients with isolated pulmonary and pulmonary plus extrapulmonary sarcoidosis (Table 3).

Discussion

The present study showed that sarcoidosis patients with pulmonary and extrapulmonary manifestations of sarcoidosis are more fatigued, more dyspneic, have poorer health status, and more impairment of activities of daily living than those with pulmonary involvement alone.

Fatigue is a common symptom of sarcoidosis. It has been hypothesized that fatigue from sarcoidosis is caused by inflammatory mediators released from the granulomatous

Table 3 Demographs and pulmonary function tests' values of patients with isolated pulmonary and pulmonary plus extrapulmonary sarcoidosis

	$X \pm$ SD, pulmonary sarcoidosis group	$X \pm$ SD, pulmonary plus extrapulmonary sarcoidosis group	t	p
N	49	32		
Sex, m/f (%)[a]	16/33 (33/67)	4/28 (12/88)		
Age, years	47.78 ± 11.18	48.41 ± 11.56	0.243	0.809
Spirometry tests				
FVC (L)	3.80 ± 1.03	3.84 ± 1.13	0.143	0.887
FVC (% predicted)	110.96 ± 17.93	116.50 ± 13.97	1.549	0.125
FEV_1 (L)	3.06 ± 0.95	3.02 ± 1.02	−0.199	0.843
FEV_1 (% predicted)	105.73 ± 18.56	108.59 ± 18.76	0.672	0.504
PEF (L/s)	8.47 ± 3.17	7.49 ± 1.90	−1.572	0.120
PEF (% predicted)	116.69 ± 24.35	110.84 ± 19.77	−1.179	0.242
TLC (L)	5.39 ± 1.11	5.42 ± 1.13	0.127	0.899
TLC (% predicted)	98.38 ± 13.13	103.22 ± 11.72	1.725	0.089
T_{LCO} (mmol/min/kPa)	7.54 ± 2.19	7.29 ± 1.71	−0.568	0.572
T_{LCO} (% predicted)	86.04 ± 14.27	85.69 ± 15.11	−0.105	0.917

N = number of patients; X = mean; SD = standard deviation; and t = t-Test for independent samples.
[a] Chi-square test value 3.214, $p > 0.05$.

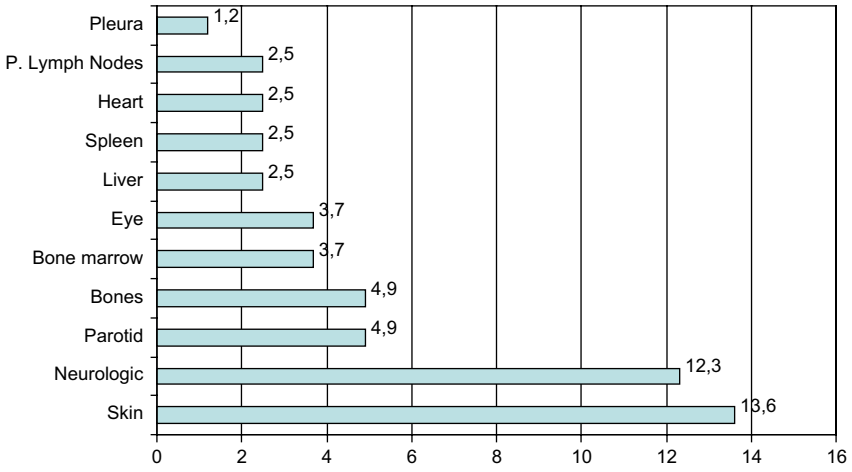

Figure 1 Extrapulmonary sarcoidosis — % of all 81 patients.

inflammation.[16] Pain also appears to be related to fatigue in sarcoidosis.[17] Pain itself and the resultant lack of mobility from pain may also contribute to fatigue. In addition, fatigue and depression may occur with sarcoidosis involvement of the central nervous system,[18] which was a frequent extrapulmonary manifestation in our patient population (12.3%). Pain, lack of mobility, depression, and central nervous system involvement with sarcoidosis might explain why fatigue was more severe in those patients with pulmonary and extrapulmonary sarcoidosis than in the group with isolated pulmonary involvement. However since pain, lack of mobility, and depression were not measured in this study, this postulation remains conjectural.

The DAL measures the ability to perform various daily activities such as eating, dressing, bathing, using the lavatory, walking, and climbing. These activities could be influenced by many extrapulmonary organs that are commonly affected by sarcoidosis including the nervous system, skin, and bones. This could explain our findings that the activities of daily living were more impaired in the pulmonary plus extrapulmonary group compared to the isolated pulmonary group.

Health status is a broad concept that is influenced by numerous factors including many extrapulmonary ones. It is likely that constitutional symptoms of sarcoidosis and extrapulmonary organ involvement contributed to

Table 4 Differences between symptoms, activities of daily living and health status scores between patients with isolated pulmonary ($N = 49$) and pulmonary plus extrapulmonary sarcoidosis ($N = 32$)

	$X \pm SD$, pulmonary sarcoidosis group	$X \pm SD$, pulmonary plus extrapulmonary sarcoidosis group	t	p
Fatigue scores				
FS—TS	2.40 ± 0.64	2.80 ± 0.62	2.797	0.007
FS—PS	2.47 ± 0.72	2.93 ± 0.66	2.924	0.005
FS—MS	2.31 ± 0.65	2.63 ± 0.79	2.015	0.047
Dyspnea scores				
BDI	8.45 ± 2.44	5.92 ± 1.84	−4.479	<0.000
MRC	1.13 ± 1.26	1.67 ± 1.07	1.844	0.070
DAL	4.33 ± 2.93	5.87 ± 2.40	2.405	0.014
SGRQ				
Total score	33.07 ± 22.81	43.69 ± 21.55	2.090	0.040
Symptoms	37.32 ± 26.21	42.19 ± 20.56	0.880	0.382
Activities	40.17 ± 26.46	55.27 ± 23.77	2.633	0.010
Impacts	27.69 ± 23.83	37.55 ± 24.39	1.772	0.081
15D	0.78 ± 0.17	0.73 ± 0.13	−1.637	0.106

N = number of patients; X = mean; SD = standard deviation; t = t-Test for independent samples; FS—TS = Fatigue Scale—total score; FS—PS = Fatigue Scale—physical component score; FS—TS = Fatigue Scale—mental component score; BDI = Baseline Dyspnea Index; MRC = Modified Medical Research Council Dyspnea Scale; DAL = List of Daily Activities; and SGRQ = The St George's Respiratory Questionnaire.

functional limitation and consequently had an important influence on health status. It is therefore not surprising that health status is more impaired in the pulmonary plus extrapulmonary group of sarcoidosis patients compared to those with isolated pulmonary involvement.

Our results showed that those with pulmonary plus extrapulmonary sarcoidosis had statistically and clinically significant worse health status in terms of SGRQ score than those with isolated pulmonary sarcoidosis. This is an interesting finding since the SGRQ is a respiratory-specific questionnaire. One possible explanation for this is that several items of the questionnaire relate to physical activities and the impact of disease on the patients' level of functioning. It is possible that extrapulmonary manifestations of sarcoidosis negatively impacted upon these items. The 15D, a generic measure of health status, did not show a statistically significant difference between the isolated pulmonary and pulmonary plus extrapulmonary groups, although the mean score reflected poorer health status in the latter group. The total SGRQ score (mean score $\pm$ SD: 37.4 ± 22.8) of our patients was comparable with a previous study of chronic sarcoidosis patients by Cox et al. (44 ± 23).[19] The total SGRQ mean score in our patients was somewhat less than the mean score (46, standard deviation not reported) in the recently published study by Baughman and coworkers.[20] However, their study population had a higher frequency of extrapulmonary involvement (73%), as compared to our patients (39.5%). This difference in the frequency of extrapulmonary sarcoidosis between the two studies probably explains the differences in the SGRQ scores.

We expected dyspnea to be similar in those with isolated pulmonary involvement and those with pulmonary plus extrapulmonary involvement. However, we found that dyspnea was more severe in the latter group. This was demonstrated using the BDI measure but not the MRC. Unlike the BDI, the MRC only addresses the level of activities that leads to dyspnea without consideration of the associated effort necessary for the performance of particular activity.[21] Furthermore, only the BDI assesses the degree of the functional impairment, which represents an important consequence of dyspnea. Since the patients' perception of dyspnea depends on the physical activities and effort they require in order to feel the breathless, those patients who have involvement of both lungs and other organ(s) may be more dyspneic because they are more functionally limited.

Although our patients were fatigued, had significant dyspnea, perceived limitations in their physical activities, and had a poor health status, they had normal pulmonary function. This confirms previous studies demonstrating that pulmonary function testing cannot function as a surrogate for these other parameters and cannot be used to assess the overall health of sarcoidosis patients.[22,23]

One limitation of this study is that the data were collected in a tertiary care setting, i.e. a specialised referral clinic for sarcoidosis patients. Based on the clinical and radiographic criteria (62.2% of the patients had radiographic stage 2 or higher), our patients had predominantly severe forms of the disease and the scores for all patient reported outcomes were probably more severe than for the average sarcoidosis patient. Therefore, our results may not be generalizable to patients in primary care settings. In addition, 80.5% of our study patients were receiving corticosteroid therapy, and this may have had a positive or negative impact upon their health status and other measured variables. Although we excluded subjects from this study with severe overt comorbidity, our results may have also been affected by unmeasured comorbidities. Finally, our criteria for the presence of extrapulmonary sarcoidosis were not standardized. We used clinical, radiographic, and pathologic criteria to define subjects as having extrapulmonary involvement. Although this classification is arguably subjective, it was performed by individuals with expertise in the clinical assessment of sarcoidosis patients (B.S.G., V.M.V.). Furthermore even a standardized measure of organ involvement such as the A Case Control Etiology of Sarcoidosis Study (ACCESS) instrument[24] relies somewhat upon the subjective clinical judgment of the assessor. In addition, the assignment of subjects in the two groups was made a priori so that it should not have influenced the study results.

We conclude that patients with pulmonary and extrapulmonary sarcoidosis are more fatigued, have more dyspnea, are more limited in their everyday physical activities, and have lower health status in comparison with those with isolated pulmonary involvement. We propose several mechanisms to explain these differences. However, our explanations remain conjectural and are potential fruitful areas for future research.

Conflict of interest statement

All authors did not disclose any potential conflicts of interest.

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