SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2012; 29; 139-146

Anxiety and depression in sarcoidosis: the influence of age, gender, affected organs, concomitant diseases and dyspnea

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Abstract. *Background*: Heightened degrees of anxiety and depression are often found in patients suffering from sarcoidosis, but the reasons for that are unclear. Furthermore, age and gender differences of anxiety and depression in sarcoidosis have not been reported with reference to normative data. *Objectives*: The aim was to test age and gender differences of anxiety and depression in a large sample, and to examine the influence of affected organs, concomitant diseases and dyspnea. *Methods*: 1197 German patients diagnosed with sarcoidosis were examined, using the Hospital Anxiety and Depression Scale (HADS) and the MRC dyspnea scale. *Results*: Patients suffering from sarcoidosis were significantly more anxious and depressed than the general population. This effect was especially strong in young age groups. The number of affected organs, the number of concomitant diseases and the degree of dyspnea significantly predicted anxiety and depression scores in univariate analyses. Among the affected organs, muscles, nerves, and bones most significantly contributed to depression. Sleep apnea, restless legs syndrome, and arterial hypertension were associated with anxiety as well as depression. In multivariate analyses including age and gender, however, only dyspnea and the number of concomitant diseases remained predictors of anxiety and depression scores. *Conclusions*: The analysis of mental distress should take into account comparisons with normative values. Young patients deserve special social support. Dyspnea proved to be an important symptom in the prediction of anxiety and depression. *(Sarcoidosis Vasc Diffuse Lung Dis 2012; 29: 139-146)*

Key words: mental distress, sarcoidosis, dyspnea, age differences, anxiety, depression

Introduction

Sarcoidosis is an inflammatory disease of unknown etiology that is characterized by multiple organ system manifestations (1). Typical symptoms are fatigue, cough, chest pain, and dyspnea. Patients suffering from sarcoidosis generally report diminished quality of life (2-5) and heightened degrees of depression. A study performed in the U.S. found a 60% prevalence of depression, measured with the CES-D and a cut-off ≥ 9 (6). Using the same instrument, another U.S. study detected an even higher prevalence of 66% (2). One Dutch study (7) reported 18% depression on the basis of the Beck Depression Inventory (BDI, cut-off ≥ 15), another Dutch study with 75 patients used the Beck Depression Inventory for Primary Care (BDI-pc) and found only 3 patients (4%) with a score above 4, indicating clinical depression (8). In New Zealand, the prevalence of depres-

Received: 26 January 2012
Accepted after Revision: 9 June 2012
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sion in a sample of 81 patients was 23%, assessed with the Hospital Anxiety and Depression Scale (HADS), cut-off ≥ 8 (9). Also measured with the HADS, a Greek study with 75 patients obtained a depression mean score of 4.9, which was markedly higher than the corresponding mean score of a control group (2.4) (10). An investigation performed in Italy (11) used clinical interviews to detect mental disorders; 25% of the 80 sarcoidosis patients met the criteria for Major Depressive Disorder.

Depression in sarcoidosis was associated with fatigue (8), with quality of life (7), with gender (higher values for females), the number of organs involved and dyspnea (6), but neither the type of treatment nor the number of medications predicted depression in that study.

The New Zealand study (9) failed to detect a relationship between depression and time since diagnosis as well as being on treatment. The domain Feelings of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) was significantly associated with FVC%, with asthenia and the use of steroids (higher scores in the subgroup with no steroids), but not with FEV1% and with multi-organ involvement (11).

Compared with depression, there are only few studies investigating anxiety in patients with sarcoidosis. In the Greek study (10), HADS anxiety was heightened with a mean HADS score of 6.6, compared with a mean score of the control group of 3.0, and one Dutch study (8) reported mean SCL-90 anxiety scores of 11.9 and 14.3 for two subgroups.

Anxiety and depression may be related to disease-specific factors (e. g., affected organs) and to concomitant diseases. Dyspnea is one symptom often observed in early to moderately advanced sarcoidosis. It is associated with several parameters of lung dysfunction (12), which may contribute to fatigue and depression. Though the prevalence rates of depression reported above embrace a wide scope, it is obvious that depression is a problem for many patients suffering form sarcoidosis. Detailed analyses, concerning the associations and putative reasons of depression including disease-specific factors, concomitant diseases and symptoms like dyspnea are hampered since the sample sizes in the studies are often too small for definite decisions. In most studies the number is below 100. Many of the studies mentioned above report mean score differences or odds ratios which are illustrative but nevertheless non-significant because of the low sample sizes. Furthermore, there are effects like gender differences [higher depression scores for females (6)] which can only be evaluated properly when the gender effects in the general population are known. Without such comparisons it remains unclear whether the gender effect found in the patients' sample is related to the disease or not. Some studies report comparisons with controls, but the sample sizes of the controls are also generally low. The aims of this study are

- to analyze the degree of anxiety and depression in a large sample (N>1000) of patients diagnosed with sarcoidosis,
- to examine age and gender effects on the basis of comparisons with normative values, and
- to investigate the influence of the organs involved, concomitant diseases and dyspnea on anxiety and depression.

Methods

Sample of patients suffering from sarcoidosis

In 2009, all members of the German Sarcoidosis Society (N=4100) were asked to take part in the study. They received a letter, together the informed consent form and a questionnaire, and they were asked to fill in the questionnaire and to return it if they were diagnosed with sarcoidosis. 1270 letters (31%) were received. Seventy-three of them could not be included in the analysis because of too many missing values or violations of the anonymization procedure. Sociodemographic features of the final sample (N=1197) are given in Table 1.

The participants were asked to indicate the affected organs (lungs, skin, lymphatic nodes, eyes, liver, muscles, nerves, bones, heart, kidneys, others) and concomitant diseases (arterial hypertension, thyroid disease, obesity, restless legs syndrome, diabetes mellitus, sleep apnea, and pulmonary hypertension). Moreover, the questionnaire contained the MRC (Medical Research Council) Dyspnea Scale (13, 14). This scale is used to assess breathlessness with five categories. Unfortunately, we had no opportunity to retrieve detailed information on the medical status of the sample.

Sample of the general population

The sample of the general population consists of two representatively selected subsamples, examined in 1998 (N=2081) and in 2009 (N=2524). Normative values derived from this total sample are published by Hinz et al. (15). The response rates were 73% (subsample 1) and 62% (subsample 2). Subjects were excluded from the analysis, when they were younger than 18 years, when they did not understand the German language well enough or when in one scale more than item was missing. This resulted in a total of 4410 persons, 1929 males and 2481 females. The sample is roughly representative of the German general population, living in private houses.

The Hospital Anxiety and Depression Scale (HADS)

The HADS was developed by Zigmond and Snaith (16) to detect increased degrees of anxiety and depression in somatically ill patients. The questionnaire comprises 14 items, with ranges from 0 to 21 for both scales. The test authors defined three ranges for each subscale: 0-7 (non-cases), 8-10 (doubtful cases) and 11-21 (cases). The HADS has been extensively used, especially in the area of heart diseases (17) and cancer (18). A review (19) summarized the results of 747 papers using the HADS, most of them attributing good psychometric properties to the questionnaire. A recent study comparing various patient-reported outcome measures of anxiety, depression and general distress found out that the HADS scored highest overall (20).

Statistics

Mean score differences between groups were tested with t-tests. Effect sizes d were calculated according to Cohen (21). Three-way ANOVAs tested the influence of gender, age group and sample (patients versus general population) on anxiety and depression scores. The combined influence of gender, age, number of affected organs, number of concomitant diseases and dyspnea was calculated with multiple regression analyses (method=Enter). The Enter method has the advantage that confounders (age and gender) are included in the model even if their contribution does not reach the significance level, and that both scales (anxiety and depression) are analyzed in the same way.

Results

Sociodemographic characteristics of the sarcoidosis sample are given in Table 1. Among the patients, 80.2% lived together with a partner, 35.7% worked full-time, 19.3% worked part-time, 5.6% were unemployed, and 39.3% were retired. The percentages of affected organs (multiple answers possible) were: lungs (90.7%), skin (24.5%), lymphatic nodes (20.8%), eyes (16.0%), liver (11.8%), muscles

Table 1. Sociodemographic characteristics of the sample (sarcoidosis)

	Total sample (N=1197)		Males (N=414)		Females (N=783)	
	N	%	N	%	N	%
Age						
Mean (SD)	54.3	(11.6)	54.0	(10.9)	54.5	(12.0)
Age group						
≤ 40 years	129	10.8	34	8.2	95	12.1
41–50 years	359	30.0	144	34.8	215	27.5
51-60 years	350	29.2	119	28.7	231	29.5
61-70 years	247	20.6	83	20.0	164	20.9
≥ 71 years	112	9.4	34	8.2	78	10.0
Education						
≥ 10 years	732	61.2	226	54.6	506	64.6
> 10 years	456	38.1	185	44.7	271	34.6
Missing	9	0.8	3	0.7	6	0.8
Time since diagnosis						
≤ 10 years	625	52.2	214	51.7	411	52.5
> 10 years	566	47.3	198	47.8	368	47.0
Missing	6	0.5	2	0.5	4	0.5

(9.4%), nerves (9.0%), bones (8.8%), heart (7.9%), kidneys (5.0%), and others (15.9%). Concerning medication, 45.8% received prednisolone, 5.0% azathioprine, 4.3% oxygen, and 2.8% methotrexat. The prevalences of concomitant diseases were as follows: arterial hypertension (38.0%), disease of thyroid gland (26.9%), obesity (26.8%), restless legs syndrome (15.7%), diabetes mellitus (11.2%), sleep apnea (8.8%), and pulmonary hypertension (3.2%). 16.3% of the participants had three or more concomitant diseases; 34.9% were completely free from these comorbidities.

Anxiety and depression of sarcoidosis patients

The mean HADS scores in the patients' sample are 7.74 ± 4.15 (anxiety) and 6.86 ± 4.17 (depression), the corresponding medians are 8 (anxiety) and 7 (depression). Given the cut-off 8+ (at least doubtful cases), the percentages of heightened anxiety and depression are 50.3% and 41.9%, respectively. Based on the cut-off 11+ (cases), the corresponding percentages are 27.2% and 19.7%.

Age and gender differences of anxiety and depression of sarcoidosis patients in relation to the general population

Figure 1 presents anxiety and depression mean scores of both samples (sarcoidosis and general population), broken down by gender and age group. Anxiety and depression scores are higher in patients compared to the general population. The largest differences between the samples are found for younger age groups.

ANOVA results are given in Table 2. The predominant effect with highest F values is the sample effect, indicating the mean score difference between patients and general population. The interaction terms describe whether there are differences between the samples concerning age and gender dependency. The Sample * Gender interaction is negligible, indicating similar gender effects in both samples. Higher anxiety mean scores for females compared to males are found in both samples in a similar way. There are, however, significant differences between the samples in age dependency, reflected in significant Sample * Age group interactions. In older age

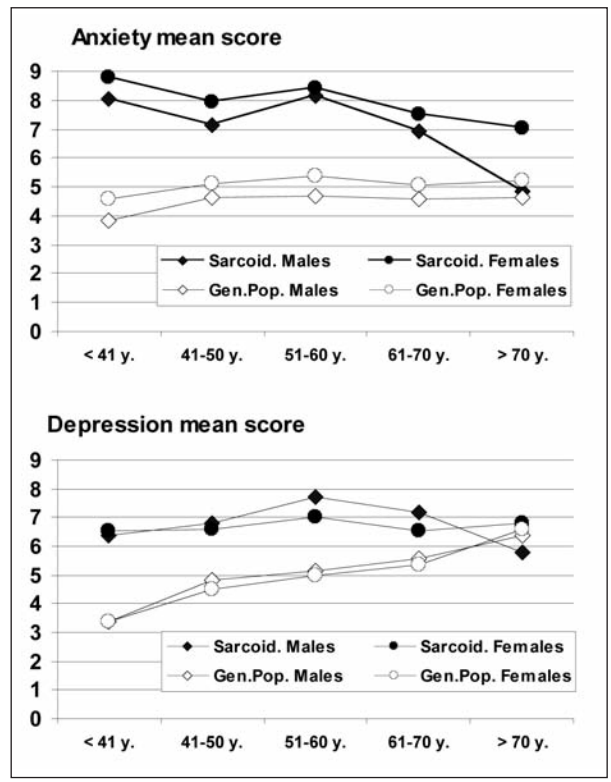

Fig. 1. Anxiety and depression mean scores, broken down by age and gender

Table 2. The effect of sample (sarcoidosis or general population), gender, and age on anxiety and depression. ANOVA results

	Anxiety			Depression		
	DF	F	Sign.	DF	F	Sign.
Main effects						
Sample	1	375.8	.001	1	136.0	.001
Gender	1	29.8	.001	1	0.2	n.s.
Age group	4	7.6	.001	4	10.9	.001
Interaction effects						
Sample * Gender	1	1.1	n.s.	1	0.0	n.s.
Sample * Age group	4	10.3	.001	4	9.9	.001
Gender * Age group	4	1.0	n.s.	4	1.3	n.s.
Sample* Gender * Age group	4	1.3	n.s.	4	0.5	n.s.

groups, the differences between the samples are less pronounced.

The influence of affected organs, concomitant diseases and dyspnea on anxiety and depression

Table 3 shows mean score differences, related to affected organs and concomitant diseases. For nearly all organs, patients with the organ affected are more anxious and depressed than patients without this affection, but the differences are generally small. There are only three organs (muscles, nerves, and bones) with a significant impact on anxiety and depression. Patients with at least three affected organs show significantly higher anxiety and depression mean scores than patients with one or two affected organs.

The effect of concomitant diseases is larger than that of the specific affected organs. With one exception (thyroid diseases), at least one of the scales (anxiety or depression) shows a significant difference between the subsamples with and without the concomitant disease. Sleep apnea has the largest impact on anxiety and depression. Patients suffering from at least three concomitant diseases are significantly more anxious and depressed than patients with fewer diseases. The 418 sarcoidosis patients who reported no comorbidity are characterized by the following scores: mean age: 50.4 years; 59% females; mean HADS anxiety: 7.34, and mean HADS depression: 6.00. Anxiety and depression scores increase with increasing degree of dyspnea (Table 4) in a nearly linear way. ANOVAs proved this effect to be significant ($p<.001$) for both dependent variables. Scores 4 (stops for breath after walking 100 m) and 5 (too breathless to leave the house or breathless when dressing) were combined in Table 4 because the frequencies (score 4: N=67; score 5: N=24) were too low for separate analyses.

Table 4. The effect of dyspnea on anxiety and depression

Dyspnea (MRC)	Anxiety		Depression	
	M	SD	M	SD
1	7.18	4.25	5.63	3.83
2	7.80	4.06	6.92	4.03
3	8.49	4.08	8.64	4.25
4-5	8.81	3.96	9.14	4.14

Table 3. The impact of affected organs, concomitant diseases and medication on anxiety and depression

	Anxiety				Depression			
	Yes	No	d	Sign.	Yes	No	d	Sign.
Affected organs								
Lungs	7.74	7.75	0.00		6.87	6.75	0.03	
Skin	8.12	7.62	0.12		6.94	6.84	0.02	
Lymphatic nodes	7.86	7.71	0.04		6.98	6.83	0.04	
Eyes	8.15	7.66	0.12		7.24	6.79	0.11	
Liver	7.82	7.73	0.02		7.01	6.84	0.04	
Muscles	8.28	7.68	0.14		7.74	6.77	0.23	.018
Nerves	8.26	7.69	0.14		8.02	6.75	0.31	.002
Bones	8.67	7.65	0.25	.017	7.73	6.78	0.23	.025
Heart	7.61	7.75	0.03		7.09	6.84	0.06	
Kidneys	8.58	7.70	0.21		7.62	6.82	0.19	
Other	7.98	7.69	0.07		7.25	6.79	0.11	
≥ 3 organs	8.38	7.44	0.23	.000	7.47	6.58	0.21	.001
Concomitant diseases								
Arterial hypertension	8.11	7.50	0.15	.013	7.56	6.43	0.27	.000
Thyroid disease	7.89	7.68	0.05		7.06	6.78	0.07	
Obesity	8.04	7.63	0.10		7.88	6.49	0.33	.000
Restless legs syndrome	8.41	7.62	0.19	.018	7.95	6.67	0.31	.000
Diabetes mellitus	8.05	7.70	0.08		7.81	6.74	0.26	.005
Sleep apnea	8.77	7.62	0.28	.007	8.72	6.67	0.49	.000
Pulmonary hypertension	8.53	7.73	0.19		8.53	6.79	0.42	.011
≥ 3 concomitant diseases	8.44	7.57	0.21	.000	8.23	6.53	0.41	.000
Medication								
Prednisolone	7.95	7.56	0.10		7.32	6.49	0.21	.001

Note: d: Effect size

Table 5. Combined effects of predictors on anxiety and depression. Results of multiple regression analyses

	Anxiety			Depression		
	Beta	T	Sign.	Beta	T	Sign.
Age	-.17	5.67	.001	-.09	3.18	.002
Gender	.05	1.87	n.s.	-.07	2.55	.011
Affected organs (number)	.05	1.80	n.s.	.03	1.09	n.s.
Concomitant diseases (number)	.07	2.24	.025	.14	4.67	.001
Dyspnea (MRC)	.15	4.70	.001	.26	8.28	.001

Combined analysis of affected organs, concomitant diseases and dyspnea on anxiety and depression

Age, gender, affected organs, concomitant diseases and dyspnea are not independent from one another. Therefore, their effects on anxiety and depression were calculated with multiple regression analyses (Table 5). Dyspnea had the largest impact on anxiety and depression. Multiple R values were .24 (anxiety) and .32 (depression).

Discussion

Anxiety and depression scores were markedly elevated in patients with sarcoidosis, compared with the *general population*. Also compared with other chronic diseases, the values were high. In a sample of 1529 cancer patients who were examined during their stay in the hospital, slightly lower mean HADS scores were found (7.19 for anxiety and 6.44 for depression) (18). The German manual of the HADS reports even lower mean scores of a sample of cardiac patients (N>6000): 6.83 for anxiety and 5.05 for depression (22). The mean values of anxiety and depression obtained in this study are similar to those found by Spruit et al., who report HADS median scores of 7 for both subscales (23), compared to 8 and 7 in our investigation. In a recent study on fatigue in sarcoidosis (24), anxiety and depression (together with several other scales) were combined to a factor called "psychoneurotic distress", and this factor was strongly associated with fatigue, a symptom often found in sarcoidosis (25, 26).

Female sarcoidosis patients were more anxious than males. However, this relationship is not specific for sarcoidosis; the same relationship holds for the general population. Anxiety showed a slightly decreasing trend with *age*, while the curve of depression was inverted-u–shaped, with highest mean scores for subjects from middle age categories. Since anxiety and depression scores are linearly correlated with age in the general population, we can conclude that the largest impact of the disease is found in the youngest age group. Figure 1 illustrates that it would be misleading to interpret age and gender effects of sarcoidosis patients without reference to the general population. It is highly recommended to compare the results (not only in sarcoidosis) with normative data of the general population to interpret age and gender effects correctly.

The type of the *affected organ* was less important for the mental distress. Though nerves, bones and muscles presented the largest mean score differences, the effect sizes were small. It might be instructive to analyze combinations of affected organs. However, given 10 organs, there are more than 100 possible combinations. Simply counting the affected organs seems to be a satisfying way to assess the impact of multi-organ affection. In the multiple regression analyses (Table 5) we see that the number of organs, which had a significant influence in Table 3, did not maintain this impact in combination with other factors.

Many participants of the study suffered from *concomitant diseases*, which also affect mental distress, especially depression. For 6 out of 7 diseases we found effect size coefficients d larger than 0.25, while the impact on anxiety was smaller. Even in the multiple regression analysis the effect of the number of concomitant diseases remained significant. Since the affected organs and the concomitant diseases were not confirmed by a physician, the results of Tables 3 and 5 should be interpreted with care. Moreover, multiple testing might have caused unsecure results in Table 3. The relatively low influence of the specific affected organs compared to the influence of concomitant diseases in Table 3 might lead to the interpretation that

concomitant diseases were more important than sarcoidosis itself. This, however, is not true. The HADS mean values of the group without reported comorbidity (7.34 and 6.00, resp.) are much larger than the corresponding mean values of the general population (4.70 and 4.67, resp.) (15). Expressed in terms of percentages above the cut-off 8+, in the sarcoidosis sample (without concomitant diseases) the percentages of patients who are at least doubtful cases were 46.9% (anxiety) and 36.8% (depression), compared to the values of the general population of 20.6% and 23.7%. Therefore, sarcoidosis is crucial, and the specific conditions seem to be less important.

Dyspnea is of importance for the development of depression (beta= .26). Several studies proved relationships between parameters of lung function and dyspnea (12, 27). A recent American study (28) proved significant correlations between dyspnea and global quality of life (SF-36).

At the beginning, we stated that the reasons of heightened degrees of anxiety and depression in sarcoidosis patients are unclear. Our study found some significant contributions of affected organs, concomitant diseases and dyspnea, which, however, explain only a relatively small part of the differences between the patients and the general population. The main reasons must, therefore, be general characteristics of the disease which are not covered by the factors analyzed here.

Limitations of this study are that it was based on self-report data, and that the representativeness of the study sample cannot be evaluated. We do not know whether sarcoidosis was confirmed according to the latest guidelines, and the analyses of affected organs and concomitant diseases were also based on self report data. We cannot assess how well the patients knew their affected organs and concomitant diseases, even if we assume that they were willing to respond correctly. Furthermore, we had no information on antidepressive medication. However, the age and gender distributions of the sample and the similarity to the results obtained by Spruit et al. (23) give no hint for a sampling bias. Since in this large sample it was also not possible to obtain clinical data on lung function, the relationship between lung function parameters and mental distress could not be analyzed.

In *conclusion*, this study was performed to identify age and gender differences in anxiety and depression, based on a large sample of sarcoidosis patients, and to explore the role of affected organs, comorbidity and dyspnea. The comparison with normative data revealed that anxiety and depression levels are especially pronounced in young patients. Moreover, dyspnea seems to be a significant predictor of these heightened mental distress scores.

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