

## Chapter 4

### Impact of pain in a Dutch sarcoidosis patient population

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## Abstract

### Background and aim

Although pain is prevalent in sarcoidosis, this has never been studied systematically. The aim of the present study was to evaluate the presence and impact of pain in sarcoidosis.

### Methods

Members from the Dutch Sarcoidosis Society without co-morbidity (n=821) participated in this study. The World Health Organisation Quality of Life assessment instrument (WHOQOL-100) was completed, as well as a symptom inventory questionnaire addressing the presence of various categories of pain, *i.e.*, muscle pain, chest pain, abdominal pain, arthralgia, and/or headache.

### Results

Pain was reported by 594 patients (72.4%). Arthralgia was experienced most frequently (53.8%), followed by muscle pain (40.2%), headache (28.0%) and chest pain (26.9%). The number of types of pain a patient was suffering from (ranging from 0-5) was related to the WHOQOL-100 Pain and Discomfort scale ( $r=0.49$ ,  $p<0.001$ ). Patients with more types of pain had lower quality of life (QOL). In addition, the total amount of experienced pain categories was associated with the WHOQOL-100 domain Level of Independence ( $r=-0.43$ ,  $p<0.001$ ), and the facet Energy and Fatigue ( $r=-0.38$ ,  $p<0.001$ ). The number of types of pain was predicted by using analgesics, psychological/neurological medication, NSAIDs, being female, indicating to feel tired, more negative feelings and less energy ( $F(7.635)=35.2$ ,  $p<0.001$ ;  $R^2=27.9\%$ ).

### Conclusion

Pain appeared to be a major problem in sarcoidosis, especially arthralgia. Although negative feelings and fatigue were related to pain, it could not fully explain pain. Future studies are needed to address mechanisms of pain, pain behaviour, and the best therapeutic approach of pain in sarcoidosis.

## Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin.<sup>1</sup> Depending on the organs involved and the severity of granulomatous inflammation, patients suffer from a broad range of persistent physical symptoms. Besides respiratory symptoms such as coughing and dyspnoea on exertion, patients often suffer from systemic non-specific symptoms such as fatigue and pain.<sup>2-5</sup> Non-specific symptoms have an important impact on the quality of life of sarcoidosis patients.<sup>6-8</sup> Assessment of quality of life (QOL) with the World Health Organisation Quality of Life assessment instrument (WHOQOL-100) appeared to be of additional value in the follow-up of sarcoidosis patients as well as patients suffering from rheumatoid arthritis.<sup>6</sup>

One of the non-specific symptoms in sarcoidosis is pain. Pain is considered to be a reflex response to underlying somatic pathology. However, pain is not a mere medical problem. There is growing evidence for the contribution of psychosocial variables in the prediction of pain and disability.<sup>9,10</sup> In the follow-up of sarcoidosis patients, results of routine tests to assess disease activity (including clinical investigation, chest radiography, lung function testing, serum angiotensin converting enzyme (sACE) measurement, gallium-67 scanning, bronchoalveolar lavage parameters) do not measure pain. Therefore, these test results do not always correlate with the well-being of the patient.<sup>11</sup> Consequently, the question arises if dysphoric symptoms are functional, *i.e.*, based on psychogenic influences or are manifestations of the underlying organic disease.<sup>12</sup> Anecdotal reports describe pain in sarcoidosis in relation to several organic disorders such as arthropathies<sup>13-17</sup>, polyneuropathy<sup>18-27</sup>, myopathy<sup>28-34</sup>, chest pain<sup>35-39</sup>, and headache.<sup>40-43</sup> However, until now pain in sarcoidosis has never been studied systematically.

The aim of the present study was to evaluate the presence of various pain categories in sarcoidosis and the relationship between pain and quality of life assessed with the WHOQOL-100.

## Materials and methods

### Study population

All 1755 members of the Dutch Sarcoidosis Society (DSS) suffering from sarcoidosis were sent a test-booklet together with a letter from the DSS in which they were asked to participate in an in-depth study on quality of life and symptoms. All data, including diagnosis, were recruited from the patients. Of the 1093 patients (62.3%) who responded, 1026 (58.5% of the total group) completed the questionnaires. The remaining

67 persons gave a number of reasons why they did not wish to participate in the study. The main reasons included (i) the innumerable list of questions, (ii) lack of time, (iii) the absence of symptoms, and (iv) the fact that the diagnosis was made quite some time ago. Eight persons returned the test-booklet without giving any reason. As we wanted to focus on pain related to sarcoidosis, only responders without co-morbidity (n=821) were included in the present study and patients with relevant co-morbidity were excluded. Co-morbidity was defined as any medical problem not related to sarcoidosis. The control group consisted of persons who were recruited through a random digit dialling method (n=178). For patient characteristics see table 4.1.

Table 4.1 Characteristics of the studied sarcoidosis patient population (n=821)

	Number of cases	Percentage of the total population
	yes /no /missing	yes /no /missing
Gender: male/female/missing	305 / 508 / 8	37 / 62 / 1
Current smoking status	67 / 714 / 40	8 / 87 / 5
Age (years)*	46 ± 12 (16-74)	
Illness duration (years)*	9 ± 9 (0-49)	
Illness duration (> 2 years)	625 / 133 / 63	76 / 16 / 8
Pulmonary involvement**	606 / 69 / 119	74 / 12 / 15
Use of NSAIDs	259 / 521 / 41	32 / 64 / 5
Use of analgesics	268 / 512 / 41	33 / 62 / 5
Use of psychological/neurological drugs	100 / 680 / 41	12 / 83 / 5
Use of oral steroids	469 / 311 / 41	57 / 38 / 5
Using oral steroids as well as NSAIDs	157 / 623 / 41	19 / 76 / 5
Fatigue	599 / 214 / 8	73 / 26 / 1
Breathlessness	628 / 147 / 46	77 / 18 / 6
Pain	594 / 209 / 18	72 / 26 / 2
Muscle pain	330 / 488 / 3	40 / 59 / 0
Chest pain	221 / 598 / 2	27 / 73 / 0
Abdominal pain	97 / 722 / 2	12 / 88 / 0
Arthralgia	442 / 377 / 2	54 / 46 / 0
Headache	230 / 575 / 16	28 / 70 / 2

Data are expressed as mean with standard deviation (SD) in parentheses.

\* Mean±standard deviation with range in parentheses;

\*\* Presence of pulmonary involvement was based on the presence of cough and/or dyspnoea and/or dyspnoea on exertion; NSAIDs= non steroidal anti-inflammatory drugs

## Questionnaires

### *Symptom inventory questionnaire*

The questionnaire consisted of 43 items including questions concerning socio-demographic and medical data such as medical history, family history, duration of disease, 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 questionnaire was not standardized or validated. It was pre-tested in a population of 10 sarcoidosis patients.<sup>2</sup>

### *WHOQOL-100*

All subjects and healthy controls completed the World Health Organization Quality of Life assessment instrument-100 (WHOQOL-100; Dutch version)<sup>11</sup>, a cross-culturally developed generic multidimensional QOL measure. It consists of 100 items assessing 24 facets of QOL within six domains (Physical health, Psychological health, Level of independence, Social relationships, Environment, and Spirituality/religion/personal beliefs) and a general evaluative facet (Overall quality of life and general health). Each facet is represented by four items. The response scale is a 5-point Likert scale. Scores on each facet and domain can range from 4 to 20. Higher scores indicate a better QOL, with the exception of the facets Pain and discomfort, Negative feelings, and Dependence on medication or treatments, where low scores indicate higher QOL. The reliability and validity of the instrument, which have also been tested in sarcoidosis, are good.<sup>11,44</sup> The test-retest reliability is satisfactory.<sup>45</sup>

## Statistical analysis

Frequencies were used for the descriptive information. Kruskal-Wallis tests were performed to establish possible differences in QOL between patients with pain (n=594; group I), patients without pain (n=209; group II), and the healthy control group (n=178). A Chi-square analysis was used to examine the relationship between shortness of breath and chest pain. Pearson correlations were used to examine the relationship between the WHOQOL-100 and the number of types of pain. Mann-Whitney U tests were performed to further establish the relationship between a type of pain and scores on the WHOQOL-100 facet Pain and Discomfort. A p-value below 0.01 was considered statistically significant. One multiple linear regression analysis (stepwise) and a series of logistic regression analyses were performed. Before the linear regression analysis was performed, the linear assumptions were tested. Normality was examined using histograms with kurtosis and skewness. All variables should be normally distributed. Subsequently, linearity and homoscedasticity were tested using (partial) plots with standardized residuals and standardized predicted values. In the present study, the linear assumptions were not violated and hence a linear regression analysis was allowed. Each regression analysis was done in block 1 with age, sex, and current

smoking status. Block 2 consisted of the use of oral steroids, the use of analgesics, psychological/neurological medication, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and illness duration. Finally, block 3 contained feeling tired (yes/no) and the WHOQOL-100 facets Energy and fatigue and Negative feelings. Pearson correlations were performed between illness duration and QOL. Due to the large sample size only correlations above 0.14 were considered statistically significant.

## Results

### Characteristics

Characteristics of the studied sarcoidosis patient population are summarized in table 4.1 (females 61.9%). The mean age was 46.3 years. Medication was used by 80.4% of the patients. The reported medication used included NSAIDs, analgesics, psychological or neurological medication, and oral steroids. Only one of the four mentioned types of drugs was used by 36.4% of the patients, whereas 44% of the patients used at least two types of drugs. The most frequently prescribed drugs were oral steroids (57.1%), followed by analgesics (32.6%). Regarding the location of sarcoid, there were 69 (11.7%) patients without pulmonary involvement and 606 (73.8%) patients with pulmonary involvement and for 119 (14.5%) patients these data were not available (pulmonary involvement was based on the presence of cough and/or dyspnoea and/or dyspnoea on exertion).

### Fatigue

A large proportion of the patients reported to feel tired (73.0%). The mean scores on the WHOQOL-100 facets Energy and Fatigue and Negative Feelings were 10.2 (SD=3.3; range 4-20) and 10.8 (SD=3.2; range 4-20), respectively. Sarcoidosis patients reported significantly more fatigue ( $p<0.001$ ;  $t=36.6$ ) and negative feelings ( $p<0.001$ ;  $t=12.5$ ) than healthy controls.

### Pain

The majority of the patients (72.4%) reported at least one type of pain. Arthralgia was experienced most frequently (53.8%) followed by muscle pain (40.2%), headache (28.0%), chest pain (26.9%) and abdominal pain (11.8%). In the age group up to 45 years 196 (48.8%) patients suffered from arthralgia and 206 (51.2%) did not, whereas in the age group above 45 years 246 (58.7%) patients suffered from arthralgia, 171 (40.8%) did not have arthralgia and 2 (0.5%) were missing. Two hundred and eleven

(25.7%) patients suffered from only one type of pain, mainly arthralgia (54.5%) or headache (21.3%). Patients with breathlessness often also reported chest pain (Chi-square=34.7;  $p<0.001$ ). Having more types of pain (possible range 0 = no pain to 5 = all types of pain) was associated with all WHOQOL-100 domains and facets except the facet Body Image and Appearance and the domain Spirituality. The correlations were strongest for the domains Physical Health ( $r=-0.48$ ) and Level of Independence ( $r=-0.43$ ) and the facets Pain and Discomfort ( $r=0.49$ ), Activities of Daily Living ( $r=-0.42$ ), Energy and Fatigue ( $r=-0.38$ ), Mobility ( $r=-0.38$ ), and Working Capacity ( $r=-0.37$ ; all  $p$ 's  $<0.001$ ). In figure 4.1 WHOQOL-100 scores per domain for sarcoidosis patients with pain ( $n=594$ ), sarcoidosis patients without pain ( $n=209$ ) and healthy controls ( $n=178$ ) are shown. QOL scores of all domains except spirituality were significantly lower in patients with (any type of) pain compared with patients without pain. Sarcoidosis patients who indicated not to suffer from pain had the same score on the facet Pain and discomfort as the control group (mean 9.7 and 9.5, respectively).

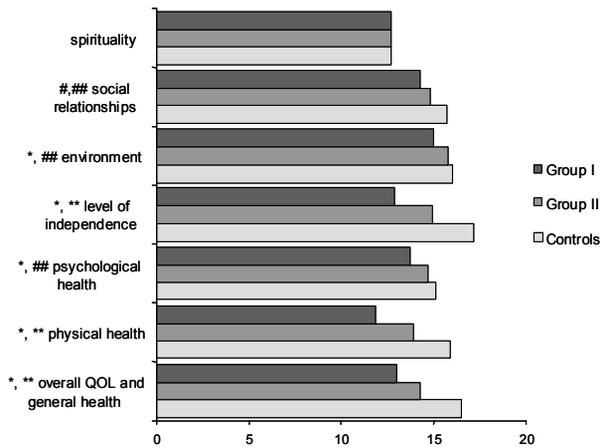


Figure 4.1 WHOQOL-100 scores in sarcoidosis patients with pain (group I), sarcoidosis patients without pain (group II) and healthy controls. \* $p<0.001$  group I vs. group II; # $p<0.01$  group I vs. group II; \*\* $p<0.001$  both group I and group II vs. controls; ### $p<0.001$  group I vs. controls.

Spirituality: Social Relationships: Personal relationships, Social support, Sexual activity; Environment: Physical safety and security, Home environment, Financial resources, Health and social care, New information and skills, Recreation/leisure, Physical environment, Transport; Level of Independence: Mobility, Activities of daily living, Medication/treatment, Working capacity; Psychological Health: Positive feelings, Cognitive functions, Self esteem, Body image, Negative feelings; Physical Health: Pain and discomfort, Energy and fatigue, Sleep and rest

Subsequently, a multiple regression analysis with the number of pain categories that a patient was suffering from (ranging from 0 to 5) as dependent variable was performed. Being female, using analgesics, psychological / neurological drugs and NSAIDs,

indicating to feel tired, scoring low on the WHOQOL-100 facet Energy and Fatigue, and scoring high on the facet Negative feelings together explained 27.9% of the variance of the number of pains ( $F(7.635)=35.2, p<0.001$ ).

The results from the logistic regression analyses are presented in table 4.2.

Table 4.2 Relation between the different types of pain and sex, medication, fatigue and negative feelings

Variables	Odds Ratio	Confidence interval	
Pain	- Sex (male)	0.54	0.37-0.80 <sup>2</sup>
	- NSAIDs	1.70	1.05-2.74 <sup>1</sup>
	- Analgesics	2.44	1.48-4.05 <sup>2</sup>
	- Feeling tired	1.59	1.00-2.54
	- WHOQOL-100 facet Energy and Fatigue	0.90	0.84-0.97 <sup>2</sup>
	- WHOQOL-100 facet Negative Feelings	1.10	1.02-1.18 <sup>1</sup>
Muscle pain	- Sex (male)	0.75	0.52-1.08
	- Illness duration: 1 - 4.9 years	1.89	1.12-3.19 <sup>1</sup>
	5 - 9.9 years	2.07	1.15-3.71 <sup>1</sup>
	≥ 10 years	2.68	1.56-4.62 <sup>3</sup>
	- NSAIDs	1.45	0.99-2.12
	- Oral steroids	0.62	0.43-0.89 <sup>2</sup>
	- Analgesics	2.40	1.64-3.51 <sup>3</sup>
	- Psychological/neurological drugs	1.40	0.83-2.34
	- WHOQOL-100 facet Energy and Fatigue	0.86	0.81-0.91 <sup>3</sup>
	- WHOQOL-100 facet Negative Feelings	1.09	1.02-1.17 <sup>1</sup>
Chest pain	- Sex (male)	0.55	0.36-0.82 <sup>2</sup>
	- Analgesics	1.81	1.23-2.65 <sup>2</sup>
	- Psychological/neurological drugs	1.27	0.75-2.15
	- Feeling tired	1.96	1.11-3.46 <sup>1</sup>
	- WHOQOL-100 facet Energy and Fatigue	0.86	0.80-0.93 <sup>3</sup>
	- WHOQOL-100 facet Negative Feelings	1.09	1.02-1.17 <sup>1</sup>
Abdominal pain	- Sex (male)	0.44	0.24-0.81 <sup>2</sup>
	- Psychological/neurological drugs	1.38	0.73-2.61
	- WHOQOL-100 facet Energy and Fatigue	0.87	0.79-0.96 <sup>2</sup>
	- WHOQOL-100 facet Negative Feelings	1.10	1.00-1.20 <sup>1</sup>
Arthralgia	- Sex (male)	0.65	0.46-0.92
	- Illness duration: 1 - 4.9 years	1.54	0.95-2.52
	5 - 9.9 years	2.20	1.25-3.85 <sup>2</sup>
	≥ 10 years	1.99	1.19-3.33 <sup>2</sup>
	- NSAIDs	1.68	1.15-2.47 <sup>2</sup>
	- Oral steroids	0.59	0.42-0.85 <sup>2</sup>
	- Analgesics	2.64	1.78-3.91 <sup>3</sup>
	- Feeling tired	2.77	1.87-4.09 <sup>3</sup>
	- WHOQOL-100 facet Energy and Fatigue	0.92	0.86-0.98 <sup>1</sup>
	- WHOQOL-100 facet Negative Feelings	1.15	1.08-1.23 <sup>3</sup>
Headache	- Sex (male)	0.74	0.50-1.09
	- Analgesics	2.12	1.45-3.08 <sup>3</sup>
	- WHOQOL-100 facet Energy and Fatigue	0.92	0.86-0.98 <sup>1</sup>
	- WHOQOL-100 facet Negative Feelings	1.15	1.08-1.23 <sup>3</sup>

Note: <sup>1</sup>  $p<0.05$ ; <sup>2</sup>  $p<0.01$ ; <sup>3</sup>  $p<0.001$ ; NSAIDs: non steroidal anti-inflammatory drugs; WHOQOL-100: World Health Organisation Quality of Life assessment instrument

Having pain was predicted by being male, using analgesics and NSAIDs, indicating to feel tired, scoring low on the WHOQOL-100 facet Energy and Fatigue and high on the WHOQOL-100 facet Negative Feelings. Looking at the type of pain reported, it appeared that the use of analgesics was related to all types of pain except abdominal pain. From the other drugs, psychological/ neurological drugs were related to chest pain, muscle pain, and abdominal pain, while the use of NSAIDs as well as not using oral steroids appeared to be related to muscle pain and arthralgia.

Illness duration played a role in muscle pain and arthralgia: patients with chronic sarcoidosis (illness duration more than 2 years) reported more often muscle pain (chi-square = 5.50,  $p < 0.05$ ) and arthralgia (chi-square = 6.97,  $p < 0.01$ ). Lower scores on the WHOQOL-100 facet Energy and Fatigue predicted muscle pain, chest pain, abdominal pain, and headache, while answering yes on the single item indicating to feel tired predicted chest pain and arthralgia. A high score on the facet Negative Feelings was related to chest pain, abdominal pain, and headache (table 4.2).

No relation was found between illness duration and QOL.

## Discussion

Pain was frequent in the studied sarcoidosis population ( $n=821$ ): 72.4% reported at least one type of pain. Furthermore, sarcoidosis patients with pain appeared to have significantly lower quality of life scores than sarcoidosis patients without pain. Pain in our sarcoidosis population involves mainly arthralgia, which seems to have a predilection for the knees, followed by ankles and shoulders. The second most prevalent pain reported appeared to be muscle pain, mostly reported in the lower limbs. A large proportion of the patients reported to feel tired and reported negative feelings. Furthermore, these feelings were related to pain. However, no indication was found that the pain was merely the result of psychogenic influences. Although negative feelings and fatigue were related to pain, they can only explain a part of the pain. Regarding the impact of gender on pain, females reported more different types of pain whereas male gender was a predictor for having one particular type of pain. Other factors involved in pain in sarcoidosis need to be explored.

Though arthralgia as well as myalgia were frequent in our sarcoidosis population, which consists mainly of Caucasians, arthritis as well as myositis and dactylitis in relation to sarcoidosis are very rare in Caucasians. Therefore, the cause of arthralgia and myalgia often remains unclear. We have the impression that the pain mostly is of non-inflammatory character: without morning- or starting stiffness and worse after exertion in comparison to the pain at rest. Furthermore, although prostaglandin  $E_2$  is a very potent stimulator of peripheral pain receptors and hyperalgia<sup>46</sup>, in most cases NSAIDs fail to

relieve pain sufficiently. This gives rise to the hypothesis that the pathophysiology is not merely prostaglandin related. In a group of sarcoidosis patients referred to our hospital we found some patients reported paraesthesias and symptoms of autonomic dysfunction along with their pain in a pattern that was highly suggestive for small fiber neuropathy. Recently, the presence of small fiber neuropathy in this subset of sarcoidosis patients was confirmed.<sup>47</sup> A more precise characterisation of different pain categories in different situations in sarcoidosis is needed to better understand the pathophysiology and underlying mechanisms leading to pain in sarcoidosis.

In treating the sarcoidosis patient with pain, symptomatic (neuropathic) pain treatment such as gabapentine or amitriptylin is indicated in case of small fiber neuropathy.<sup>47</sup> However, optimal treatment should be beneficial in both the inflammation process and the subjective symptoms such as fatigue and pain. It was suggested that in sarcoidosis, as in other immune mediated disorders, constitutional symptoms, especially fatigue and pain, may be caused by circulating cytokines such as TNF- $\alpha$  and interleukin (IL)-1.<sup>1,48</sup> Several effective treatment regimens for sarcoidosis such as steroids and more recently infliximab, suppress TNF- $\alpha$  production or release.<sup>49,50</sup> Therefore, these might be beneficial in reducing disease activity as well as in reducing pain and fatigue.

Using patient organisations provides the opportunity to gather information concerning a large number of patients in a short time span. However, critics point out that it is not known whether members of a certain patient organisation are representative of the particular patient population at large. Previously, it was demonstrated that members of the sarcoidosis patient organisation had lower QOL than non-members.<sup>44</sup> However, after correction for the presence of symptoms, most differences disappeared. Another problem might be the fact that members of a patient organisation more often suffer from chronic disease and QOL may vary with disease chronicity. However, we found no relation between illness duration and QOL. In the present study 76.1% of the cases suffered from chronic disease (time since onset two or more years), whereas 16.2% suffered from a disease history of less than two years (7.7% missing) (table 4.1). The chronic cases reported more arthralgia and muscle pain compared to those with a shorter disease history. Although the members of the DSS members are not completely representative of sarcoidosis patients in general, in the large group of patients studied (821 patients), which might be representative for chronic sarcoidosis patients, pain appeared to be a substantial problem. Another limitation of the study might be the acquisition of pain by the symptom inventory questionnaire. This questionnaire is not a validated or standardized tool. However, this questionnaire was used to make a pain inventory. Now that pain appears a major problem in sarcoidosis more detailed pain studies with in-depth pain questionnaires are needed. Furthermore, there might be a lack of specificity in this study, *i.e.*, it cannot be excluded that arthralgia was partly due to coexistent degenerative joint disease. Similarly, abdominal discomfort could be

medication induced. However, sarcoidosis patients with any type of co-morbidity were excluded from the study. This approach ensures that existing co-morbidity interferes with pain as reported in the present study. Besides, in our experience degenerative joint disease is extremely rare in sarcoidosis. Moreover, 44.3% of all patients suffering from arthralgia are under 45 years of age. Arthrosis is highly unlikely at this age. Therefore, we consider it unlikely that degenerative joint disease causes arthralgia in a large proportion of our sarcoidosis patients. Regarding the relation between abdominal pain and medication, abdominal pain was in contrast to other types of pain not related to the use of analgesics or NSAIDs. Therefore, abdominal discomfort due to medication also appears unlikely.

Generally, the management of a sarcoidosis patient is coordinated by a pulmonologist. However, sarcoidosis is a multisystem disorder in which many other organ systems may be involved. Extrapulmonary symptoms appeared to be a common problem in chronic sarcoidosis and do not always correlate with pulmonary symptoms. Moreover, lack of an objective system for assessment of sarcoidosis to evaluate disease course and effectiveness of therapy is a major problem.<sup>51,52</sup> Therefore, in the evaluation of the efficacy of treatment, extrapulmonary parameters such as pain and fatigue need more attention, including sufficient questionnaires to add to the regular investigations. More knowledge is warranted to better understand the impact of extrapulmonary symptoms.

## Conclusions

Pain is a major problem in sarcoidosis, especially arthralgia. Although negative feelings and fatigue are related to pain, they cannot fully explain the pain. Future studies are needed to address the precise characteristics and the underlying mechanisms of pain, pain behaviour and coping, and the most appropriate therapeutic approach in sarcoidosis. As pain is a substantial problem in sarcoidosis, appropriate questionnaires gaining information about pain might be helpful. The simultaneously use of these questionnaires, lung function tests, imaging procedures and other clinical markers of disease activity and severity may provide a framework for understanding how to correctly manage the intriguing disease sarcoidosis.

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