Clinical presentation of sarcoidosis in the Netherlands
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Clinical presentation of sarcoidosis in the Netherlands
An epidemiological study

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Abstract

Background: Patients suffering from sarcoidosis may present with a wide range of symptoms. The aim of this study was to make an inventory of the clinical presentation of the sarcoidosis population in the Netherlands.

Methods: Symptom inventory questionnaires were sent to all members of the Dutch Sarcoidosis Society. Of these 1755 sarcoidosis patients, 1026 (58%) aged 46.7 ± 11.6, female 63% completed the questionnaire.

Results: Familial sarcoidosis was reported by 170 patients (16.3%). In 57% of the cases the first diagnosis was sarcoidosis. Other diagnoses included rheumatoid arthritis (5.1%) and tuberculosis (4.8%). Treatment with systemic corticosteroids was reported by 565 patients (55.1%). The most frequently reported symptom was fatigue (71%), followed by dyspnea (70%), arthralgia (52%), muscle pain (39%), chest pain (27%), and general weakness (22%). Moreover, 26% of patients suffered from disease-related tension and strain. No relationship was found between the reported symptoms and treatment with corticosteroids.

Conclusions: Sarcoidosis patients suffered from a broad range of persistent physical symptoms. In this study fatigue appeared to be the most commonly reported symptom. Intervention programs should focus on physical health as well as psychosocial aspects such as teaching patients how to cope with the disease. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Sarcoidosis; Symptoms; Epidemiology; Dutch population

1. Introduction

In sarcoidosis, a disseminated granulomatous disease of unknown origin, practically every organ can be involved [1]. Depending on the organs involved and the severity of granulomatous inflammation, symptoms can vary considerably. Besides respiratory symptoms such as coughing and dyspnea on exertion, patients often suffer from systemic symptoms such as fever, weight loss, and fatigue [2,3].

In the follow-up of sarcoidosis patients, routine tests to assess disease activity include clinical investigation, chest radiography, and lung function testing [4]. Serum angiotensin converting enzyme (sACE), gallium-67 scanning, high resolution computed tomography, and bronchoalveolar lavage parameters may also be useful as indicators of disease activity [4], although they do not necessarily reflect well-being of the patient. For example, even if pulmonary...
function tests, sACE, and radiographic abnormalities return to normal or show only small impairment, nonspecific symptoms, such as fatigue and reduced exercise capacity may persist.

In other chronic respiratory disorders such as chronic obstructive pulmonary disease (COPD) the correlation of quality of life (QOL) and physiological measures of disease severity such as forced expiratory volume in one second (FEV₁) have been found to be either weak [5–8] or not existent [9], although respiratory symptoms such as wheezing, dyspnea, and subjective severity of breathing problems were more strongly related to QOL [7,10]. In a previous study of 64 sarcoidosis patients, we also found that QOL was not associated with pulmonary function tests and sACE [11]. The presence of symptoms, however, influenced QOL considerably [12]. The number and severity of symptoms may therefore provide more accurate information on the degree of impairment and the well-being of patients with sarcoidosis than the routinely performed physiological measures of disease activity and severity.

Other epidemiological studies have shown that there are considerable differences between countries, not only in the prevalence of sarcoidosis but also in the clinical presentation [13]. For the Netherlands, no extensive epidemiological data exist on the clinical presentation of sarcoidosis. Since the symptoms of sarcoidosis vary considerably, it is essential that pulmonary physicians and other physicians such as general practitioners, internists, and rheumatologists are aware of the possible forms of presentation of this disorder.

Therefore, the aim of the present study was to make an extensive inventory of sarcoidosis-related symptoms in order to gain more information on the presentation of this disorder. Data on family history, duration of the disease, diagnostic procedures, and treatment were also analyzed.

2. Methods

2.1. Patients

All members of the Dutch Sarcoidosis Society (n = 1975) were sent the questionnaire by mail together with a letter from the Dutch Sarcoidosis Soci-
Table 1
Characteristics of the Dutch sarcoidosis patient population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>1026</td>
</tr>
<tr>
<td>Gender: male/female</td>
<td>380/646 (37/63)</td>
</tr>
<tr>
<td>Actual age, years</td>
<td>46.7 ± 11.6</td>
</tr>
<tr>
<td>Age at the time of diagnosis, years</td>
<td>36.5 ± 10.9</td>
</tr>
<tr>
<td>Years since diagnosis</td>
<td>945/81 (92/8)</td>
</tr>
<tr>
<td>more/less than 2 years</td>
<td>170/856 (16.5/83.5)</td>
</tr>
<tr>
<td>Familiar sarcoidosis yes/no</td>
<td>170/856 (16.5/83.5)</td>
</tr>
<tr>
<td>Symptoms at the time of diagnosis yes/no</td>
<td>923/54 (90/5)</td>
</tr>
<tr>
<td>Symptoms at the time of the study yes/no</td>
<td>938/88 (91/9)</td>
</tr>
<tr>
<td>Current smoking yes/no</td>
<td>115/875 (11/86)</td>
</tr>
<tr>
<td>Corticosteroids yes/no</td>
<td>565/367 (55/36)</td>
</tr>
</tbody>
</table>

Data are expressed as total numbers with percentages in parentheses.

* Data are expressed as mean ± SD.

pared with only 11.3% of the men. Mean age at diagnosis for women was 37.6 years and for men 34.7 years (unequal variance t-value 4.2, p < 0.001). Also at the time of the study the women were significantly older than the men (unequal t-value 3.1, p < 0.01).

With respect to marital status, 715 patients (69.7%) were married, 101 (9.8%) were single, 35 (3.4%) were divorced, and 28 (2.7%) were widowed. It appeared that more men than women were living together with a partner (χ² = 8.49, p < 0.005). With respect to ethnic origin, only 0.5% of the study population were of African descent, all others were Caucasians.

The time interval between the onset of symptoms and the diagnosis was less than three months in 25.5% of cases, three to six months in 17.6% of cases, six to twelve months in 11.6% of cases, and more than one year in 24.5% of cases. This information was missing in 20.8% of cases. A correlation was found between age and time interval between onset of symptoms and diagnosis (Pearson’s correlation coefficient 0.15, p < 0.001), older patients were diagnosed later.

In the course of their disease 565 patients (55.1%) were treated with systemic corticosteroids, 322 (31.4%) with inhaled corticosteroids, and 323 (31.5%) with nonsteroidal anti-inflammatory drugs. No data were available with respect to doses and/or duration of treatment.

Familial sarcoidosis was reported by 170 patients (16.5%). In 106 of these cases (62%) a first-degree relative was affected (in 47 cases brother/sister, in 28 cases the mother, in 20 cases the father, and in 11 cases a child). In 75 cases second-degree relatives suffered from sarcoidosis and in 14 cases two or three relatives were affected by sarcoidosis.

A positive family history with respect to Crohn’s disease was reported by 66 patients (6.4%). In 50 of these cases (75.7%) first-degree family members were affected. Four patients (0.4%) of this study population suffered from both sarcoidosis and Crohn’s disease.

Table 2 summarizes the symptoms reported by the patients at onset of the disease and at the time of the study. The most frequent symptom at presentation of the sarcoidosis as well as at the time of the study was fatigue. No correlation was found between the symptom fatigue and age. Other frequently reported symptoms were coughing, arthralgia, reduced exercise capacity, muscle pain, and dyspnea. Heart-re-

Table 2
The most common symptoms related to sarcoidosis at the time of diagnosis as well as at the time of this study (n = 1026)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>At time of diagnosis</th>
<th>At time of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>771</td>
<td>75.1</td>
</tr>
<tr>
<td>Cough</td>
<td>548</td>
<td>53.4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>275</td>
<td>26.8</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>321</td>
<td>37.3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>791</td>
<td>77.1</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>535</td>
<td>52.1</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>349</td>
<td>34.0</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>323</td>
<td>31.5</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>383</td>
<td>37.3</td>
</tr>
<tr>
<td>General weakness</td>
<td>262</td>
<td>25.5</td>
</tr>
<tr>
<td>Starting problems</td>
<td>330</td>
<td>32.2</td>
</tr>
<tr>
<td>Reduced exercise capacity</td>
<td>498</td>
<td>48.5</td>
</tr>
<tr>
<td>Increased need for sleep</td>
<td>529</td>
<td>51.6</td>
</tr>
<tr>
<td>Headache</td>
<td>278</td>
<td>27.1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>250</td>
<td>24.4</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>218</td>
<td>21.2</td>
</tr>
<tr>
<td>Tension, strain</td>
<td>317</td>
<td>30.9</td>
</tr>
</tbody>
</table>
lated problems—including arrhythmias, palpitations, angina pectoris, orthopnea and paroxysmal nocturnal dyspnea—were reported by 9.6% of patients at the onset of the disease and by 9.9% at the time of the study, and a dry mouth by 15.1% of patients at the onset of the disease, and 15.7% at the time of the study. At the time of the study only 171 patients (16.6%) did not report any dyspnea, while 396 patients (38.6%) reported dyspnea at heavy exertion, 314 patients (30.6%) experienced dyspnea when performing routine daily activities, and 7 patients (0.7%) while at rest. The remaining 138 patients (13.5%) did not answer this question.

Women reported more symptoms than men, when age and marital status were entered as covariates ($F = 20.5, \ p < 0.001$). Moreover, results indicated that more women than men had symptoms ($\chi^2 = 5.62, \ p < 0.05$). Women suffered more frequently from arthralgia ($\chi^2 = 18.95, \ p < 0.001$), muscle pain ($\chi^2 = 7.91, \ p < 0.01$), chest pain ($\chi^2 = 16.77, \ p < 0.001$), fatigue ($\chi^2 = 5.44, \ p < 0.05$), starting problems ($\chi^2 = 12.56, \ p < 0.001$), a dry mouth ($\chi^2 = 3.22, \ p < 0.01$), as well as skin lesions ($\chi^2 = 5.84, \ p < 0.05$).

At the onset of the disease only 8.7% of patients suffered from just one symptom, 13.8% suffered from two symptoms, 16.4% from three symptoms, and 12.5% from four symptoms. These percentages did not change significantly over the course of the disease. Correlations were found between the duration of the disease and the symptoms muscle pain ($r = 0.14, \ p < 0.01$), arthralgia ($r = 0.11, \ p < 0.01$), heart problems ($r = 0.14, \ p < 0.001$), skin lesions, e.g., erythema nodosum ($r = 0.12, \ p < 0.001$), visual impairment ($r = 0.10, \ p < 0.01$), dry mouth ($r = 0.10, \ p < 0.01$), and reduced exercise capacity ($r = 0.09, \ p < 0.01$), respectively.

Table 3 summarizes the diagnostic procedures that were performed to establish the diagnosis of sarcoidosis in these patients. The most frequent tests were chest radiographs in 908 patients (88.5%), laboratory tests in 794 patients (77.4%), and pulmonary function tests in 712 patients (69.4%). Ga scans were performed in four cases. Various correlations were found between the duration of the disease and the use of diagnostic procedures. In 50% of the patients who were diagnosed within the previous four years (high resolution) computed tomography

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>908</td>
<td>88.5</td>
</tr>
<tr>
<td>(HR)CT-scan of the thorax</td>
<td>390</td>
<td>38.0</td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>794</td>
<td>77.4</td>
</tr>
<tr>
<td>Lung function test</td>
<td>712</td>
<td>69.4</td>
</tr>
<tr>
<td>Exercise tests</td>
<td>352</td>
<td>34.3</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>573</td>
<td>55.8</td>
</tr>
<tr>
<td>Bronchoalveolar lavage</td>
<td>248</td>
<td>24.2</td>
</tr>
<tr>
<td>Mediastinoscopy</td>
<td>200</td>
<td>19.5</td>
</tr>
<tr>
<td>Thoracoscopy</td>
<td>272</td>
<td>26.5</td>
</tr>
<tr>
<td>Liver biopsy</td>
<td>82</td>
<td>8.0</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>37</td>
<td>3.6</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td>160</td>
<td>15.6</td>
</tr>
<tr>
<td>Eye check</td>
<td>284</td>
<td>27.7</td>
</tr>
</tbody>
</table>

HRCT: (High resolution) computed tomography.

Sarcoidosis was the first diagnosis in 57% of the patients. Others were first diagnosed as suffering from tuberculosis (4.8%) and rheumatoid arthritis (5.1%). In 3.1% of cases a psychological cause was first considered responsible for the reported symptoms. In the remaining cases ($\pm 30\%$) a large range of disorders was first diagnosed, such as bronchus carcinoma, non-Hodgkin lymphoma, diabetes mellitus, hypertension, and pathology of the oesophagus. Of these diagnoses, bronchus carcinoma was the most frequently reported (2%), the others consisted of a large number of different, isolated diagnoses.

Seventy-five percent of this study population indicated that they regularly visited a chest physician and/or other physicians such as the internist (24.3%).
ophthalmologist (29.2%), rheumatologist (9.8%),
dermatologist (10.1%), neurologist (5.9%), cardiologist
(5.7%), and ear–nose–throat physician (5.8%) on a regular basis, while 34% of the patients visited
the general practitioner regularly. A relationship was
found between the duration of the disease and the
number of physicians that were visited on a regular basis ($r = 0.07, p < 0.03$).

Treatment with systemic corticosteroids correlated
with duration of the disease (unequal $t$-value $-4.44, p < 0.001$) and age (equal $t$-value $-3.34, p < 0.001$). No relationship was found between the re-
ported symptoms and treatment with systemic corticosteroids. No significant differences with respect to
symptoms were found between patients, who had
and those who had not been treated with systemic
corticosteroids in the course of their disease.

4. Discussion

In this study, the symptoms, diagnostic proce-
dures, treatment, and course of disease were evalu-
ed in a large number of sarcoidosis patients.

This survey of members of the Dutch Sarcoidosis
Society showed that persistent fatigue was found to
be the most common symptom. Remarkably, fatigue
was reported more frequently than respiratory symp-
toms or any other symptom, in contrast with the
results of a recent study comparing the clinical pic-
ture of sarcoidosis in Finland and Japan [14]. In
Finland the main presenting symptoms were coughing (33%) and in Japan eye symptoms (41%),
whereas fatigue was reported in 21% of patients in
Finland and none in Japan [14]. In our recent study
of 64 sarcoidosis patients in the Netherlands, 58%
appeared to have actual symptoms. Of this sub-group
80% reported fatigue at the time of diagnosis and
77% still suffered from it at the time of the study
[12]. In the present study the patients were allowed
to report more than one symptom which was present
at the onset of the disease and led to medical exami-
nation and the correct diagnosis. Moreover, in about
half of the patients of the Finish/Japanese study the
disease was detected by mass chest radiograph sur-
veys. In the Netherlands no mass chest radiograph
surveys are performed, and this may account for the
differences between the sarcoidosis population in the
Netherlands and these countries.

Sarcoidosis is a disorder that affects the relatively
young. The peak incidence for men and women
occurs between 20 and 40 years [15]. In agreement
with this, in our patient group the mean age was 36
years at the onset of the disease. At this age, persist-
ent fatigue and reduced exercise capacity can be
expected to interfere severely not only with patients’
daily activities but also with their working life.

Although fatigue is a common symptom of many
chronic diseases [3], neither the frequency nor the
physiological basis of this symptom in sarcoidosis
has been studied. Fatigue can be assessed by appro-
priate QOL instruments such as the World Health
Organization Quality of Life assessment instrument
(WHOQOL-100) [16], or special fatigue measures
such as the Profile of Fatigue-Related Symptoms
(PFRS) [17], designed for the chronic fatigue syn-
drome (CFS). However, data obtained by means of a
questionnaire have to be regarded as subjective. If
fatigue remains the main symptom, it may be diffi-
cult to demonstrate that the patient’s impairment is
due to sarcoidosis, e.g., for insurance purposes or
questions of patients’ work capability. Therefore, the
physiological basis of fatigue in sarcoidosis needs to
be studied and markers must be found in order to
assess this symptom more objectively. Recently, we
found a relationship between the level of acute phase
response proteins and fatigue in sarcoidosis patients
[18].

A number of other persistent physical symptoms
such as reduced exercise capacity, arthralgia, weak-
ness, starting problems, and muscle pain were re-
ported. The question then arises as to whether these
could be expression of muscle involvement. This
would be remarkable, considering that symptomatic
muscle involvement in sarcoidosis is estimated to
occur in only 1.4–2.3% of cases [19]. Asymptomatic
muscle involvement, however, has been reported in
50–80% of cases [20]. In a previous study we showed
that reduced respiratory muscle endurance time was
related to impaired mobility in a group of sarcoidosis
patients, although, no such relationship was found
with peripheral muscle strength [11].

Although in this study the patients reported mainly
physical symptoms, almost a third of patients also
suffered from psycho-social problems such as feeling
depressed, tension and strain at the onset of the disease. These problems improved only slightly over time. The latter symptoms were attributed to sarcoidosis by the patients themselves. Previously, we demonstrated that QOL factors were associated with depressive symptoms in sarcoidosis [12]. Thus sarcoidosis patients may benefit from psycho-social support and learning different coping strategies as well as attention to the somatic aspects of the disease [12]. Further intervention research is needed here, however.

In this study population, 46% had suffered from sarcoidosis for more than eight years. This group reported symptoms such as arthralgia and muscle pain as well as reduced exercise capacity more frequently than patients who were diagnosed less than six years ago. Surprisingly, the same tendency was found for skin lesions such as erythema nodosum. These findings suggest that such persistent symptoms not only impair health status and quality of life of patients with a chronic course of sarcoidosis, but also represent a large demand on health facilities. This demand may mean that the patients make frequent visits to various physicians and require prolonged medication. This may also have economical implications. However, for this patient group no data are available on frequency of visits to the various physicians. Duration of the disease was related only moderately to the number of physicians visited on a regular basis.

Sarcoidosis is thought to occur more frequently in women than in men [21]. The study population of Pietinalho and Ohmichi consisted of 59% and 55% women in Finland and in Japan, respectively [14]. A recent epidemiological study from Spain, where sarcoidosis is a rare disorder, reported 85% women in their study population [22]. In our study 63% of the study population were women.

In a study in the USA, familial sarcoidosis was estimated to occur in 5% of cases among Caucasians and in 19% among African Americans [23]. In the present patient group the percentage of familial sarcoidosis was much higher (16.5%) than expected, since only 0.5% of patients were of African descent. In a study of the members of the German sarcoidosis patient organization, a familial sarcoidosis was found in 7.5% of cases [24]. In the clinical practice, however, familial sarcoidosis is seen only occasionally and large-scale epidemiological studies are needed to identify ‘sarcoidosis families’ and undertake the necessary genetic research.

Both sarcoidosis and Crohn’s disease are disorders of unknown origin and are characterized by granulomatous inflammation. As the histological characteristics of sarcoidosis and Crohn’s disease are similar, a pathogenic relationship has been suggested [25]. In one family Grönhagen-Riska et al. found an accumulation of both [26]. Cases have also been described, in which patients met the criteria for both, Crohn’s disease and sarcoidosis [25]. In our study population only four patients reported suffering from both diseases.

In this present study sarcoidosis was the initial diagnosis in only 57% of cases, suggesting that the diagnosis of the disease can be difficult. Other first diagnoses included a wide range of somatic disorders. Also psychological problems were considered to be the cause of the symptoms in a number of patients. Furthermore, only about 25% of the patients were correctly diagnosed within the first three months after the onset of symptoms and in another 25% it took more than one year. A relationship was found with the age of the patients; older people experienced longer delay.

Among the diagnostic procedures used computed tomography appeared relatively little used (38%), although especially its high resolution form (HRCT) is much more sensitive than plain radiographs and can demonstrate early fibrosis and distortion of the lung parenchyma [4,27]. Also, bronchoalveolar lavage (BAL) was relatively little used, considering its importance in the diagnosis of sarcoidosis [28]. Lung biopsies obtained by thoracoscopy and mediastinoscopy were performed relatively often, even though these tests are much more invasive. However, when the use of these tests was correlated with the duration of the disease, we found that in patients with a shorter time since diagnosis, (HR)CT and BAL were performed more often and mediastinoscopy and thoracoscopy less often than in those diagnosed more than eight years ago. This reflects recent shifts in management strategies resulting from the development of new diagnostic techniques. The use of BAL together with (HR)CT obviates the need for more invasive diagnostic procedures such as thoracoscopy and mediastinoscopy in sarcoidosis.
There are several limitations to the present study. Since the data were collected by means of questionnaires completed only by the patients themselves, medical data from their physicians with respect to severity and stage of the disease are lacking. In this patient population it appears that a large number of tests were performed to obtain histological evidence of granulomatous inflammation.

Corticosteroids are regarded as the most effective treatment options for severe symptoms or involvement of eyes, central nervous system or the heart [21]. For pulmonary sarcoidosis, objective evidence of deterioration in pulmonary functions has been suggested as an indication of the need for supportive treatment [29]. Recently, small long-term advantages from prolonged treatment with systemic corticosteroids were found for patients with pulmonary sarcoidosis and persistent radiographic shadowing [30]. In contrast, two other studies have found that the rate of relapse was higher for patients treated with corticosteroids than for untreated patients [31,32]. In the present study, 55.1% of patients have received systemic corticosteroids, this is within the range of 30% to 100% reported in various other studies [13]. In the present study no relationship was found between the number and kind of symptoms and treatment with corticosteroids. Duration of disease and age, however, were found to be related to treatment with systemic corticosteroids. Inhaled corticosteroids had been used at some time in the course of the disease by 31% of patients, even though these are generally not recommended for the treatment of sarcoidosis [33]. However, bronchial hyperresponsiveness is assumed in about 30% of patients with sarcoidosis [34], and this may explain the positive effect of inhaled corticosteroids on respiratory symptoms [35]. Moreover, 31% of patients received non steroidal anti-inflammatory drugs (NSAIDs). NSAIDs are sometimes used to treat minimal disease [36], they may not only help to relieve arthralgia and muscle pain but also have an anti-inflammatory effect in sarcoidosis.

In conclusion, the results of this study within a sarcoidosis patient population in the Netherlands indicated that patients present a wide range of physical symptoms, the most common being persistent fatigue. A considerable number of patients suffered from depressive feelings, tension, and strain, many of which persisted over time. No relationship was found between the reported symptoms and treatment with systemic corticosteroids. As the symptom fatigue is difficult to assess objectively, the physiological basis of fatigue in sarcoidosis has to be studied and markers are needed for its accurate assessment. Due to the broad range of possible symptoms, patients with sarcoidosis may consult the family doctor, pulmonologist or any other physician. Therefore, physicians in general should be aware of the many possible presentations of this disorder. Large-scale prospective studies are needed to gain more insight into sarcoidosis, which may be facilitated by a data base, since sarcoidosis remains a relatively rare disorder. In addition, the quality of life and health status should form part of the monitoring of this patient group.

Acknowledgements

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