Delayed diagnosis of sarcoidosis is common in Brazil*

Diagnóstico tardio da sarcoidose é comum no Brasil

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Abstract

Objective: To determine the frequency of and the factors related to delayed diagnosis of sarcoidosis in Brazil. **Methods:** We evaluated patients with a biopsy-proven diagnosis of sarcoidosis, using a questionnaire that addressed the following: time since symptom onset and since the first medical visit; and the number and specialty of the physicians visited. We divided the patients by the timeliness of the diagnosis—timely (< 6 months) and delayed (≥ 6 months)—comparing the two groups in terms of systemic and pulmonary symptoms; extrathoracic involvement; spirometric data; radiological staging; level of education; income; and tuberculosis (diagnosis and treatment). **Results:** We evaluated 100 patients. The median number of physicians consulted was 3 (range, 1-14). In 11 cases, sarcoidosis was diagnosed at the first visit. In 54, the first physician seen was a general practitioner. The diagnosis of sarcoidosis was timely in 41 patients and delayed in 59. The groups did not differ in terms of gender; race; type of health insurance; level of education; income; respiratory/systemic symptoms; extrathoracic involvement; and radiological staging. In the delayed diagnosis group, FVC was lower (80.3 ± 20.4% vs. 90.5 ± 17.1%; p = 0.010), as was FEV_1 (77.3 ± 19.9% vs. 86.4 ± 19.5%; p = 0.024), misdiagnosis with and treatment for tuberculosis (≥ 3 months) also being more common (24% vs. 7%, p = 0.032, and 20% vs. 0%; p = 0.002, respectively). **Conclusions:** The diagnosis of sarcoidosis is often delayed, even when the imaging is suggestive of sarcoidosis. Delayed diagnosis is associated with impaired lung function at the time of diagnosis. Many sarcoidosis patients are misdiagnosed with and treated for tuberculosis.

Keywords: Sarcoidosis; Sarcoidosis, pulmonary/diagnosis; Tuberculosis.

Resumo

Objetivo: Avaliar a frequência do diagnóstico tardio de sarcoidose no Brasil e os fatores relacionados a esse atraso. **Métodos:** Avaliamos pacientes com diagnóstico de sarcoidose confirmado por biópsia utilizando um questionário que abordava o tempo entre o início dos sintomas e a data da primeira consulta médica; e o número e especialidades dos médicos consultados. Sintomas sistêmicos e pulmonares, envolvimento extratorácico, dados espirométricos, estadiamento radiológico, escolaridade, renda individual e diagnóstico/tratamento de tuberculose foram comparados entre os pacientes com diagnóstico precoce (< 6 meses até o diagnóstico) e tardio (≥ 6 meses). **Resultados:** Foram incluídos 100 pacientes. A mediana do número de médicos consultados foi 3 (variação: 1-14). O diagnóstico de sarcoidose foi feito na primeira consulta em 11 casos. Um clínico geral foi inicialmente consultado em 54 casos. O diagnóstico de sarcoidose foi precoce em 41 casos e tardio em 59. Não houve diferença entre os grupos no tocante ao gênero, raça, tipo de seguro saúde, escolaridade, renda, sintomas sistêmicos e respiratórios, envolvimento extratorácico e estadiamento radiológico. Os pacientes com diagnóstico tardio apresentavam menor CVF (80,3 ± 20,4% vs. 90,5 ± 17,1%; p = 0,010) e VEF_1 (77,3 ± 19,9% vs. 86,4 ± 19,5%; p = 0,024), além de mais frequentemente receberem diagnóstico de tuberculose (24% vs. 7%; p = 0,032) e tratamento para tuberculose (≥ 3 meses; 20% vs. 0%; p = 0,002). **Conclusões:** O diagnóstico de sarcoidose é tardio em muitos casos, mesmo quando há achados de imagem sugestivos. O diagnóstico tardio está associado a menor função pulmonar na época do diagnóstico. Vários pacientes com sarcoidose recebem diagnóstico e tratamento de tuberculose.

Descritores: Sarcoidose; Sarcoidose pulmonar/diagnóstico; Tuberculose.

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Tel. 55 11 5543-8070. E-mail: pereirac@uol.com.brFinancial support: None.
Submitted: 15 April 2013. Accepted, after review: 16 July 2013.

Introduction

A diagnosis of sarcoidosis is established when clinical and radiological findings are associated with the histological presence of granulomas and causes other than sarcoidosis have been excluded.[1,2] The diagnosis of sarcoidosis is often delayed for various reasons. The disease is uncommon and can affect any organ system. The clinical presentation of sarcoidosis can be typical[1,3,4] or atypical.

In countries in which the number of cases of tuberculosis is high, such as Brazil, a diagnosis of tuberculosis is always considered in patients in whom a biopsy shows granulomas, and such patients often receive treatment for tuberculosis (even without bacteriological confirmation). Similarly to tuberculosis, sarcoidosis predominantly affects the upper lobes, and parenchymal fibrosis can cause architectural distortion, hilar retraction, and upper lobe volume loss.[5] Patients with sarcoidosis can present with systemic symptoms, such as fever, weight loss, and night sweats, which can lead physicians to misdiagnose such patients as having tuberculosis.[6] Sarcoidosis is asymptomatic in many cases. In symptomatic patients, the symptoms are generally nonspecific. Finally, economic barriers and difficult access to specialists can affect the time to diagnosis. In a study conducted in the United States and involving 189 patients, the diagnosis was delayed (> 6 months after symptom onset) in 31%.[7] The presence of pulmonary symptoms and radiological findings indicative of advanced disease were associated with a longer time to diagnosis. In contrast, the presence of skin lesions resulted in earlier diagnosis.

The objective of the present study was to determine the frequency of and the factors related to delayed diagnosis of sarcoidosis in patients seeking treatment at specialized centers in Brazil.

Methods

The study protocol was approved by the Research Ethics Committee of the Federal University of São Paulo, located in the city of São Paulo, Brazil. All patients gave written informed consent. Clinical and biopsy findings were consistent with sarcoidosis in all of the patients included in the present study. Other conditions were excluded on the basis of the results of ancillary tests, including special stains for mycobacteria and fungi on biopsy slides. Patients were recruited from among those treated at any of the following facilities in the city of São Paulo, Brazil: the *Hospital São Paulo* Outpatient Clinic for Interstitial Diseases (n = 68); the São Paulo Hospital for State Civil Servants (n = 22); and a private clinic owned by one of the authors of the present study (n = 10).

A standardized questionnaire was administered at diagnosis or retrospectively, up to one year after diagnosis. Data were collected between June of 2007 and May of 2011.

We excluded patients who were unable to remember the time of symptom onset or the number of physicians consulted, as well as those who were unable to perform acceptable spirometric maneuvers.

In the initial evaluation, patients underwent history taking, detailed physical examination, and ancillary tests to determine whether there was multiple organ involvement by sarcoidosis.[1] Chest X-rays and CT scans taken closest to the date of biopsy were reviewed. The chest X-ray findings were classified in accordance with the criteria proposed by Scadding[8]: stage 0, no thoracic involvement; stage I, hilar adenopathy alone; stage II, hilar enlargement with interstitial lung disease; stage III, interstitial lung disease alone; and stage IV, pulmonary fibrosis.

All spirometric tests met the acceptability and reproducibility criteria proposed by the Brazilian Thoracic Association, and the results were expressed as predicted values for the Brazilian population.[9,10] Abnormal patterns were classified as obstructive (reduced FEV_1/FVC ratio with normal FVC), restrictive (reduced FVC and FEV_1 with normal FEV_1/FVC ratio), or mixed (reduced FVC and FEV_1/FVC ratio). Dyspnea was assessed by the baseline dyspnea index.[11] Dyspnea was considered severe when the score was ≤ 6.

Patients answered questions regarding the date of symptom onset, the date of the first medical visit, the number of physicians visited (and their specialty), and the specialty of the physician who made the diagnosis of sarcoidosis. Physicians were classified as general practitioners or generalists (including emergency room physicians), pulmonologists, dermatologists, ophthalmologists, or others.

The clinical presentation of sarcoidosis was classified as asymptomatic (abnormal radiological findings without symptoms), pulmonary symptoms, cutaneous symptoms, ocular symptoms, systemic symptoms (fever, weight loss, and night sweats), or others.

Patients were classified as Black or White on the basis of their skin color. The level of education was classified as illiterate, elementary school, high school, or college. The monthly individual income was quantified by the number of times the average minimum wage at the time of the study: 1-3 (600-1,800 Brazilian reals); 4-10; and > 10. Health insurance was classified as public or private.

The diagnosis of sarcoidosis was classified as timely (< 6 months) or delayed (≥ 6 months) on the basis of the time elapsed between the first medical visit and the date of the visit in which the diagnosis of sarcoidosis was established.

Variables with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution were expressed as median and range. The chi-square test was used in order to compare the timely diagnosis and delayed diagnosis groups regarding categorical variables. Regarding variables with normal distribution, the two groups of patients were compared by the Student's t-test. Regarding those with non-normal distribution, they were compared by the Kruskal-Wallis test or the Mann-Whitney test. Correlations of FVC% with the time elapsed between symptom onset and diagnosis were determined by Spearman's test.

A preliminary analysis of sarcoidosis patients showed that approximately half had had a delayed diagnosis. Considering a difference of 20% in the frequency of findings between the two groups relevant, with values of $\alpha = 0.05$ and power $(1 - \beta)$ of 0.80, we found that a sample of 97 cases was required.[12] Statistical analysis was performed with the Statistical Package for the Social Sciences, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$ (two-tailed).

Results

One hundred patients were included in the present study. The overall findings are shown in Table 1. White females constituted the majority of the sample. The mean age was 48 years, being higher for females than for males (50.1 ± 12.1 years vs. 43.9 ± 11.4 years; t = 2.57; p = 0.012).

Of the sample as a whole, 79% had public health insurance, 52% had finished college, and 60% had a monthly income of less than 2,000 Brazilian reals.

Table 2 shows the clinical, functional, and radiological findings, as well as the biopsy sites in which granulomatous lesions were found. The diagnosis was based on incidental chest X-ray findings in 13% of the cases. Systemic symptoms were common: 46% of the patients reported weight loss; 35% reported night sweats; and 20% reported fever. Increased dyspnea was reported by 19%.

Mean FVC and FEV_1 values (as assessed by spirometry) were close to the lower limit of the reference range, and the mean FEV_1/FVC ratio was normal. Spirometric values were within the reference range in 44 cases; 29 cases were classified as restrictive, 19 were classified as obstructive, and 8 were classified as mixed.

In 49 cases, the diagnosis of sarcoidosis was based on transbronchial biopsy findings. Skin lesions and extrathoracic adenopathy were common, and one third of the cases were diagnosed on the basis of biopsy findings in those sites.

The median number of physicians consulted was 3 (range, 1-14). The first physician consulted was a general practitioner in 54 cases; a pulmonologist, in 13; a dermatologist, in 7; and other specialists, in 24. Sarcoidosis was diagnosed at the first visit in only 11 patients; 6 patients were diagnosed by a dermatologist, 3 were diagnosed a pulmonologist,

Table 1 - General characteristics of 100 patients with sarcoidosis.[a]

Variable	Result
Age, years[b]	47.6 ± 12.1
Gender	
Male	40
Female	60
Race	
White	79
Black	21
Health insurance	
Private	21
Public	79
Level of education	
Illiterate	8
Elementary school	40
High school	33
University	19
Monthly income, no. of times the national minimum wage[c]	
≤ 1	6
1-3	54
4-10	29
> 10	11

[a]Values expressed as n of patients, except where otherwise indicated. [b]Value expressed as mean ± SD. [c]National minimum wage, in Brazilian reals (R$) = R$ 600.00.

Table 2 - Clinical, functional, and radiological findings, as well as biopsy sites showing granulomas, in 100 patients with sarcoidosis.[a]

Variable	Result
Symptoms	
Absent	13
Systemic	59
Fever	20
Weight loss	46
Night sweats	35
Pulmonary	70
Extrathoracic adenopathy	23
Skin lesions	30
Ocular disease	12
Baseline dyspnea index[c]	
> 6	79
≤ 6	19
Spirometry[b]	
FVC, % of predicted	84.5 ± 19.7
FEV_1, % of predicted	81.1 ± 19.9
FEV_1/FVC	0.79 ± 0.10
Radiological staging	
0/I/II/III/IV	8/21/35/29/7
Biopsy site/type[d]	
Transbronchial biopsy	49
Skin	17
Extrathoracic adenopathy	16
Surgical lung biopsy	11
Mediastinoscopy	8
Testicle	1

[a]Values expressed as n of patients, except where otherwise indicated. [b]Values expressed as mean ± SD. [c]n = 98. [d]A total of 102 biopsies were performed in 100 patients.

and 2 were diagnosed by a general practitioner. In 26 cases, five or more physicians were consulted before the correct diagnosis was made.

All patients visited one of our facilities, meaning that, by the end of the study, all patients had consulted with a pulmonologist. Before that, 68 patients had consulted with 90 pulmonologists, the diagnosis having been established in 28 patients (31%).

The median time elapsed from the onset of symptoms or from an abnormal radiological finding to the first visit was 1 month; the median time elapsed from the first visit to the diagnosis of sarcoidosis was 7.5 months; and the median time elapsed from the onset of symptoms or from an abnormal radiological finding to the diagnosis of sarcoidosis was 12 months. Fifty-three patients consulted with a physician within 1 month after the onset of symptoms, and 82 patients consulted with a physician within 6 months after the onset of symptoms.

Fifty-nine patients (59%) were diagnosed late (≥ 6 months after the first visit), whereas the remaining 41 (41%) were diagnosed timely. The time elapsed from the onset of symptoms to the first visit was similar between the two groups. The median duration of symptoms was 1 month in the group of patients with timely diagnosis group and 2 months in the delayed diagnosis group ($z = 0.24$; $p = 0.81$).

The time elapsed from the onset of symptoms to the first visit and from the onset of symptoms to the diagnosis of sarcoidosis did not differ between the genders, races, or types of health insurance, or among levels of education or incomes (data not shown).

Table 3 shows a comparison between the timely and delayed diagnosis groups in terms of clinical, functional, and imaging findings. Those in the delayed diagnosis group had a higher mean age, a lower FVC, and a lower FEV_1, as well as having been more commonly misdiagnosed with and treated for tuberculosis. Of the 59 patients in the delayed diagnosis group, 24 (40.7%) had restrictive lung disease, when compared with 6 (14.6%) of the 41 patients in the timely diagnosis group ($p = 0.005$).

There were no differences between the patients in the timely diagnosis group and those in the delayed diagnosis group regarding systemic symptoms, respiratory symptoms, or the frequency of extrathoracic involvement. In addition, there were no differences between the two groups of patients regarding radiological staging. In 97 patients, CT scans were available for review. After the application of the Scadding classification system to the CT scans, there were changes in the radiological staging of 50 patients, 36 of whom moved to a higher stage. Only 1 of the 8 cases classified as stage 0 on the basis of routine chest X-ray findings remained at that stage after HRCT staging.

In 21 cases, the disease stage changed from I, II, or III to IV. There were no differences between the patients in the timely diagnosis group and those in the delayed diagnosis group regarding CT staging (Table 3). When the disease stages were grouped into 0/I/II vs. III/IV and compared regarding diagnosis (timely or delayed), no differences were observed.

Table 3 - Clinical, functional, and radiological findings in 100 patients with sarcoidosis, by time to diagnosis—timely (< 6 months) or delayed (≥ 6 months).[a]

Variable	Timely diagnosis (n = 41)	Delayed diagnosis (n = 59)	p
Age, years[b]	44.9 ± 10.7	49.4 ± 12.7	0.069
Symptoms			
Absent	4 (9.8)	9 (16.9)	0.421
Systemic	24 (58.5)	35 (59.3)	0.937
Pulmonary	26 (63.4)	44 (74.6)	0.231
Extrathoracic adenopathy	11 (26.8)	12 (20.3)	0.575
Skin lesions	9 (22.0)	21 (35.6)	0.143
Ocular disease	3 (7.3)	9 (15.2)	0.230
Baseline dyspnea index[c]	6 (14.3)	13 (22.6)	0.303
≤ 6	8 (18.2)	14 (22.0)	0.833
Spirometry[b]			
FVC, % of predicted	90.5 ± 17.1	80.3 ± 20.4	0.010
FEV_1, % of predicted	86.4 ± 19.5	77.3 ± 19.9	0.024
FEV_1/FVC	0.79 ± 0.11	0.79 ± 0.10	0.981
Radiological staging			
0/I/II/III/IV	2/11/17/10/1	6/10/18/19/6	0.251
HRCT staging	(n = 39)	(n = 58)	
0/I/II/III/IV	0/8/19/3/9	1/9/22/7/19	0.585
Diagnosis of tuberculosis	3 (7.3)	14 (23.7)	0.032
Treatment of tuberculosis for ≥ 3 months	0 (0)	12 (20.3)	< 0.002

[a]Values expressed as n (%), except where otherwise indicated. [b]Values expressed as mean ± SD. [c]n = 98.

Seventeen patients were diagnosed with tuberculosis, none of whom had bacteriological confirmation. All 17 initially received treatment for tuberculosis, 12 of whom received it for 3 months or more. As expected, those who were treated for 3 months or more had a delayed diagnosis (Table 3). Ten patients were diagnosed as having tuberculosis by pulmonologists, 4 were diagnosed as having tuberculosis by general practitioners, and 3 were diagnosed as having tuberculosis by other professionals. Of the 17 patients who were diagnosed with tuberculosis, 15 (88.2%) had systemic symptoms, compared with 44 (53.0%) of the 83 patients not having been so diagnosed ($\chi^2 = 7.24$; p = 0.007).

Discussion

The present study confirms that delayed diagnosis of sarcoidosis is common. The diagnosis of sarcoidosis was delayed by 6 months or more in approximately 60% of the cases. Only 11% of the patients were diagnosed by the first physician consulted. In 26% of the cases, five or more physicians were consulted before the correct diagnosis of sarcoidosis.

The present study was inspired by another study,[7] which showed that the time elapsed from the onset of symptoms to diagnosis, as well as the time elapsed from the first medical visit to diagnosis, was longer in patients with pulmonary symptoms; the presence of skin involvement was associated with a shorter time to diagnosis of sarcoidosis. In the present study, the abovementioned findings had no influence on the time to diagnosis.

The time to diagnosis of sarcoidosis (from the onset of symptoms and from the first medical visit) was not affected by gender, race, individual income, or type of health insurance. According to the Brazilian Institute of Geography and Statistics,[13] the mean monthly individual income in São Paulo at the time of the study was approximately 850 Brazilian reals, which is similar to the mean value found in the present study (approximately 800 Brazilian reals).

In most cases, a general practitioner was the first physician consulted. However, the diagnosis of sarcoidosis was made at the first visit in only 1 case. Pulmonologists were the first physicians consulted in 13 cases, and the diagnosis of sarcoidosis was made in only 3 of those cases.

Two biases in the present study merit consideration. One is a recruitment bias; it is possible that the sarcoidosis patients included in the present study are not representative of sarcoidosis patients in general. Regarding age and gender, our findings are similar to those of two epidemiological studies, one in Holland and the other in Japan.[14,15] A study conducted in the United States, designated A Case Control Etiologic Study of Sarcoidosis,[16] involved a large, representative sample of patients with sarcoidosis. The results of that study showed similarities and differences in comparison with those of the present study. As occurred in our study, the mean age was higher for females, and the proportions of skin involvement, extrathoracic lymph nodes, and ocular involvement were very similar between the two studies. However, the proportion of patients with stage III/IV sarcoidosis was higher in our sample (36% vs. 16%), whereas that of those with stage I sarcoidosis was lower (21% vs. 40%).[16]

In Brazil, there have been no population-based studies investigating sarcoidosis. Two studies conducted at referral centers in two different cities (Porto Alegre and Rio de Janeiro) showed overall findings in patients with sarcoidosis.[17,18] Both studies showed that the disease is more common in female patients, most patients having stage II or III sarcoidosis. In one of those studies,[18] 6 of 100 sarcoidosis patients had initially been diagnosed with tuberculosis. The time to diagnosis was not reported in those studies. Therefore, the present study is similar to other Brazilian studies conducted at referral centers. However, the patients with sarcoidosis investigated in those studies are probably not representative of those in the general population. It is possible that patients with earlier stage disease were not referred to those centers. However, in the present study, the number of patients with stage I or II sarcoidosis (n = 28) was the same in both groups (with and without delayed diagnosis). Therefore, the fact that the number of patients with stage I or II sarcoidosis was lower in our study than in population-based studies does not explain the findings.

Another potential bias in our study is a recall bias due to the fact that, in many cases, the questionnaires were administered retrospectively. We tried to minimize that by excluding patients who were unable to recall the details of their cases. However, this is a subjective task, and we did not record the number of patients excluded on the basis of that criterion.

In those patients in whom the time elapsed from the onset of symptoms to diagnosis was longer, FVC was lower. This finding suggests that a delayed diagnosis of pulmonary sarcoidosis results in worsening of lung dysfunction in the absence of treatment. Unfortunately, we did not record long-term changes in pulmonary function tests after treatment.

In the present study, we found no relationship between radiological staging and delayed diagnosis. Although HRCT is superior to chest X-ray for detecting nodules and mediastinal lymph node enlargement,[19] these findings were not useful for earlier diagnosis. In the absence of pathologic confirmation, clinical and radiological findings can be useful for the diagnosis of stage I sarcoidosis (reliability, 98%) and stage II sarcoidosis (reliability, 89%), being, however, less accurate for the diagnosis of stage III sarcoidosis (reliability, 52%) and stage 0 sarcoidosis (reliability, 23%).[1,3] Asymptomatic bilateral hilar lymphadenopathy without systemic findings or with acute symptoms (uveitis, polyarthritis, or erythema nodosum) is highly suggestive of sarcoidosis,[4,20] histological confirmation being therefore unnecessary. A combination of pulmonary nodules with hilar/mediastinal adenopathy should immediately raise the suspicion of sarcoidosis. In this context, nodules with a lymphatic distribution on HRCT scans constitute further evidence for a diagnosis of sarcoidosis. In a retrospective review of 91 cases of patients with hilar adenopathy and pulmonary nodules in our registry of interstitial lung disease cases, sarcoidosis was diagnosed in 76 (84%), silicosis was diagnosed in 10 (11%), and other diseases were diagnosed in 5 (5%; unpublished data). In the present study, this combination was not useful for earlier diagnosis.

A total of 17 patients were misdiagnosed as having tuberculosis. Of those, 12 were treated for more than 3 months and 4 completed the standard 6-month treatment established in Brazil. This shorter treatment duration probably reflects a reconsideration of the diagnosis after a lack of response to tuberculosis treatment.

During the study period, in the three facilities involved, only 1 patient initially treated as having sarcoidosis was later confirmed as having

tuberculosis. The patient in question was excluded from the present study.

In patients with sarcoidosis, the only finding associated with more frequent diagnosis of tuberculosis was the presence of systemic symptoms. Weight loss, fever, and night sweats are common findings in patients with sarcoidosis.[6] Fatigue, which is another common finding in patients with sarcoidosis,[21] was not evaluated in the present study.

The risks of treating sarcoidosis as tuberculosis are not negligible.[22] In addition, potentially serious forms of sarcoidosis, such as cardiac sarcoidosis, can go undetected because of the lack of systematic investigation. Ten of the 17 patients treated as having tuberculosis had bilateral hilar lymphadenopathy, which is a rare finding in patients with tuberculosis and should therefore suggest the correct diagnosis.

One study evaluated the usefulness of PCR in biopsy specimens in differentiating between patients with sarcoidosis and those with tuberculosis.[23] In all 31 cases of patients with tuberculosis, PCR was positive, as it was in 20 of 104 cases of patients with sarcoidosis. A quantitative analysis was able to distinguish between the two groups. However, these findings should be confirmed at other centers.

In conclusion, the diagnosis of sarcoidosis is delayed in many cases, even when there are imaging findings suggestive of sarcoidosis. Delayed diagnosis is associated with lower lung function at diagnosis. In some cases, patients are diagnosed with and treated for tuberculosis. This delays the correct diagnosis. General practitioners and even pulmonologists should become more familiar with the findings that are suggestive of sarcoidosis.

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