Factor analysis of sarcoidosis phenotypes at two referral centers in Brazil


1 Paulista School of Medicine, Federal University of São Paulo, São Paulo, Brazil, 2 São Paulo Hospital for State Civil Servants, São Paulo, Brazil

Abstract. Background: In sarcoidosis, clinical presentations and outcomes vary widely. Objective: To characterize the clinical phenotypes of sarcoidosis, by factor analysis, in a series of cases with long-term follow-up. Methods: We conducted a retrospective study involving 137 patients with biopsy-confirmed sarcoidosis, recruited from two referral centers in São Paulo, Brazil. Organ involvement was evaluated in accordance with a previously established protocol. Sarcoidosis phenotypes were characterized by factor analysis. Results: Follow-up ranged from 6 to 144 months. Four factors (phenotypes) were identified: relevant residual pulmonary fibrosis; relapse; residual airflow limitation; and acute disease. The four factors collectively accounted for 66% of the total variance. Patients with relevant residual pulmonary fibrosis were older and presented with the following: greater symptom duration; skin involvement; low forced vital capacity; low forced expiratory volume in one second/forced vital capacity ratio; and more advanced radiographic stages at baseline. The relapse phenotype was associated with chronic disease, greater dyspnea severity, neurologic involvement, and cardiac involvement. Patients with residual airflow limitation more often had airflow obstruction at baseline, chronic disease, and relevant residual pulmonary fibrosis. Acute disease was associated with being younger, weight loss, scoring lower for dyspnea, and having extensive involvement. Abnormal calcium metabolism was associated with acute disease and with relapse. Conclusions: Sarcoidosis can be categorized into four different clinical phenotypes: three that are chronic; and one that is acute and self-limiting. In many cases, these phenotypes can be easily recognized. (Sarcoidosis Vasculitits Diffuse Lung Dis 2011; 28:34-43)

Key words: sarcoidosis, phenotyping, classification, interstitial lung diseases

Introduction

There is evidence that sarcoidosis, rather than being a single disease, consists of several overlapping clinical syndromes, each with its own specific pathogenesis (1). In A Case-Control Etiologic Study of Sarcoidosis (ACCESS), the initial presentation of the disease was found to be related to gender, race, and age (2). The prognosis of sarcoidosis is uncertain and is affected by several classes of human leukocyte antigen (HLA) alleles, as well as by race, age at disease onset, initial clinical features (significant dyspnea and extrathoracic findings portend a worse prognosis), lung function parameters, radiographic stage, high-resolution computed tomography (HRCT) findings, appropriate treatment (to achieve remission), and ethnic origin of the patient (1-13). The prognosis of Löfgren's syndrome (one form of sar-
Sarcoidosis phenotypes: factor analysis

Sarcoidosis (sarcoidosis) is favorable, especially in White patients who are carriers of the HLA-DRB1*03 allele (5, 7, 14). Skin lesions (excluding erythema nodosum), nephrocalcinosis, and bone sarcoidosis are most often associated with chronic sarcoidosis (7). Some studies have shown that the prognosis of sarcoidosis is worse for African-American patients than for White patients (6, 15, 16). A recent study investigated clinical phenotypes of sarcoidosis in a large group of cases (8). However, the authors employed previously established definitions of disease severity (6). Factors associated with severe sarcoidosis include African descent, reduced forced vital capacity (FVC), reduced forced expiratory volume in one second/forced vital capacity ratio (FEV₁/FVC ratio), gas exchange abnormalities, extrapulmonary involvement, and pulmonary hypertension (6, 8, 15).

The clinical presentation and outcome of sarcoidosis vary by region and ethnicity. The obstructive pattern is more prevalent and severe in African-American patients than in those of European or Japanese descent (17-19). Therefore, the prognosis of sarcoidosis varies by region (7, 13). To date, there have been no studies of the severity and prognosis of sarcoidosis in Brazil.

The aim of the present study was to evaluate the clinical phenotypes of sarcoidosis, by factor analysis, in a series of cases with long-term follow-up.

**Methods**

This was a retrospective analysis of 137 patients treated between September 1989 and January 2009 at two tertiary-care facilities in São Paulo, Brazil. The following inclusion criteria were applied: a histological diagnosis of sarcoidosis; having undergone functional evaluation (by spirometry) and imaging studies of the chest (by X-ray or HRCT); and having been followed up for at least six months. The study design was approved by the research ethics committees of the two institutions involved.

We reviewed standardized questionnaires for interstitial lung disease (ILD), which had been applied to all of the patients. The baseline dyspnea index (BDI) was used in order to quantify dyspnea (20). Individuals with a smoking history of at least 10 pack-years were classified as smokers (21).

The diagnosis of sarcoidosis was based on the following criteria: clinical, radiographic, and biochemical findings consistent with the disease; histological evidence of typical sarcoid granuloma; and negativity for mycobacteria and fungi. Cases of hypersensitivity pneumonitis were excluded, as were those of pulmonary reactions to drugs or metals.

**Clinical evaluation of patients**

The diagnosis of sarcoidosis was made by consensus between two pulmonologists. Slides from biopsies were reviewed by two pathologists specializing in ILD. For difficult cases, the diagnosis was reached after a panel discussion involving clinicians, radiologists, and pathologists. If a consensus was not reached, the case in question was excluded.

Organ involvement was evaluated in accordance with the ACCESS protocol (22). Extensive disease was defined as systemic involvement of two or more organs, excluding extrathoracic lymph nodes and independent of erythema nodosum. Radiologically, sarcoidosis was divided into five stages, in accordance with the staging system devised by Scadding (23), and into three groups by lung parenchyma involvement: absent (radiographic stage 0 or I); present without fibrosis (radiographic stage II or III); and present with fibrosis (radiographic stage IV). Sarcoidosis outcomes were classified as follows: residual dysfunction (obstructive or restrictive pattern on the most recent spirometry); significant fibrosis (occupying ≥ 1/3 of the area of at least one lung) on the most recent chest X-ray; use of drugs other than corticosteroids to achieve disease remission after having used corticosteroids for at least one year; disease relapse after initial remission or in the tapering phase of treatment with prednisone or equivalent at doses < 20 mg/day; or death from sarcoidosis.

The functional diagnosis was based on the assessment of FVC, FEV₁, and the FEV₁/FVC ratio. All tests were performed in accordance with the American Thoracic Society guidelines (24). The predicted values were those proposed for the adult population of Brazil (25). Airflow limitation was defined as an FEV₁/FVC ratio below the 5th percentile of the predicted value; and the restrictive pattern was defined as FVC below the predicted lower limit, with a normal FEV₁/FVC ratio.
**Statistical analysis**

All statistical analyses were carried out with the Statistical Package for the Social Sciences, version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used. Medians, means, and standard deviations were calculated for continuous variables, whereas frequencies and percentages were determined for categorical variables. Baseline characteristics and outcome measures were compared using two-tailed t-tests or the Mann-Whitney test, as needed, for continuous variables and the chi-square test for categorical variables. Values of \( p \leq 0.05 \) were considered significant. Sarcoidosis phenotypes were characterized by factor analysis, which included the following variables: disease duration; weight loss; smoking history; extent of the disease; calcium metabolism disturbance; baseline percentage of predicted FVC (FVC%); baseline FEV1/FVC ratio; residual restriction; residua airflow limitation; relapse; treatment with drugs other than corticosteroids; radiographic stage; and relevant residual pulmonary fibrosis. We performed the factor analysis using principal component analysis with varimax rotation.

A correlation matrix was constructed, and the principal components were derived. A correlation coefficient > 0.30 was considered significant. Factors with an eigenvalue > 1 in the principal component analysis were included in the varimax rotation. For the final model, a scree plot was employed in order to select the factors, and four factors were retained. The varimax rotation was aimed at maximizing the correlations between certain variables and a single factor, and minimizing those correlations with the remaining factors (26). The next step in the factor analysis was to construct a new factor matrix in order to examine the weight assigned to each variable, by factor. The criterion adopted for inclusion in the model was a value greater than 5.152 = \( \sqrt{(N-2)} \), resulting in a value of \( \leq -0.44 \) (27).

**Results**

The final sample comprised 137 patients with sarcoidosis. The diagnosis was established by transbronchial biopsy (n = 72), surgical lung biopsy (n = 20), mediastinoscopy (n = 23), skin biopsy (n = 18), extrathoracic lymph node biopsy (n = 20), or biopsy of other organs (n = 9). In 12 patients, the diagnosis was confirmed by biopsy of two or more organs.

Table 1 shows the general characteristics of the study population. The mean age was 49.5 ± 11.4 years, and most (73.7%) were female. Females were

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>101 (73.7)</td>
</tr>
<tr>
<td>Age in years, mean ± SD</td>
<td>49.5 ± 11.41</td>
</tr>
<tr>
<td>Race - White/Black/ND, n</td>
<td>94/35/8</td>
</tr>
<tr>
<td>Symptom duration in month, median (range)</td>
<td>14 (0–420)</td>
</tr>
<tr>
<td>Recent disease/chronic disease/ND</td>
<td>71/58/8</td>
</tr>
<tr>
<td>BDI &gt; 6/BDI ≤ 6/ND, n</td>
<td>78/45/14</td>
</tr>
<tr>
<td>Weight loss - yes/no/ND, n</td>
<td>49/58/30</td>
</tr>
<tr>
<td>Smoking - yes/no/ND, n</td>
<td>32/90/15</td>
</tr>
<tr>
<td>Exposure to birds - yes/no/ND, n</td>
<td>53/70/14</td>
</tr>
<tr>
<td>Exposure to mold - yes/no/ND, n</td>
<td>40/72/25</td>
</tr>
<tr>
<td>Extrapulmonary involvement - yes/no/ND, n</td>
<td>90/46/1</td>
</tr>
<tr>
<td>Extensive disease* - yes/no/ND, n</td>
<td>74/61/2</td>
</tr>
<tr>
<td>Radiographic stage† - 0/I/II/III/IV/ND, n</td>
<td>7/18/46/32/29/5</td>
</tr>
<tr>
<td>Tomographic stage† - 0/I/II/III/IV/ND, n</td>
<td>3/9/54/21/28/22</td>
</tr>
<tr>
<td>Follow up time in months, median (range)</td>
<td>35 (6–144)</td>
</tr>
<tr>
<td>FVC (% of predicted), mean ± SD</td>
<td>85.31 ± 19.33</td>
</tr>
<tr>
<td>FEV1 (% of predicted), mean ± SD</td>
<td>81.11 ± 20.44</td>
</tr>
<tr>
<td>FEV1/FVC, mean ± SD</td>
<td>77.21 ± 10.56</td>
</tr>
<tr>
<td>Normal/obstructive/ restrictive spirometry pattern, %</td>
<td>44.5/29.2/26.3</td>
</tr>
<tr>
<td>No treatment/corticosteroid/chloroquine/methotrexate/other drugs/ND, %</td>
<td>10.4/75.9/33.6/24.1/8.7/1.6</td>
</tr>
</tbody>
</table>

ND, no data; BDI, baseline dyspnea index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second
* Defined as systemic involvement of two or more organs, excluding extrathoracic lymph nodes and erythema nodosum
† Scadding staging system
older than males (50.84 ± 11.59 vs. 45.86 ± 10.16 years; t=2.28, p =0.02). The majority of the patients (73.0%) were White. Disease duration varied widely (0 - 420 months). Sarcoidosis was classified as recent (duration<2 years) in 51.8%. The median BDI was 8 (interquartile range = 5.0-9.5), dyspnea being mild/moderate (BDI > 6) in 57.0%. Environmental exposure to birds or mold was common (in 39.0 and 29.0%, respectively). In those cases, we carefully ruled out hypersensitivity pneumonitis by reviewing clinical, radiological, and pathological data.

Chest X-rays and HRCT scans were reviewed in 132 and 115 cases, respectively. Follow-up ranged from 6 to 144 months. Spirometry revealed ventilatory impairment in 55.5 % of the cases (restrictive in 26.3% and obstructive in 29.2%).

Systemic involvement is shown in Table 2. The lungs and intrathoracic lymph nodes were involved in 94.9% of the cases. Extrapulmonary involvement was seen in 65.7% of the cases, calcium metabolism disturbance being identified in 20.4% and the most common specific locations being the skin (in 29.2%), peripheral lymph nodes (in 19.0%), heart (in 17.1%), and eye (in 11.7%). Systemic involvement and lung function did not differ by gender, race, or age. Baseline spirometry values were 85.3 ± 19.3 for FVC%, 81.1 ± 20.4 for FEV1%, and 77.2 ± 10.5% for the FEV1/FVC ratio. Restrictive and obstructive patterns were both more common in smokers (χ² = 8.35, p = 0.02, OR = 3.73, 95% CI = 1.47-9.51), who also showed lower FVC than did nonsmokers (76± 18% vs. 86± 18%; t = 2.60, p = 0.01). Smoking was marginally associated with airflow obstruction (χ² = 3.51, p = 0.06, OR = 2.25, 95% CI = 0.95-5.30). Patients with abnormal spirometry values more often showed greater dyspnea severity (χ² = 6.62, p = 0.01, OR =

### Table 2. Specific involvement

<table>
<thead>
<tr>
<th>Organ/component</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs - with EN/without EN</td>
<td>130</td>
<td>94.9</td>
</tr>
<tr>
<td>Skin</td>
<td>7/33</td>
<td>5.1/24.1</td>
</tr>
<tr>
<td>Peripheral lymphatic system</td>
<td>30</td>
<td>21.9</td>
</tr>
<tr>
<td>Abnormal calcium metabolism</td>
<td>28</td>
<td>20.4</td>
</tr>
<tr>
<td>Heart</td>
<td>24</td>
<td>17.1</td>
</tr>
<tr>
<td>Eyes</td>
<td>16</td>
<td>11.7</td>
</tr>
<tr>
<td>Nervous system</td>
<td>10</td>
<td>7.3</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Osteoarticular system</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>6</td>
<td>4.4</td>
</tr>
<tr>
<td>Spleen</td>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>Muscles</td>
<td>4</td>
<td>2.9</td>
</tr>
<tr>
<td>Ear, nose, and throat</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>2.2</td>
</tr>
<tr>
<td>Parotid and salivary glands</td>
<td>2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

EN, erythema nodosum

### Table 3. Phenotypes of sarcoidosis defined by factor analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>RRPF</th>
<th>Relapse</th>
<th>RAL</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% of predicted)</td>
<td>-0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scadding stage</td>
<td>0.67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relevant residual pulmonary fibrosis*</td>
<td>0.65</td>
<td></td>
<td></td>
<td>-0.33</td>
</tr>
<tr>
<td>Residual restriction†</td>
<td>0.62</td>
<td></td>
<td>-0.49</td>
<td></td>
</tr>
<tr>
<td>Smoking history ≥ 10 pack-years</td>
<td>0.45</td>
<td></td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Use of drugs other than corticosteroids‡</td>
<td>-</td>
<td>0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse§</td>
<td>-</td>
<td>0.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extensive disease</td>
<td></td>
<td></td>
<td>-</td>
<td>0.57</td>
</tr>
<tr>
<td>Abnormal calcium metabolism</td>
<td>-</td>
<td>0.52</td>
<td></td>
<td>0.48</td>
</tr>
<tr>
<td>Residual airflow limitation</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Baseline FEV1/FVC ratio</td>
<td>-</td>
<td></td>
<td>-0.74</td>
<td></td>
</tr>
<tr>
<td>Recent disease</td>
<td>-</td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
</tbody>
</table>

RRPF, relevant residual pulmonary fibrosis; RAL, residual airflow limitation; AD, acute disease; FVC, forced vital capacity

* Fibrosis in ≥ 1/3 of the area of at least one lung
† Restrictive pattern on the most recent spirometry
‡ For disease remission after having used corticosteroids for at least one year
§ After initial remission or in the tapering phase of treatment with prednisone or equivalent at doses ≤ 20 mg/day
|| Systemic involvement of two or more organs, excluding extrathoracic lymph nodes and erythema nodosum
‡ Obstructive pattern on the most recent spirometry
2.72, 95% CI = 1.26-5.89), a higher radiographic stage ($\chi^2 = 16.25$, $p = 0.03$), and involvement of the lung parenchyma ($\chi^2 = 13.95$, $p = 0.001$).

Although 2 patients died before the end of the period studied, neither death was directly attributed to sarcoidosis.

In the factor analysis, the eigenvalues for the five most important factors (with cumulative variance, in %) were as follows: 2.41 (18.6%) for recent disease; 2.06 (34.4%) for weight loss; 1.84 (48.5%) for smoking history ≥ 10 pack-years; 1.23 (58%) for extensive disease; and 1.10 (66.5%) for abnormal calcium metabolism. Table 3 shows the principal components and the significant interrelated variables in each domain after varimax rotation. Four factors (phenotypes) were identified: relevant residual pulmonary fibrosis; relapse; residual airflow limitation, and acute disease.

Patients with relevant residual pulmonary fibrosis (Table 4) showed lower FVC and more advanced radiographic stages at baseline.

Patients who relapsed (Table 5) showed greater dyspnea severity, as well as more often having calcium metabolism disturbance and extrathoracic involvement, including that of the nervous system and heart.

Patients with residual airflow limitation (Table 6) more often showed airflow obstruction at baseline and residual pulmonary fibrosis.

The fourth phenotype, acute disease (Table 7), was associated with lower age at disease onset, lesser dyspnea severity, and baseline radiographic stage II.

Table 4. Variables associated with the relevant residual pulmonary fibrosis phenotype of sarcoidosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relevant residual pulmonary fibrosis*</th>
<th>Relevant residual pulmonary fibrosis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (years) ± SD</td>
<td>Yes 52.2 ± 10.6</td>
<td>No 48.2 ± 11.6</td>
</tr>
<tr>
<td>Disease duration (months), median (range)</td>
<td>24 (0-312)</td>
<td>12 (0-420)</td>
</tr>
<tr>
<td>Calcium, %</td>
<td>Yes 86.3</td>
<td>No 28.8</td>
</tr>
<tr>
<td>No erythema nodosum, %</td>
<td>Yes 36.7</td>
<td>No 20</td>
</tr>
<tr>
<td>FVC (% of predicted), mean ± SD</td>
<td>Yes 77.57 ± 20.27</td>
<td>No 90.09 ± 15.69</td>
</tr>
<tr>
<td>Residual restriction‡, %</td>
<td>Yes 27.4</td>
<td>No 10.2</td>
</tr>
<tr>
<td>FEV₁/FVC, mean ± SD</td>
<td>Yes 74.74 ± 15.53</td>
<td>No 78.93 ± 9.42</td>
</tr>
<tr>
<td>Residual obstruction§, %</td>
<td>Yes 54.2</td>
<td>No 20.2</td>
</tr>
<tr>
<td>Scadding stage - 0/I/II/III/IV, %</td>
<td>Yes 3.8/1.9/23.1/21.2/50</td>
<td>No 6.6/22.3/42.7/25.3/2.7</td>
</tr>
</tbody>
</table>

FVC, forced vital capacity; FEV₁, forced expiratory volume in one second
* Fibrosis in ≥ 1/3 of the area of at least one lung
† Mann-Whitney test/Student’s t-test
‡ Restrictive pattern on the most recent spirometry
§ Obstructive pattern on the most recent spirometry

Table 5. Variables associated with the relapse phenotype in sarcoidosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes 33 (0-420)</th>
<th>No 12 (0-144)</th>
<th>$-3.27$</th>
<th>0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease duration (months), median (range)</td>
<td>67.2</td>
<td>40.4</td>
<td>8.33</td>
<td>0.004</td>
</tr>
<tr>
<td>Chronic disease, %</td>
<td>48.9</td>
<td>22.6</td>
<td>8.28</td>
<td>0.004</td>
</tr>
<tr>
<td>BDI ≤ 6, %</td>
<td>54.4</td>
<td>35.8</td>
<td>4.13</td>
<td>0.04</td>
</tr>
<tr>
<td>Extensive disease‡, %</td>
<td>34.0</td>
<td>14.1</td>
<td>6.47</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcium, %</td>
<td>27.3</td>
<td>10.4</td>
<td>5.78</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac involvement, %</td>
<td>12.5</td>
<td>3.0</td>
<td>4.07</td>
<td>0.04</td>
</tr>
<tr>
<td>Neurological involvement, %</td>
<td>96.4</td>
<td>77.6</td>
<td>8.86</td>
<td>0.03</td>
</tr>
<tr>
<td>Corticosteroid use, %</td>
<td>63.6</td>
<td>10.6</td>
<td>37.23</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BDI, baseline dyspnea index
* After initial remission or in the tapering phase of treatment with prednisone or equivalent at doses < 20 mg/day
† Mann-Whitney test/Student’s t-test
‡ Systemic involvement of two or more organs, excluding extrathoracic lymph nodes and erythema nodosum
§ Use of alternative drugs to corticosteroid therapy for disease remission after corticosteroid use for at least one year
Patients with acute disease were also less likely to have residual fibrosis ($\chi^2 = 4.53, p = 0.03$).

**Discussion**

Using factor analysis, we identified four different phenotypes in 137 patients with biopsy-confirmed sarcoidosis.

The first phenotype was residual pulmonary fibrosis. This phenotype was characterized by relevant fibrosis on the most recent chest X-ray. Recent studies have suggested that, in sarcoidosis, a variety of genetic abnormalities are more common and fibrogenic cytokine levels are elevated, leading to irreversible pulmonary fibrosis (28, 29). In the present study, as expected, we found that patients with residual pulmonary fibrosis were at the more advanced radiographic stages at baseline. Although half of all such patients presented with fibrosis, approximately 40% were at stages II or III. Although cases at stages 0 and I rarely progress to fibrosis (30), this was seen in 6% of the cases evaluated here. Some studies have reported poor prognosis and higher likelihood of disease progression in cases with pulmonary infiltration (3, 7, 30, 31). Reich and Johnson staged sarcoidosis patients at diagnosis and found that 17% and 44% of those at stages II and III, respectively, progressed to fibrosis, suggesting a worse prognosis for stage III (30). In our sample, the prevalence of skin lesions (excluding erythema nodosum) was higher among patients with fibrotic pulmonary sarcoidosis. Neville noted that specific skin lesions have a chronic fibrotic course (7), which might explain the correlation found between pulmonary fibrosis and skin involvement in our study; both are manifesta-
tions of chronic fibrotic sarcoidosis. In the present study, the patients with residual pulmonary fibrosis had longer symptom duration and were older at diagnosis. Longer symptom duration is well known to be associated with chronic progression, although the effect that age at symptom onset has on prognosis is controversial (13, 16, 32). We found that the residual pulmonary fibrosis phenotype was associated with smoking. At baseline, smoking was associated with lower FVC% and was marginally associated with airflow obstruction. We also found that smoking affected residual lung dysfunction.

The second phenotype was relapse. The reported frequency of relapse in sarcoidosis ranges from 16% to 74%, and relapse typically occurs during corticosteroid tapering (33). In the present study, patients with relapse were more often treated with corticosteroids and alternative drugs. In a large sample of sarcoidosis patients, Gottlieb noted that 74% of relapse episodes were associated with previous use of corticosteroids, occurring in only 8% of untreated cases (12). These findings can be explained by the higher initial severity seen in the treated cases, although some authors have suggested that corticosteroid therapy predisposes to clinical relapse (12, 33). In the present study, the patients experiencing relapse had longer symptom duration, more often had extensive systemic involvement, and showed greater dyspnea severity. Similarly, Hunninghake et al followed a group of treatment-naive sarcoidosis patients and found that those presenting with clinical and functional worsening had had longer symptom duration at diagnosis (34). Various studies of pulmonary sarcoidosis have demonstrated a correlation between symptom duration and prognosis (12, 13, 16, 35). Spontaneous resolution of radiographic lesions is more common in asymptomatic patients (12, 13). Another study found that sarcoidosis patients in whom dyspnea worsened over a two-year period were more likely to develop involvement of multiple organs (16). In a large longitudinal study of 254 sarcoidosis patients, respiratory symptoms at diagnosis were correlated with mortality (35).

Various studies have reported poor prognoses in patients with calcium metabolism abnormalities, cardiac involvement, or neurological involvement (6, 7, 10). In our study, those same variables were associated with relapse and with the use of drugs other than corticosteroids.

The third phenotype was residual airflow obstruction. Patients with residual obstruction showed lower FEV1/FVC ratios and longer symptom duration. At baseline, the prevalence of the restrictive pattern was similar to that of the obstructive pattern. In other studies, the reported prevalence of the obstructive and restrictive patterns is 4–67% and 6–100%, respectively (36). A common finding in pulmonary sarcoidosis is nodular thickening along the airway (or bronchovascular bundle), from the lobar to the subsegmental level, due to non-caseating granulomas in the bronchial mucosa (37). In an HRCT and bronchoscopy study of 60 sarcoidosis patients, conducted by Lenique et al (38), 65% of the patients had nodular or uniform thickening of the airways from the lobar to the subsegmental level. The authors found that bronchial abnormalities were associated with the presence of bronchial granulomas. In another study, pulmonary sarcoidosis was found to be accompanied by bronchomalacia in 11 (61%) of the 18 patients evaluated (39). Given the affinity of sarcoid granulomas for the airways, the bronchial and peribronchial granulomatous inflammation seen in sarcoidosis might weaken the bronchial walls, increasing their susceptibility to collapse (37). An interesting finding of our study was that residual obstruction was more common than was residual restriction (31% vs. 17%), suggesting that airflow limitation is most often irreversible. Residual restriction and obstruction were associated with significant pulmonary fibrosis in the final evaluation. These findings stress the value of spirometry for the evaluation of sarcoidosis patients. Wasfi et al found that functional parameters such as FVC%, FEV1/FVC ratio, and percentage of predicted diffusing capacity of the lung for carbon monoxide (DLCO%) are markers of sarcoidosis severity (6). Viskum showed that, in sarcoidosis, the degree of pulmonary dysfunction (total lung capacity < 80% and FEV1/FVC ratio < 70%) correlates with greater mortality (9).

The fourth phenotype was acute sarcoidosis, which was positively associated with recent disease, weight loss, lesser dyspnea severity, and the lower radiographic stages, especially stage II. This phenotype was correlated with a lower risk of progression to fibrosis. Acute sarcoidosis is typically associated with a high rate of spontaneous resolution (8, 10, 40). However, there is a special subgroup of individuals...
with acute onset of symptoms that progress to chronic disease, requiring long-term immunosuppressive therapy (8).

Relapse and acute disease were both associated with abnormal calcium metabolism, suggesting that, in these two situations, the granuloma burden is greater (41).

Extensive disease was more common in cases of recent sarcoidosis. This is probably attributable to the definition of extensive systemic disease employed in our study, which included calcium metabolism abnormalities (a component of the acute disease phenotype). When we excluded calcium from the definition of extensive sarcoidosis, we found no association between extensive and recent disease ($\chi^2 = 2.18$, $p = 0.14$). The calcium metabolism abnormalities seen in acute sarcoidosis indicate a marked acute phase response, likely associated with the high granuloma burden.

Constitutional symptoms are seen in a significant number of sarcoidosis patients. In a review of ten case series, the prevalence of weight loss, which typically occurred during the early stages of illness, was 16 - 54% (42). Weight loss was reported by 36% of our patients and was associated with acute disease and with a good prognosis.

Our study has one limitation inherent to retrospective analyses: the management of the selected cases did not follow a standardized protocol. For example, DLCO and gas exchange assessments during exercise were performed in a small number of cases and were therefore excluded from the analysis. Another limitation was selection bias, because the patients were treated at outpatient clinics that are referral centers for ILD, and our sample was therefore not representative of the general population of sarcoidosis patients. Conditions typically associated with a favorable prognosis, such as erythema nodosum and stage I, were uncommon. Stage IV disease was seen in 21% of the patients, a higher proportion than the 5 - 8% reported in large case-control studies (2, 43). However, our sample included many cases of chronic sarcoidosis with long-term follow-up, allowing us to identify phenotypes of sarcoidosis with complicated outcomes.

In recent years, the heterogeneity of sarcoidosis has aroused interest in investigating its phenotypes. In various diseases, the characterization of phenotypes is crucial to genetic mapping and correlation analysis with environmental variables. This has been shown in many studies of sarcoidosis (1, 5, 6, 44-46). None of the four phenotypes identified in our study correlated with environmental exposure to birds or mold.

The main phenotyping studies of sarcoidosis were based on previously defined phenotypes (6, 8). Such phenotypes have the disadvantage of not always adequately expressing the disease genotype (47).

Wasfi et al defined the phenotype of severe sarcoidosis using backward multiple linear regression, then creating and validating a disease severity scale. Variables included in the model were selected by an expert panel. The multivariable model for severity included cardiac involvement, neurological involvement, current therapy with nonsteroidal immunosuppressive agents, DLCO%, FEV1/FVC ratio, African-American race, FVC%, and skin involvement (6). Prasse et al described a protocol for clinical classifications of sarcoidosis activity considering the mode of disease onset (acute or chronic), as well as the need for and duration of treatment (8). The authors found that patients with acute disease more often had extrapulmonary involvement than did those with chronic disease. Patients with acute disease also required long-term treatment less often than did those with chronic disease, and the indication to treat was due predominantly to extrapulmonary involvement. Patients who were initially diagnosed with acute disease but later relapsed were reclassified as having chronic disease. Patients with stage IV disease had lower FVC and FEV1 values. In patients who required long-term treatment, there was a trend toward decreased pulmonary function at baseline. All patients with stage IV disease were classified as having chronic refractory disease, although the authors also included some stage 0, I, II, and III patients in this category.

From a statistical perspective, factor analysis is the best method of phenotype identification. Although our findings bear some similarity to those of the two studies cited above (6, 8), our sarcoidosis phenotypes, being derived from factor analysis, were more appropriate. Unlike other statistical methods, factor analysis does not use data for comparison or prediction, but follows an exploratory principle of analysis of variance. Its purpose is to examine the common nature, typically hidden, of the interrela-
tionships between multiple variables. The role of fac-
tor analysis is to reduce a large number of variables
to a smaller number of factors, which are grouped by
statistical association (26, 27).

In conclusion, sarcoidosis, including its chronic
form, can be categorized into different clinicalphe-
notypes. Phenotypes associated with chronic pro-
gression were more common in patients with longer
symptom duration at baseline. The most chronic
phenotype is that associated with relevant residual
pulmonary fibrosis. This phenotype can be predicted
by low FVC% and by more advanced radiographic
stage at presentation. The airflow limitation pheno-
type is also related to chronic disease, including pul-
monary fibrosis, and patients with this phenotype
more often present with baseline airflow obstruction.
Relapses are more common in patients with extra-
pulmonary involvement or greater baseline dyspnea
severity. The acute disease phenotype is associated
with better prognosis and a lower likelihood of de-
veloping pulmonary fibrosis.

The methodology used in the present study
should be applied to larger samples in order to con-
firm and expand upon our findings. Defining the
clinical phenotypes of sarcoidosis will make it possi-
ble to identify their genetic, immunological, and
pathological biomarkers, which will lead to the de-
velopment of safer, more appropriate, and more ef-
fective treatments for each phenotype.

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