Epidemiologic patterns of disease expression in sarcoidosis: age, gender and ethnicity-related differences

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Abstract

Objective

To evaluate the influence of age, gender and ethnicity in the clinical presentation of sarcoidosis in a cohort of Spanish patients.

Methods

We analysed 175 consecutive patients diagnosed with sarcoidosis between 1990 and 2014 in the Hospital Clinic of Barcelona, Spain. Sarcoidosis was diagnosed according to the 1999 WASOG criteria. Organ involvement was defined using the 2014 WASOG organ assessment instrument.

Results

There were 110 women and 65 men, with a mean age at diagnosis of 47.31 ± 15.46 years (range, 16-92); 23% of patients were born outside Spain. Women had a higher mean age (p=0.027), a higher frequency of cutaneous (OR=2.28) and musculoskeletal (OR=2.73) symptoms at diagnosis, and a lower frequency of cumulated WASOG involvements including renal involvement (OR=0.17), hypercalcaemia (OR=0.20) and raised ACE levels (OR=0.30). Patients aged ≥65 years had a lower frequency of cutaneous (OR=0.23) and musculoskeletal (OR=0.13) symptomatology at diagnosis and a higher frequency of cumulated WASOG involvements including renal involvement (OR=18.70) and calcium/vitamin D abnormalities (OR=5.31). According to ethnicity, non-Spanish-born patients had a lower mean age (40 vs. 49 years, p=0.001), a higher predominance of females (68% vs. 54%, p=0.036) and a higher frequency of radiographic stages I/II at diagnosis (97% vs. 78%, p=0.041) in comparison with Spanish-born patients.

Conclusion

Using the new 2014 WASOG organ assessment instrument, we found that epidemiological features (age at diagnosis, gender and ethnicity) play a significant role in the presentation of sarcoidosis. Variations in these epidemiological features may aid early diagnostic suspicion, the search for histopathological confirmation and the prompt introduction of the appropriate therapy.

Key words

sarcoidosis, ethnicity, epidemiology

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Introduction

Sarcoidosis is a systemic disease of unknown etiology characterised by the development of noncaseating epitheloid cell granulomas. The most commonly involved organ is the lung in more than 90% of cases, followed by the lymph nodes, the skin, and the eyes (1). The estimated prevalence varies from 1 to 40 cases per 100,000 individuals, and often affects young adults between 20 and 40 years of age, with a predominance in women (female:male ratio 1.2 to 1.5:1) (2). The diagnosis is established when clinical and radiologic findings are supported by histologic evidence of non-caseating granulomas (3). However, none of the diagnostic tests are pathognomonic. The natural history of sarcoidosis is highly variable: spontaneous remission is frequent and may occur in two out of three patients, while remaining cases have a chronic, progressive disease (3).

As in other systemic diseases, epidemiological profiles seem to have a significant influence on the disease presentation (4). Both the clinical presentation and the disease course may be extremely variable depending on the epidemiological features of patients. The age at diagnosis (5), gender (6), ethnicity (7) and geographical / environmental factors (8) have been reported as significant game-changers with respect to the clinical presentation of the disease. This often complicates an appropriate, prompt diagnosis of sarcoidosis, a disease that frequently mimics a wide variety of processes and which is often diagnosed after the exclusion of other diseases.

This study evaluates the influence of the main epidemiological features (age, gender and ethnicity) in the clinical presentation of sarcoidosis in a cohort of patients diagnosed at a Spanish urban tertiary teaching hospital.

Methods

Patients

We analysed 175 consecutive patients diagnosed with sarcoidosis (130 biopsy-proven, 45 clinically proven) between 1990 and 2014 in the Hospital Clinic of Barcelona (Spain), an urban tertiary teaching hospital. Sarcoidosis was diagnosed in agreement with the criteria proposed by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis (3): a) clinical or radiologic findings consistent with sarcoidosis, such as pulmonary disease, uveitis, mediastinal bilateral hilar lymphadenopathy (BHL), or erythema nodosum; b) tissue biopsy with histologic evidence of noncaseating granulomas; c) absence of other causes of granulomatous disease. However, most experts allow the inclusion of patients without histopathological studies, and thus patients with a clinically-proven diagnosis were included after fulfilling the following two criteria: a) clinical and/or radiographic features suggestive of sarcoidosis; and b) at least one diagnostic test suggestive of sarcoidosis, including elevated serum angiotensin-converting enzyme (ACE), raised liver and/or muscle serum enzymes, hypercalcaemia, abnormal uptake on gallium-67 citrate scintigraphy, elevated lymphocyte count, or elevated CD4/CD8 ratio in bronchoalveolar lavage fluid.

Variables

Variables were retrospectively collected at the time of diagnosis of sarcoidosis (defined as the date of the first positive histopathological result or, in cases without a positive or with no histopathology, the date of the clinical diagnosis of sarcoidosis). Variables included were: age, gender, country of birth, clinical manifestations at diagnosis (individual symptoms), radiographic stages classified as stage 0 (normal), stage I (BHL without pulmonary infiltrates), stage II (BHL plus pulmonary infiltrates), stage III (parenchymal infiltrates without BHL) and stage IV (extensive fibrosis with distortion or bullae), and laboratory parameters such as, ACE (>114 U/L), liver enzymes (aspartate aminotransferase -AST-, alanine aminotransferase -ALT- and/or gamma glutamyl transpeptidase >40 UI/L), muscle enzymes (creatinine kinase >105 U/L) and hypercalcaemia (serum calcium >10.5 mg/dL).

Organ involvement was retrospectively determined in each patient (at the time of diagnosis and cumulated during the

follow-up) using the 2014 WASOG organ assessment instrument (9). This recently proposed instrument may serve as guidance as to whether a clinical diagnosis of extrathoracic involvement can be made without performing a biopsy to demonstrate granulomatous inflammation. Clinical scenarios are classified into four categories (highly probable, at least probable, possible and indeterminate). For all of the 16 organs evaluated, the experts reached consensus that organ involvements classified as "highly/at least probable" represent sarcoidosis.

Statistical analysis

Descriptive data were presented as mean (S.D.) for continuous variables and number (%) for categorical variables. Categorical data were compared using the χ^2 and Fisher's exact tests. Continuous variables were analysed using the Student's *t*-test. Logistic multivariate regression models were constructed to analyse the association between the main clinical features identified as statistically-significant in the univariate comparisons ($p<0.05$) and the following independent epidemiological variables: gender (women *vs*. men), age at diagnosis (≤40 years, 40–65 years, ≥65 years) and country of birth (Spain vs other countries). The odds ratios (ORs) and their 95% CIs obtained in the logistic multivariate regression models were calculated. All significance tests were two-tailed and values of $p<0.05$ were considered significant. All analyses were conducted using the R v. 3.2.1 for Windows statistical software package.

Results

Clinical presentation at diagnosis

The cohort consisted of 175 patients, including 110 (63%) women and 65 (37%) men (female:male ratio, 1.7:1), with a mean age at diagnosis of 47.31±15.46 years (range, 16–92) (Table I). Forty-one (23%) patients were born outside Spain (16 in South America, 12 in Asia, 10 in Africa and 3 in other European countries).

Clinical features at the time of diagnosis are summarised in Table I. The most frequent symptoms at presentation con-

Table I. Clinical characterisation of 175 patients with sarcoidosis.

Variables at diagnosis	n=175 n (%)
Gender (male)	65 (37)
Age (mean ± SD)	47.31 ± 15.46
Country of birth	
- Spain	134 (76.6)
- South America	16 (9)
- Asia	12 (7)
- Africa	10 (6)
- Other European countries	3 (1.7)
Asymptomatic patients at diagnosis	21 (12)
Symptoms at diagnosis	
- Fever (>37.5 ºC)	40 (22.9)
- Fatigue	18 (10.3)
- Weight loss	16 (9.1)
- Cough	55 (31.4)
- Dyspnea	33 (18.9)
- Chest pain	3 (1.8)
- Erythema nodosum	51 (29.1)
- Other cutaneous lesions	39 (22.3)
- Joint pain	39 (22.3)
- Arthritis/periarthritis	8 (4.6)
- Myalgia	9 (5.1)
- Peripheral lymphadenopathies	21 (12.0)
- Sicca syndrome	14 (8.0)
- Uveitis	10 (5.7)
- CNS involvement	8 (4.6)
- Parotid enlargement	7 (4.0)
- Renal involvement	5 (2.9)
- Cardiac involvement	4 (2.3)
- Hypercalcaemia	3 (1.8)
- Testicular involvement	2 (1.1)
Radiological stages at diagnosis	170/175
- Normal	16 (9.4)
- Stage I	56 (32.9)
- Stage II	85 (50.0)
- Stage III	12 (7.1)
- Stage IV	1 (0.6)
Laboratory abnormalities at diagnosis	
- Liver enzymes (AST, ALT and/or GGT >40 UI/L)	71/156 (45.5)
- Muscle enzymes (creatinine kinase >105 U/L)	20/132 (15.2)
- Hypercalcaemia (> 10.5 mg/dL)	17/132 (12.9)
ACE (> 114 U/L)	43/97 (44)
Histological non-caseating granulomas	130/141 (92)
Cumulated organ involvement*	
Pulmonary involvement	162 (93)
Extrathoracic involvement	131 (75)
- Cutaneous involvement	59 (34)
- Extrathoracic lymph node involvement	31 (18)
- Calcium/Vitamin D	23 (13)
- Ocular involvement	16 (9)
- Liver involvement	14 (8)
- Salivary gland involvement	13 (7)
- Splenic involvement	11 (6)
- Renal involvement	11 (6)
- Neurological involvement	8 (5)
- Muscle involvement	4 (2)
- ENT involvement	3 (2)
- Bone/joint involvement	2 (1)
- Other involvements**	8 (5)

CNS: central nervous system, ENT: ear nose and throat.
*2014 WASOG organ assessment instrument (9); only included organ involvements classified as "highly/at least probable". **Testes (2), bone marrow (2), pancreas, gastrointestinal tract, tongue, breast.

Table II. Characterisation of sarcoidosis according to gender, age at diagnosis and country of birth: univariate comparison analysis.

Variables	Gender			Age at diagnosis				Country of birth		
	Male (n=65)	Female (n=110)	*p*-value	≤ 40 (n=67)	41 - 64 (n=84)	≥ 65 (n=24)	*p*-value	Non-Spain (n=41)	Spain (n=134)	*p-value*
Features at presentation										
Asymptomatic presentation	11 (16.9)	10 (9.1)	0.150	7 (10.4)	11 (13.1)	3 (12.5)	0.902	4 (9.8)	17 (12.7)	0.786
General symptoms	20 (30.8)	30 (27.3)	0.729	24 (35.8)	20 (23.8)	6 (25)	0.249	17 (41.5)	33 (24.6)	**0.048**
Pulmonary symptoms	27 (41.5)	50 (45.5)	0.639	32 (47.8)	34 (40.5)	11 (45.8)	0.661	19 (46.3)	58 (43.3)	0.858
Cutaneous symptoms	13 (20)	40 (36.4)	**0.027**	21 (31.3)	29 (34.5)	3 (12.5)	0.118	9 (22)	44 (32.8)	0.244
Musculoskeletal symptoms	11 (16.9)	30 (27.3)	0.141	26 (38.8)	13 (15.5)	2 (8.3)	**0.001**	13 (31.7)	28 (20.9)	0.205
Liver enzymes†	32/59 (54.2)	39/97 (40.2)	0.099	23/60 (38.3)	38/73 (52.1)	10/23 (43.5)	0.295	18/40 (45)	53/116 (45.7)	1.000
Muscle enzymes‡	12/49 (24.5)	8/83 (9.6)	**0.026**	10/52 (19.2)	7/60 (11.7)	3/20 (15)	0.542	8/36 (22.2)	12/96 (12.5)	0.180
Hypercalcaemia (>10.5 mg/dL)	10/44 (22.7)	7/88 (8)	**0.026**	3/47 (6.4)	9/63 (14.3)	5/22 (22.7)	0.155	2/32 (6.2)	15/100 (15)	0.242
ACE (>114 U/L)	23/39 (59)	20/58 (34.5)	**0.022**	13/37 (35.1)	22/43 (51.2)	8/17 (47.1)	0.360	15/29 (51.7)	28/68 (41.2)	0.378
Radiological stages			**0.002**				0.304			**0.041**
Normal	1/63 (1.6)	15/107 (14.0)		3/63 (4.8)	9/83 (10.8)	4/24 (16.7)		0	16/130 (12.3)	
Stage I	24/63 (38.1)	32/107 (29.9)		24/63 (38.0)	25/83 (30.1)	7/24 (29.2)		17/40 (42.5)	39/130 (30.0)	
Stage II	36/63 (57.1)	49/107 (45.8)		33/63 (52.4)	42/83 (50.6)	10/24 (41.7)		22/40 (55.0)	63/130 (48.5)	
Stage III	1/63 (1.6)	11/107 (10.3)		3/63 (4.8)	7/83 (8.5)	2/24 (8.3)		1/40 (2.5)	11/130 (8.5)	
Stage IV	1/63 (1.6)	0		0	0	1/24 (4.1)		0	1/130 (0.7)	
Cumulated WASOG organ involvement¶										
Pulmonary involvement	64 (98.5)	98 (89.1)	**0.033**	64 (95.5)	76 (90.5)	22 (91.7)	0.483	41 (100)	121 (90.3)	**0.040**
Cutaneous involvement	16 (24.6)	43 (39.1)	0.068	23 (34.3)	32 (38.1)	4 (16.7)	0.141	10 (24.4)	49 (36.6)	0.187
Liver involvement	6 (9.2)	8 (7.3)	0.774	6 (9)	6 (7.1)	2 (8.3)	0.929	4 (9.8)	10 (7.5)	0.742
Ocular involvement	4 (6.2)	12 (10.9)	0.417	8 (11.9)	5 (6)	3 (12.5)	0.337	7 (17.1)	9 (6.7)	***0.061***
Splenic involvement	5 (7.7)	6 (5.5)	0.540	1 (1.5)	7 (8.3)	3 (12.5)	**0.050**	1 (2.4)	10 (7.5)	0.462
Salivary gland involvement	4 (6.2)	9 (8.2)	0.770	4 (6)	7 (8.3)	2 (8.3)	0.788	5 (12.2)	8 (6)	0.187
ENT involvement	1 (1.5)	2 (1.8)	1.000	2 (3)	0 (0)	1 (4.2)	0.165	1 (2.4)	2 (1.5)	0.553
Calcium/Vitamin D	11 (16.9)	12 (10.9)	0.258	4 (6)	13 (15.5)	6 (25)	**0.032**	3 (7.3)	20 (14.9)	0.293
Bone/joint involvement	0 (0)	2 (1.8)	0.530	0 (0)	1 (1.2)	1 (4.2)	0.256	0 (0)	2 (1.5)	1.000
Muscle involvement	2 (3.1)	2 (1.8)	0.628	1 (1.5)	2 (2.4)	1 (4.2)	0.627	1 (2.4)	3 (2.2)	1.000
Extrathoracic lymph node	12 (18.5)	19 (17.3)	0.840	13 (19.4)	14 (16.7)	4 (16.7)	0.926	5 (12.2)	26 (19.4)	0.356
Renal involvement	8 (12.3)	3 (2.7)	**0.020**	1 (1.5)	7 (8.3)	3 (12.5)	**0.050**	4 (9.8)	7 (5.2)	0.287
Neurological involvement	6 (9.2)	2 (1.8)	***0.053***	6 (9)	2 (2.4)	0 (0)	0.136	3 (7.3)	5 (3.7)	0.393

†AST, ALT and/or GGT >40 UI/L; ‡creatinine kinase >105 U/L; ENT: ear, nose and throat involvement. ¶2014 WASOG organ assessment instrument (9); only included organ involvements classified as "highly/at least probable".

sisted of cough in 55 (31%) patients, erythema nodosum in 51 (29%), fever in 40 (23%) and joint pain in 39 (22%) patients. In 21 (12%) patients, sarcoidosis was diagnosed in asymptomatic patients due to incidental radiological findings; there were 10 women and 11 men, with a mean age at diagnosis of 49 years and all but 4 were born in Spain. With respect to diagnostic tests, data on the radiographic stage at diagnosis was available in all but five patients, with stage II (50%) and stage I (33%) being the most frequently-reported patterns. With respect to laboratory abnormalities, 71/156 (45%) patients had raised liver enzymes, 43/97 (44%) raised ACE levels, 20/132 (15%) raised muscle enzymes and 17/132 (13%) hypercalcaemia (Table I). Histopathological studies showed a biopsy at diagnosis compatible with sarcoidosis in 130/141 (92%) patients; in the remaining 34 patients, no biopsy was performed or information was not available; multiple biopsies were made 28/141 (20%) patients. The organs most-frequently biopsied were the lungs (n=73), skin (n=26), extrathoracic lymph nodes (n=17) and the liver (n=15).

Cumulative organ-specific involvement according to the 2014 WASOG classification is summarised in Table I. Pulmonary involvement was reported in 162 (93%) patients. Extrathoracic involvement was reported in 131 (75%) patients, with the most frequent sites being the skin (34%), extrathoracic lymph nodes (18%) and calcium/vitamin D abnormalities (13%).

Sarcoidosis in men

Of the 175 patients with sarcoidosis, 65 (37%) were men. At diagnosis, men had a lower mean age (44 *vs*. 49 years, *p*=0.027), a lower frequency of cutaneous symptoms (20% *vs*. 36%, *p*=0.027), a higher frequency of radiographic stages I/II (95% *vs*. 76%, *p*=0.002) and a higher frequency of laboratory abnormalities including raised ACE levels (59% *vs*. 34%, *p*=0.022), raised muscle enzymes (24% *vs*. 10%, *p*=0.026) and hypercalcaemia (23% *vs*. 8%, *p*=0.026) in comparison with women (Table II). With respect to the cumulative organ-specific involvement classified according to the 2014 WASOG criteria, men had a higher frequency of pulmonary (98% *vs*. 89%, *p*=0.033), renal (12% *vs*. 3%, *p*=0.02) and neurological (9% *vs*. 2%, *p*=0.053) involvements in comparison with women (Table II).

Age at diagnosis

In 67 (38%) patients, sarcoidosis was diagnosed before the age of ≤40, in 84 (48%) between 41 and 64 years and in 24 (14%) after the age of ≥65. At diagnosis, patients aged ≤40 years had a greater frequency of musculoskeletal symptomatology (39% *vs*. 15% *vs*. 8%, *p*=0.001). With respect to the cumulative organ-specific involvement classified according to the 2014 WASOG

criteria, patients aged ≤40 years had a lower frequency of splenic involvement (1% *vs*. 8% *vs*. 12%, *p*=0.05), calcium/vitamin D abnormalities (6% *vs*. 15% *vs*. 25%, *p*=0.032) and renal involvement (1% *vs*. 8% *vs*. 12%, *p*=0.05) (Table II). Radiographic stages I/II were more frequently seen in younger patients (Fig. 1).

Sarcoidosis in non-Spanish patients

Of the 175 patients with sarcoidosis, 41 (23%) were born outside Spain. At diagnosis, non-Spanish-born patients had a lower mean age (40 *vs*. 49 years, *p*=0.001), a higher predominance of females (68% *vs*. 54%, *p*=0.036), and a higher frequency of general symptomatology (41% *vs*. 25%, *p*=0.048) (Table II). The radiographic presentation consisted of stages I/II in all cases but one (97% *vs*. 78% in Spanish-born patients, *p*=0.041), especially in non-Spanish men, while Spanish women had a differentiated pattern of pulmonary involvement with a higher frequency of stage 0 but also a higher frequency of stage III in comparison with Spanish men (*p*=0.017) (Fig. 2). In addition, females from Latin America and Europe had more-advanced radiographic stages (III), while African males showed a predominance of the least-severe stage (I) (Fig. 3).

With respect to the cumulative organ-specific involvement classified according to the 2014 WASOG criteria, non-Spanish-born patients had a higher frequency of pulmonary involvement (100% *vs*. 90%, *p*=0.04) and a trend for a higher frequency of ocular involvement (17% *vs*. 7%, *p*=0.06) in comparison with Spanish-born patients (Table II).

Epidemiological multivariate regression model

Logistic multivariate regression models analysed the association between the main clinical features and the epidemiological variables, and found that women had a higher frequency of cutaneous (OR=2.28) and musculoskeletal (OR=2.73) symptoms, and lower frequency of hypercalcaemia (OR=0.20) and raised ACE levels (OR=0.30) at diagnosis and a lower frequency of 2014 WASOG renal involvement (OR=0.17), while patients aged ≥65 years had a lower frequency of cutaneous (OR=0.23) and musculoskeletal (OR=0.13) symptomatology at diagnosis and a higher frequency of 2014 WASOG renal involvement (OR=18.70) and calcium/vitamin D abnormalities (OR=5.31) (Table III).

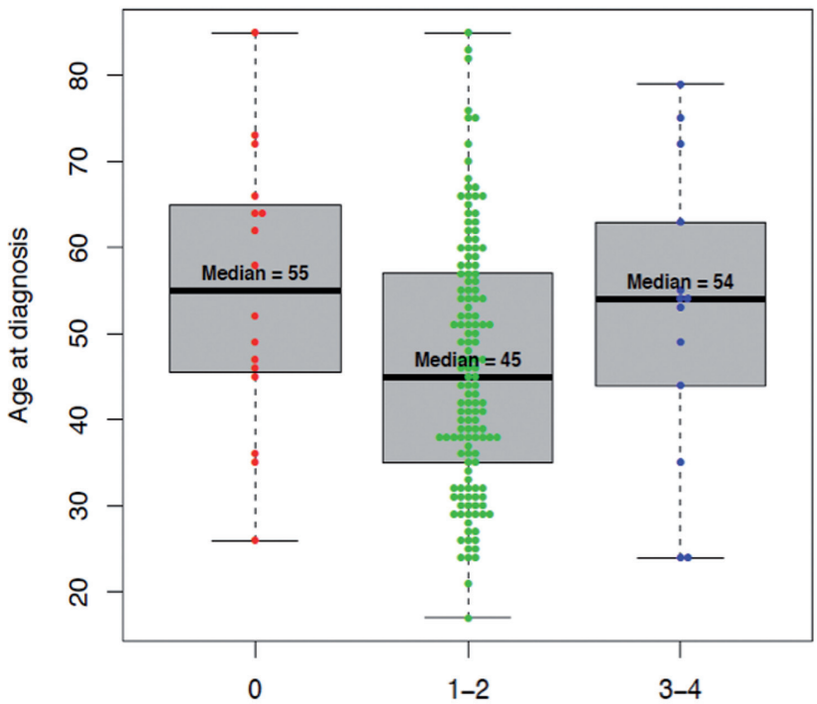

Fig. 1. Mean age at diagnosis according to radiographic pulmonary stages.

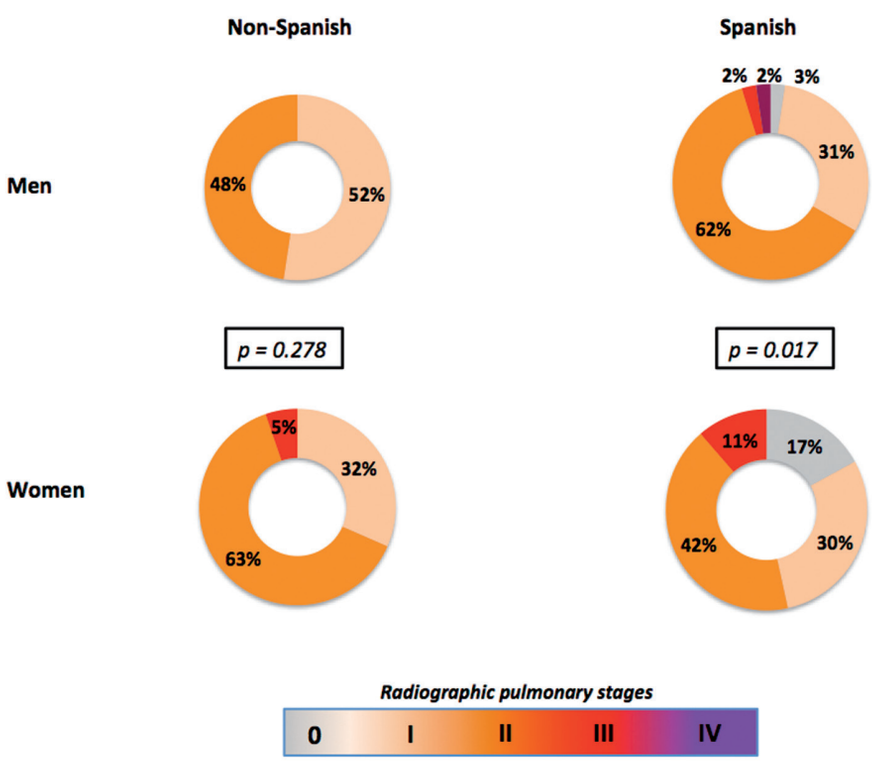

Fig. 2. Radiographic pulmonary stages at diagnosis according to gender and country of birth.

Discussion

Sarcoidosis is probably one of the systemic diseases in which epidemiologi-

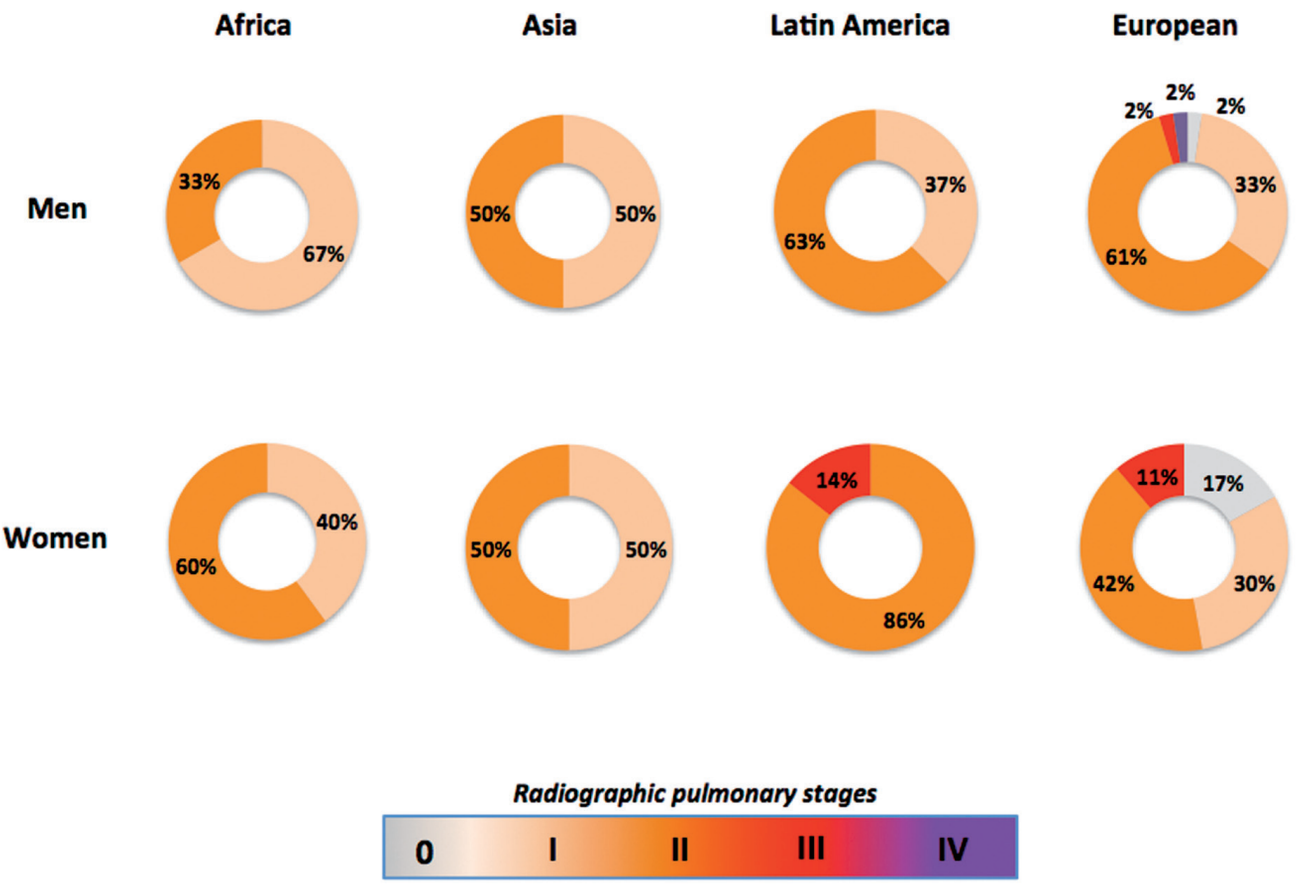

Fig. 3. Radiographic pulmonary stages at diagnosis according to gender and continent of birth.

Table III. Independent epidemiological variables associated with the main clinical features (logistic multivariate regression).

Variables	Gender[a] Female	Age at diagnosis[b] 41 - 64	Age at diagnosis[b] ≥ 65	Country of birth[c] Spain
Features at presentation				
General symptoms	1.02 [0.50 - 2.06]	0.60 [0.29 - 1.24]	0.74 [0.25 - 2.18]	0.49 [0.23 - 1.06]
Cutaneous symptoms	**2.28 [1.08 - 4.81]**	0.97 [0.48 - 1.98]	**0.23 [0.06 - 0.88]**	1.79 [0.76 - 4.21]
Musculoskeletal symptoms	**2.73 [1.17 - 6.38]**	**0.25 [0.11 - 0.57]**	**0.13 [0.03 - 0.64]**	0.63 [0.27 - 1.48]
Muscle enzymes[‡]	0.38 [0.14 - 1.04]	0.71 [0.24 - 2.10]	1.07 [0.24 - 4.75]	0.60 [0.21 - 1.73]
Hypercalcaemia (>10.5 mg/dL)	**0.20 [0.06 - 0.61]**	3.29 [0.77 - 14.00]	4.65 [0.91 - 23.82]	3.20 [0.62 - 16.58]
ACE (>114 U/L)	**0.30 [0.12 - 0.75]**	**2.76 [1.02 - 7.47]**	2.53 [0.69 - 9.30]	0.60 [0.23 - 1.58]
Cumulated organ involvement[¶]				
Pulmonary involvement	0.16 [0.02 - 1.32]	0.62 [0.15 - 2.52]	0.91 [0.14 - 6.05]	0 [0 - Inf]
Splenic involvement	0.48 [0.13 - 1.72]	6.25 [0.73 - 53.15]	8.83 [0.84 - 93.01]	2.84 [0.33 - 24.60]
Calcium/Vitamin D	0.44 [0.17 - 1.12]	3.11 [0.94 - 10.30]	**5.31 [1.29 - 21.92]**	2.07 [0.55 - 7.89]
Renal involvement	**0.17 [0.04 - 0.70]**	**8.95 [1.03 - 77.99]**	**18.70 [1.59 - 219.28]**	0.46 [0.11 - 1.97]

All values are OR (95% CI). Reference level: a Male, b ≤40, c Non-Spain. [‡]creatinine kinase >105 U/L, [¶]2014 WASOG organ assessment instrument (9); only included organ involvements classified as "highly/at least probable".

cal and environmental factors have a capital influence on the disease aetiopathogenesis. The clinical presentation of sarcoidosis is heterogeneous, due to the high variability caused by epidemiological factors that include age at onset, gender, ethnicity, geographical factors and exposure to infections/toxics. The seasonal clustering of the diagnosis of cases of sarcoidosis, a higher incidence rate in specific occupations (healthcare/military professionals, agricultural workers, fire/rescue workers, professions with high exposure to organic dust/wood dust/wood burning/metal dust), and the strong association found with lower income groups, are epidemiological findings that support a close link between the environment and sarcoidosis (8, 11, 12).

Age clearly influences the clinical expression of sarcoidosis (13), as does ethnicity and the healthcare settings where studies are conducted. We found a mean age at diagnosis of 47 years in our cohort, significantly higher than the mean found in large Danish (14)

and German (15) studies but similar to that reported in UK studies (16, 17). A diverse ethnic mix or the study setting (hospital *vs*. primary care) may be possible explanations, as some non-complicated, self-limiting cases (Löfgren syndrome, which predominates at younger ages and in some ethnic groups) may be seen and followed exclusively in primary care centres (18).

We found that patients diagnosed before the age of ≤40 had a higher frequency of musculoskeletal symptoms and neurological involvement, but a lower frequency of renal and splenic involvement, while patients with disease onset after the age of ≥65 had a lower frequency of cutaneous/musculoskeletal symptoms and less or no neurological involvement. With respect to pulmonary involvement, radiographic stages I/II were more frequently seen in younger patients. Previous studies in different settings and populations have found very similar results. In Japan, epidemiological surveys suggested a gradual increase in the incidence of sarcoidosis in women after 50 years of age, a reduced occurrence of bilateral hilar lymphadenopathy and an increase in ocular/cardiac involvement (19). Yanardag *et al*. (20) found that arthritis, Löfgren syndrome, erythema nodosum, and uveitis were less frequent in older patients, while Lenner *et al*. (21) found that patients with late-onset and young-onset were statistically similar in terms of other extrapulmonary involvements, clinical pulmonary signs, radiographic stage, and pulmonary function tests.

Gender is also a significant epidemiological determinant in the presentation of sarcoidosis. As with many other systemic autoimmune diseases, sarcoidosis more frequently affects females than males. The largest studies found a female:male ratio ranging from 1.1 (16, 22) to 1.4 (15). A more-recent study of patients evaluated at a tertiary referral centre found that 65.5% were female (23), a very similar percentage to our cohort. In this study, males developed the symptoms of sarcoidosis and were diagnosed approximately two years earlier than females (23): in our study the difference was five years. A second gender-related feature is the second peak of sarcoidosis incidence in women diagnosed after 50 years of age (24, 25). Late-onset sarcoidosis is more common in females than in males, which may explain the increased mean age at diagnosis reported in females compared with males (23), as in our study. One study reported that 70.3% of women were diagnosed at ≥ 70 years of age (26), while Varron et al (5) found that 83% of patients with sarcoidosis were diagnosed at ≥65 years of age; our study found a rate of 71%, confirming that sarcoidosis affects females an older age than males. The older age at diagnosis in females was more frequently associated with a lack of pulmonary involvement (extrathoracic sarcoidosis) or with more-severe pulmonary stages (stage III) (Fig. 1); previous studies have found that females are more likely to have systemic disease (27, 28) and more-severe pulmonary involvement than males (29).

Our results show that gender was the most powerful epidemiological determinant influencing the clinical presentation of sarcoidosis: women had a higher mean age at diagnosis, a higher frequency of cutaneous symptoms, and a lower frequency of pulmonary stages I/II, renal and neurological involvement and abnormal laboratory parameters (including raised ACE levels, hypercalcaemia and raised muscle levels) compared with males. Studies have found that males tended to have higher rates of pulmonary and cardiac involvement, while female patients tended to present greater peripheral lymph node, skin, eye, and liver involvement (23, 30, 31). A prospective US study of patients with newly- diagnosed sarcoidosis reported that females were more likely to have erythema nodosum than males, although no significant differences were found in other cutaneous manifestations (24).

Sarcoidosis occurs worldwide, although there are large regional variations in prevalence. The estimated prevalence in Europe ranges between

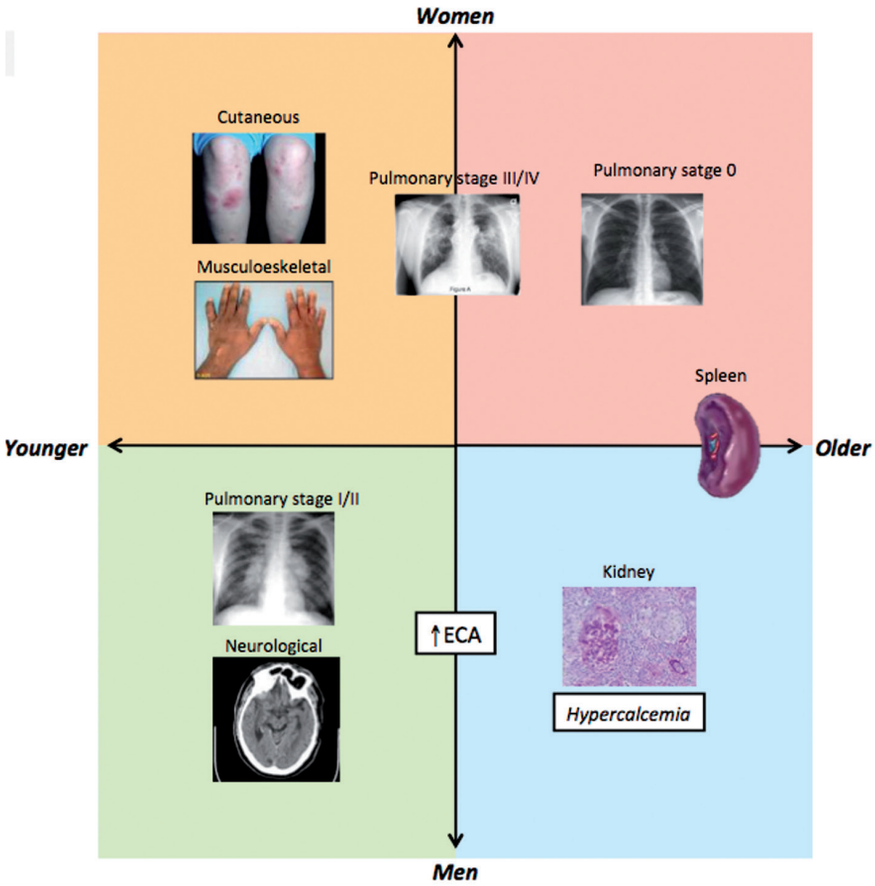

Fig. 4. Clusters of association of the main clinical, radiological and laboratory abnormalities according to the combination of gender and age at diagnosis of sarcoidosis.

4 and 11 cases per 100,000 inhabitants, with a significantly higher rate in countries such as Ireland (21-85 cases) and Sweden (64 cases) (8). In multiethnic cohorts from London, there was a wide variation according to ethnic background, with higher figures for West Indian (58 cases), Irish (21 cases), and Asian (14 cases) patients with respect to UK-born (4 cases) patients (32). In US multiethnic populations, sarcoidosis is more common in African Americans, with rates as high as 40 cases per 100,000 inhabitants, higher than people of white European origin (5-11 cases) (33). An African study found a similar disproportion in the prevalence among blacks (23.2/100,000), whites (3.7/100,000), and persons of mixed race (11.6/100,000) (34). In Latin-America, sarcoidosis has been rarely reported in Mexico, Costa Rica, Cuba and Argentina (35, 36); the largest studies have been reported in Brazil (37, 38), including some series in which mestizos and African-American patients accounted for more than 75% of cases (39). Differences in the prevalence and phenotype between racial groups might also be influenced by socioeconomic disparity leading to greater environmental exposure (40). Surprisingly, nearly 25% of our patients were born outside Spain, an epidemiological feature unreported until now, and one that might suggest that non-Europeans from Latin America, Africa and Asia may be at higher risk of sarcoidosis. The proportion of immigrants in Spain in 2014 was half the proportion found in our cohort with sarcoidosis (13%). Patients born outside Spain were younger (mean age 40 years), more frequently female and had a higher frequency of musculoskeletal symptomatology, pulmonary involvement (with the radiographic presentation being stages I/II in all cases but one, Fig. 2) and ocular involvement compared with Spanish patients. We found more-advanced radiographic stages in females from Latin America and Europe, and a predominance of the least-severe stage (I) in African males (Fig. 3). This suggests that non-Spanish immigrants have a very-specific clinical and radiographic pattern, which may aid the diagnosis.

Epidemiological features play a key role in the clinical, laboratory and radiological features presented at diagnosis. Figure 4 summarises the complex heterogeneity of clinical, radiological and laboratory abnormalities according to the combination of gender and age at diagnosis: young women predominantly have erythema nodosum and musculoskeletal involvement, young men pulmonary stages I/II and neurological involvement, older women no pulmonary involvement and older men hypercalcaemia.

In conclusion, age, gender and ethnicity play a significant role in the presentation of sarcoidosis and the variations in these factors may aid early diagnostic suspicion, the search for histopathological confirmation and the prompt introduction of the appropriate therapy.

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