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Influence of Gender on Epidemiology and Clinical Manifestations of Sarcoidosis: A Population-Based Retrospective Cohort Study 1976-2013

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Abstract

Purpose—The influence of ethnicity on epidemiology and clinical manifestations of sarcoidosis is well recognized. However, data on the role of sex are limited.

Methods—The current study utilized the resource of the Rochester Epidemiology Project to identify all residents of Olmsted County, Minnesota, United States, with new diagnosis of sarcoidosis from 1976 to 2013. Diagnosis was verified by medical record and histopathological report review.

Results—345 incident cases of sarcoidosis were identified; 174 (50%) females and 171 (50%) male. The age at diagnosis was significantly higher among females than males (48.3 years versus 42.8 years; $p < 0.001$). Intra-thoracic disease was seen in the great majority of patients (98% among females and 96% among males; $p = 0.50$). However, pulmonary symptoms were significantly more frequent among males than females (51% versus 36%; $p = 0.006$). The frequency of individual extra-thoracic organ involvement was not significantly different between females and males except for cutaneous involvement and uveitis that were significantly more common among females (6% versus 1% for uveitis, $p = 0.012$ and 25% versus 12% for cutaneous involvement, $p = 0.002$). The frequency of elevate angiotensin converting-enzyme level and hypercalcemia was not significantly different between the 2 sexes.

Conclusions—Females tended to be older at the age they developed sarcoidosis, and had more uveitis and cutaneous involvement than males.

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Keywords

Sarcoidosis; epidemiology; sex; clinical manifestation

Introduction

Sarcoidosis is a chronic granulomatous disorder that primarily affects the lungs and intra-thoracic lymph node. Extra-thoracic involvement is also common. The pathogenesis of sarcoidosis is not well-understood and its etiologies are yet to be identified. A large case-control study has reported an association between sarcoidosis and several occupational and environmental exposures such as insecticides, birds and molds [1]. Further investigations are still required to examine the role of these and other exposures in the etiopathogenesis of the disease.

The influence of ethnicity on epidemiology of sarcoidosis is well recognized. Sarcoidosis is commonly seen in blacks in whom the incidence is approximately 4 to 10 times higher than whites [2, 3]. It is rare among Asians [4]. The clinical phenotype of sarcoidosis varies among different ethnic groups. For example, eye, skin and bone marrow involvement are more common among blacks, while hypercalcemia is more prevalent among whites [5].

The influence of sex on epidemiology and clinical phenotype of several autoimmune disorders, such as systemic lupus erythematosus, ankylosing spondylitis and multiple sclerosis, is well known [6]. However, data on the role of sex on sarcoidosis are limited. The current study aimed to better characterize the epidemiology and clinical disease manifestation of females and males with sarcoidosis using the cohort of patients with incident sarcoidosis in Olmsted County, Minnesota (MN), United States from 1976 to 2013.

Patients and methods

Participants and study design

This study utilized the resources of the Rochester Epidemiology Project (REP) which provided a comprehensive access to medical records of residents of Olmsted County, MN, from all local health care providers including the Mayo Clinic, the Olmsted Medical Center and their affiliated hospitals, local nursing homes and the few private practitioners for over six decades. The REP database collects diagnostic codes from every encounter between residents of Olmsted County, Minnesota, USA and all local healthcare providers. Therefore, virtually, all clinically recognized cases of sarcoidosis could be identified from this database, ensuring complete case ascertainment. The potential use of this record linkage system for population-based epidemiologic studies has previously been described [7].

Potential cases of sarcoidosis from 1976 to 2013 were retrieved using diagnosis codes related to sarcoid, sarcoidosis and noncaseating granuloma. Medical records of these potential cases were individually reviewed. Inclusion required physician diagnosis supported by presence of non-caseating granuloma on histopathology, radiologic features of intrathoracic sarcoidosis, compatible clinical presentation and exclusion of other granulomatous diseases such as tuberculosis and fungal infection. The only exception to the

requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only evidence of symmetric bilateral hilar adenopathy on radiographic imaging in the absence other identifiable alternative causes. Isolated granulomatous disease of a specific organ except for the skin was also classified as sarcoidosis given that there was no better alternative diagnosis [8]. Cases with known diagnosis of sarcoidosis prior to residency in Olmsted County were not included.

A standardized data extraction form was used to record the following information: demographic data (age at diagnosis, sex and self-reported ethnicity), length of follow up, status at last follow up (death or alive), presence of intrathoracic disease, presence of symptoms related to intrathoracic disease (cough, dyspnea and chest pain), presence of extrathoracic disease (uveitis, arthritis/arthralgia, nervous system, skin rash, gastrointestinal, liver, spleen, heart, bone, kidney, endocrine gland and exocrine gland), angiotensin converting enzyme (ACE) level and calcium level.

Statistical analysis

Descriptive statistics (percentages, mean, etc.) were used to summarize the characteristics of each cohort. Comparisons between cohorts were performed using Chi-square and rank sum tests. ACE and calcium level were categorized as high versus normal/low. A logistic regression model was used to assess the association between presence of pulmonary symptoms and sex adjusted for smoking status. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population estimates for adults (age ≥ 18 years) based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years. Overall incidence rates were age- and/or sex-adjusted to the 2010 white population of the United States. A p-value of less than 0.05 was considered statistically significant for all analyses. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

345 incident cases of sarcoidosis were identified. 174 (50%) of them were female and 171 (50%) of them were male, corresponding to the incidence rate of 11.0 per 100,000 population for females and 10.5 per 100,000 population for males. The age at diagnosis was significantly higher among females (48.3 years) than males (42.8 years; $p < 0.001$). Among females, there were 154 (90%) Caucasians, 7 (4%) African-Americans and 5 (3%) Asians. Among males, there were 147 (90%) Caucasians, 11 (7%) African-Americans and 1 (1%) Asians. The ethnical composition was not significantly different between the 2 sexes ($p = 0.15$). Among females, at diagnosis, there were 108 (64%) never smokers, 38 (22%) ex-smokers and 24 (14%) current smokers. Among males, at diagnosis, there were 90 (55%) never smokers, 33 (20%) ex-smokers and 39 (24%) current smokers.

Intra-thoracic disease was seen in the great majority of patients (98% among females and 96% among males; $p = 0.50$). However, pulmonary symptoms, including cough, dyspnea and chest pain, were significantly more frequent among males than females (51% versus 36%; $p = 0.006$). This difference persisted after adjustment for smoking status ($p=0.007$).

The frequency of individual extra-thoracic organ involvement was not significantly different between females and males except for cutaneous involvement and uveitis that were significantly more common among females (6% versus 1% for uveitis, p = 0.012 and 25% versus 12% for cutaneous involvement, p = 0.002). The frequency of high ACE level and hypercalcemia was similar between the 2 sexes. High ACE level was observed in 42% of females and 42% of males (p = 0.98). Hypercalcemia was observed in 9% of females and 12% of males (p = 0.40). The data on laboratory investigations and clinical manifestations of sarcoidosis by sex are summarized in **Table 1**.

Discussion

The current study is the first population-based study with comprehensive medical record review to investigate clinical phenotypes of sarcoidosis in females and males. There was no sex predilection for sarcoidosis in this cohort, with the female to male incidence rate ratio of 1:1. This observation is different from previous studies, which generally describe a slightly higher incidence among females, ranging from the female to male incidence rate ratio of 1.3 to 1.8 [2, 4, 9]. Differences in the demographic background of this to other studied populations may be responsible for the variability in the incidence estimates. As well, differences in the ratio of males to females may relate to study design, as the current study utilized a population-based cohort while most of the previous studies were referral-based. The mean age at diagnosis was higher in females than males. This age difference has been observed in other cohorts as well [9-11].

The vast majority of patients in this cohort had intra-thoracic disease. However, only half of males and approximately one-third of females had pulmonary symptoms. It is unclear why asymptomatic disease was more common among females. Among possible explanations may be the different patterns of healthcare utilization between the 2 sexes, as females might have a higher likelihood to undergo screening examination than males and, thus, a higher likelihood of detecting asymptomatic lesions.

The frequency of extra-thoracic organ involvement was similar between females and males except for uveitis and skin rash. The higher prevalence of ocular and cutaneous involvement has been observed in other populations with different ethnic backgrounds [4, 10-13]. Differences in the prevalence of sarcoidosis involvement have been reported in other organs such as heart, liver and extra-thoracic lymph node as well [4, 10, 11]. However, these differences have not been consistently observed across different cohorts and were not observed in the current study. It is also possible that the higher frequency of ocular and cutaneous involvement among females could lead to more thoracic imaging and detection of asymptomatic pulmonary involvement.

The prevalence of high ACE level and hypercalcemia were similar between females and males in this cohort. Interestingly, one study has reported a higher percentage of elevated ACE level and hypercalcemia [10] in males than females, but this observation is not consistent across studies [4, 11].

The major strengths of this study include that it is a population-based study using a comprehensive diagnostic index that allows identification of nearly all of the clinically recognized cases of sarcoidosis in the community. This approach minimizes the likelihood of referral bias toward more severe cases. Risk of misclassification is also minimized as the diagnosis of sarcoidosis in this study was confirmed by individual medical record and histopathology report review, unlike administrative database-based studies that usually relied on diagnostic codes.

The major limitations are those associated with the retrospective nature of the study. Data on clinical manifestations as well as laboratory investigations of the patients were not systematically obtained and recorded. Therefore, some of the pertinent data might not be available. For example, data on ACE and calcium levels were not available in 17% and 15% of patients, respectively. The ethnic background of this cohort is predominately of Northern European ancestry. Therefore, the results might not be generalizable to other populations, as the influence of sex on the clinical phenotype of patients with other ethnicity could be different. Moreover, there is a higher proportion of health-care workers in Olmsted County which might affect the pattern of healthcare utilization and disease detection.

Conclusion

There is no difference in sex predilection for developing sarcoidosis. In this study, females tended to be older at the age they developed sarcoidosis, and had more uveitis and cutaneous involvement than males.

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Table 1

Clinical characteristics of females and males with sarcoidosis

	Females (N=174)	Males (N=171)	p value
Mean age at diagnosis in years (SD)	48.3 (14.1)	42.8 (12.6)	< 0.001
Ethnicity			0.15
Caucasian	154 (90%)	147 (90%)	
African-American	7 (4%)	11 (7%)	
Asian	5 (3%)	1 (1%)	
Native American	0 (0%)	2 (1%)	
Other	5 (3%)	2 (1%)	
Unknown	3	8	
Smoking status at diagnosis			0.068
Never	108 (64%)	90 (56%)	
Ex-smoker	38 (22%)	33 (20%)	
Current smoker	24 (14%)	39 (24%)	
Unknown	4	9	
Intra-thoracic involvement			
Any intra-thoracic involvement	170 (98%)	165 (96%)	0.50
Lung parenchymal disease	78 (46%)	91 (55%)	0.09
Intra-thoracic lymphadenopathy	151 (89%)	142 (86%)	0.45
Pulmonary symptoms	61 (36%)	84 (51%)	0.006
Extra-thoracic involvement			
Uveitis	11 (6%)	2 (1%)	0.012
Joint	24 (14%)	18 (11%)	0.35
Nervous system	6 (3%)	6 (3%)	0.78
Cutaneous	43 (25%)	20 (12%)	0.002
Gastrointestinal	0 (0%)	1 (1%)	0.31
Hepatic	10 (6%)	10 (6%)	0.97
Spleen	6 (3%)	7 (4%)	0.75
Cardiac	3 (2%)	1 (1%)	0.32
Bone	1 (1%)	0 (0%)	0.32
Renal	6 (3%)	6 (4%)	0.98
Endocrine gland	1 (1%)	1 (1%)	0.99
Exocrine gland	4 (2%)	3 (2%)	0.72
Laboratory measures			
High ACE level	60 of 142 tested patients (42%)	61 of 145 tested patients (42%)	0.98
Hypercalcemia	14 of 150 tested patients (9%)	18 of 145 tested patients (12%)	0.40

SD, standard deviation; ACE, angiotensin converting enzyme