

Prevalence of atopic diseases in patients with sarcoidosis

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ABSTRACT

It remains unclear whether atopy is associated with the occurrence of sarcoidosis or affects its severity. The purpose of this study was to compare the lifetime prevalence of atopic eczema, asthma, and hay fever in sarcoidosis patients with controls and to assess whether atopy influences the severity of sarcoidosis. The prevalence of atopic disorders assessed with a validated postal questionnaire in sarcoidosis patients with pulmonary, uveitis, and cutaneous sarcoidosis was compared with that of their domestic partners in a case-control study. The serological parameters, the pulmonary function tests, and the high-resolution computed tomography (HRCT) scans of atopic and nonatopic sarcoidosis patients were compared in a nested cohort. Multivariate logistic regression models were used to calculate the odds ratios (ORs) and the 95% confidence intervals (CIs). Two hundred twenty-five sarcoidosis patients and 177 controls were included. The prevalences of atopic eczema, asthma, and hay fever were comparable between patients and controls (12.4% versus 12.4%, 5.3% versus 5.6%, and 16.9% versus 15.8%, respectively). After adjusting for gender and ethnicity, those with sarcoidosis and a history of atopic eczema were significantly less likely to have uveitis (OR, 0.30; 95% CI, 0.13–0.71). Within the sarcoidosis cohort, the distributions of serological markers, the lung function tests, and the HRCT scans were similar between atopic and nonatopic patients. Atopy is not associated with the occurrence of sarcoidosis, but atopic eczema may decrease the likelihood of eye involvement.

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Sarcoidosis is a systemic granulomatous disease of variable clinical presentation and course. Over 90% of the patients have thoracic involvement, but the skin, eyes, and other organs may also be affected.¹ The annual incidence is estimated at 20/100,000.² It is thought to be mainly T-helper type 1 (Th1) driven, but the exact etiology is unknown. Predisposing factors for sarcoidosis are black race, female sex, age between 20 and 40 years, and a family history of sarcoidosis.³ An uncontrolled study in 41 Turkish sarcoidosis patients revealed a lower prevalence of asthma and positive skin-prick tests when compared with the expected rate based on national data.⁴ Two studies by Hattori *et al.*, reported lower total serum immunoglobulin E (IgE) in sarcoidosis patients and fewer parenchymal lung lesions in chest x rays in atopic sarcoidosis patients (19% versus 37%; $p = 0.018$).^{5,6} However, no evidence of a lower prevalence of atopic asthma was found in a cross-sectional survey among 136 sarcoidosis patients.⁷ Therefore, it remains unclear whether the prevalence of atopic disorders is decreased in sarcoidosis patients and whether atopy affects the severity of sarcoidosis. In this case-control study, the association between

atopic disorders, sarcoidosis, and detailed sarcoidosis characteristics in the largest cohort to date was investigated.

PATIENTS AND METHODS

Study Population

We approached by 371 consecutive patients with sarcoidosis diagnosed between 2000 and 2012 at the Clinical Immunology Outpatient Clinic at the Erasmus Medical Center (Rotterdam, the Netherlands). Our center is a tertiary referral center with expertise in sarcoid uveitis and cutaneous sarcoidosis. Patients' medical records were available to the study team. The spouses/partners of the contacted patients were asked to act as controls. Participants were considered to be of Dutch ancestry if both of their parents were born in the Netherlands. Caribbean and Suriname subjects were those in whom one of the parents was born either in Suriname or the Caribbean. This study was conducted in accordance with the Declaration of Helsinki and the medical Ethical Committee of the Erasmus Medical Center provided a waiver for this single-subject questionnaire-based study.

Patient-Reported Atopic Features

Patients were sent an invitation letter, the questionnaire, and a prepaid return envelope. Nonresponders were contacted a second time *via* mail. The definitions of the atopic features (*i.e.*, atopic eczema, hay fever, and asthma) were self-reported and based on items from the European Community Respiratory Health

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Table 1 Subject characteristics

	Sarcoidosis Patients <i>n</i> = 225	Controls <i>n</i> = 177	<i>p</i> Value
Median age, yr (IQR)	50 (41–61)	52 (40–63)	0.928
Male sex	88 (39%)	96 (54%)	0.003
Family history of atopy	127 (56%)	99 (56%)	0.918
Ancestry			
Dutch	152 (69%)	137 (79%)	0.022
Caribbean and Suriname	43 (19%)	18 (10%)	0.013
Other	30 (13%)	22 (13%)	0.796
Pulmonary sarcoidosis	166 (74%)		
Scadding score*			
Stage 0	26 (16%)		
Stage 1	45 (27%)		
Stage 2	59 (36%)		
Stage 3	9 (5%)		
Stage 4	18 (11%)		
no HRCT	9 (5%)		
Sarcoidosis uveitis	126 (60%)	n/a	
Cutaneous sarcoidosis	92 (45%)	n/a	
Median duration of sarcoidosis, yr	5.0 (IQR, 2.0–10.0)	n/a	

*0, normal chest HRCT; 1, bilateral hilar lymphadenopathy; 2, stage 1 + pulmonary infiltrates; 3, pulmonary infiltrates without hilar lymphadenopathy; 4, pulmonary fibrosis.

IQR = interquartile range; HRCT = high-resolution computed tomography; n/a = not applicable.

Survey and International Study of Asthma and Allergies in Children protocol.^{8,9} Subjects were considered to have had asthma if they answered the question, “Have you ever been diagnosed with asthma by a doctor?” positively and if the answer to the question, “How old were you when you were diagnosed with asthma?” was <25 years. The criteria for the diagnosis of atopic dermatitis were atopic dermatitis diagnosed by a physician before the age of 25 and for a duration of >1 year. For diagnosis of hay fever patients had to answer the next question affirmatively, “Have you ever had hay fever before the age of 25 years?” The age of 25 years was used as cutoff to increase the specificity as atopic disorders mainly have their onset during childhood and adolescence. This prevents misclassification of other forms of eczema as atopic eczema and of chronic obstructive pulmonary disease as atopic asthma. Patients were also asked about the use of topical corticosteroids for their atopic dermatitis, inhalants for the asthma, and nasal sprays or antihistaminics for the hay fever. The presence of atopic features in the first-degree relatives was also assessed through this questionnaire.

Sarcoidosis Types, Activity, and Severity

Sarcoidosis patients were further classified into non-exclusive three groups: pulmonary sarcoidosis, sarcoid uveitis, and cutaneous sarcoidosis. The diagnosis of

sarcoidosis was established according to the guidelines of the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis, and other Granulomatous Disorders statement on sarcoidosis.¹⁰ The diagnosis of (posterior or anterior) uveitis was made by certified immunologists and confirmed by ophthalmologic examination. The diagnosis of cutaneous sarcoidosis was confirmed by biopsy.

To assess the disease activity and severity (*i.e.*, organ involvement and serological markers), radiological, serological, and pulmonary function tests were performed on clinical indication. Serological tests included erythrocyte sedimentation rate, T-lymphocyte levels, serum angiotensin-converting enzyme (ACE), and serum calcium (CA). All patients suspected of having sarcoidosis routinely undergo high-resolution computed tomography (HRCT) scanning at our center. Modified Scadding scoring system was applied to HRCT to assess pulmonary sarcoidosis.¹¹ All HRCTs were graded according to the Scadding system by a certified radiologist.¹² Defined by the Scadding scale, 0 represents a normal chest HRCT; stage 1, bilateral hilar lymphadenopathy; stage 2, stage 1 + pulmonary infiltrates; stage 3, there are pulmonary infiltrates without hilar lymphadenopathy; and stage 4, shows pulmonary fibrosis.

In pulmonary sarcoidosis, pulmonary functioning may be impaired even in the absence of radiological

Table 2 Prevalence of self-reported atopic disorders and their medication use

	Sarcoidosis <i>n</i> = 225	Control <i>n</i> = 177	<i>p</i> Value
Atopic eczema			
Ever	28 (12.4%)	22 (12.4%)	0.996
Current topical corticosteroid use	39 (18.6%)	21 (12.0%)	0.124
Family history	70 (30.1%)	50 (28.2%)	0.534
Atopic asthma			
Ever	12 (5.3%)	10 (5.6%)	0.890
Current use of inhalators	6 (2.7%)	5 (2.8%)	0.923
Family history	56 (25.0%)	43 (24.3%)	0.891
Hay fever			
Ever	38 (16.9%)	18 (15.8%)	0.774
Current use of nasal spray/antihistaminics	37 (17.6%)	26 (14.7%)	0.437
Family history	89 (39.6%)	67 (37.9%)	0.725
Any atopic disorder	60 (26.7%)	44 (24.9%)	0.681

Table 3 Uni- and multivariate logistic analyses of the risk of sarcoidal uveitis

<i>n</i> = 402	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Eczema	0.32 (0.14–0.73)	0.30 (0.13–0.71)
Age, yr (per 10 yr)	1.12 (0.95–1.31)	1.16 (0.98–1.37)
Dutch ancestry	0.50 (0.31–0.79)	0.50 (0.31–0.81)
Male sex	0.42 (0.27–0.66)	0.42 (0.27–0.67)

Adjusted for all the variables in table 3.

CI = confidence interval; OR = odds ratio.

abnormalities. Transfer factor for carbon monoxide and total lung capacity are characteristically affected but the forced vital capacity and forced expiratory volume in 1 second are also frequently decreased.^{13,14} Pulmonary function tests were performed according to the local protocol at the Pulmonology Department. The values of the parameters were expressed as a percentage of the expected value corrected for ethnicity, sex, age, and hemoglobin levels. The classic serological parameters of the disease activity are ACE, CA, and T-cell numbers. These were performed at the time of diagnosis according to the protocol of the Medical Laboratory at the Erasmus Medical Center.

Patients were also asked to report the name of their current medication for sarcoidosis. If patients stated that no medication was currently used the sarcoidosis was considered resolved.

Statistics

For sample size calculations, we assumed a prevalence of 20% of atopic disorders in our control group, as previously found,¹⁵ and expected one-half of this proportion in sarcoidosis patients. A convenience sam-

ple of ~200 cases was deemed reasonable. We compared the prevalence of atopic features between the patients and the controls. In the cohort of sarcoidosis patients we also investigated whether the presence of atopic features was related to specific organ involvement in sarcoidosis (*i.e.*, pulmonary, uveitis, and cutaneous sarcoidosis).

The chi-squared test was used to test for statistical differences in proportions and Mann-Whitney *U* tests for nonparametric testing. Age, sex, and ancestry were considered confounders in the relation between sarcoidosis and atopy. Multivariate logistic regression models were used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Variables with *p* < 0.20 in the univariate analysis were included in multivariate models. Values of *p* < 0.05 were considered significant. All data were analyzed using IBM SPSS Version 19.0 (2011; SPSS, Inc., Chicago, IL).

RESULTS

Subject Characteristics

Of the 371 patients, 225 (61%) replied to our mailing with 177 control partners. The median age was 50 years for patients and 52 years for controls. The controls were significantly more often male subjects (54% versus 39%; *p* = 0.003) and of Dutch ancestry (79% versus 69%; *p* = 0.022) when compared with patients (Table 1). Almost twice as many patients were of Surinam or Caribbean descent when compared with their partners (19% versus 10%; *p* = 0.013).

Pulmonary involvement was found in 166 (74%) and 157(95%) of these patients HRCT scanning was performed. Uveitis and cutaneous sarcoidosis were seen in 126 (60%) and 92 (45%) of patients, respectively.

Table 4 Pulmonary sarcoidosis activity and severity in atopic patients vs nonatopic patients at the time of diagnosis sarcoidosis

	Any Atopy <i>n</i> = 43	No Atopy <i>n</i> = 123	<i>p</i> Value
Serum ACE, µg/L	52 (IQR, 26–112)	47 (IQR, 30–86)	0.325
Serum CA, mmol/L	2.35 (IQR, 2.29–2.43)	2.40 (IQR, 2.33–2.47)	0.211
Erythrocyte sedimentation rate, mm/hr	12 (IQR 6.0–24)	15 (IQR, 6.0–31)	0.958
T cells, * 10 ⁹ /L	0.75 (0.41–1.02)	0.73 (IQR, 0.53–1.22)	1.000
Total lung capacity, %ref	86 (IQR, 68–97)	79 (IQR, 17–90)	0.297
Forced vital capacity, %ref	96 (IQR, 72–103)	100 (IQR, 89–112)	0.247
Forced expiratory volume in 1 s, %ref	86 (IQR, 64–99)	92 (IQR, 76–105)	0.938
Transfer factor for carbon monoxide/diffusion capacity for carbon monoxide, %ref	74 (IQR, 52–91)	72 (IQR, 52–82)	0.938
Sarcoidosis Scadding stage HRCT	<i>n</i> = 39	<i>n</i> = 118	
0	8 (21%)	18 (15%)	
1	7 (18%)	38 (33%)	
2	15 (38%)	44 (37%)	
3	4 (10%)	5 (4%)	
4	5 (13%)	13 (11%)	0.341*

*The *p* value for trend.

IQR = interquartile range; HRCT = high-resolution computed tomography; ACE = angiotensin-converting enzyme; %ref = expressed as percentage of reference group.

Atopic Features and Sarcoidosis

Sarcoidosis patients with pulmonary sarcoidosis did not differ from their partners regarding frequency of self-reported diagnoses of asthma, hay fever, or eczema (Table 2). Moreover, drug use for atopic disorders and proportions of positive family histories did not differ across patients and controls. The same was the case for patients with cutaneous sarcoidosis. Adjusting for the confounders did not alter these results. However, patients with sarcoidosis uveitis reported eczema less often than the controls (26% versus 12%; *p* = 0.045; Table 2).

This association yielded an unadjusted OR of 0.32 and 95% CI of 0.14–0.73 and after adjusting for age, ancestry, and sex OR was 0.30 and 95% CI was 0.13–0.71 (Table 3).

Sarcoidosis in Atopic Patients

We also analyzed the differences in the activity and the severity of sarcoidosis in atopic and nonatopic patients. No statistically significant differences were found in the distribution of serum ACE, CA, erythrocyte sedimentation rate, T-cell numbers, and lung function tests (and total lung capacity, forced vital capacity, forced expiratory volume in 1 second, and transfer factor for carbon monoxide; Table 4). The HCRT modified Scadding scores were comparable between atopic and nonatopic sarcoidosis patients. A history of atopic diseases did not affect resolution rates (15% versus 20%; *p* = 0.895), TNF-α blocker use (20% versus 21%;

p = 0.8990), and methotrexate use (20% versus 30%; *p* = 0.340) among patients with sarcoidosis.

DISCUSSION

No association between atopy and the development of sarcoidosis was found in this study. Having an atopic disorder was also not associated with attenuated disease. However, atopic eczema is associated with a lower occurrence of sarcoidal uveitis. This strong negative association remained after adjusting for confounders. Our study also confirmed the classic risk factors (black race and female sex) for sarcoidosis. Sarcoidosis is currently perceived as a Th1-mediated disease, whereas atopic disorders are categorized as exclusively Th2 conditions. Antagonism between Th1 and Th2 axes has been the subject of previous studies and atopy has been linked to a lower prevalence and a less severe course of autoimmune diseases such as diabetes mellitus type 1, rheumatoid arthritis, and multiple sclerosis.¹⁶ The A Case Controlled Etiologic Study of Sarcoidosis study also revealed that sensitization to household animal dust and feathers conferred a lower risk for the development of sarcoidosis.¹⁷

The Turkish and Japanese studies reported a lower prevalence of positive tests for atopy, including skin-prick tests and total serum IgE levels, in subjects with sarcoidosis.^{4,5} In contrast, another questionnaire-based study performed in New Zealand did not confirm these findings.¹⁸ Questionnaire-based studies may be more appropriate in this setting because atopic dis-

orders, especially atopic eczema, are generally more active during childhood. Moreover, negative skin-prick tests and lower total serum IgE levels may reflect an anergy of sarcoidosis instead of an absence of atopy. Anergy in sarcoidosis is a well-recognized phenomenon. Nevertheless, no single impairment has been pinpointed to be the cause. The anergy of sarcoidosis has been ascribed to the generally increased numbers of T regulatory cells¹⁹ and inert dendritic cells.²⁰ Clinically, it results in reduced efficacy of vaccination²¹ and suppression of cell-mediated hypersensitivity.^{22–24} It is plausible that this anergy affects the expression of atopy or reactivity to *in vivo* and *in vitro* atopy tests.

Our results showed that atopic eczema was negatively associated with uveitis. How eczematous skin may contribute in the protection of physically and immunologically isolated eyes is not clear from this study. This association was independent of traditional risk factors gender and ancestry, which suggests a nongenetic effect. However, this unexpected finding warrants replication in other studies.

The major weakness of our data is the dependence of self-reporting and retrospective assessment, with inherent recall bias. This is caused by the nature of atopic disorders, which mostly tend to wane in adulthood. Recall bias could have played a role in the reporting of atopy. In addition, we have reported a cohort of patients referred to our university clinic with a relatively high incidence of uveitis, which could also bias our results.

This is the first controlled study assessing the history of atopy. This is also the first study of sarcoidosis and atopy that takes into account the three major types of sarcoidosis patients. The prevalence of atopic features in our control group is in concordance with prevalence found in a previous study.¹⁵ In future studies we recommend further investigation into the association of sarcoidosis uveitis and atopic eczema and if confirmed, investigation of the possible mechanisms.

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