

Total serum IgE levels and atopic status in patients with sarcoidosis

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ABSTRACT

To date, two studies have reported lower total serum immunoglobulin E (IgE) levels and lower prevalence of atopy in patients with sarcoidosis compared with healthy subjects. However, those reports did not consider age or gender differences between cases and controls. In addition, the association between total serum IgE levels and clinical manifestations of sarcoidosis has not been clarified. This study assessed total serum IgE levels and prevalence of atopy in patients with sarcoidosis after taking age and sex differences into account and evaluated associations between total serum IgE levels and clinical manifestations of sarcoidosis. Total serum IgE levels and prevalence of atopy on initial visits were compared between 189 patients with sarcoidosis and 378 age- and sex-matched controls. Associations between total serum IgE levels and involvement of each affected organ were evaluated. Changes in total serum IgE levels during the clinical course of sarcoidosis were also evaluated. Total serum IgE levels were significantly lower in patients with sarcoidosis than in controls, independent of atopic status (atopic subjects, $p = 0.025$; nonatopic subjects, $p < 0.001$). Total serum IgE levels did not differ according to the involvement of different organs. Total serum IgE levels decreased further, albeit only slightly, after disease remission ($p < 0.001$). Increased susceptibility to sarcoidosis may be attributable to several underlying genetic or environmental factors that result in lower total serum IgE levels.

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Sarcoidosis is a systemic disorder of unknown origin characterized by the development of cell-mediated immune response, resulting in the formation of noncaseating granulomas and accumulation of activated T cells and macrophages at sites of inflammation.¹ T helper (Th)1 cytokines such as interferon γ , which is produced by activated CD4⁺ T cells, appear essential for granuloma formation.² Conversely, increased levels of total serum immunoglobulin E (IgE) and atopy are associated with an immune response characterized by production of Th2 cytokines such as interleukin (IL)-4 and IL-13.³ Th1- and Th2-mediated immune responses have been reported to negatively cross-regulate each other, both *in vitro* and in experimental animal studies.⁴

Several epidemiological studies have shown inverse relationships between increased total serum IgE levels

or risk of atopy and various Th1-mediated diseases, such as multiple sclerosis and tuberculosis.^{5,6} Yagura *et al.* reported that in a Japanese population, total serum IgE levels were lower in subjects with sarcoidosis than in healthy controls.⁷ Another study found that the prevalence of atopy was lower in patients with sarcoidosis compared with healthy subjects in a Turkish population.⁸ However, age and gender distributions are known to differ between patients with sarcoidosis and general populations.⁹ According to the recent increase in the incidence of several allergic diseases, younger adults display a higher prevalence of atopy than older adults.¹⁰ Thus, when assessing total serum IgE levels and the prevalence of atopy in subjects with sarcoidosis, consideration of age and gender difference between cases and controls is crucial.

In addition to comparisons of these allergic parameters in serum from healthy subjects, associations with several clinical manifestations of the disease are also intriguing. We have recently reported that atopic subjects with sarcoidosis show a lower prevalence of lung parenchymal lesions and favorable prognosis for pulmonary involvement compared with nonatopic subjects.¹¹ However, no reports have clarified the relationship between total serum IgE levels and several clinical manifestations of sarcoidosis.

Given this background, the present study had two goals. The first was to compare total serum IgE levels and prevalence of atopy between patients with sarcoid-

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osis and age- and sex-matched controls. The second was to evaluate the association of total serum IgE levels with clinical manifestations of sarcoidosis, including affected organs and disease activity.

MATERIALS AND METHODS

Study Populations

A total of 567 unrelated Japanese subjects were evaluated for this study (189 patients with sarcoidosis and 378 age- and sex-matched controls). Based on a digital data system and medical records, patients newly diagnosed with sarcoidosis between January 2000 and December 2008 at the pulmonary clinic in the First Department of Medicine at Hokkaido University Hospital were retrospectively analyzed. In all patients, diagnosis of sarcoidosis was based on compatible clinical findings, histological demonstration of noncaseating epithelioid cell granuloma, and exclusion of other diseases capable of producing a similar histological or clinical picture, as recommended by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders statement.¹² Patients with sarcoidosis who had a history of any other pulmonary diseases, including asthma, were excluded. Patients who had been treated with oral corticosteroids at their initial visits were also excluded from the analysis.

As part of our research into genetic factors contributing to susceptibility to sarcoidosis and asthma,^{13–15} we had recruited control subjects between January 2000 and December 2008. These were individuals with no history of asthma or any other chronic pulmonary diseases who visited the clinic for annual routine health checkups or students at the School of Medicine at Hokkaido University. We selected two age- and sex-matched (up to 5 years older or younger) controls per case ($n = 378$). Subjects were all unrelated and of Japanese descent. All study protocols were approved by the Clinical Research Ethics Committee of Hokkaido University Hospital.

Total and Specific IgE Measurements

Total serum IgE levels and specific IgE responses to common inhaled allergens, including *Dermatophagoides farinae*, grass pollens, animal dander, and molds, were determined in controls and patients with sarcoidosis at their initial visits. We defined atopy based on positive multiple antigen simultaneous test scores (>1.01 lumicount) to at least one common inhaled allergen.^{11,14,16,17}

Evaluation of the Clinical Course of Sarcoidosis

To evaluate changes in total serum IgE levels according to changes in disease activity, we selected patients

who had clearly shown “remission” or “persistence” of the disease within 1–5 years after the initial visit. We defined “remission” of disease as all of the affected organs showing improvement without systemic glucocorticoid therapy. Criteria for the improvement of each affected organ were as follows: ocular involvement, improvement of ocular impairment such as blurred vision, pulmonary involvement, clear disappearance of lung parenchymal lesions or hilar/mediastinal lymphadenopathy on chest radiography, cutaneous involvement, improvement of skin conditions, and subjective symptoms. A total of 32 patients were categorized as in remission according to this definition. Because total serum IgE levels might change due to activity of existing allergic diseases in atopic subjects, changes in total serum IgE levels were also evaluated only in nonatopic subjects. We defined “persistence” of the disease based on confirmation that no affected organs showed any improvement during follow-up. We excluded subjects with improvement of even one organ from this definition. A total of 13 patients were categorized as showing disease persistence according to this definition.

Statistical Analysis

Statistical analyses were performed using R version 2.12.1 software (www.R-project.org/).¹⁸ For analyses, categorical variables were compared using the χ^2 -test with Yates' correction and continuous variables were compared using the Mann-Whitney U test. Total serum IgE levels were log-transformed to approximate normal distributions. One-way analysis of variance was used to compare total serum IgE levels between groups. Changes in total serum IgE levels according to disease remission were assessed using the paired t -test. For all statistical analyses, values of $p < 0.05$ were considered significant.

RESULTS

Characteristics of controls and patients with sarcoidosis are presented in Table 1. The male-to-female ratio was 0.28 in both groups and the median age was 55 years in controls and 56 years in patients with sarcoidosis. Prevalence of atopy tended to be lower in patients with sarcoidosis than in controls, but no significant difference was present (controls, 52.9%; sarcoidosis, 45.5%; $p = 0.116$). Total serum IgE levels on initial visits were significantly lower in patients with sarcoidosis than in controls ($p < 0.001$). This difference remained significant even after stratification into atopic and nonatopic patients (atopic subjects, $p = 0.025$; nonatopic subjects, $p < 0.001$; Table 2). Prevalences of ocular, cutaneous, and cardiac involvements were 70.9, 15.3, and 4.2%, respectively. Total serum IgE levels were not associated with the presence of any specific organ involvements (Table 3).

Table 1 Characteristics of control subjects and patients with sarcoidosis

	Control (n = 378)	Sarcoidosis (n = 189)	p Value
Male, n (%)	106 (28.0)	53 (28.0)	—
Age (median, range)	55, 18–79	56, 18–78	—
Atopy, n (%)*	200 (52.9)	86 (45.5)	0.116
log (IgE) (log [IU/mL]; mean, SD)#	2.01, 0.63	1.72, 0.65	<0.001
Stage (0/I/II/III/IV)	—	35/101/42/11/0	—
Ocular involvement, n (%)	—	134 (70.9)	—
Cutaneous involvement, n (%)	—	29 (15.3)	—
Cardiac involvement, n (%)	—	8 (4.2)	—
Serum ACE activity (U/mL; median, range)	—	23.1, 12.7–49.4	—
Systemic steroids treatment, n (%)§	—	41 (21.7)	—

* χ^2 -test.#Student's *t* test

§Sixteen sarcoidosis patients were treated for ocular involvement, seven for cardiac involvement, seven for neural involvement, five for pulmonary involvement, two for renal involvement, one for cutaneous involvement, and three for another disease (malignant lymphoma, rheumatoid arthritis, and nephritis).

ACE = angiotensin-converting enzyme; IgE = immunoglobulin E.

Table 2 Total serum IgE levels in control subjects and subjects with sarcoidosis

	Atopic Subjects			Nonatopic Subjects		
	Control (n = 200)	Sarcoidosis (n = 86)	p Value*	Control (n = 178)	Sarcoidosis (n = 103)	p Value*
log (IgE) (log [IU/mL]; mean, SD)	2.27, 0.56	1.95, 0.64	0.025	1.72, 0.57	1.53, 0.60	<0.001

*ANOVA, adjusted by sex and age.

IgE = immunoglobulin E.

Table 3 Associations between total serum IgE levels and presence of organ involvement

	Presence of Affected Organ Involvement		Absence of Affected Organ Involvement		p Value#
	n	mean, SD*	n	mean, SD*	
Chest radiographic abnormality	154	1.68, 0.64	35	1.89, 0.68	0.200
Lung parenchymal involvement	53	1.62, 0.71	136	1.76, 0.63	0.288
Extrapulmonary involvement	156	1.73, 0.66	33	1.69, 0.62	0.988
Ocular involvement	134	1.72, 0.66	55	1.73, 0.63	0.943
Cutaneous involvement	29	1.60, 0.63	160	1.74, 0.66	0.408
Cardiac involvement	8	2.08, 0.74	181	1.70, 0.65	0.340

*Total serum IgE levels, log (IgE) (log [IU/mL]).

#ANOVA, adjusted by sex, age, and atopic status.

Despite lower total serum IgE levels at initial visits in patients with sarcoidosis compared with controls, levels decreased further, albeit only slightly, after remission of the disease ($n = 32$; $p = 0.001$; before, 67.4 IU/mL [mean value]; after, 50.8 IU/mL; Fig. 1 A). Decreases in total serum IgE levels with remission were apparent in all

subjects when atopic subjects were excluded from analysis ($n = 17$; $p = 0.006$; before, 55.8 IU/mL; after, 37.2 IU/mL; Fig. 1 B). In contrast, changes in total serum IgE levels were not consistent in the patients who showed persistence of the disease ($n = 13$; $p = 0.334$; before, 18.0 IU/mL; after, 13.1 IU/mL; Fig. 1 C).

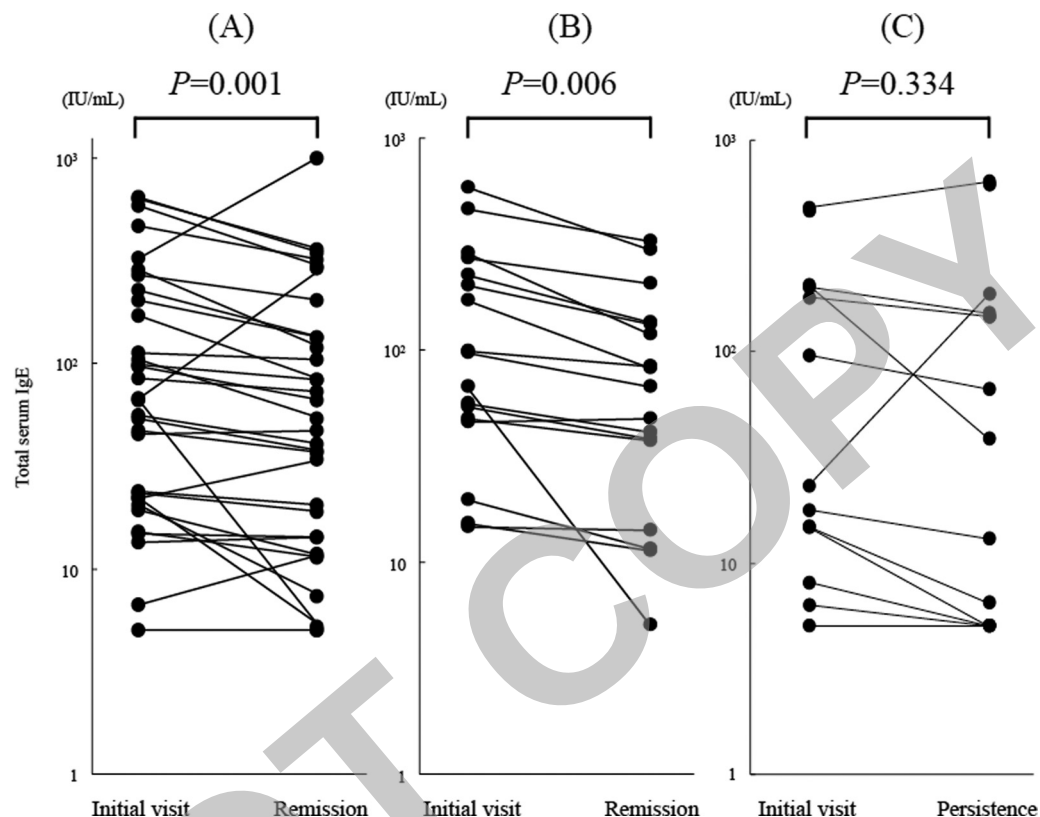


Figure 1. Changes in total serum immunoglobulin E (IgE) levels with clinical improvement of sarcoidosis. (A) All patients showing "remission" ($n = 32$; paired t -test, $p = 0.001$). (B) Nonatopic patients showing "remission" ($n = 17$; paired t -test, $p = 0.006$). (C) Patients showing "persistence" ($n = 13$; paired t -test, $p = 0.334$).

DISCUSSION

Two previous reports have shown that total serum IgE levels and prevalence of atopy are lower in patients with sarcoidosis than in healthy subjects among Japanese and Turkish populations.^{7,8} However, neither age nor gender distributions were considered in those investigations. To clarify these issues, the present study compared total serum IgE levels and prevalences of atopy between patients with sarcoidosis and sex- and age-matched controls. We found that total serum IgE levels at initial visits were significantly lower in patients with sarcoidosis than in controls ($p < 0.001$). Prevalence of atopy tended to be lower in patients with sarcoidosis than in controls, but this difference was not statistically significant ($p = 0.116$).

Because reciprocal regulation of Th1 and Th2 responses is a well-documented phenomenon, Th1-induced immunologic activity associated with sarcoidosis may potentially play a role in decreasing total serum IgE levels. However, when we assessed IgE levels in 32 patients who showed disease remission, total serum IgE levels showed further slight reductions. This finding indicates that lower serum IgE levels observed in patients with sarcoidosis compared with controls may not be the consequence of the development of sarcoidosis. Alternatively, factors underlying lower total serum IgE levels may confer susceptibility to sarcoidosis. Of interest, individuals carrying a C allele at position 159 in the promoter region of the

CD14 gene ($-159C/T$), a mutation that is more prevalent in patients with sarcoidosis, display significantly lower total serum IgE levels compared with noncarriers^{19,20} and these findings may support our speculation.

The fact that total serum IgE levels decreased after clinical improvement of the disease suggest that clinical activity of sarcoidosis is associated with elevation of total serum IgE levels from the baseline. There are several potential explanations for this phenomenon. Alveolar macrophages from subjects with sarcoidosis show higher expression of IL-13, a critical cytokine that induces IgE production.²¹ Levels of platelet-activating factor and IL-18, also known as a stimulus for IgE production, are higher in bronchoalveolar lavage fluid (BALF) from subjects with sarcoidosis.^{22,23} These factors may be involved in the regulation of total serum IgE levels in patients with sarcoidosis. In contrast, Milburn *et al.* reported that IL-4 levels in BALF were lower in patients with sarcoidosis than in normal controls.²⁴ They also showed that IL-4 and IgE levels in BALF increased after treatment with oral corticosteroids, whereas total serum IgE levels decreased after such treatment, indicating reciprocal regulation between local and systemic immune responses in sarcoidosis. Measurement of IgE levels in both serum and BALF may clarify the mechanisms underlying this phenomenon.

In conclusion, we have established lower total serum IgE levels in patients with sarcoidosis compared with age- and sex-matched healthy controls. In addition, we found interesting associations between total serum IgE levels and disease activity of sarcoidosis. The mechanisms underlying these relationships are not apparent from this study and remain to be determined by future studies. Genetic studies may provide more mechanistic insights into this association and prospective studies are needed to clarify changes in total serum IgE levels according to the activity of sarcoidosis.

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