

Allergy to dust mites may contribute to early onset and severity of alopecia areata

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Summary

Background. A higher risk of allergic diseases such as rhinitis, asthma and atopic eczema (atopic dermatitis) has been reported for patients with alopecia areata (AA) compared with the general population, but the significance of this is still largely unclear.

Aim. To determine whether serum total or specific IgE play a role in the onset and severity of AA.

Methods. We tested 461 serum samples from 351 patients with AA and 110 healthy controls (HC) for total IgE (tIgE) and specific IgE (sIgE) by ImmunoCAP-100 or *in vitro* test (IVT).

Results. The absolute value of tIgE was higher in patients with AA than in normal controls ($P < 0.001$), although the prevalence of raised tIgE (> 120 IU/mL) detected in patients with AA (29.3%) was similar to that of HC (21.8%). Prevalences of raised sIgE against various allergens detected by ImmunoCAP-100 showed that *Dermatophagoides pteronyssinus* (Der p; 31.1%) and *Dermatophagoides farinae* (Der f; 29.0%) were the most common allergens. Similar results were found by IVT, with the most common response being against Der p/Der f (29.0%). However, the prevalences of tIgE and sIgE against dust mites (Der p and Der f) in patients with early-onset AA and severe AA were significantly higher than those with late-onset AA and mild AA ($P = 0.02$, $P = 0.02$ vs. $P = 0.03$ and $P = 0.001$, respectively). Notably, the increases in tIgE and sIgE were independent of atopy history.

Conclusions. Allergy to dust mites may have an effect on the immune response in AA, and may contribute to its early onset and severity in patients of Chinese origin.

Introduction

Alopecia areata (AA) is an unpredictable, recurrent, nonscarring hair-loss condition, which affects 0.1–0.2% of people worldwide,¹ with a calculated lifetime risk of approximately 2%,² making it one of the most prevalent autoimmune diseases. Because of its

substantial disease burden, its often devastating effects on a patient's quality of life and self-esteem, and its potential pathogenic sequelae, AA is not simply a 'cosmetic' problem.^{3,4} Although AA usually occurs in apparently healthy individuals without other skin disorders, patients with AA have a higher risk of developing allergic diseases such as allergic rhinitis, asthma and atopic dermatitis/eczema compared with healthy people without AA.^{5–7}

Allergic diseases caused by dust mites are abundant.⁸ *Dermatophagoides pteronyssinus* (Der p) and *Dermatophagoides farinae* (Der f) are the most common species of dust mite in China. Given that Der p and Der f share some common antigen epitopes, people

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sensitized to Der p also tend to be sensitized to Der f, and *vice versa*.^{8,9} In routine clinical work, we found that many patients with AA were also allergic to dust mites, but the prevalence and level of response are, to a large degree, unknown.

The aim of this study was to investigate levels of total and specific IgE (tIgE and sIgE) in patients with AA, and their correlation with clinical features.

Methods

All the procedures in this study were approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University (no. [2009]4), and informed consent was obtained from all participants before blood samples were taken.

Participants

The study group consisted of 351 patients (181 male, 170 female; mean $\pm$ SD age 25.7 ± 13.6 , range 1–59) clinically diagnosed with AA, and 110 age- and sex-matched healthy controls (HC).

Data collection

Patient sex, age at disease onset and age at the time of evaluation were recorded. The pattern of hair loss and severity were evaluated using AA Foundation guidelines (grades S1 or S2 considered mild; grades S3–S5 considered severe).¹⁰ Any concomitant allergic diseases, including atopic dermatitis (atopic eczema; AE), allergic rhinitis and asthma, were also recorded. Patients with one or more than one allergic disease mentioned above were considered to have a positive history of atopy for the purposes of this study.

Testing

The level of tIgE in the sera of all participants was measured by an automated system (BN ProSpec Automatic Specific Protein Analyzer; Siemens, Marburg, Germany) and was regarded as raised when it was greater than the cutoff point of 120 IU/mL.

Levels of sIgE in the sera of 251 patients with AA and 110 healthy subjects were also measured by a fluorescence enzyme immunoassay system (ImmunoCAP-100; Phadia, Uppsala, Sweden). Values were divided into seven classes according to concentration: class 0, < 0.35 KU/L; class 1, 0.35 – 0.7 KU/L; class 2, 0.7 – 3.5 KU/L; class 3, 3.5 – 17.5 KU/L; class 4, 17.5 – 50.0 KU/L; class 5, 50.0 – 100.0 KU/L; and class 6,

> 100 KU/L. Classes 1–6 were all considered positive responses.

ImmunoCAP-100 was not available for testing for the remaining 100 patients, who were later recruits. Instead, levels of sIgE in the remaining 100 patients with AA were measured by *in vitro* Test (IVT; Arlington Scientific, Springville, UT, USA). This test had previously been compared with ImmunoCAP, and the results were not significantly different. The IVT results were classified as –, negative; +/-, weakly positive; +, positive and ++, strongly positive; the latter three were all considered positive responses.

Statistical analysis

Data were analyzed using SPSS Statistics (v.17.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean $\pm$ SD. Mann–Whitney *U*-test or χ^2 test were used for statistical analysis between two groups. $P < 0.05$ was considered statistically significant.

Results

Alopecia areata

The area of scalp hair loss ranged from 1 to 100%, with a median of 30%. Of the 351 patients, 143 (40.7%) had severe AA (grades S3–S5). Clinical subtypes included 205 cases of patchy AA (58.4%), 43 cases of diffuse pattern (12.3%), 12 cases of ophiasis pattern (3.4%), and 91 cases of alopecia totalis/alopecia universalis (AT/AU, 25.9%). Of the 351 patients, 93 (26.5%) reported having at least one kind of allergic disease other than AA, and this rate did not correlate age of onset ($P = 0.47$) or severity ($P = 0.48$) of AA.

Determination of total and specific IgE

The absolute value (mean $\pm$ SD) of tIgE was higher in patients with AA (235.2 ± 575.1) than in HC (110.4 ± 183.8) ($P < 0.001$). However, a raised tIgE level (> 120 U/mL) was found in 29.3% (103/351) of patients with AA, similar to that in HC (21.8%; 24/110) ($P = 0.12$).

ImmunoCAP-100 results showed that the most common allergen eliciting a response was Der p (31.1%), followed by Der f (29.0%), and cockroach (20.3%) (Table 1). Similar results were found using IVT, with the most common response being against Der p/Der f (29.0%), followed by cockroach (20.0%), and house dust (10.0%) (Table 2). In the control group, the positive response rate for Der p by ImmunoCAP-100

Table 1 Distribution of specific IgE (sIgE) by ImmunoCAP-100 test.

			Positive response samples, <i>n</i>							
			Class							
Groups	slgE	Samples, <i>n</i>	1	2	3	4	5	6	Total	Prevalence, %
AA	d1	251	15	28	17	8	4	6	78	31.1
	d2	145	8	16	9	4	2	3	42	29
	i6	246	11	28	8	3	0	0	50	20.3
	e1	136	1	0	0	0	0	0	1	0.7
	e5	136	4	2	1	0	0	0	7	5.1
	t18	105	2	2	1	0	0	0	5	4.8
	m3	107	2	2	0	0	0	0	4	3.7
	f13	105	1	0	0	0	0	0	1	1
Control	d1	110	7	6	11	1	2	2	29	26.4

d1, *Dermatophagoides pteronyssinus*; d2, *Dermatophagoides farinae*; i6, cockroach (German); e1, cat epithelium and dander; e5, dog dander; t18, *Eucalyptus* pollen; m3, *Aspergillus fumigatus*; f13, peanut.

Table 2 Distribution of specific IgE by *in vitro* test.

Specific IgE	Samples, <i>n</i>	Positive response samples, <i>n</i>			Total	Prevalence, %
		Grade				
		+/-	+	++		
d1/d2	100	6	10	13	29	29
i6	20	0	3	1	4	20
h1	100	0	9	1	10	10
m1/m6/m11	100	0	6	0	6	6

d1, *Dermatophagoides pteronyssinus*; d2, *Dermatophagoides farinae*; i6, cockroach (German); h1, house dust; m1, *Penicillium*; m6, *Alternaria*; m11, *Rhizopus nigricans*.

was 26.4%, which was not significantly different from patients with AA ($P > 0.05$).

Correlation between total IgE and clinical features of alopecia areata

There was a significantly ($P = 0.02$) higher prevalence of raised tIgE in patients with AA onset at 0–19 years of age (53/147, 36.1%) than in patients with AA onset at 20–59 years (50/204, 24.5%) (Fig. 1a). Similarly, there was a significantly ($P < 0.01$) higher prevalence of raised IgE in patients aged 0–19 years at the time of study (44/110, 40.0%) than in patients aged 20–59 years (59/241, 24.5%) (Fig. 1b).

In addition, the absolute level of tIgE was greater in patients with AA onset at 0–19 years old than in those with AA onset at 20–59 years of age ($P = 0.03$), and was also higher in patients aged 0–19 years than in patients aged 20–59 years at the time of study ($P = 0.01$).

Raised levels of tIgE were also more prevalent in patients with AT/AU (34/91, 37.4%) than in patients with patchy alopecia (48/205, 23.4%) ($P = 0.01$) (Fig. 1c). Raised tIgE was also more common in patients with severe AA (51/143, 35.7%) than in patients with mild AA (52/208, 25.0%) ($P = 0.03$) (Fig. 1d), and patients with severe AA had higher absolute levels of tIgE than patients with mild AA ($P < 0.04$).

Correlation between specific IgE against Der p and/or Der f and clinical features of alopecia areata

Prevalence of sIgE against Der p and/or Der f was higher in patients with onset of AA at 0–19 years (56/147, 38.1%) than in patients with AA onset at 20–59 years (53/204, 26.0%) ($P = 0.02$) (Fig. 2a). Patients aged 0–19 years old at the time of study were more likely to have raised sIgE (45/110, 40.9%) than patients aged 20–59 years old (64/241, 26.6%) ($P = 0.001$) (Fig. 2b).

Prevalence of sIgE was higher in patients with AT/AU (35/91, 38.5%) than in patients with patchy alopecia (51/205, 24.9%) ($P = 0.02$) (Fig. 2c), and was also higher in patients with severe AA (59/143, 41.3%) than in those with mild AA (50/208, 24.0%) ($P = 0.001$) (Fig. 2d).

Increases in total and specific IgE were independent of the history of atopy

As to the atopy history, the prevalence of raised tIgE was not statistically different in patients with atopy (34/93, 36.6%) and those without (69/258, 26.7%) ($P = 0.08$). Similarly, the frequency of raised sIgE also

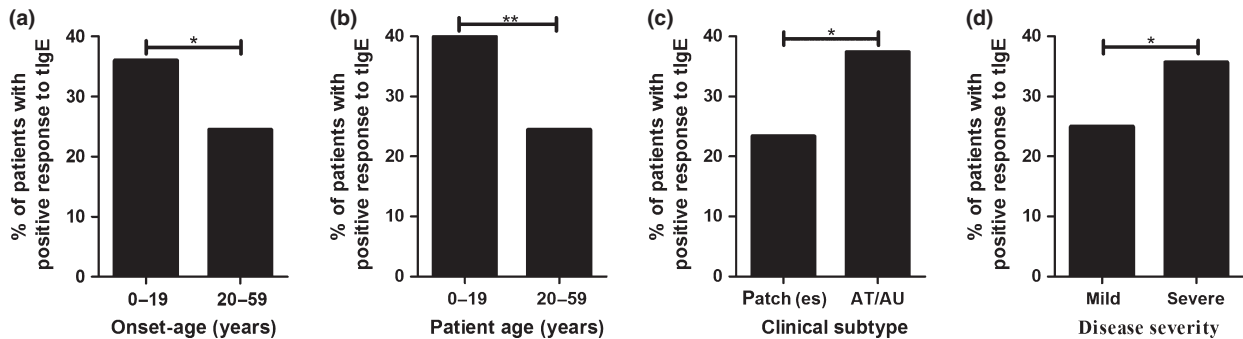


Figure 1 Percentages of patients with raised total IgE (tIgE) categorized by the clinical features of alopecia areata (AA). The prevalence of tIgE was significantly higher (a) in the group with AA onset at 0–19 years than in the group with AA onset at 20–59 years; (b) in the group aged 0–19 years at study entry than in the group 20–59 years; (c) in the group with alopecia totalis/alopecia universalis (AT/AU) than in the group with patchy alopecia; and (d) in the group with severe AA than in the group with mild AA. * $P < 0.05$; ** $P < 0.01$.

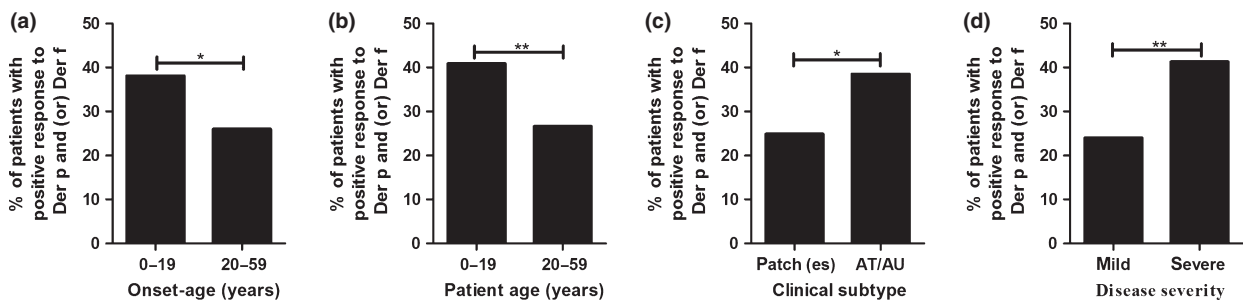


Figure 2 Percentages of patients with raised specific IgE (sIgE) categorized by the clinical features of alopecia areata (AA). The prevalence of sIgE was significantly higher (a) in the group with AA onset at 0–19 years than in the group with AA onset at 20–59 years; (b) in the group aged 0–19 years at study entry than in the group 20–59 years; (c) in the group with alopecia totalis/alopecia universalis (AT/AU) than in the group with patchy alopecia; and (d) in the group with severe AA than in the group with mild AA. * $P < 0.05$; ** $P < 0.01$.

did not differ between patients with (36/93, 38.7%) and without (73/258, 28.3%) a history of atopy ($P = 0.06$).

Discussion

AA is an inflammatory nonscarring hair loss that affects people of all ages, without a clear sex predilection.^{2,11} Although diagnosing AA is usually easy, treating it is not, because the pathogenesis of AA is still largely unknown.² Based on previous studies and the clinical findings in the current study, we speculate that AA may be associated with allergy, either by genetic or immunological processes. First, the prevalence of concomitant allergic diseases in patients with AA is higher than that in the general population, and the more severe AA types (AT and AU) are often linked to atopy.^{5–7} Second, recurrence of AA in the same annual season, in a similar manner to seasonal

rhinitis, was observed for some patients attending our clinic (unpublished observations). Finally, eosinophils and mastocytes can be found in at least some AA lesions.^{12,13}

Previous research has shown that serum levels of tIgE are raised in patients with AA compared with healthy subjects.^{14,15} In the current study, we confirmed that this was the case for the absolute level of tIgE, but not the prevalence. The lack of statistical significance for prevalence may due to the larger sample size of this study, or to ethnic or regional environmental differences. In China, the prevalence of allergic diseases generally is increasing, partly due to industrialization and increased air pollution. Lastly, we believe that AA may have different causes (environmental and genetic) in each individual. The disease may be caused and further influenced by a wide variety of pathogenic factors, such as autoimmunity, atopy and allergy, with different factors influencing different

subgroups. In fact, our previous study did show a significant difference in the prevalence of raised tIgE level between HC and patients with AA, but only in the group with diffuse AA.¹²

Dust mites are the most common cause of allergic rhinitis, asthma and other allergic disorders in China, and high levels of sIgE against dust mites are common.^{8,16} Our findings in patients with AA are in line with these previous observations. Previous studies have also suggested that fungal infection, seasonal allergens and other allergens may associate with, and potentially trigger, autoimmunity in AA.^{12,17,18} If allergens can induce AA, then dust mite-derived antigens may possibly be an inciting agent. Thus, allergy may contribute to AA via immunological processes, and this may influence the onset of the immune response in AA.

Our study revealed that there were higher levels and prevalence of tIgE and higher prevalence of sIgE in patients with early-onset and severe hair loss than in patients with late-onset and mild hair loss, respectively. In agreement with some of our results, Attia *et al.* reported that levels of serum tIgE were higher in AU than in other forms.¹⁵ There are links between atopy and AA, including that both can involve genetic predisposition, and that severe AA is likely to happen in people with AE traits.¹⁹ In large-scale clinical aetiology studies, Ikeda *et al.* observed that patients with atopy have AA onset at a relatively younger age.^{18,20} The main components of AE are cutaneous or mucosal defects and changes in the immune system. In the current study, we found that only raised tIgE and sIgE levels, but not atopy status, were associated with early age of onset and more severe AA. This divergence between IgE and atopy significance in this study is unexpected, and suggests that it is allergy rather than atopy that we should address in patients with AA. Potentially, the low general incidence of AE disease in the Chinese population is due to the genetic background,²¹ while the high prevalence of allergic disease due to a polluted environment may contribute to this divergence. Therefore, findings of this study in a Chinese population in the South China region might not apply to other populations.

Patients with AA can be divided into two groups; a group with early-onset and severe AA, and a second group with late-onset and milder AA.^{22,23} In this study, in the group with early-onset and severe AA, we found increased tIgE and sIgE levels, and these observations were independent of a history of atopy. Therefore, we speculate that increased tIgE and sIgE

may affect the magnitude and duration of the immune response in AA in these patients.

The balance of cytokines secreted by T helper (Th)1 and Th2 cells may play a role in AA. Antihistamine drugs were included in the recent guidelines for the management of AA published by the Japanese Dermatological Association.²⁴ Interleukin (IL)-4, a Th2 cytokine, is raised in severe AA,¹⁵ and raised IL-4 levels could be related to the human leucocyte antigen profile, which contributes to disease susceptibility and severity.^{15,23,25} Thus, allergy may contribute to AA by a genetic process. These findings confirm a role of allergy in the susceptibility and severity of AA.

Conclusion

Allergy to dust mites may contribute to the time of onset and severity of AA by a genetic or immunological process. Our results provide additional support and an experimental basis for future treatments focused on allergy-related inflammatory mechanisms.

What's already known about this topic?

- AA is an autoimmune disorder with a genetic predisposition.
- It has been reported that there is a higher risk of patients with AA developing allergic conditions.

What does this study add?

- Higher percentages of total IgE and dust mite-specific IgE were detected in patients with early-onset and severe AA.
- Allergy to dust mite may contribute to the early onset and severity of AA in an immunological or genetic process.

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