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Specific IgE Response to *Trichophyton* and Asthma Severity*

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Background: Sensitization to *Trichophyton*, a major dermatophyte, has been associated with asthma. Whether such sensitization is generally associated with the severity of asthma, like other molds such as *Alternaria*, is unknown.

Methods: We compared 258 patients with asthma, which was classified by severity as mild ($n = 123$), moderate (101), or severe (34), and 114 healthy control subjects, with regard to specific IgE titers against *Trichophyton rubrum* and other common allergens such as mixed molds, house-dust mite, cat dander, dog dander, Japanese cedar pollen, mixed Gramineae pollens and mixed weed pollens.

Results: Positive rate of *Trichophyton*-specific IgE was higher in the patients with moderate asthma (15.8%) than in the control subjects (7.0%, $p = 0.04$) and patients with mild asthma (4.9%, $p < 0.006$), and it was also higher in the patients with severe asthma (32.4%) than in control subjects ($p = 0.0001$), and patients with mild asthma ($p < 0.0001$) and moderate asthma ($p = 0.04$), but it did not differ between the control subjects and patients with mild asthma. The positive rates of mixed molds, cat dander, and dog dander were almost invariably higher in patients in all asthma subgroups than in the control subjects but did not differ among patients in the three asthma subgroups. The positive rates of other allergens were not different in all groups. Reanalysis of positive rate of *Trichophyton*-specific IgE after excluding 52 subjects with positive results for mixed molds showed a similar statistical trend to that of the original cohort. This may negate the potential effect of cross-reactivity to these molds. Multivariate analysis of asthma subgroups identified positive IgE results for *Trichophyton* as an independent determinant of asthma severity.

Conclusions: Specific IgE response to *Trichophyton* may be associated with more severe asthma.

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Key words: asthma; dermatophyte; sensitization; severity; *Trichophyton*

Abbreviations: ANOVA = analysis of variance; UA = unit of allergen

Severe or difficult asthma is an important clinical issue, and sensitization and exposure to specific allergens may play essential roles in its pathogenesis.¹ Molds such as *Alternaria*, *Penicillium*, *Aspergillus*, and *Cladosporium* are important allergens in asthma,² and sensitivity to these molds is associated with increased asthma exacerbations and severity.^{2–6} Admission to intensive care for asthma was strongly associated with skin-test reactivity to one or more fungi (*Alternaria tenuis*, *Cladosporium cladosporioides*, *Helminthosporium maydis*, and *Epicoccum nigrum*) in 87 patients.³ Adults with severe asthma (defined as an admission to the hospital with acute asthma at least twice) were more likely to be skin-test

positive for at least one of the molds *Aspergillus fumigatus*, *Penicillium notatum*, *Cladosporium herbarum*, or *Alternaria alternata*, or the yeast *Candida albicans* (76%) vs adults with mild-to-moderate asthma (16 to 19%; $p < 0.0001$).⁴ In a study of 108

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young adults, sensitization to *Alternaria* was associated with severity of asthma as defined by FEV₁, frequency of exacerbations, and treatment requirements. There were not enough positive results on skin-prick tests to investigate the effect of other molds.⁵ A subsequent cross-sectional study of 1,132 adults with asthma found

that sensitization to *A alternata* or *C herbarum* is a significant risk factor for severe asthma in several countries.⁶ No such association was found for pollens or cats.⁶

Trichophyton is well known as a major dermatophyte worldwide.^{7,8} In Japan, dermatophyte infection is almost exclusively caused by Trichophyton species. Among them, *Trichophyton rubrum* is the most common pathogen.⁹ Trichophyton was also associated with asthma in previous small studies. A case series of 12 asthma patients with dermatophyte infections revealed sensitization to Trichophyton, as demonstrated by skin tests and bronchial provocation with Trichophyton extracts. Antifungal treatment resulted in an improvement of asthma in a subset of patients.¹⁰ The same authors later conducted a randomized, placebo-controlled study in 11 patients with moderate-to-severe asthma with Trichophyton dermatophyte infections and its hypersensitivity.¹¹ Treatment with fluconazole, 100 mg daily, resulted in a highly significant decrease in bronchial sensitivity to Trichophyton and in oral steroid requirement. Symptoms of asthma, pulmonary function, and signs of fungal skin infection also improved.¹¹ These results suggested an association of Trichophyton dermatophyte infection with specific sensitization and deterioration of asthma. Such evidence has been supported by a number of anecdotal case reports.^{12–14} Efficacy of antifungal treatment was also reported in other airway disorders associated with sensitization to molds.^{15,16}

Because it is unknown whether sensitization to Trichophyton is generally associated with the severity of asthma like other molds,^{2–6} we examined the degree of specific IgE response to Trichophyton and other common allergens in a large series of asthma patients and healthy subjects, and we analyzed the relations of these variables to asthma severity.

MATERIALS AND METHODS

Subjects and Design

Consecutive adult patients with asthma were prospectively recruited in our asthma clinic of Kyoto University from Novem-

ber 2002 to November 2004. Patients were classified by asthma severity, as assessed by the 2004 Global Initiative for Asthma guidelines according to clinical features and lung function before treatment and medication required to maintain control, as mild (steps 1 and 2), moderate (step 3), or severe (step 4).¹⁷ None had evidence of COPD. Healthy adult volunteers were recruited from our hospital staff as control subjects. They had no allergic diseases such as asthma or rhinitis. None of the participants were considered immunocompromised or had smoked ≥ 10 pack-years. Patients with asthma of each severity and healthy control subjects were compared in a cross-sectional manner with regard to gender, age, disease duration, FEV₁, and serum total and specific IgE results.

Specific IgE Measurement

Allergen-specific IgE antibodies were detected with a capsulated hydrophilic carrier polymer radioallergosorbent test fluoroenzyme immunoassay (Phadia; Uppsala, Sweden) at an external laboratory (Mitsubishi Kagaku Bio-Clinical Laboratories; Kyoto, Japan), for *T rubrum*, mixed molds (*Candida*, *Alternaria*, *Penicillium*, *Aspergillus*, *Helminthosporium*, and *Cladosporium*), house-dust mite, cat dander, dog dander, Japanese cedar pollen, mixed graminea pollens (orchard grass, sweet vernal grass, Bermuda grass, timothy, and reeds), and mixed weed pollens (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy).

With regard to the cutoff level of specific IgE, 0.35 unit of allergen (UA)/mL, 0.7 UA/mL, or both has been used in adults as well as in children.¹⁸ In this study, specific IgE levels ≥ 0.7 UA/mL were considered positive.^{19–21} The higher cutoff 0.7 UA/mL was chosen to avoid the possibility of false-positive results, which we considered more important than to avoid false negatives in this study that aimed to propose a potentially relevant allergen involved in asthma pathophysiology.

As for Trichophyton, specific IgE levels as well as positive rates were compared among groups. Because the working range of assay was 0.35 to 100 UA/mL, the values less than the detection limit (0.35) were arbitrarily set at a nominal value of 0.35 UA/mL.

Statistical Analysis

Variables are expressed as the mean (SD) unless otherwise stated. For comparison of multiple groups, analysis of variance (ANOVA) followed by Fisher protected least significant difference post hoc test was used for parametric data, when significant difference was found. For nonparametric data, the Kruskal-Wallis test followed by the Mann-Whitney *U* test was applied instead. The χ^2 test was used for categorical data. Logistic regression analysis was performed to test for independent effects of age and positive IgE results of Trichophyton on disease severity. Analyses were performed by using a statistical software package (StatView; SAS Institute Inc; Cary, NC). A *p* value of < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the subjects' characteristics and results. Healthy control subjects were significantly younger and more predominantly male than the patients in the asthma subgroups. Patients with mild asthma were significantly younger than those with severe asthma. Total IgE levels were significantly increased in the three asthma subgroups as compared with the control subjects but did not differ among these subgroups.

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Table 1—Characteristics of Healthy Control Subjects and Three Subgroups of Asthma Patients*

Characteristics	Healthy Control Subjects	Patients			p Value
		Mild Asthma	Moderate Asthma	Severe Asthma	
Patients, No.	114	123	101	34	
Gender, M/F (F%)	66/48 (42.1)	55/68 (55.3)†	37/64 (63.4)†	14/20 (58.8)†	0.02‡
Age, yr	38.5 ± 19.0	49.3 ± 18.0†	52.9 ± 17.0†	58.1 ± 15.5†§	< 0.001
Disease duration, yr		8.4 ± 11.3	10.8 ± 12.9	13.8 ± 14.9	0.20
FEV ₁ , % predicted	103.1 ± 13.0	94.3 ± 14.9†	86.1 ± 18.4†§	73.6 ± 21.8†§¶	< 0.001
IgE, IU/mL	98 (2–1,600)	169 (2–11,683)†	207 (2–6,428)†	253 (4–8,126)†	< 0.001#
Positive specific IgE response					
Trichophyton	8 (7.0)	6 (4.9)	16 (15.8)§**	11 (32.4)†§	< 0.001‡
Mixed molds	5 (4.4)	19 (15.4)†	18 (17.8)†	10 (29.4)†	< 0.001‡
House-dust mites	43 (37.7)	62 (50.4)	50 (49.5)	14 (41.2)	0.18‡
Cat dander	7 (6.1)	26 (21.1)†	20 (19.8)**	6 (17.6)**	< 0.01‡
Dog dander	8 (7.0)	28 (22.8)†	16 (15.8)**	6 (17.6)	0.01‡
Japanese cedar pollens	70 (61.4)	59 (48.0)	48 (47.5)	14 (41.2)	0.07‡
Mixed graminea pollens	34 (29.8)	30 (24.4)	26 (25.7)	5 (14.7)	0.30‡
Mixed weed pollens	10 (8.8)	15 (12.2)	12 (11.9)	5 (14.7)	0.70‡

*Values are given as the mean ± SD, No. (%), or median (range), unless otherwise stated. M = male; F = female.

†p < 0.001 vs control subjects.

‡χ² test.

§p < 0.01 vs patients with mild asthma.

||ANOVA.

¶p < 0.05 vs patients with moderate asthma.

#Kruskal-Wallis test.

**p < 0.05 vs control subjects.

The positive rate of specific IgE against *Trichophyton* was significantly higher in the patients with moderate asthma than in the control subjects and patients with mild asthma, and it was also higher in

the patients with severe asthma than in all other groups but was similar in the control subjects and patients with mild asthma (Table 1). Specific IgE antibody titers against *Trichophyton* similarly dif-

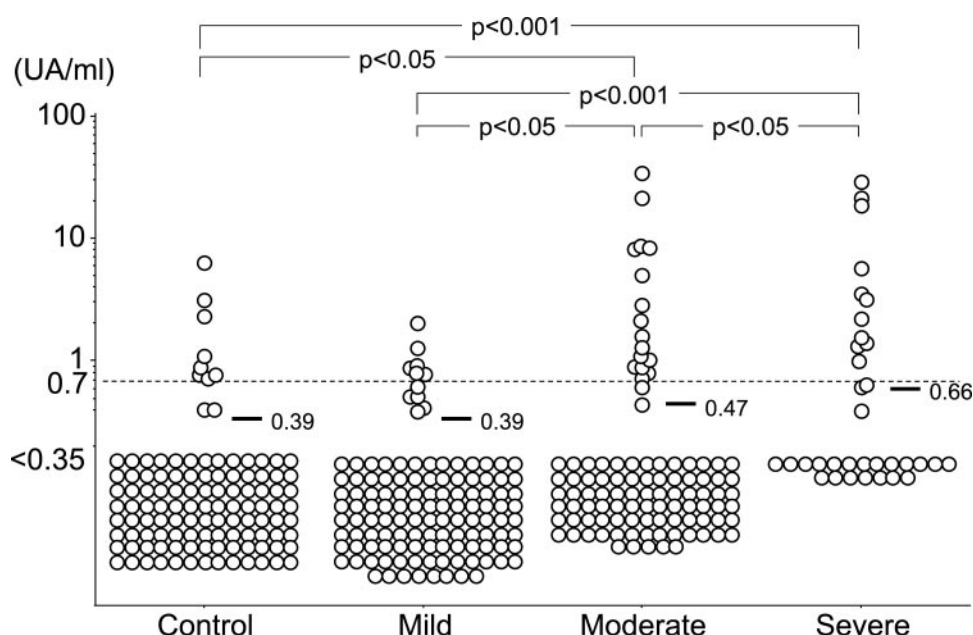


FIGURE 1. Specific IgE titers against *T rubrum* in healthy control subjects and subgroups of patients with asthma. The cutoff level of 0.7 UA/mL is indicated by a broken line. Bars represent geometric means. The differences among the four groups were significant by the Kruskal-Wallis test ($p = 0.01$).

ferred significantly among the four groups (Fig 1). The positive rates of specific IgE for mixed molds, cat dander, and dog dander were almost invariably higher in all asthma subgroups than in the control subjects but did not significantly differ among patients in the three asthma subgroups. The positive rates of specific IgE for house-dust mite, Japanese cedar pollen, mixed Gramineae pollens, and mixed weed pollens did not significantly differ in all groups (Table 1).

When gender, age, total IgE, and positive rates of specific IgE for each allergen were separately compared among the three asthma subgroups, age ($p = 0.028$ by ANOVA) and the positive rate of specific IgE against *Trichophyton* ($p < 0.0001$ by χ^2 test) differed significantly, whereas total IgE ($p = 0.37$ by Kruskal-Wallis test), rates of positive specific IgE against mixed molds ($p = 0.17$ by χ^2 test), and other variables did not (data not shown). Multiple logistic regression analysis was performed by including age and the positive rate of *Trichophyton*-specific IgE as possible predictors of asthma severity (Table 2). The probability of severe vs mild asthma was significantly associated with a positive *Trichophyton* IgE response and age. The probability of severe vs moderate asthma was associated only with a positive *Trichophyton* IgE response (Table 2).

The positive rate of specific IgE against *Trichophyton* was reanalyzed among four groups after excluding 52 subjects with positive IgE results for mixed molds, to exclude the potential effect of cross-reactivity to these molds. The positive rate of *Trichophyton*-specific IgE was higher in the patients with moderate asthma (8.4%) than in the patients with mild asthma (1.9%, $p = 0.04$) and marginally higher than in the control subjects (2.8%, $p = 0.07$). It was also higher in the patients with severe asthma (20.8%) than in the control subjects ($p = 0.0007$) and patients with mild asthma ($p = 0.0002$), marginally higher than in the patients with moderate asthma ($p = 0.08$), but similar in the control subjects and patients with mild asthma.

DISCUSSION

Our study shows that the positive rate and titers of specific IgE antibody to *Trichophyton* are signifi-

cantly higher in patients with moderate and severe asthma, but not in those with mild asthma, as compared with healthy control subjects. Both the prevalence and titers of these antibodies increased with increasing severity of asthma. Such a trend was not found for other allergens. Multivariate analysis of the three asthma subgroups indicated that the positive results of *Trichophyton*-specific IgE is an independent determinant of asthma severity. These results demonstrate that *Trichophyton* may be an important allergen associated with more severe asthma. We assessed "sensitization" solely on the basis of specific IgE results, but IgE levels for *Trichophyton* as examined by radioallergen sorbent test show a good correlation with the results of skin test or provocation test examined with *Trichophyton* extracts.^{10,22}

An association between the positive results of specific IgE against mixed molds and asthma severity was not demonstrated in this study, in contrast with previous reports.³⁻⁶ The reason for this is unclear, but it might be related to geographic differences in the frequency of sensitization.² Unlike most previous reports addressing the association between sensitization to molds and asthma severity,³⁻⁶ our study included healthy control subjects. Our data clearly demonstrated increased specific IgE response to *Trichophyton* in patients with moderate and severe asthma but not in those with mild asthma compared with control subjects. This response was associated with asthma severity. These results contrasted with the results obtained for mixed molds, showing increased specific IgE responses for patients in the three asthma subgroups as compared with control subjects but no statistically significant difference among patients in these subgroups.

When the specific IgE results against different molds are analyzed together, cross-reactivity among the molds may need to be considered.^{23,24} A previous report demonstrated that specific IgE antibody to *Trichophyton tonsurans* is unlikely to cross-react with other molds,²² but no specific study has addressed the cross-reactivity of *T. rubrum*-specific IgE. We compared the four subject groups including control subjects for the rate of positive specific IgE response against *Trichophyton* before and after exclusion of 52 subjects with positive IgE results for mixed molds. Because the results of two cohorts showed a

Table 2—Adjusted Odds Ratios for the Effects of Positive Specific IgE Against *Trichophyton* and of Age on Asthma Severity (Multiple Logistic Regression Analysis)*

Variables	Severe vs Mild Asthma			Severe vs Moderate Asthma		
	OR	95% CI	p Value	OR	95% CI	p Value
<i>Trichophyton</i>	7.83	2.52–24.32	< 0.001	2.67	1.04–6.86	0.04
Age	1.03	1.00–1.06	0.03	1.02	1.00–1.05	0.10

*CI = confidence interval; OR = odds ratio.

similar statistical trend, we feel that the cross-reactivity to molds is unlikely to have affected the results. However, a high degree of amino acid sequence identity has been identified in an allergen of *T rubrum* and that of *Penicillium citrinum*,^{7,25,26} so potential effects of cross-reactivity cannot be excluded completely.

The presence of Trichophyton infection has been suggested to be an important determinant of sensitization to Trichophyton,^{27,28} and inhalation or dermal absorption of Trichophyton antigens is considered a possible route of exposure.^{7,10,27} Fungal skin infections are more frequent in immunocompromised patients with conditions such as HIV infection, systemic treatment with corticosteroids, and diabetes mellitus.⁷ Six of our patients with severe asthma were continuously receiving oral corticosteroids to control asthma, but the prevalence of this treatment did not differ between Trichophyton IgE-positive and IgE-negative patients (3 of 11 [27%] vs 3 of 23 [13%], respectively; $p = 0.30$). Diabetes mellitus was more commonly present in patients with severe asthma (11 of 34; 32%) than in those with moderate (9 of 101; 8.9%) and mild disease (11 of 123; 8.9%; $p = 0.003$ by χ^2 test), but the need of insulin treatment (severe: 1 of 11 [9%]; moderate: 2 of 9 [22%]; mild: 3 of 11 [27%]) and levels of hemoglobin A1c (severe, $6.8 \pm 0.8\%$; moderate, $6.2 \pm 0.8\%$; mild, $7.3 \pm 1.4\%$) were similar among diabetes patients in the three groups ($p = 0.51$ by χ^2 test and $p = 0.12$ by ANOVA). Moreover, specific IgE antibody titers against Trichophyton did not differ between patients with diabetes mellitus ($n = 31$; 0.55 ± 5.76 UA/mL by geometric mean $\pm$ SD) and those without it ($n = 227$; 0.43 ± 3.02 UA/mL) when all asthma patients were analyzed ($p = 0.32$ by Mann-Whitney U test). The increased specific IgE response to Trichophyton in our patients with severe asthma is unlikely to be caused by corticosteroid-induced or diabetes mellitus-induced immunosuppression with resultant skin infection. We recognize it as a significant limitation of this study that the presence or absence of Trichophyton infection was not examined in all of our subjects, and that we cannot discuss in detail the effect of Trichophyton dermatophyte infection on the IgE response and asthma severity based on our own data. Despite this limitation, however, we believe the difference in the specific IgE response to Trichophyton among patients with asthma of varying severity and control subjects is relevant. We assume that Trichophyton may be involved in patients with more severe disease as an intrinsic allergen that may deteriorate asthma, although the exact route of exposure (inhalation or dermal absorption in patients with infection) is unknown.

The positive rates of specific IgE to house-dust mite or pollens did not differ among the healthy

subjects and asthmatic subgroups. It has been recognized that the proportion of subjects sensitized to aeroallergens such as house-dust mite, pollens, animal danders, and molds decrease consistently from younger to older cohorts.^{2,29} A study³⁰ from Japan has shown that specific IgE responses to *Dermatophagoides farinae* and timothy (defined as a capsulated hydrophilic carrier polymer radioallergosorbent test result > 0.35 UA/mL) were found in 66% and 41% of young (< 41 years of age) healthy volunteers and in 26% and 6% of older (≥ 41 years of age) healthy volunteers and even in 38% and 15% of older asthma patients, respectively. Because our healthy control subjects were significantly younger than all of the asthma subgroups, potentially greater rates of positive IgE response to some allergens, such as Japanese cedar pollen, might have been missed in the asthma patients. Moreover, assessment of specific IgE using pollen and mold mixes, which is another limitation of this study, could have masked differences in specific IgE response between asthma patients and control subjects. However, a higher positive rate of Trichophyton-specific IgE in the patients with moderate and severe asthma than in the control subjects and patients with mild asthma, who were younger than the former two groups, certainly demonstrates the relation between increased specific IgE response to Trichophyton and more severe disease.

In conclusion, specific IgE response to Trichophyton increases with increasing severity of asthma. This is still true even when subjects with positive IgE results for other (mixed) molds are excluded. Trichophyton may therefore be an important allergen associated with the development of severe asthma. Examinations for sensitization to Trichophyton may be indicated in patients with refractory asthma.

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