

Analysis of the Serum Levels of Fungi-Specific Immunoglobulin E in Patients with Allergic Diseases

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Key Words

Atopic dermatitis · Respiratory allergic disease · Fungi-specific IgE

Abstract

Background: Atopic patients are exceptionally sensitive to airborne allergens. Sensitization to fungal allergens may be associated with respiratory allergic disease (RAD) and atopic dermatitis (AD). This study investigates the relationship between sensitization to different fungal allergens and the clinical manifestations of atopic disease. **Methods:** We retrospectively reviewed the medical records of atopic patients from the National Taiwan University Hospital from 2004 to 2009. A total of 133 atopic patients were found who were sensitive to at least 1 of the 3 most common fungi (*Candida albicans*, *Aspergillus fumigatus*, *Penicillium chrysogenum*) in Taiwan and were enrolled in the study. These patients were further divided into subgroups of isolated AD, isolated RAD and AD + RAD. The association between sensitization to fungi and allergic disease was analyzed by logistic regression analysis. **Results:** The sensitization rate to *Candida*-specific IgE was 81.2%, followed closely by *Aspergillus* at 69.2% and *Penicillium* at 63.2%. Isolated AD was the most common diagnosis. The levels of specific IgE antibodies against *Aspergillus*, *Candida* and *Penicillium* were highest in patients with isolated AD. Logistic regression revealed that isolated AD

was highly associated with sensitization to *Candida* [odds ratio (OR) 10.45, 95% confidence interval (CI) 2.37–45.9]. In contrast, sensitization to *Penicillium* (OR 0.34, 95% CI 0.13–0.87) and *Candida* (OR 0.30, 95% CI 0.10–0.92) showed a negative association with isolated RAD. **Conclusions:** Fungal sensitization is more closely associated with AD than RAD. Our results suggest that specific sensitization to fungal allergens plays a critical role in the pathogenesis of atopic disease.

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Introduction

The prevalence of asthma and allergic diseases in Asian populations is increasing over time [1, 2]. Airborne allergens are important predisposing factors to these allergic diseases. House dust mites are the most common allergens triggering atopic disease in the Taiwan area [3]. Recent reports have demonstrated that fungal allergens also play an important role in allergic disease.

Fungal spores are ubiquitous in outdoor and indoor environments [4–6]. The outdoor fungal allergens are predominantly composed of spores [7] from *Cladosporium* and *Alternaria*. *Aspergillus* spp. and *Penicillium* spp. are well-known indoor fungi, and their occurrence is not affected by seasonal changes [8]. Taiwan is located in a subtropical region with optimal environmental condi-

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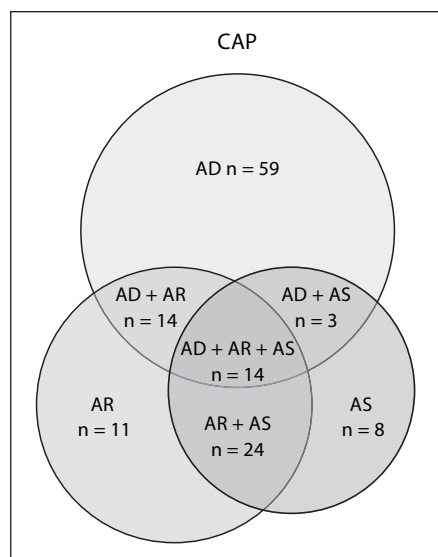


Fig. 1. The diagnostic subgroups in our patients enrolled from the National Taiwan University Hospital. AS = Asthma; AR = allergic rhinitis.

tions for fungal growth such as high temperature and relative humidity [4]. Several species and genera are known to cause allergic disease. Exposure to airborne fungi and spores contributes to rhinitis, asthma and atopic dermatitis (AD) [6, 9–11]. Fungal allergens have been implicated as aggravating factors in both respiratory allergic disease (RAD) and AD [12, 13]. Fungal allergens are more numerous and antigenically variable than other allergens. Because of their ubiquitous nature, they are exceedingly difficult to avoid [14].

The purpose of our study was to determine the sensitization rate and degree of sensitization to the 3 most common fungal allergens (*Candida albicans*, *Aspergillus fumigatus*, *Penicillium chrysogenum*) and their role in both AD and RAD patients.

Patients and Methods

Patients

A total of 133 patients visiting the outpatient clinics of the Departments of Pediatrics, Dermatology, ENT and Internal Medicine at the National Taiwan University Hospital for atopic diseases were enrolled in this study. Patients (male to female ratio 1.6; mean age 16.4 years, range 1–67 years) were enrolled if their serum allergen-specific IgE levels were elevated in response to at least 1 of the following fungal allergens: *C. albicans*, *A. fumigatus* or *P. chrysogenum*. Exclusion criteria were an uncertain diagnosis and incomplete medical records. Most patients were selected from the Departments of Dermatology and Pediatrics.

The inclusion criterion was the presence of atopic disease (including asthma and/or rhinitis and/or AD). Asthma was diagnosed using the criteria of the Global Initiative For Asthma 2007 guidelines. The diagnosis of allergic rhinitis was based on symptoms of long-term itching, sneezing, watery rhinorrhea and/or nasal stiffness [15]. The diagnosis of AD was based on the presence of a chronic pruritic skin rash. The patients diagnosed with asthma and/or allergic rhinitis were grouped as having RAD.

The 133 patients were sorted into 3 groups according to their diagnoses (fig. 1): group 1, the isolated AD group (n = 59); group 2, patients with allergic rhinitis/asthma or isolated asthma or isolated allergic rhinitis, who were labeled the isolated RAD group (n = 43), and group 3, patients with both AD and RAD (n = 31).

Determination of Total IgE and Allergen-Specific Antibodies

Levels of serum IgE specific for 1 of the 3 fungi (*C. albicans*, *A. fumigatus* and *P. chrysogenum*) were measured by the CAP system (Pharmacia, Uppsala, Sweden). The severity of sensitization to individual allergens was categorized into 6 classes (0–6). A result equal to or greater than class 2 was considered positive. The total serum IgE level was also measured by the CAP system in all patients.

Statistical Analysis

Continuous data are shown as means and categorical data are shown as frequencies (percentiles). The differences in percentages between the atopic groups were analyzed by the χ^2 test. We compared the values of mean class levels between groups by using the nonparametric Mann-Whitney U test. The distribution of serum specific IgE (mean class levels) for an individual fungus and different disease groups is shown using a box plot. The associations between independent covariates, such as different individual fungus sensitization, and dependent variables (isolated AD, isolated RAD, AD + RAD groups) were further analyzed by binary logistic regression. A value of $p < 0.05$ was considered statistically significant. All analyses were performed using SPSS 15.0 software (SPSS, USA).

Results

Distribution of Subjects according to Diagnosis

One hundred and thirty-three atopic patients were enrolled in this cross-sectional study, as shown in table 1. There were significantly fewer females than males (males 62.4% vs. females 37.6%; $p < 0.05$). Positive sensitization to fungi was very prevalent among young children (<10 years) in the isolated RAD group. The prevalence of sensitization to fungal allergens in the isolated AD group peaked at 11–20 years and then declined substantially in the following decade. The most common diagnosis was AD (59/133). The number of patients in the isolated RAD group (43/133) was modestly higher than in the dual diagnosis group, i.e. AD + RAD (31/133). Total serum IgE levels were significantly higher in patients with isolated AD than in the other groups ($p < 0.05$). The isolated

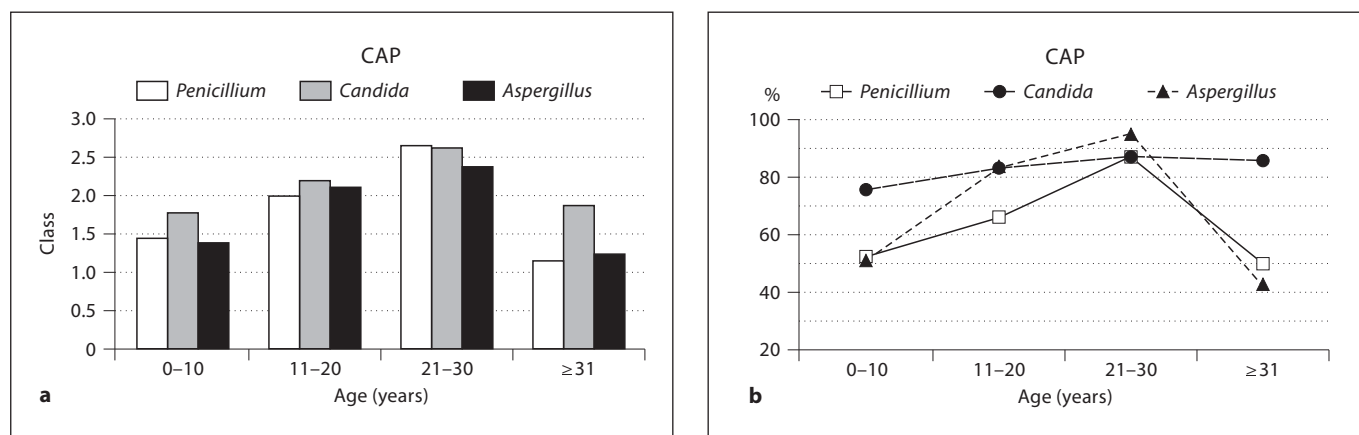


Fig. 2. Positive sensitization rates for individual fungi and distribution of serum-specific IgE levels in different age groups. **a** The class level for individual fungi is indicated on the y-axis, and age groups are shown on the x-axis. **b** The percentages of positive sensitization for individual fungi are indicated on the y-axis, and age groups are shown on the x-axis.

Table 1. Patient characteristics and prevalence of sensitization to different fungi according to diagnosis

Characteristics	Total (n = 133)	Isolated AD (n = 59)	Isolated RAD (n = 43)	AD + RAD (n = 31)	p value
Males	83 (62.4)	37 (62.7)	32 (74.4)	14 (45.2)	0.037
Females	50 (37.6)	22 (37.3)	11 (25.6)	17 (54.8)	
Age, years					
0-10	49 (36.8)	8 (13.6)	20 (46.5)	21 (67.7)	
11-20	47 (35.3)	24 (40.7)	15 (34.9)	8 (25.8)	
21-30	24 (18.1)	21 (35.5)	1 (2.3)	2 (6.5)	
31-40	4 (3)	3 (5.1)	1 (2.3)	0	
>41	9 (6.8)	3 (5.1)	6 (14.0)	0	
Mean total IgE, kU/liter	1,698	1,958	1,206	1,894	<0.05 ¹
<i>Penicillium</i> sensitization	84 (63.2)	44 (74.6)	18 (41.9)	22 (71)	0.002
<i>Aspergillus</i> sensitization	92 (69.2)	48 (81.4)	22 (51.2)	22 (71)	<0.005
<i>Candida</i> sensitization	108 (81.2)	56 (94.9)	31 (72.1)	21 (67.7)	0.001

Values represent numbers of patients, except where indicated otherwise. Figures in parentheses are percentages. A p value <0.05 was considered to be statistically significant.

¹ Mann-Whitney U test.

RAD group had the lowest total serum IgE level ($p < 0.05$).

Candida was the most common sensitizing agent of the 3 fungi tested in all patients. *Candida*-specific IgE was detected in 81.2% of patients; *Aspergillus*-specific IgE was observed in 69.2% of patients and *Penicillium*-specific IgE in 63.2%. We found that patients were rarely sensitized to a single fungal species.

The serum of patients with isolated AD had a higher prevalence of sensitization (94.9%) to *Candida* compared

to patients with only RAD (72.1%). Patients who only had RAD showed a significantly lower prevalence of sensitization to *Aspergillus* and *Penicillium* ($p = 0.005$).

Positive Sensitization Rate to Fungal Allergens and Distribution of Serum Fungi-Specific IgE Classes in Different Age Groups

The sensitization rate to each fungal species demonstrated strikingly similar age-dependent prevalence patterns (fig. 2). Regardless of the type of fungus, the highest

Fig. 3. Comparison of fungi-specific IgE levels among the 3 disease groups. Each box indicates the 25th–75th percentiles of the individual fungi-specific IgE level. The horizontal line marks the median.

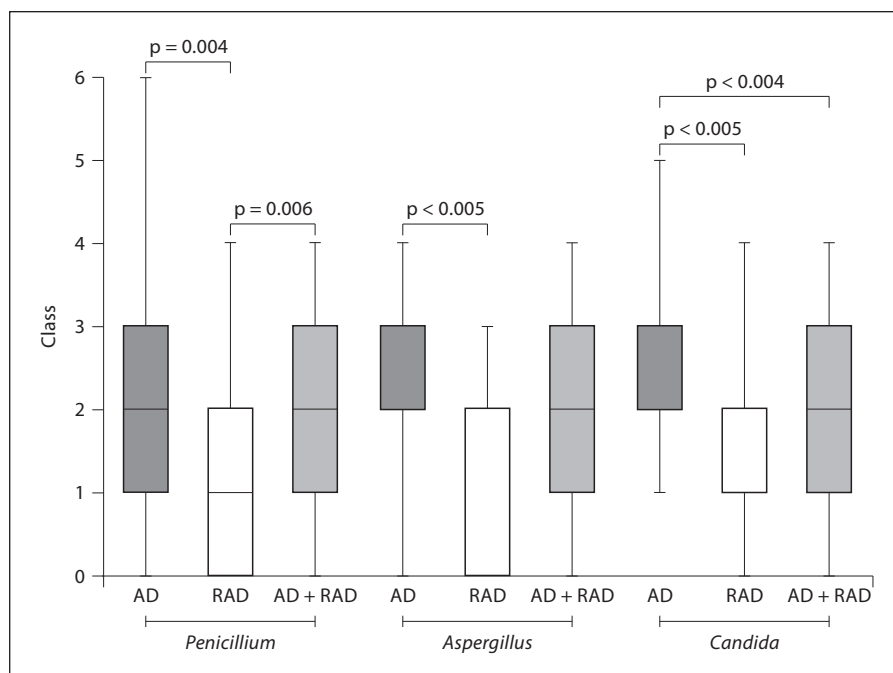


Table 2. Numbers of patients sensitized to other airborne allergens according to diagnosis

Patient group	Sensitization to airborne allergens			
	mites (n = 123)	pollen (n = 55)	animal dander (n = 82)	cockroaches (n = 70)
AD only	55 (44.7)	27 (49.1)	45 (54.9)	34 (48.6)
RAD only	37 (30.1)	18 (32.7)	20 (24.4)	23 (32.8)
AD + RAD	31 (25.2)	10 (18.2)	17 (20.7)	13 (18.6)

Figures in parentheses are percentages.

specific IgE levels (fig. 2a) and the highest prevalence rates (fig. 2b) were observed in 21- to 30-year-old patients. The sensitization rates to *Aspergillus* and *Penicillium* declined thereafter.

Comparison of Serum Fungi-Specific IgE Levels among the 3 Disease Groups

In figure 3, it can be seen that the fungi-specific IgE levels (as shown by class level) differed among the 3 patient groups. The fungi-specific IgE levels were lowest in the isolated RAD patients. The levels of specific IgE antibodies against *Penicillium*, *Aspergillus* and *Candida* were

significantly higher in patients with isolated AD than with isolated RAD ($p < 0.05$). Levels of specific IgE against those fungal allergens inhaled through the respiratory tract, namely *Penicillium* and *Aspergillus*, were not significantly different between the patients with isolated AD and those with AD + RAD. However, sensitization to *Candida*, which colonizes on the skin, was significantly higher in the patients with isolated AD than in the patients with isolated RAD or AD + RAD.

Sensitization to Other Airborne Allergens

Patients were tested for sensitization to dust mites, pollen, animal dander and cockroaches (table 2). Nearly all of the patients (123/133, 92.5%) were positively sensitized to mite allergens (including Der p and Der f) and had class IV sensitization (data not shown). Most atopic patients were sensitized to other allergens. It seems to be a common pattern for these subjects to react to many species.

Association between Sensitization to Fungi and Allergic Disease

As illustrated in table 3, sensitization to *Candida*, *Penicillium* and *Aspergillus* was associated with isolated AD by univariate analysis. After adjusting for confounding factors in multivariate analysis, such as age, sex and sensitization to pollen, mites, cockroaches, animal dander

Fig. 4. Correlation between the body surface area involvement and sensitization to different fungi in AD. The lines mark the means. The mean proportion of body surface involvement was 59% for *Aspergillus*, 61% for *Penicillium* and 57% for *Candida*.

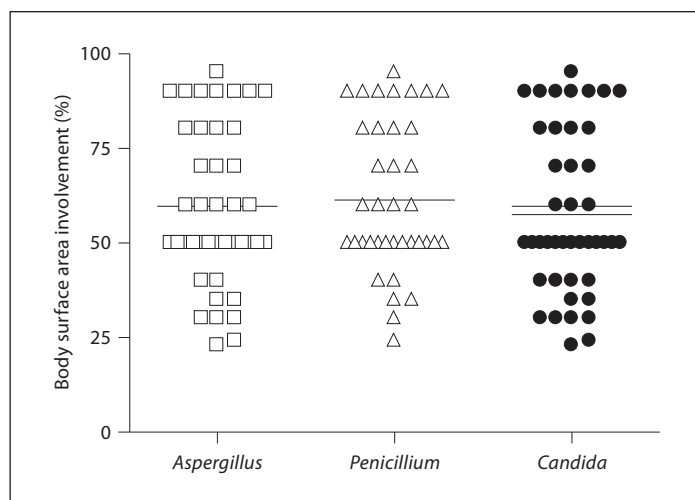


Table 3. Logistic regression analysis of the association of isolated AD and isolated RAD with sensitization to individual fungi

Factors	Isolated AD		Isolated RAD	
	OR (95% CI)	adjusted OR (95% CI)	OR (95% CI)	adjusted OR (95% CI)
Male	0.97 (0.48–1.98)	1.64 (0.66–4.07)	2.22 (0.99–4.96)	0.35 (0.14–0.88)*
Age 0–10 years	0.12 (0.53–0.3)*	0.01 (0.03–0.29)*	0.07 (0.01–0.53)*	1.34 (0.52–3.45)
Sensitization to				
<i>Penicillium</i>	2.49 (1.18–5.24)*	1.43 (0.47–4.36)	0.26 (0.12–0.56)*	0.34 (0.13–0.87)*
<i>Aspergillus</i>	2.97 (1.33–6.64)*	1 (0.27–3.53)	0.29 (0.13–0.65)*	0.46 (0.16–1.36)
<i>Candida</i>	7.89 (2.23–27.95)*	10.45 (2.37–45.9)*	0.43 (0.17–1.06)	0.30 (0.1–0.92)*
Pollen	1.38 (0.69–2.77)	1 (0.37–2.79)	1.03 (0.49–2.15)	2.2 (0.79–6.13)
Mites	1.21 (0.32–4.51)	0.89 (0.17–4.57)	0.28 (0.07–1.07)	0.31 (0.05–1.65)
Cockroaches	1.43 (0.72–2.85)	0.86 (0.31–2.35)	1.05 (0.50–2.18)	1.94 (0.73–5.13)
Animal dander	3.21 (1.51–6.62)*	4.73 (1.52–14.7)*	0.39 (0.18–0.83)	0.46 (0.17–1.27)

Adjusted OR = OR adjusted for sex, age 0–10 years and sensitization to mites, pollen, animal dander, cockroaches and fungal allergens. * $p < 0.05$.

and different fungi, *Candida* sensitization was still significantly associated with AD [$p < 0.05$; odds ratio (OR) 10.45, 95% confidence interval (CI) 2.37–45.9]. The ORs for RAD patients were significantly lower with regard to *Penicillium* and *Aspergillus* sensitization ($p < 0.05$) by univariate analysis. In multivariate analysis, sensitization to *Penicillium* (OR 0.34, 95% CI 0.13–0.87) and *Candida* (OR 0.30, 95% CI 0.10–0.92) had significantly decreased ORs for RAD patients ($p < 0.05$). Taken together, our results showed that fungal sensitization was associated with AD rather than RAD.

Correlation between Body Surface Area Involvement and Sensitization to Different Fungi in AD

The results shown in figure 4 reveal the close relationship between fungal sensitization and AD. We analyzed the data for an association between sensitization to different fungi and the body surface area involvement in AD patients. In 68 of the 90 AD patients analyzed, no association was detected between the size of the body surface area involvement and the type of fungi. The mean percentage of body surface involvement was 59% for *Aspergillus*, 61% for *Penicillium* and 57% for *Candida*.

Discussion

Fungi are among the most common and important airborne allergens. Exposure to allergenic fungi may lead to IgE-mediated allergic respiratory disease [16] and AD [9], yet few studies have examined fungal sensitization in Asian populations. Our study showed comparable findings with regard to age dependency of mold sensitization to those reported in the literature [16–18]. The sensitization pattern revealed that fungal allergy was extremely common among children with RAD, especially in those <10 years of age. One possible reason is that younger children may be less efficient in clearing airway fungal spores, which results in higher and longer antigenic stimulation [16]. The higher specific IgE titers to fungi in adults compared to children may reflect a difference in cumulative exposure or poor elimination. The relatively rapid fall in sensitization to fungi with increased age may be due to an increase in immunological memory promoting the production of alternative antibody isotypes (e.g. secretory immunoglobulin against fungal spores [18]).

Several species of fungi, such as *C. albicans*, *Trichophyton rubrum*, *Penicillium notatum*, *A. fumigatus* and *Malassezia*, have been associated with AD [9, 10, 19–23]. Recent studies described autoreactivity to human proteins such as manganese superoxide dismutase (MnSOD), which may be involved in IgE-mediated auto-reactivity [23]. The MnSOD in allergic patients showed sequence identity and similarity of >50 and 70%, respectively, to the corresponding allergens of *A. fumigatus*. The identical residues are scattered over the sequence of the MnSOD and may indicate putative conformational IgE-binding epitopes that could play a role in exacerbation of atopic eczema [22, 23]. In addition to the fungi tested in this study, *Malassezia* spp. also represent an important contributing factor to eczema [9, 21]. By molecular mimicry leading to cross-reactivity, such sensitization might be induced primarily by exposure to environmental fungal MnSOD of *Malassezia sympodialis* [24]. However, the limited data about *Malassezia* spp. sensitization in AD in Taiwan reflect its unexplored potential association with skin diseases in Taiwan and warrant further research.

Most of our patients (90/133) had a diagnosis of AD. The absolute class level of specific IgE against *Candida*, which colonizes the skin, was significantly higher in patients with isolated AD than in those with AD and RAD or isolated RAD. Most of our AD patients exhibited IgE specific for dust mites or other aeroallergens. After controlling for most of the confounding factors such as age, sex and sensitization to pollen, mites, cockroaches, ani-

mal dander and different fungi, *Candida* sensitization was still significantly associated with isolated AD ($p < 0.05$; OR 10.45, 95% CI 2.37–45.9) by multivariate analysis. Recent reports have suggested that the T cell immune response shifts from T helper type 1 to T helper type 2 cells in the immune response to *C. albicans* antigen in AD [25]. Since *Candida* species usually colonize the skin, it is difficult for AD patients to control and treat them by avoiding *Candida*. Thus, a report suggested that antifungal treatment may provide symptomatic improvement in some patients with AD [21].

Exposure to fungal spores is one of the important contributing factors in the development of allergic respiratory disease [8, 26]. Three studies suggest that elevated levels of fungi-specific IgE are important causes of asthma and allergic rhinitis [27–29]. This association is caused by colonization of the mucus-epithelial surface with fungi or an extreme response to exogenous spores [18]. Worldwide variations in the prevalence of fungi sensitization in RAD patients suggest that environmental factors, different criteria for population selection and different characteristics of diagnostic extracts play important roles [30–33].

Among the RAD patients in our study, *Candida* (72.1%) was the most common sensitizing agent, followed by *Aspergillus* (51.2%) and *Penicillium* (41.9%). Similar results were reported by Ezeamuzie et al. [16], although their study was conducted in a desert area, whereas our study was conducted in a subtropical region characterized by high temperature and humidity.

On the other hand, according to multivariate logistic regression analysis, we found that sensitization to *Penicillium* and *Candida* has a significantly decreased association with RAD (ORs of 0.34 and 0.30). Previous studies observed that exposure to fungal spores may have a protective effect on atopic asthma and some species may play beneficial roles in health outcome [34, 35]. Furthermore, Schubert and Goetz [36] reported elevated total serum IgE but no elevation of fungus-specific IgE serum levels in 67 patients with allergic fungal sinusitis. In another smaller series of 14 patients with allergic fungal sinusitis, none had a positive serum IgE response to *Aspergillus* [37]. These contradictory observations may be due to localized effects of *Aspergillus* in the airway even if no immunological response to *Aspergillus* can be detected in the serum. Besides, serum IgE tests have not always demonstrated a good correlation between allergic fungal sinusitis and allergic reactions [37]. Moreover, fungal exposure may result in an alternative immunological event, similar to exposure to bacterial endotoxins that favor the T helper type 1-mediated cytokine re-

sponse, and may underline the lack of allergic sensitization in children [38].

Most of our patients were sensitized to multiple fungi, and thus possible cross-reactions among the various fungi should be addressed. If IgE from the serum of an allergic patient exhibits reactivity to multiple allergens, it would cause a problem. The existence of cross-reactivity between various fungi could be determined by assays such as CAP inhibition [24]. Cross-reactivity between *A. fumigatus* and *Penicillium* using similar inhibition methods demonstrated that the binding to *Penicillium* of IgE antibodies in sera from patients with allergic bronchopulmonary aspergillosis could be inhibited by *A. fumigatus* almost as effectively as by *Penicillium* [39]. By using affinity-purified antibodies and a sensitive and quantitative assay with untreated antigens [40], the cross-reactivity between *Stachybotrys*, *Aspergillus* and *Penicillium* was determined to be approximately 10%, which is lower than previously believed. The relationship between cross-reactivity of various fungi and clinical manifestation of allergic disease requires further evaluation.

One of the limitations of our study is the lack of post hoc tests in the nonparametric analysis, and an α error might have been included. Moreover, the study enrolled patients from a single medical center and there was no healthy control group. Thus, our observations may have a selection bias. These limitations might have underestimated the prevalence of fungal sensitization in the general population in Taiwan.

Conclusion

The routes of exposure to fungal allergens and the involvement of different organs are important in the outcome of allergic diseases, even though genetic and environmental factors also play important roles. In this study, patients who were sensitized to fungi also had a tendency to be sensitized to other aeroallergens. Fungal sensitization was associated with AD rather than RAD.

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