

Increased Levels of Serum-Specific Immunoglobulin E to Staphylococcal Enterotoxin A and B in Patients with Allergic Rhinitis and Bronchial Asthma

Jyh-Hong Lee^a Yu-Tsan Lin^a Yao-Hsu Yang^a Li-Chieh Wang^a
Bor-Luen Chiang^{a,b}

^aDepartment of Pediatrics, National Taiwan University Hospital, and ^bGraduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan, ROC

Key Words

Staphylococcal enterotoxin A and B · Allergic rhinitis ·
Bronchial asthma · Logistic regression analysis

Abstract

Background: The association between staphylococcal enterotoxins and atopic dermatitis (AD) is well characterized. We aim to evaluate the association between sensitization to staphylococcal enterotoxin A (SEA) and/or B (SEB) and the development of allergic airway disease. **Methods:** Two hundred and seventy-four patients were grouped into allergic rhinitis (AR) and/or bronchial asthma (BA) only, AD only and AR/BA+AD. The AR/BA only group was further divided into AR only, AR and airway hyperresponsiveness (AR+AHR) and BA. The allergen-specific and total immunoglobulin E (IgE) antibodies were determined by the CAP system. The associations of sensitization to SEA/SEB with allergic airway disease were analyzed by logistic regression analysis. **Results:** The overall rate of sensitization to SEA/SEB was 25.7%, whereas the rate of the AD only group (45.5%) was significantly higher than that of the AR/BA only group (24.5%, $\chi^2 = 8.1$). After sensitization to SEA/SEB, the geo-

metric mean total IgE levels were significantly elevated in patients with AR+AHR and BA, but not in those with AR only. BA patients had higher geometric mean values of SEA- and SEB-specific IgE than AR only and AR+AHR patients. Logistic regression revealed that AR/BA only was more associated with sensitization to SEA/SEB (odds ratio 6.57) than AD only and AR/BA+AD (odds ratio 2.44 and 1.72). **Conclusions:** Atopic status after sensitization to SEA/SEB was more closely associated with BA than with other airway allergy, implying that SEA/SEB may play a role in exacerbating airway allergy and increasing the risk of allergic airway disease. Our study suggests that staphylococcal enterotoxins play a prominent role in the pathogenesis of allergic airway disease as well as AD.

Copyright © 2005 S. Karger AG, Basel

Introduction

Staphylococcus aureus-derived enterotoxins (SAEs) are superantigens that possess potent stimulatory activity for T lymphocytes. SAEs cross-link the V β chain of the T cell receptor with major histocompatibility complex

class II molecules on accessory or target T cells outside the peptide-binding groove area [1]. SAEs are a family of structurally related, heat-stable proteins comprising several major serologic types; among these are 5 prototypic SAEs (types A through E) and toxic shock syndrome toxin 1. These SAEs have activity related to that of both immunomodulatory and proinflammatory effector cell types; therefore, they may have an important role in the pathogenesis of chronic inflammatory diseases, such as atopic eczema/dermatitis syndrome, rhinitis, nasal polypsis and possibly asthma [2].

Unlike atopic dermatitis (AD), *S. aureus* and its superantigens are not well studied in terms of their role in allergic airway disease. In individuals with asthma and in those allergic to house dust mites (*Dermatophagoides pteronyssinus*) or birch pollen, *S. aureus* can induce the release of histamine from leukocytes [3, 4]. Among patients with poorly controlled asthma, samples obtained during bronchoalveolar lavage show significantly increased expression of T cell receptor V β 8+ T cells, suggesting that staphylococcal superantigens are potential triggers of T cell activation [5]. Animal studies have shown that staphylococcal enterotoxin B (SEB) triggers the recruitment of several proinflammatory cells and cytokines associated with increased airway responsiveness [6].

S. aureus is one of the predominant bacteria in the nasal airways, and its superantigen may aggravate perennial allergic rhinitis (AR) [7]. Approximately 25–33% of patients with AR are sensitized to staphylococcal enterotoxin A (SEA) and/or SEB [8]. In patients with allergy to house dust mites as well as persistent AR and/or bronchial asthma (BA), 9.1% have SEA-specific immunoglobulin E (IgE), 15.1% have SEB-specific IgE and 24.24% have both [9]. IgE antibodies to SAEs are more common in patients with severe asthma than in those with mild asthma, suggesting a relationship between the presence of IgE antibody to SAEs and the severity of asthma [10].

We aimed to evaluate the association between specific sensitization to SEA and/or SEB and allergic airway disease and to draw a parallel with this relationship in AD, in comparison with sensitization to other aeroallergens.

Methods

Study Groups

From May to September 2004, 425 subjects with physician-referred or self-reported symptoms of allergic disease came to the outpatient department of our hospital. We excluded patients with an uncertain diagnosis, those without available data from aeroal-

lergen sensitization tests and those with infection (bacterial, viral, fungal and parasite), systemic disease (malignancy, immunodeficiency) or conditions (except AD) associated with unusually high serum IgE levels (e.g., Kimura disease, allergic bronchopulmonary mycosis, hyper-IgE syndrome, Netherton syndrome). Therefore, we retrospectively reviewed the charts of 327 subjects who had undergone allergen sensitization tests for various allergens by using the CAP system.

Fifty-three cases (16.2%) whose condition did not meet the clinical and laboratory criteria for allergic disease formed the group of nonallergic controls. Patients without positive allergic laboratory testing results but with severe, persisting or recurrent possible allergic symptoms and with a need for continuous pharmacological treatment and a positive family history of allergy were excluded from the control group.

The remaining 274 subjects were divided into 3 groups according to their diagnosis. Group 1, the AR/BA only group, included 188 patients (57.5%) with AR and/or BA diagnosed on the basis of clinical symptoms and pulmonary function tests. AR was diagnosed if nasal itching, sneeze, watery rhinorrhea or nasal stiffness occurred at least twice and was induced by an IgE-mediated response [11]. Patients with concurrent AR and allergic conjunctivitis were included. BA was defined as chronic inflammation and increased airway hyperresponsiveness (AHR) that led to recurrent wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning [12]. The baseline lung function test forced expiratory volume in 1 s (FEV₁) and peak expiratory flow rate were performed using a spirometry. Group 2, the AD only group, included 55 patients (16.8%) with atopic eczema/dermatitis syndrome [13]. Group 3, the AR/BA+AD group, included 31 patients (9.5%) with concurrent AR/BA and AD.

The AR/BA only group was further divided into 3 subgroups: those with AR only (n = 134), those with AR+AHR (n = 37) and those with BA (n = 17). AHR was measured by methacholine chloride (Brantford, Canada) inhalation using the 2-min tidal breathing dosing protocol with a starting concentration of 0.0625 mg/ml [14]. Subjects who had a decline in FEV₁ of 20% or more after 2 mg/ml or less methacholine were defined as having AHR. Subjects with AHR caused by smoking-induced chronic airway obstruction, congestive heart failure, cystic fibrosis and infectious bronchitis were excluded. Patients with AR+AHR but without clinical asthma or symptoms such as wheeze and/or cough at resting state were included in the AR+AHR subgroup. Patients with clinical asthma with or without AR were included in the BA subgroup. The baseline percent of predicted values of FEV₁ and peak expiratory flow rate (mean $\pm$ SD) in BA patients were 91.1 $\pm$ 21.4 and 79.5 $\pm$ 20.3%, respectively.

Determination of Total and Allergen-Specific Serum IgE Levels

Levels of total serum IgE and allergen-specific serum IgE to aeroallergens were measured by using the CAP FEIA system (Pharmacia, Uppsala, Sweden) according to the manufacturer's instructions, and values were represented as mean $\pm$ standard deviation. The assay was calibrated against the World Health Organization standard for total serum IgE, with a range of 0.35–100 kU/l for allergen-specific IgE and 2–2,000 kU/l for total serum IgE. Titers were defined as being positive for sensitization when the observed allergen-specific serum IgE level was $\geq$ 0.35 kU/l.

Table 1. Demographic, serologic characteristics of the study population

Characteristics	Total (n = 327)	Control (n = 53)	AR/BA only (n = 188)	AD only (n = 55)	AR/BA+AD (n = 31)
Sex, F:M	166:161	30:23	92:96	30:25	14:17
Age group, %					
0–10 years	65.8	71.7	64.4	56.4	80.7
11–20 years	12.5	5.7	12.1	20.0	12.9
21–30 years	8.3	5.7	7.5	14.6	6.4
31–40 years	7.3	11.2	7.5	7.2	0
>40 years	6.1	5.7	8.5	1.8	0
Geometric mean of total IgE, kU/l	490.0	64.5	438.8	949.4	799.2
SEA/SEB sensitization, n (%)	84 (25.7)	2 (3.8)	46 (24.5)	25 (45.5)	11 (35.5)

Table 2. Comparison of total serum IgE, *D. pteronyssinus*- and *D. farinae*-specific IgE levels with or without SEA/SEB sensitization

	AR/BA only		AD only		AR/BA+AD	
	SAE (–)	SAE (+)	SAE (–)	SAE (+)	SAE (–)	SAE (+)
Total IgE, kU/l	338.5 ± 429.4	712.8 ± 674.9*	568.8 ± 674.7	1,363.1 ± 693.3*	406.2 ± 435.0	1,467.3 ± 663.8*
<i>D. pteronyssinus</i> -specific IgE, kU/l	31.9 ± 38.2	50.9 ± 44.8*	36.7 ± 43.1	72.9 ± 42.1*	57.0 ± 45.5	65.4 ± 48.0*
<i>D. farinae</i> -specific IgE, kU/l	28.9 ± 35.5	46.7 ± 42.1*	34.4 ± 41.6	70.3 ± 43.0*	51.2 ± 43.2	59.8 ± 45.4*

Data are indicated as mean ± SD. SAE (+) = Patients with SEA/SEB sensitization; SAE (–) = patients without SEA/SEB sensitization.

* $p < 0.001$, SAE (+) versus SAE (–).

Statistical Analysis

IgE levels were statistically analyzed with a nonparametric Mann-Whitney U test. A χ^2 test was used to compare the rate of sensitization to SEA/SEB among groups.

Aeroallergens are grouped into 6 groups: SAEs (SEA, SEB), mites (*D. pteronyssinus*, *Dermatophagoides farinae*, *Blomeia tropicalis*), fungi (*Penicillium notatum*, *Aspergillus fumigatus*, *Candida albicans*), cockroaches, animal dander (cat, dog) and pollen (common ragweed, Bermuda grass). The association of allergen-specific IgE to these 6 groups with the risk of AR/BA, AD and concurrent AR/BA and AD were studied by means of logistic regression.

Patient sex, age and allergen-specific IgEs for the 6 groups of aeroallergens were included as categorical variables. Patients were stratified according to sex and 10-year age groups. Female sex, age in the first decade, IgE ≤ 150 kU/l and specific aeroallergen sensitization of control subjects were considered a reference group for calculation. Odds ratios (ORs) and 95% confidence intervals for the ORs were derived accordingly. Stepwise multiple logistic regression analysis was performed to evaluate the independent effects of sensitization to allergens as a risk factor for the various disease groups. Adjustments were made for the effect of the following confounding variables: age, sex, total serum IgE value and any allergen sensitivity. p values ≤ 0.05 were regarded as indicating a statistically significant difference. Collinearity was tested by examining the variance inflation factor. The analyses were performed using the SAS software (SAS Institute Inc., N.C., USA).

Results

Demographic and Serologic Characteristics of Participants

The sex and age distributions of the 327 subjects were evenly matched, as shown in table 1, except that the AR/BA+AD group was younger than the others (geometric mean: 13.0 years for control, 13.9 years for AR/BA only, 12.6 years for AD only, 7.5 years for AR/BA+AD).

In table 1, the overall rate of sensitization to SEA and/or SEB was 25.7% and the AD only group had a significantly higher rate of sensitization than the AR/BA only group (45.5 vs. 24.5%, $\chi^2 = 8.1$, $p = 0.005$).

Effects of Total Serum IgE and Mite-Specific IgE Levels after Sensitization to SEA/SEB on All Disease Groups

The levels of total serum IgE, *D. pteronyssinus*-specific and *D. farinae*-specific IgE in those who were sensitized to SEA/SEB were significantly higher than the levels of those who were not sensitized (table 2).

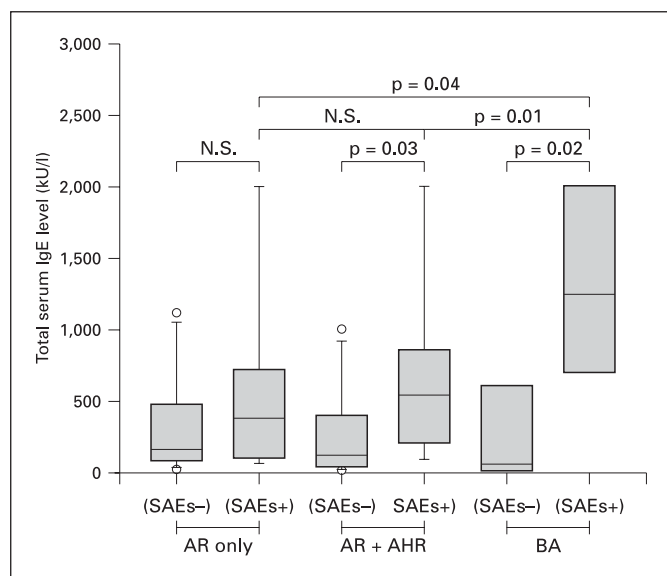


Fig. 1. Comparison of total serum IgE levels between subgroups of the AR/BA only group with (SAEs+) or without (SAEs-) sensitization to SEA/SEB. The boundary of the box indicates the 25th–75th percentile of the total serum IgE level, the line marks the median. N.S. = Not significant.

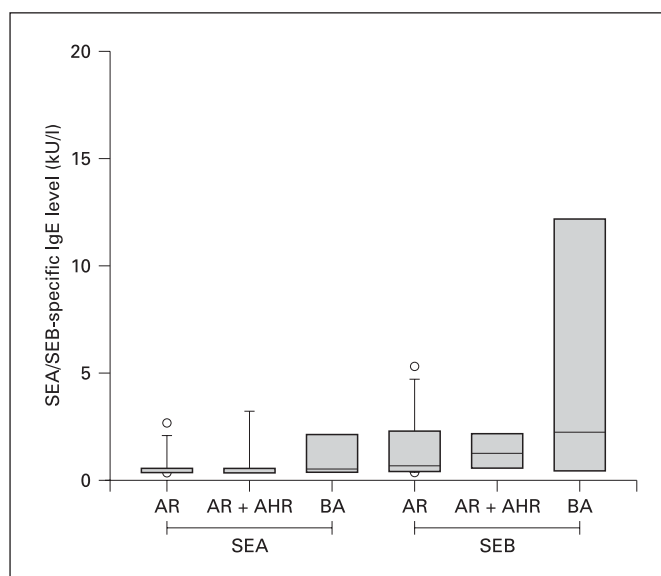


Fig. 2. Comparison of SEA- and SEB-specific IgE levels between subgroups of the AR/BA only group. The boundary of the box indicates the 25th–75th percentile of the SEA/SEB-specific IgE level, the line marks the median.

Comparison of Serum SEA- and SEB-Specific IgE Levels among All Disease Groups

The SEA- and SEB-specific IgE levels among all patient groups were not significantly different, only in that the AD only group had significant higher serum SEA-specific IgE levels than the AR/BA only group ($p = 0.03$). The serum SEA-specific IgE levels (mean $\pm$ SD) in patients with AR/BA only, AD only and AR/BA+AD were 0.7 ± 1.7 , 1.3 ± 2.3 and 1.1 ± 1.5 kU/l, respectively. The SEB-specific IgE levels were 2.0 ± 3.5 , 1.5 ± 1.6 and 2.4 ± 3.0 kU/l, respectively.

The Subgroup Comparisons of AR/BA Only Patients

The rate of sensitization to SEA/SEB was gradually increased from AR only to BA. Thirty-two (23.9%) of 134 patients with AR only, 9 (24.3%) of 37 patients with AR+AHR and 5 (29.4%) of 17 patients with BA were sensitized.

The effect of sensitization to SEA/SEB on elevation of total serum IgE was more pronounced in BA patients than in others. In figure 1, patients with AR+AHR and with BA, but not patients with AR only, had significant higher levels of total serum IgE than those who were not sensitized. Among sensitized patients, BA patients had a much higher total serum IgE level ($1,326.4 \pm 738.7$ kU/l) than

AR only and AR+AHR patients (562.2 ± 629.6 and 639.8 ± 590.3 kU/l, respectively). The difference in total serum IgE level among patients without sensitization was not significant.

Patients with BA had higher values of SEA- and SEB-specific IgE levels than the others. As shown in figure 2, SEA- and SEB-specific IgE levels in BA, AR only and AR+AHR patients were 0.9 ± 1.1 and 5.4 ± 8.9 , 0.7 ± 2.0 and 1.7 ± 2.1 , and 0.5 ± 1.0 and 1.5 ± 1.4 kU/l, respectively.

Association of Sensitization to SEA/SEB with Allergic Airway Disease

Sensitization to SEA/SEB carries an increased risk for patients with AR/BA only, more than for those with AD only and AR/BA+AD. Table 3 shows the ORs for patient groups relative to the controls by sex, age, total serum IgE and specific aeroallergen sensitization. On univariate analysis, patients sensitized to SEA/SEB had a significantly increased risk for all patient groups, while after adjustment for confounding factors, the odds for AR/BA only (6.57) were greater than those for AD only (2.44) and AR/BA+AD (1.72). The variance inflation factors for the model covariates ranged from 1.26 to 1.68, indicating that collinearity was not a major concern.

Table 3. Logistic regression analysis of the association of AR/BA only, AD only and AR/BA+AD with sex, total IgE and specific sensitization

Factors	AR/BA only		AD only		AR/BA+AD	
	OR (95% CI)	adjusted OR (95% CI)	OR (95% CI)	adjusted OR (95% CI)	OR (95% CI)	adjusted OR (95% CI)
Male	1.36 (0.74–2.52)	1.36 (0.49–3.78)	1.09 (0.51–2.32)	0.65 (0.16–2.69)	1.58 (0.65–3.86)	1.34 (0.18–10.16)
IgE >150 kU/l	20.57 (4.70–90.06) ^a	8.14 (1.61–41.11) ^c	69.33 (13.97–344.07) ^a	34.04 (5.14–225.67) ^b	45.71 (8.62–242.31) ^a	29.84 (2.68–332.11) ^c
SEA/SEB	8.26 (1.94–35.25) ^c	6.57 (0.71–60.89) ^d	21.25 (4.70–96.10) ^a	2.44 (0.19–31.90)	14.02 (2.85–68.97) ^c	1.72 (0.11–26.85)
Mite	17.29 (8.08–37.0) ^a	8.37 (2.92–23.99) ^a	12.34 (4.97–30.64) ^a	4.38 (4.38–18.66) ^c	114.51 (14.03–934.92) ^a	69.19 (3.83–999) ^c
Pollen	1.89 (0.41–8.67)	0.18 (0.1–2.47)	7.89 (1.69–36.95) ^c	1.04 (0.30–31.57)	2.73 (0.43–17.33)	0.36 (0.30–43.79)

Adjusted OR = Odds ratios adjusted for sex, age, total serum IgE and any allergen sensitization; CI = confidence interval.

^a $p < 0.0001$; ^b $p < 0.001$; ^c $p < 0.05$; ^d $p < 0.1$, borderline significance.

We also showed that AR/BA only, AD only and AR/BA+AD were significantly associated with a total serum IgE value >150 kU/l and sensitization to mites. Sensitizations to fungi, cockroaches and animal dander were rarely observed in our controls; therefore, sensitization for these allergens failed to pass logistic analysis.

Discussion

We believe that this is the first study to determine whether sensitization to SEA/SEB contributes to AD as well as to allergic airway disease using an epidemiological study. Our results showed that AD patients had a higher rate of sensitization and higher serum-specific IgE levels only to SEA. AR/BA patients as well as AD patients had elevated levels of total serum IgE and serum-specific IgE to mites after sensitization to SEA/SEB. BA patients had a higher rate of sensitization, higher levels of SEA- and SEB-specific IgE and higher levels of total serum IgE than AR only and AR+AHN patients. Sensitization to SEA/SEB was independently associated with AR/BA patients, more than with AD patients. We suggest that sensitization to SEA/SEB is associated with an increased airway allergic status and an increased risk for allergic airway disease.

The prevalence of sensitization to SEA/SEB is higher in AD patients (34.5–80.2%) than in those with allergic airway disease [15–18]. The reported prevalence in patients with AR and in those with BA is 25–33 and 49%, respectively [9, 10, 19]. Our results confirmed these observations (table 1). Differences in the sensitization between AD and AR may reflect the rate at which toxin-producing *S. aureus* bacteria colonize at the site of allergic inflammation [19]. However, with the environment en-

riched with *S. aureus* and an overall prevalence of 25.7% in our study, their colonization in human airways and sensitization to superantigens might impose an important issue in airway allergy.

In our patients with SEA/SEB sensitization, total serum IgE, *D. pteronyssinus*-specific and *D. farinae*-specific IgE levels were significantly increased, which is in consistency with previous reports suggesting that exposure to SEA/SEB and subsequent sensitization may be involved in the polyvalent sensitization of serum IgE [9, 10, 16]. SEB is known to induce IgE production in vitro in atopic patients via upregulation of interleukin-4 and/or down-regulation of interferon- γ [6, 20]. More superantigens from *S. aureus* such as staphylococcal enterotoxin C, staphylococcal enterotoxin D, staphylococcal protein A and the toxic shock syndrome toxin 1 may also play a role [9, 10, 21, 22]. This would explain why a multiclonal IgE response due to SAEs might affect not only total serum IgE levels but also levels of specific IgE to individual allergens. We suggest that such polyvalent sensitization of serum IgE observed after SEA/SEB sensitization is associated with increased IgE reactivity to environmental allergens and leading to increased allergic response (atopy). Bacterial toxins including the lipopolysaccharide from gram-negative bacteria or the lipoteichoic acid from gram-positive bacteria are also associated with allergic disease [23, 24]. Furthermore, both pathogenic bacteria and ordinary commensals, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *S. aureus*, *Moraxella catarrhalis* and *Hemophilus influenzae*, could increase histamine released by basophils and mast cells within the airways and lead to bronchial hyperreactivity in asthmatic patients [25]. These studies explore more possible bacteria, and a different mechanism might contribute to the pathogenesis of allergic airway diseases.

It is known that SEB-specific IgE titers are well correlated with the severity of AD [16, 17, 26]. Lin et al. [27] also showed that positive rates of SEA-/SEB-specific IgE are correlated with the severity of AD. However, reports of such observations in allergic airway disease are rare. Recently, Bachert et al. [10] established a relation between the positive rate of specific IgE to SAE mix and the severity of asthma and also observed a significant correlation between concentrations of total serum IgE and specific IgE to SAE mix. In our study, patients with BA were more frequently sensitized to SEA/SEB than to other allergic airway diseases and had higher SEA/SEB-specific IgE levels (fig. 2). Moreover, a higher total serum IgE level was also observed in sensitized BA patients, and the significance of differences in total serum IgE levels after sensitization gradually increased from AR only to BA (p trend: N.S. $\rightarrow$ 0.034 $\rightarrow$ 0.018) (fig. 1). Our findings imply that worsening airway allergy was associated with SEA/SEB-induced total serum IgE elevation, which is known to be closely linked to AHR, asthmatic symptoms and the diagnosis of asthma [28]. In addition, allergen exposure results in increased airway responsiveness in nonasthmatic subjects with AR (i.e., AR+AHR) [29], whereas AR often precedes the development of BA [30]. It seems that BA and AR result from similar inflammatory processes induced by allergens in the upper and lower airways [31]. Taken together, our observations suggest that patients with BA are more frequently and markedly affected by SEA/SEB sensitization than patients with AR only or those with AR+AHR. The results imply that sensitization to SEA/SEB might play a role in increased airway allergy and possible exacerbating allergic airway disease in our patients, in consistency with the findings of Bachert et al. [10].

Many studies have shown that sensitization to mite results in an OR of 3.8–19.7 for asthma [32]. The OR for AR in patients with sensitization to at least 1 aeroallergen (including mites) is 2.9 [33]. Most patients in the AR/BA group only had AR. Therefore, an OR of 8.37 for AR/BA resulting from mite sensitization was consistent with previous reports. A dust mite-specific IgE value >30 kU/l was strongly associated with AD (OR approximately 30) [34]. Mean values of *D. pteronyssinus*- and *D. farinae*-specific IgE in our patients with AD only or with AR/BA+AD without SEA/SEB sensitization were about 35 and 50 kU/l, respectively. Therefore, the ORs of 4.38 and 69.19 for AD patients and for AR/BA+AD patients sensitized to mites were also reasonable. AD is the most common condition associated with greatly elevated total serum IgE values [16]. The ORs for an association between

IgE levels >100 kU/l with asthma and with AR is 4.7–18 [35] and 3.3 [33], respectively. Our patients with a total serum IgE level >150 kU/l had ORs of 8.14 (AR/BA only), 34.04 (AD only) and 29.84 (AR/BA+AD), in accordance with the reported results. Due to sensitization to mite and elevated total serum IgE known to be strongly associated with AR, BA and AD, we suggest that those (confounding) factors should be considered seriously in determining the contributions of specific aeroallergen to the risk of allergic airway disease.

Our data revealed that sensitization to SEA/SEB does not seem to be independently associated with an increased risk of AD, but rather, it is more likely to be related to allergic airway disease (table 3). The possible explanation is that most methods used to establish the association of sensitization to SEA/SEB with AD are based on individual markers responsible for the association, such as sensitization rate, SEA- and/or SEB-specific IgE levels, colonization and/or infection with *S. aureus*, and the severity of AD. Those characterized associations were confirmed in our univariate logistic regression analysis (table 3). When most of the confounding effects were considered, the effects of sensitization to SEA/SEB were balanced in the specific disease group, implying that sensitization to staphylococcal superantigens has at least the same contributions to the development of AD as well as allergic airway disease.

In summary, our study showed that sensitization to SEA/SEB is common in patients with allergic airway diseases, although this is less prevalent than in AD patients. Among allergic airway diseases, the effects of sensitization to SEA/SEB on BA patients were more pronounced than on the others, implying that SEA/SEB might play a role in exacerbating allergic airway disease. We suggest that SEA/SEB have important contributions to the pathogenesis and development of allergic airway diseases.

References

- Fleischer B: Superantigens. *Acta Pathol Microbiol Immunol Scand* 1994;102:3–12.
- Bachert C, Gevaert P, van Cauwenberge P: *Staphylococcus aureus* enterotoxins: a key in airway disease? *Allergy* 2002;57:480–487.
- Clements P, Jensen CB, Jarlov JO, Hannoun C, Soborg M, Norn S: Influenza A virus enhances *Staphylococcus aureus*-induced basophil histamine release in normal individuals and patients with intrinsic asthma. *Allergy* 1989;44:39–44.
- Oehling A, Aguila de la Caba R, Fernandez M, Leyva J, Sanz ML, Resano A: Potentiation of histamine release against inhalant allergens (*Dermatophagoides pteronyssinus*) with bacterial antigens in bronchial asthma. *J Invest Allergol Clin Immunol* 1997;7:211–216.
- Hauk PJ, Wenzel SE, Trumble AE, Szefer SJ, Leung DY: Increased T-cell receptor V β 8+ T cells in bronchoalveolar lavage fluid of subjects with poorly controlled asthma: a potential role for microbial superantigens. *J Allergy Clin Immunol* 1999;104:37–45.
- Herz U, Ruckert R, Wollenhaupt K, Tschernig T, Neuhaus-Steinmetz U, Pabst R, Renz H: Airway exposure to bacterial superantigen (SEB) induces lymphocyte-dependent airway inflammation associated with increased airway responsiveness – A model for non-allergic asthma. *Eur J Immunol* 1999;29:1021–1031.
- Shiomori T, Yoshida S, Miyamoto H, Makishima K: Relationship of nasal carriage of *Staphylococcus aureus* to pathogenesis of perennial allergic rhinitis. *J Allergy Clin Immunol* 2000;105:449–454.
- Alho OP, Karttunen TJ, Karttunen R, Tuokko H, Koskela M, Suramo I, Uhari M: Subjects with allergic rhinitis show signs of more severely impaired paranasal sinus functioning during viral colds than nonallergic subjects. *Allergy* 2003;58:767–771.
- Rossi RE, Monasterolo G: Prevalence of serum IgE antibodies to the *Staphylococcus aureus* enterotoxins (SEA, SEB, SEC, SED, TSST-1) in patients with persistent allergic rhinitis. *Int Arch Allergy Immunol* 2004;133:261–266.
- Bachert C, Gevaert P, Howarth P, Holtappels G, van Cauwenberge P, Johansson SG: IgE to *Staphylococcal aureus* enterotoxins in serum is related to severity of asthma. *J Allergy Clin Immunol* 2003;111:1131–1132.
- Howarth PH: Allergic and nonallergic rhinitis; in Adkinson NF Jr, Yunginger JW, Busse WW, Bochner BS, Holgate ST, Simons FER (eds): *Middleton's Allergy: Principles and Practice*, ed 6. Philadelphia, Mosby, 2003, pp 1391–1410.
- National Asthma Education and Prevention Program. Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma Update on Selected Topics – 2002. *J Allergy Clin Immunol* 2002;110:S141–S219.
- Johansson SG, Hourihane JO, Bousquet J, Brujinzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wuthrich B, EAACI (the European Academy of Allergology and Clinical Immunology) nomenclature task force: A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–824.
- Cfzapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS: Guidelines for methacholine and exercise challenge testing – 1999. *Am J Resp Crit Care Med* 2000;161:309–329.
- Leung DY, Harbeck R, Bina P, Reiser RF, Yang E, Norris DA, Hanifin JM, Sampson HA: Presence of IgE antibodies to staphylococcal exotoxins on the skin of patients with atopic dermatitis. Evidence for a new group of allergens. *J Clin Invest* 1993;92:1374–1380.
- Bunikowski R, Mielke M, Skarabis H, Herz U, Bergmann RL, Wahn U, Renz H: Prevalence and role of serum IgE antibodies to the *Staphylococcus aureus*-derived superantigens SEA and SEB in children with atopic dermatitis. *J Allergy Clin Immunol* 1999;103:119–124.
- Nomura I, Tanaka K, Tomita H, Katsunuma T, Ohya Y, Ikeda N, Takeda T, Saito H, Akasawa A: Evaluation of the staphylococcal exotoxins and their specific IgE in childhood atopic dermatitis. *J Allergy Clin Immunol* 1999;104:441–446.
- Tada J, Toi Y, Akiyama H, Arata J, Kato H: Presence of specific IgE antibodies to staphylococcal enterotoxins in patients with atopic dermatitis. *Eur J Dermatol* 1996;6:552–554.
- Okano M, Takishita T, Yamamoto T, Hattori H, Yamashita Y, Nishioka S, Ogawa T, Nishizaki K: Presence and characterization of sensitization to staphylococcal enterotoxins in patients with allergic rhinitis. *Am J Rhinol* 2001;15:417–421.
- Neuber K, Steinrucke K, Ring J: Staphylococcal enterotoxin B affects in vitro IgE synthesis, interferon-gamma, interleukin-4 and interleukin-5 production in atopic eczema. *Int Arch Allergy Immunol* 1995;107:179–182.
- Kristiansen SV, Pascual V, Lipsky PE: Staphylococcal protein A induces biased production of Ig by VH3-expressing B lymphocytes. *J Immunol* 1994;153:2974–2982.
- Hofer MF, Harbeck RJ, Schlievert PM, Leung DY: Staphylococcal toxins augment specific IgE responses by atopic patients exposed to allergen. *J Invest Dermatol* 1999;112:171–176.
- Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E, Allergy and Endotoxin Study Team: Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–877.
- Matsui K, Nishikawa A: Lipoteichoic acid from *Staphylococcus aureus* enhances allergen-specific immunoglobulin E production in mice. *Clin Exp Allergy* 2003;33:842–848.
- Cazzola M, Matera MG, Rossi F: Bronchial hyperresponsiveness and bacterial respiratory infections. *Clin Ther* 1991;13:157–171.
- Breuer K, Wittmann M, Bosche B, Kapp A, Werfel T: Severe atopic dermatitis is associated with sensitization to staphylococcal enterotoxin B (SEB). *Allergy* 2000;55:551–555.
- Lin YT, Shau WY, Wang LF, Yang YH, Hwang YW, Tsai MJ, Tsao PN, Chiang BL: Comparison of serum specific IgE to staphylococcal enterotoxins between atopic children with and without atopic dermatitis. *Allergy* 2000;55:641–646.
- Sears MR, Burrows B, Flannery EM, Herbison GP, Hewitt CJ, Holdaway MD: Relation between airway responsiveness and serum IgE in children with asthma and in apparently normal children. *N Engl J Med* 1991;325:1067–1071.
- Ramsdale EH, Morris MM, Roberts RS, Hargreave FE: Asymptomatic bronchial hyperresponsiveness in rhinitis. *J Allergy Clin Immunol* 1985;75:573–577.
- Linneberg A, Nielsen NH, Frolund L, Madsen F, Dirksen A, Jorgensen T, Copenhagen Allergy Study: The link between allergic rhinitis and asthma: a prospective population-based study. *The Copenhagen Allergy Study. Allergy* 2002;57:1048–1052.
- Boulay ME, Boulet LP: The relationships between atopy, rhinitis and asthma: pathophysiological considerations. *Curr Opin Allergy Immunol* 2003;3:51–55.
- Platts-Mills TAE, Rakes G, Heymann PW: The relevance of allergen exposure to the development of asthma in childhood. *J Allergy Clin Immunol* 2000;105:S503–S508.
- Celedon JC, Soto-Quiros ME, Hanson LA, Weiss ST: The relationship among markers of allergy, asthma, allergic rhinitis, and eczema in Costa Rica. *Pediatr Allergy Immunol* 2002;13:91–97.
- Scalabrini DM, Bavbek S, Perzanowski MS, Wilson BB, Platts-Mills TA, Wheatley LM: Use of specific IgE in assessing the relevance of fungal and dust mite allergens to atopic dermatitis: a comparison with asthmatic and non-asthmatic control subjects. *J Allergy Clin Immunol* 1999;104:1273–1279.
- Sunyer J, Anto JM, Castellsague J, Soriano JB, Roca J: Total serum IgE is associated with asthma independently of specific IgE levels: the Spanish Group of the European Study of Asthma. *Eur Respir J* 1996;9:1880–1884.