

Role of staphylococcal superantigen-specific IgE antibodies in aspirin-intolerant asthma

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ABSTRACT

IgE antibodies specific for staphylococcal superantigens (SAg) have been implicated in the pathology of several allergic diseases such as rhinosinusitis, nasal polyposis, asthma, and aspirin intolerance. We sought to determine whether SAg-specific IgE levels associate with clinical parameters in patients with aspirin-intolerant asthma (AIA), as compared with patients with aspirin-tolerant asthma (ATA) and nonatopic controls. Eighty patients with AIA, 62 patients with ATA, and 52 normal controls were enrolled in this study. Total serum IgE and IgE specific for staphylococcal enterotoxin A, staphylococcal enterotoxin B, and staphylococcal toxic shock syndrome toxin 1 (TSST-1) were measured using the CAP system (Pharmacia, Uppsala, Sweden). The prevalence of staphylococcal enterotoxin B-specific IgE and TSST-1-specific IgE was significantly higher in the asthma patients than in the healthy controls. The prevalence of SEB-specific IgE was slightly higher in patients with AIA than in those with ATA (22.5% versus 14.5%), although this difference was not statistically significant. No significant difference in staphylococcal enterotoxin A-specific or TSST-1-specific IgE was found between AIA and ATA subjects. Total serum IgE levels were higher in asthma patients with detectable SAg-specific serum IgE than in those without. Airway hyperresponsiveness, as measured by PC20 methacholine, was significantly increased in asthma patients with detectable SAg-specific IgE than in asthma patients without ($p = 0.038$). There were no significant differences in other clinical parameters between AIA and ATA patients with and without detectable SAg-specific antibody responses. These findings suggest that the staphylococcal SAg may contribute to airway inflammation and the development of airway hyperresponsiveness in asthma.

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Bacterial superantigens (SAg) are the most powerful known T-cell stimulants. Concentrations of <0.1 pg/mL of SAg are sufficient to stimulate an uncontrolled activation of $CD4^+$ T lymphocytes that can result in fever, shock, and death.^{1–3} The SAg bind to the class II major histocompatibility complex molecules that are expressed on antigen-presenting cells. The SAg cross-link T cells and antigen-presenting cells by simultaneously binding to a region of the class II major histocompatibility complex molecule that is outside the peptide-binding groove and to the variable region of the T-cell receptor β -chain.

Staphylococcus aureus--derived enterotoxins (SE) are a family of structurally related proteins of high molecular weight that act as SAg. Most of the well-known SE trigger staphylococcal food poisoning, causing vomiting and diarrhea within 1–2 hours after ingestion. Another member of the staphylococcal SAg family, the *S. aureus* toxic shock syndrome toxin 1 (TSST-1), is the causative agent of toxic shock syndrome.⁴ To date, 18 different SE have been described in the literature.³

There is increasing evidence for an association between staphylococcal infection and the pathogenesis of allergic diseases such as atopic dermatitis, rhinitis, nasal polyposis, and possibly bronchial asthma. In one study, 25% of patients with allergic rhinitis had serum IgE antibodies specific for SE, compared with only 6.3% of controls.⁵ In another study, 44% of patients with perennial allergic rhinitis were found to harbor *S. aureus* in their nasal cavities, compared with 20% of controls. In addition, SAg-producing *S. aureus* was detected more often in patients (22%)

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Table 1 Comparison of the clinical characteristics of the aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA) patients and normal control (NC) subjects

	AIA (n = 80)	ATA (n = 62)	NC (n = 52)	p value	
				AIA versus ATA	NC versus AIA
Age (yr)	44.8 ± 14.0	42.5 ± 13.7	33.7 ± 13.0	p = 0.333	p < 0.001
Asthma duration (yr)	6.2 ± 5.4	4.4 ± 5.8	NA	p = 0.114	NA
Gender (m/f)	31/49	23/39	20/32	p = 0.840*	p = 0.973*
Atopy ± (%)	36/44 (45.0)	36/27 (56.5)	0/52 (0.0)	p = 0.176*	p < 0.001*
FEV ₁ (%)	79.7 ± 22.8	85.8 ± 23.1	ND	p = 0.187	NA
PC20 methacholine (mg/mL)	2.7 ± 4.5	6.2 ± 10.4	ND	p = 0.057	NA
Total IgE (kU/mL)	323.2 ± 382.5	373.3 ± 626.2	94.6 ± 182.9	p = 0.557	p < 0.001
sCD23 (U/mL)	33.6 ± 16.5	29.9 ± 19.9	ND	p = 0.385	NA

P values were calculated by Student's *t* test'' except *, which were calculated by Pearson's χ squared test.

ND: not done. NA: not applicable.

than in control subjects (6.7%), reinforcing a possible role for SE in allergic disease.⁶ Bachert *et al.* recently reported that IgE antibodies specific for *S. aureus* enterotoxin A (SEA) and/or *S. aureus* enterotoxin B (SEB) were present in approximately one-half of polyp tissues from patients with nasal polyposis, and the presence of enterotoxin-specific IgE correlated with the presence of polyclonal IgE antibodies specific for inhaled allergens. In that study, the samples that tested positive for SEA/SEB-specific IgE antibodies also contained more eosinophils and higher levels of eosinophil cationic protein, IL-5, eotaxin, and cys-leukotrienes. Not surprisingly, these patients were more likely to suffer from asthma and/or aspirin sensitivity.⁷ Recently, we also reported that the levels of SEA- and SEB-specific IgE antibodies in nasal polyps were higher in subjects with aspirin-intolerant asthma (AIA) than in those with aspirin-tolerant asthma (ATA) and that the levels of enterotoxin-specific IgE correlated with the degree of eosinophilic inflammation.⁸ In this study, we measured serum IgE antibodies specific for staphylococcal SAg in patients with AIA and ATA and in normal controls, and we examined possible associations between IgE levels and various clinical parameters of disease.

METHODS

Subjects

We evaluated 142 patients with a diagnosis of bronchial asthma (80 patients with AIA and 62 patients with ATA) according to the criteria of the American Thoracic Society. Study subjects were selected from among the patients who visited the Allergic Clinic of Ajou University Hospital, Suwon, Korea, complaining of asthma symptoms. The diagnosis of AIA was confirmed using lysine-aspirin bronchoprovocation tests

during the patient's stable asthmatic state, as previously described.⁹ Positive results were defined as a 20% decrease in forced expiratory volume in 1 second (FEV₁). ATA patients had a clinical diagnosis of asthma but had negative results on the lysine-aspirin bronchoprovocation test. Control subjects had no history of either respiratory disease or positive skin-prick tests in response to common inhaled allergens (Bencard, Brentford, UK). A diagnosis of atopy after the skin-prick test was defined as a positive response (wheal diameter, ≥ 3 mm) to one or more allergens. The clinical details of the asthma patients and control subjects are shown in Table 1. The study was approved by the Ethics Committee of the Ajou University Hospital, and written informed consent was obtained from each subject.

Measurement of Specific IgE and Other Inflammatory Markers

Venous blood was collected from the antecubital vein, allowed to clot for 1–3 hours at 4°C, and centrifuged at $1500 \times g$ for 10 minutes at 4°C. The serum was aspirated, separated, and stored in aliquots at –20°C until analysis. The levels of total serum IgE and IgEs specific for SEA, SEB, and TSST-1 were measured by the CAP system (Pharmacia, Uppsala, Sweden), according to the manufacturer's instructions.

Statistical Analysis

Clinical markers, including IgE antibodies specific for SEA, SEB, and TSST-1, were compared among AIA, ATA, and control groups using the Kruskal-Wallis test. Total IgE levels and PC20 methacholine values were compared among the groups with and without detectable SAg-specific IgE responses, using the Mann-Whitney *U* test. Spearman's correlations were calculated to define the relationships between the level of SAg-specific IgE and inflammatory markers. A value of $p \leq$

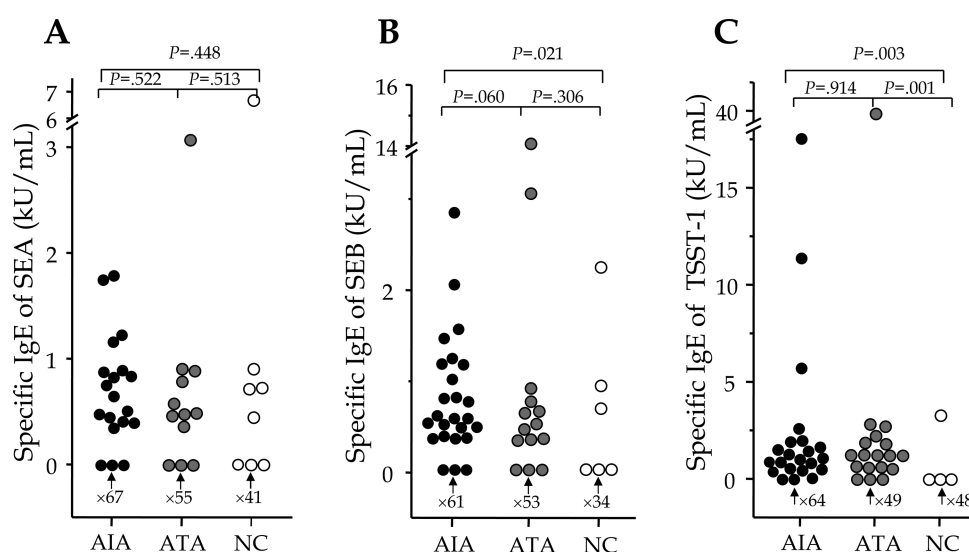


Figure 1. Serum levels of the IgE antibodies specific for staphylococcal SAg in AIA patients, ATA patients, and normal controls (NC). Panels A, B, and C show serum levels of the IgE antibodies for staphylococcal enterotoxin A (SEA), staphylococcal B (SEB), and staphylococcal toxic shock syndrome toxin 1 (TSST-1), respectively.

Table 2 Prevalence of IgE antibodies specific for three staphylococcal superantigens in sera from aspirin-intolerant asthma (AIA) and aspirin-tolerant asthma (ATA) patients and normal control subjects (NC)

	AIA (n = 85)	ATA (n = 67)	NC (n = 52)	p value	
				AIA versus ATA	NC versus AIA
SEA	15 (18.8%)	9 (14.5%)	5 (10.2%)*	p = 0.504	p = 0.193
SEB	22 (27.5%)	9 (14.5%)	3 (7.5%)#	p = 0.063	p = 0.016
TSST-1	19 (23.8%)	14 (22.6%)	1 (1.9%)	p = 0.871	p < 0.001

*, For tested subjects, n = 49. #, For tested subjects, n = 40.

0.05 was considered significant. The data were analyzed and processed using SPSS version 11.5 (SPSS, Inc., Chicago, IL) on a Windows XP operating system.

RESULTS

Clinical Characteristics of the Study Patients

The clinical characteristics of the AIA, ATA, and control groups are shown in Table 1. There were no significant differences in gender, age, duration of symptoms, atopy, lung function (expressed as percent predictive value of FEV₁), airway hyperresponsiveness, or serum IL-5 levels between the AIA and ATA groups. Patients with AIA or ATA were significantly older ($p < 0.001$) and had higher total IgE levels ($p < 0.001$) than controls.

Serum IgE Specific for Staphylococcal SAg

The prevalence of SEB-specific IgE antibodies in the serum tended to be higher in AIA patients than in ATA patients (27.5% versus 14.5%), but this difference was not significant ($p = 0.063$). There also were no significant differences in the prevalence of SEA- or TSST-1-specific

IgE between patients with AIA and patients with ATA (Fig. 1). However, when compared with healthy controls, patients with AIA had significantly higher serum levels of both SEB- and TSST-1-specific IgE antibodies ($p = 0.016$ and $p < 0.001$, respectively; Table 2). In addition, there was no difference between the AIA and ATA groups in the number of patients who had detectable antibody responses to at least one of the SAg tested. However, more AIA patients had antibody responses to at least one SAg than did healthy controls.

Correlations among Clinical Parameters

Spearman's correlations were used to examine the relationships among clinical parameters, including levels of SAg-specific IgE, total serum IgE, percent predictive FEV₁, and airway hyperresponsiveness in all of the study subjects (Table 3). The levels of serum IgE specific for SEA, SEB, and TSST-1 were positively correlated with each other. The level of IgE specific for SEB, but not of IgE for other SE, was negatively correlated with the PC20 methacholine response, but this

Table 3 Correlations among serum total IgE, IgEs specific for each staphylococcal superantigen, and selected asthma parameters

	SEA	SEB	TSST-1	Total IgE	FEV1	PC20
SEA	1 <i>n</i> = 191	0.436* <i>n</i> = 181	0.346* <i>n</i> = 181	0.302* <i>n</i> = 191	−0.103 <i>n</i> = 106	−0.098 <i>n</i> = 98
SEB		1 <i>n</i> = 182	0.427* <i>n</i> = 182	0.355* <i>n</i> = 182	0.037 <i>n</i> = 106	−0.197# <i>n</i> = 98
TSST-1			1 <i>n</i> = 194	0.406* <i>n</i> = 194	0.057 <i>n</i> = 106	−0.172 <i>n</i> = 98
Total IgE				1 <i>n</i> = 194	0.075 <i>n</i> = 106	−0.031 <i>n</i> = 98
FEV ₁					1 <i>n</i> = 106	0.389* <i>n</i> = 88
PC20						1 <i>n</i> = 98

Data are expressed as Spearman's ρ .

*, Significant at the 0.01 level (2-tailed). #, $p = 0.052$.

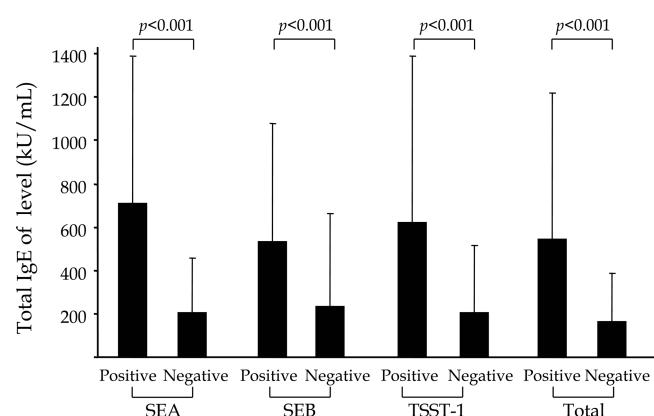


Figure 2. Total serum IgE antibodies. Patients (AIA and ATA) and normal controls were grouped according to the presence (positive) or absence (negative) of detectable IgE antibody responses specific for each staphylococcal SAg.

was not statistically significantly (Spearman's $\rho = -0.197$; $p = 0.052$).

Correlation of Staphylococcal SAg-Specific IgE Responses with Airway Hyperresponsiveness Status

We stratified the study subjects according to the presence or absence of SAg-specific IgE antibodies. The total IgE levels were significantly higher in patients who had detectable SAg-specific IgE antibodies than in those who did not (Fig. 2). An increased airway hyperresponsiveness was noted in asthmatic subjects who had IgE antibodies specific for one or more staphylococcal SAg than in asthmatic subjects who lacked detectable SE-specific antibodies (PC20 methacholine = 2.75 ± 4.44 and 4.98 ± 9.06 , respectively; $p = 0.038$; Fig. 3).

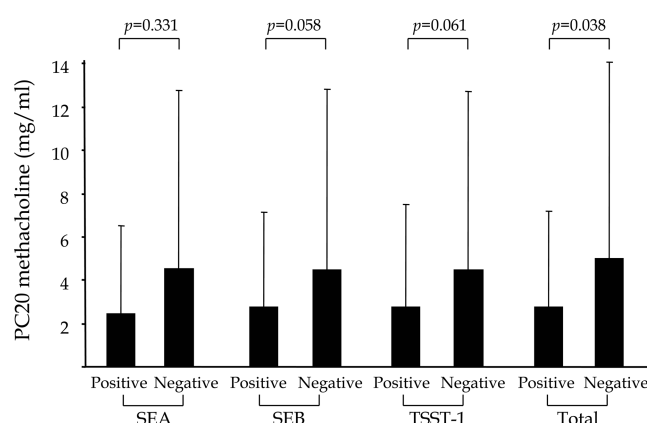


Figure 3. Airway hyperresponsiveness expressed as mean PC20 methacholine values. Patients AIA and ATA were grouped according to the presence (positive) or absence (negative) of detectable IgE antibody responses specific for each staphylococcal SAg.

DISCUSSION

In this study, we showed that the prevalence of serum IgE antibodies specific for staphylococcal SAg was higher in patients with AIA and ATA than in healthy control subjects. Among asthmatic patients, the prevalence of SAg-specific IgE was slightly higher in patients with AIA than patients with ATA, with the largest difference in levels of SEB-specific antibodies. Airway hyperresponsiveness was more prevalent in patients with detectable SAg-specific IgE antibody responses than in patients without detectable responses. These results support the hypothesis that staphylococcal SAg play a role in the pathogenesis of asthma. To the best of our knowledge, this is the first study to establish an association between increased airway hyperresponsiveness and the presence of serum IgE antibodies specific for staphylococcal SAg.

Considerable evidence suggests that infectious agents are involved in the etiology and pathogenesis of airway diseases. For example, a close association between the pathogenesis of asthma and viral airway infection has been shown.¹⁰⁻¹³ In a study conducted by the European Network on Aspirin-Induced Asthma, a typical pattern of symptom development in AIA was described. Persistent rhinitis was an early symptom, followed by asthma, aspirin intolerance, and nasal polyposis.¹⁴ An author of this study suggested that a latent viral infection might contribute to the pathogenesis of the disease.¹⁵ Organisms other than viruses have been suggested to contribute to AIA, including atypical pathogens such as *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Adults with recently diagnosed asthma were found to have evidence of chronic respiratory tract infections with *C. pneumoniae*,¹⁶ and acute illness caused by *C. pneumoniae* infections often heralds the development of chronic asthma in previously asymptomatic individuals.¹⁷ *Mycoplasma* and/or *Chlamydia* species, accompanied by increased numbers of mast cells, were detected in the airways of a significant number of patients with chronic stable asthma.¹⁸ Patients with adult-onset nonatopic asthma and IgG responses specific for *C. pneumoniae* suffered a significantly faster decline in lung function than did asthmatic patients lacking these antibody responses.¹⁹

In addition to viral and atypical pathogens, *S. aureus* enterotoxins have been implicated in the initiation and progression of rhinitis, nasal polyposis, and asthma, particularly AIA. *S. aureus* infections are more common among patients with allergic diseases, and the presence of SE-specific antibodies has been correlated with the degree of eosinophilic inflammation in patients with asthma.^{6,7} Tripathi *et al.* recently showed that the prevalence of serum IgE specific for staphylococcal SAg was significantly greater among patients with chronic sinusitis/nasal polyposis than among healthy controls.²⁰ The increased serum IgE level probably was the result of local IgE synthesis.²¹ Recently, Bachert *et al.* also indicated that aspirin sensitivity was associated with increased concentrations of eosinophil-related mediators as well as IgE antibodies specific for staphylococcal SAg in nasal polyp tissue.²² In a previous study, our group showed that total IgE and IgE specific for both SEA and SEB were markedly higher in nasal polyps from AIA subjects than in nasal polyps from ATA subjects.⁸ Bachert *et al.* suggested that IgE antibodies to staphylococcal SAg were found more often in sera from patients with severe asthma than in sera from patients with mild asthma, but those results were not statistically significant.²³ In another study, SE-specific IgE antibodies were increased in patients with severe persistent asthma and were related to eosinophil cationic protein and FEV₁.²³

In this study, the prevalence of serum IgE specific for SEB tended to be higher in AIA subjects than in ATA subjects. This finding was not shown in previous studies.^{8,22-24} One possible reason for this discrepancy is that most of the previous studies measured IgE antibody responses to a mixture of staphylococcal SAg (SEA, AEB, and TSST-1) rather than to individual SE. We also found that the prevalence of TSST-1-specific IgE was higher in patients with asthma than in normal controls, although no difference was seen between patients with AIA and ATA. These results suggest the possibility that SEB plays a more significant role in aspirin sensitivity than other SAg. Taken together, the data suggest that staphylococcal SAg may trigger eosinophilia and IgE-mediated inflammation in asthma, rhinitis, and nasal polyposis.

The mechanisms by which staphylococcal SAg cause ongoing eosinophilic and IgE-mediated inflammation in airway disease remain to be elucidated. Staphylococcal SAg have been implicated in the pathogenesis of atopic eczema/dermatitis syndrome; it has been suggested that the polyclonal activation of T cells and the activation of antigen-specific CD4⁺ T cells promotes the activation of IgE-producing B cells, thus promoting allergic reactions.²⁵ Staphylococcal SAg, which are known to activate CD4⁺ T cells, may trigger inflammation in a similar way.²¹ Studies have shown that the numbers of TCR-V β 8(+) T cells in bronchoalveolar lavage of patients with poorly controlled asthma are significantly increased²⁶ and that staphylococcal SAg can induce steroid insensitivity in peripheral blood mononuclear cells.²⁷ However, it is still unclear how these SAg drive ongoing inflammation in airway diseases.

In conclusion, the data show that the prevalence of serum IgE antibodies specific for staphylococcal SAg is higher in patients with asthma (both AIA and ATA) than in control subjects. Among patients with asthma, the prevalence of SEB-specific IgE was slightly higher in AIA patients than in ATA patients. More importantly, the study showed that airway hyperresponsiveness, as measured by PC20 methacholine responses, is greater in asthma patients with detectable SAg-specific IgE antibody responses than in asthma patients who lack these specific IgE. These findings suggest that staphylococcal SAg may play a role in the pathogenesis of airway diseases by exacerbating airway hyperresponsiveness.

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