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Staphylococcus Aureus Enterotoxin A and Enterotoxin B Specific IgE Antibodies in Atopic Dermatitis

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ABSTRACT

Objective: A correlation between the intensity of S. aureus colonization and skin inflammation has been demonstrated. 30-60% of S. aureus bacteria in patients with atopic dermatitis (AD) generate exotoxins, specifically superantigen-like enterotoxins A-B-C-D and toxic shock syndrome toxin-1. This study aimed to determine the role of serum staphylococcal enterotoxin A (SEA) and staphylococcal enterotoxin B (SEB)-specific IgE antibodies in children with AD.

Materials and Methods: Forty-four children with AD, 30 with allergic respiratory disease (ARD) without AD, and 25 nonatopic healthy children were included in this study. AD cases were diagnosed according to Hanifin and Rajka criteria. The severity of AD was evaluated by the "Eczema Area and Severity Index". Serum total IgE (tIgE), SEA-specific IgE and SEB-specific IgE levels were analyzed in all children.

Results: Serum tIgE levels were significantly elevated in children with ARD without AD compared to children with AD and healthy children (p=0.041). However, there was no significant difference in the levels and the rates of positive SEA-specific IgE and SEB-specific IgE for children with AD, children with ARD without AD, and healthy children. A significantly positive correlation was detected between the EASI scores and SEA-IgE levels in children with AD (p=0.002).

Conclusion: Although the role of SEA in the pathogenesis of AD through IgE-mediated mechanisms is not fully known, the data in our study seems to provide support to the role of SEA on the severity of AD. To conclude, adding antistaphylococcal treatment to anti-inflammatory therapy may be helpful in obtaining an effective clinical response in children with moderate to severe AD.

Keywords: Atopic dermatitis, severity of atopic dermatitis, Staphylococcus aureus enterotoxin A, Staphylococcus aureus enterotoxin B

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that is intensely pruritic. It is the most common skin disease in infancy and childhood and frequently coexists with asthma and allergic rhinitis (1-3).

The diagnosis of AD is made clinically and is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. One of the earliest and most recognized sets of diagnostic criteria is the Hanifin and Rajka Criteria that is useful for the diagnosis of AD in hospital-based and experimental studies (4-6).

The pathogenesis of AD consists of a complex interaction between several factors such as genetics, skin barrier defects, impairment in immune response, and environmental factors such as allergens and exposure to microorganisms (7,8).

Recent studies have emphasized the role of *S. aureus* in the pathogenesis of AD. While 60-100% of AD patients have colonization of *S. aureus* in the skin, healthy controls show a rate of up to 30%. It was also shown that nasal colonization of *S. aureus* in infants is associated with AD (9-14). Alsterholm et al. (15) have demonstrated that 71% of patients were colonized with *S. aureus* on lesional skin,

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and 90% of them were colonized on non-lesional skin. Tomczak et al. (11) have reported that the skin colonization rate of *S. aureus* was 45% in children with AD, and the nasal carriage rate was 47%. In a study from Turkey, Uysal et al. (16) have reported that the nasal *S. aureus* colonization rate was 32.8% in children with AD, while it was 14.2% in healthy children. In recent studies, *S. aureus* colonization was associated with exacerbation and severity of AD (16-18). It is commonly accepted that *S. aureus* plays a role in AD; however, its role in promoting the disease is still debated. *S. aureus* produces enterotoxins with superantigenic character such as staphylococcal enterotoxins A-D (SEA-D) and the toxic shock syndrome toxin, overstimulating the Th lymphocytes (9,11,18-21). It has been emphasized in the literature that especially SEA and SEB play a role in the exacerbation of AD (20-23). In a meta-analysis that included twenty-six studies, Wit et al. (24) have reported that the prevalence of IgE against SEA and SEB was higher in patients with AD.

The aim of this study was to compare SEA and SEB-specific IgE levels between children with AD, children with allergic respiratory disease (ARD) without AD, and nonatopic healthy children, and thus to determine the role of *S. aureus* enterotoxins in AD pathogenesis.

MATERIALS and METHODS

Study Subjects

This prospective cross-sectional study was conducted at the Pediatric Allergy Department between June 2005 and October 2006. The cases included in this study were aged between 3 months and 17 years. The study group consisted of three groups: Forty-four children with AD as group I, thirty children with ARD without AD as group II, and twenty-five healthy children without a history of recurrent infection or allergy selected as controls as group III. Atopic dermatitis was diagnosed by a pediatric allergist according to the criteria defined by Hanifin and Rajka, including detailed clinical history and physical examination (4). The severity of AD was assessed according to the "Eczema Area and Severity Index" (EASI) (25). Patients with a diagnosis of allergic rhinitis and/or asthma were included in the ARD group. There was no difference for age and gender between the groups. Patients with a systemic or local infection or an immune deficiency were excluded.

Determination of tIgE and SEA/SEB- Specific IgE Levels and the AlaTOP Panel

Four cc blood samples were taken into the biochemistry tube to determine the tIgE, SEA-IgE, and SEB-IgE levels in all children on admission. Blood samples were centrifuged at 4000 rpm and placed in 2 cc Eppendorf tubes and then stored at -20 degrees for a maximum of 6 months until they were examined. Samples were frozen not later than one hour of collection.

In all children, the tIgE levels were measured by chemiluminescent immunoassay (CIA) (Immulite 1000, DPC, Los Angeles, USA) with a 300 µl serum sample and a 40-minute incubation period. tIgE positivity was defined as tIgE levels over the cut-off levels according to the age (26).

In all children, serum total SEA- specific IgE and SEB-specific IgE levels were measured by chemiluminescent immunoassay (CIA), (Immulite 2000 Allergy; Diagnostic Products Corp., Los Angeles, USA), with a 300 µl serum sample and a 70-minute incubation period. Results over the detection limit of >0.35 kU/l was defined as SEA/SEB-specific IgE positivity.

In children with AD and ARD, the inhalant screening allergens (AlaTOP) panel was measured by chemiluminescent immunoassay (CIA), (Immulite 2000 Allergy; Diagnostic Product Corporation DPC, Los Angeles, CA, USA). The AlaTOP test comprises inhalant allergens from 12 sources: house dust mite (*Dermatophagoides pteronyssinus*), cat dander epithelium, dog dander epithelium, Bermuda grass, timothy grass, *Penicillium notatum*, *Alternaria tenuis*, birch tree, Japanese cedar tree, common ragweed (*Ambrosia artemisiifolia*), English plantain, and *Parietaria officinalis*. The AlaTOP test is designed for qualitative detection of serum specific IgE antibodies to inhalant allergens. It was defined as positive or negative.

Statistical Analysis

Statistical analysis of the data was evaluated with the SPSS-22 (Chicago, II, USA) program. The compatibility of the continuous variables with the normal distribution was analyzed by the Kolmogorov-Smirnov test. Normally distributed continuous variables were given as mean ± standard deviation (SD), non-normally distributed continuous

variables as median (minimum, maximum), and categorical variables as percentage (%). One-Way ANOVA and Kruskal-Wallis tests were used for the analysis of numeric variables, and the Chi-Square test was used for the analysis of categorical variables. Spearman correlation coefficient was used for the association between variables. $p< 0.05$ was considered significant.

Approval was obtained from the local university Ethics Committee (approval date: 24.03.2005, approval number: 2005/038) before the study was started. The study was conducted in accordance with the principles set forth in the Helsinki Declaration. Written informed consent was taken from the legal guardians of the children.

Table I: Clinical features of patients with atopic dermatitis

	n (%)
EASI	
Mild (1.1-7)	33 (75)
Moderate (7.1-21)	9 (20.5)
Severe (21.1-50)	2 (4.5)
Stage of the lesions	
Acute	6 (13.6)
Subacute	15 (34.1)
Chronic	23 (52.3)
Characteristic of the lesions	
Erosion	39 (88.6)
Lichenification	38 (86.4)
Pruritus	34 (77.3)
Erythema	32 (72.7)
Incrustation	32 (72.7)
Infiltration	28 (63.6)
Discharge	2 (4.5)
Impetigo	2 (4.5)
Furuncles	1 (2.3)

EASI: Eczema Area and Severity Index

RESULTS

Demographic and Clinical Findings

Ninety-nine children were included in this study. Of the forty-four children of Group I, 29 (69.5%) were male; of the 30 children of Group II, 19 (63.3%) were male; and of the 25 children of Group III, 14 (56%) were male. The mean age and standard deviations for age of the children of Group I, II and III were 5.40±4.36, 6.52±3.30, and 5.02±4.38 years, respectively. There was no difference in terms of sex and age among the groups (p=0.507, p=0.372, respectively).

In 16 (36.4%) of the children in Group I, symptoms of AD had started before the age of 1 year. The clinical characteristics of the patients with AD are demonstrated in Table I.

Laboratory Findings

The AlaTOP results were compared between Group I and II. They were significantly higher in Group II ($p<0.001$). Total IgE levels, enterotoxin A-B specific IgE levels, tIgE and specific IgE positivity were compared between Group I, II and III. There was the only a significant difference in the tIgE levels between the groups (p=0.041) (Table II).

Table II: Laboratory finding of children in the study groups.

	Group I (n=44)	Group II (n=30)	Group III (n=25)	P
Total IgE IU/ml*	49.75 (1.6-2000)	117.5 (6.7-2000)	38.3 (1-374)	0.041[k]
SEA-IgE KU/l*	0.1 (0.1-3.97)	0.1 (0.1-1.35)	0.1 (0.1-0.15)	0.402[k]
SEB-IgE KU/l*	0.1 (0.1-100)	0.1 (0.1-2.20)	0.1 (0.1-0.79)	0.109[k]
AlaTOP (+)**	5 (11.4%)	16 (53.3%)	-	< 0.001[#]
Total IgE positivity**	23 (52.3%)	17 (56.7%)	10 (40%)	0.446[#]
SEA-IgE ≥ 0.35KU/l**	3 (6.8%)	4 (13.3%)	0	0.157[#]
SEB-IgE ≥ 0.35KU/l**	7 (15.9%)	6 (20%)	1 (4%)	0.214[#]
SEA and SEB-IgE ≥ 0.35KU/l**	2 (4.5%)	3 (10%)	0	0.236[#]
SEA and/or SEBIgE ≥ 0.35KU/l**	8 (18.2%)	7 (23.3%)	1 (4%)	0.442[#]

Group I: Children with AD, Group II: Children with ARD without AD. Group III: Healthy children
*Median (minimum-maximum) **number (positive rate) [k]Kruskal-Wallis test [#]Chi-Square test (Fischer exact test when< 5)
SEA-IgE: Staphylococcal enterotoxin A-specific IgE, **SEB-IgE:** Staphylococcal enterotoxin B-specific IgE

Spearman's correlation test was performed to show the association between serum specific SEA/SEB- specific IgE levels and the EASI score. There was a significant correlation between the EASI score and serum SEA-specific IgE levels (Spearman's r=0.46, p=0,002). However, no significant correlation was detected between the EASI score and serum SEB-specific IgE levels (Spearman's r=-0.05, p=0.974).

DISCUSSION

The pathogenesis of AD is not completely explained, although it is the most common inflammatory skin disease. In previous studies, the role of Staphylococcal enterotoxins on the pathogenesis of AD was mentioned. In this study, we demonstrated a positive correlation between the EASI score and SEA-specific IgE levels. Therefore, we thought that SEA might play an IgE-mediated role on the clinical severity of AD.

In their study Lin et al. (27) have reported that serum tIgE levels in cases with AD (60 cases) were statistically higher than cases with ARD without AD (55 cases) and the healthy group (24 cases). Comparing the cases of ARD without AD and the healthy group, they found that serum tIgE levels in cases of ARD without AD were statistically higher than the healthy group. Comparing the median serum tIgE levels of Group I, II, and III in our study, we found that the serum tIgE levels in group II were statistically significantly higher than group I and III, unlike Lin et al.'s (27) study. This result may be due to the fact that the sensitivity to inhalant allergens in the patients with ARD was found to be higher than the patients with AD in our study. On the other hand, Lin et al. (27) have found no difference in terms of sensitivity to inhalant allergens between the patients with AD and the patients with ARD.

Lin et al. (27) have shown that serum SEA- specific IgE and SEB-specific IgE levels and positivity rate were significantly higher in AD cases compared to ARD cases without AD and non-atopic cases in their study. Also, it was reported that there was no significant difference between serum SEA- and SEB-specific IgE levels and positivity rates among children with AD who had or did not have a previous skin infection. In addition, they detected no significant difference in terms of serum SEA-specific IgE and SEB-specific IgE levels and positivity rates between ARD cases without AD and non-atopic cases. With these findings, they suggested that serum SEA-specific IgE and SEB-specific IgE antibodies could be specific for AD and play a major role in the pathogenesis of the disease. On the other hand, a meta-analysis conducted by Muluk et al. (9) has demonstrated that SEA and SEB play a role not only in the course of atopic dermatitis, but also allergic rhinitis and asthma. In another previous study, Ide et al. (28) have found that the ratio of SEA/SEB - specific IgE positivity was 33.6% in all patients with AD. In a recent study, Tomczak et al. (11) have reported the percentage of positive SEA-sIgE, SEB-sIgE, and SEA-sIgE or SEB-sIgE values as 32.8%, 32.8%, and 41% , respectively in patients with AD.

In the study performed by Morishita et al. (29), the positivity rate of SEA- and/or SEB-specific IgE was reported as 71.7% in 149 patients with AD between age of 1-73 years. When they compared AD patients with control groups that included patients with nonatopic skin disease and healthy subjects, they showed that specific IgE antibodies for SEA and/or SEB were significantly higher in AD patients. Additionally, researchers investigated the relationship between AD and staphylococcal enterotoxins by detecting the enterotoxins of *S. aureus* by genotyping analysis. Na et al. (30) mentioned that the most common toxin gene identified in AD patients was SEA. It was detected alone in 52.6% of patients and together with TSST in 42.1%. In a recent study, Ogonowska et al. (21) have noted that the most common gene detection in *S. aureus* isolated from AD patients was SEC. In addition, they determined that the SEA gene was more frequent in patients with AD, while SEB genes more frequent in nonatopic patients. On the other hand, Blicharz et al. (31) have identified the rate of presence of SEA on lesional skin as 7%, and SEB as 2.3%, while the rate of staphylococcal enterotoxin-like superantigen X(selX) was 53.5%. In addition, they noticed there was a positive correlation between the number of superantigens detected on lesional skin and the severity of the disease (31).

In our study, there was no significant difference between the groups in terms of the serum SEA/SEB-specific IgE positivity rate. The fact that 75% of the patients in Group I were mild AD cases led to the conclusion that the SEA/SEB IgE positivity was not significantly high in this group.

Nomura et al. (32) found that serum SEB-specific IgE antibodies were significantly higher in patients with severe AD than those with mild and moderate AD in their study. In addition, levels of serum anti-SEB-specific IgE were significantly higher in the cases with severe AD than in the

cases with mild and moderate AD in cases under 7 seven years of age. Bunikowski et al. (33) have shown that the severity of the skin lesion in AD patients was correlated with SEA/SEB-specific IgE levels. Also, Ide et al. (28) have mentioned that the ratio of SEA/SEB-specific IgE positivity was higher in patients with severe AD than in patients with mild and moderate AD. Breuer et al. (34) have demonstrated a correlation between the severity of the skin lesion and SEB-specific IgE positivity in adult patients with AD. However, they could not show the same relationship for serum SEA-specific IgE. As a result of these findings, they argued that SEB had higher immunogenicity than SEA in patients with AD. Tomczak et al. (11) have noticed that the patients with the highest SEA-sIgE and SEB-sIgE values had a more severe AD course. In contrast, Rojo et al. (35) have reported there was no significant association between serum SEA-sIgE and SEB-sIgE levels and the severity of the disease. In addition, Dahal et al. (17) and Na et al. (30) demonstrated a positive relation between *S. aureus* colonization and the severity of the disease. Similarly, Simpson et al. (36) have mentioned that patients with AD colonized with *S. aureus* on their skin had more severe disease.

In our study, we found no significant difference when we compared mild AD cases, moderate-severe AD cases, Group II, and Group III with each other in terms of serum the SEA/SEB-specific IgE levels and positivity rate. The reason may be related to the fact that the number of cases with moderate-severe AD (11 cases) is very low compared to the number of cases with mild AD (33 cases). On the other hand, we demonstrated a positive relationship between serum SEA- specific IGE levels and the EASI score in patients with AD. This result shows a reasonable positive relationship between high serum SEA-specific IgE levels and disease severity, consequently showing the importance of *S. aureus* in AD pathogenesis.

The most important limitation of our study was the small number of moderate and severe AD patients. On the other hand, the strong side of study is that it is a prospective study.

In conclusion, this study suggests that staphylococcal exotoxins, particularly SEA, may contribute to exacerbation of AD. In patients with moderate and severe AD, a more effective clinical response may be obtained by adding anti-staphylococcal therapy to anti-inflammatory therapy. We believe studies including a larger number of moderate and severe AD patients should be conducted in order to determine the role of SEA-specific IgE and SEB-specific IgE in the pathogenesis of AD.

Conflict of Interest

The authors declare no conflict of interest.

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Authorship Contributions

Concept: **Mehtap Yazicioglu,** Design: **Mehtap Yazicioglu,** Data collection or processing: **Sema Yildirim, Sukran Ciftci** Analysis or Interpretation: **Sema Yildirim, Mehtap Yazicioglu,** Literature search: **Sema Yildirim,** Writing: **Sema Yildirim,** Approval: **Sema Yildirim.**

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