Association of staphylococcal superantigen-specific IgE with mild and moderate atopic dermatitis

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Abstract

Objective—To examine the frequency of allergic sensitization to staphylococcal superantigens in young children with mild to moderate atopic dermatitis (AD).

Study design—AD severity was assessed by objective Scoring AD (SCORAD). Serum IgE to staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin-1 (TSST-1) were measured by ImmunoCAP. Comparisons between mild and moderate AD were performed using logistic regressions.

Results—The prevalence of allergic sensitization to staphylococcal superantigens in patients with mild and moderate AD was 38% and 63%, respectively. Allergic sensitization to staphylococcal superantigens, particularly SEA and SED, was found to be associated with moderate AD, compared with mild AD.

Conclusions—Our results suggest that allergic sensitization to staphylococcal superantigens is common even among young children with mild to moderate AD, and such sensitization may contribute to the disease severity of these patients.

Keywords

allergic sensitization; enterotoxin; *Staphylococcus aureus*; staphylococcal superantigens; young children

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Staphylococcus aureus (*S. aureus*) is believed to play a significant role in the pathogenesis of atopic dermatitis (AD).[1] Up to 57% of *S. aureus* isolated from children with AD were found to secrete exotoxins with superantigen activity.[2] These exotoxins are known as staphylococcal superantigens, which include staphylococcal enterotoxin (SE) A, SEB, SEC, SED and toxic shock syndrome toxin-1 (TSST- 1).[2] In addition to their superantigen activity, staphylococcal superantigens also have been shown to induce inflammation via the production of superantigen-specific IgE in patients with AD.[3] Although it is known that nearly 80% of patients with severe AD produce specific IgE against staphylococcal superantigens,[2] the association of these specific IgE molecules among young children with mild and moderate AD has not been studied

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in detail. In this study, we analyzed the frequency of allergic sensitization to staphylococcal superantigens in patients with mild and moderate AD.

METHODS

Patients and IgE Measurement

The study was approved by the hospital's local Institutional Review Board. Written and informed consent was obtained from all parents/guardians when appropriate. Fifty children from age 1 to 6 years who fulfilled the U.K. Working Party's diagnostic criteria for AD were recruited.[4] AD severity was measured by objective Scoring AD (SCORAD).[5] Subjects were divided into 2 groups: mild AD, in which subjects had objective SCORAD of 15 or less; and moderate AD, in which subjects had objective SCORAD of more than 15, but less than 40. [6] Total serum IgE and specific IgE to staphylococcal enterotoxin (SEA), SEB, SEC, SED and toxic shock syndrome toxin (TSST)-1 were assayed in a commercial laboratory (Specialty Lab., Valencia, California). Specific IgE to a panel of common food and inhalant allergens also was assessed. The panel consisted of cow's milk, egg white, soybean, wheat, peanut, house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), *Aspergillus fumigatus*, *Cladosporium herbarum*, cockroach, cat, dog, western ragweed and Bermuda grass. The specific IgE assays were based on the ImmunoCAP system (Phadia, USA). Specific IgE concentrations of more than 0.35 kU/L were considered to be positive.

Statistical Analysis

The association between allergic sensitization to staphylococcal superantigens and total serum IgE or allergic sensitization to common food/inhalant allergens was analyzed by the Fisher exact test. Logistic regressions were performed for comparing the moderate AD group with the mild AD group. Subjects with positive IgE to staphylococcal superantigen(s) were assigned a value of 1 and those with negative IgE to staphylococcal superantigen(s) a value of 0. The analyses were performed by controlling for patients with AD with "high total IgE" (defined as subjects with total serum IgE > 150 IU/mL), as these patients have been shown to have more severe disease than patients with "low total IgE" (i.e. total serum IgE < 150 IU/mL).[7] Odds ratios with 95% confidence were expressed. A *p* value of 0.05 or less was considered to be statistically significant.

RESULTS/DISCUSSION

The mean objective SCORADs for the mild and moderate AD groups were 9.9 ± 3.7 and 19.9 ± 2.5, respectively. Our results showed that the prevalence of allergic sensitization to staphylococcal superantigens in mild and moderate AD was 38% and 63%, respectively (Table I). These observations confirm previous beliefs that the prevalence of allergic sensitization to staphylococcal superantigens increases with the severity of AD.[8]

Our results are also in keeping with a previous study that showed nearly 80% allergic sensitization to staphylococcal superantigens among children with severe AD.[2] Allergic sensitization to SEA and TSST-1 was the most common sensitization to staphylococcal superantigens among our population of mild and moderate AD (Table I).

The prevalence of subjects with AD with high total IgE in our study was 66% (33/50). Among patients with AD with high total IgE, 58% (19/33) had allergic sensitization to at least one staphylococcal superantigen, compared with only 23% (4/17) of patients with AD with low total IgE (*p*<0.04)(Figure 1). These results are consistent with recent data showing an association of allergic sensitization to microbial antigens with patients with AD who have high total serum IgE,[7,8] rather than low total serum IgE.[9] We further analyzed whether allergic

sensitization to staphylococcal superantigens may be associated with a subgroup of patients with AD with low total IgE, but with allergic sensitization to common food/inhalant allergen(s). Our data shows that 71% (12/17) of subjects with AD with low total IgE have allergic sensitization to at least one or more common food/inhalant allergens, compared with all the subjects with high total IgE. Our results confirmed that allergic sensitization to cow's milk, egg white, house dust mites (*D. farinae* or *D. pteronyssinus*) and house pets (dog or cat) are among the most common food/inhalant allergic sensitizations in children with AD.[10,11,12] As shown by Reefer et al in adults,[7] we found no association between allergic sensitization to staphylococcal superantigens and common food/inhalant allergens among children with AD with low total IgE (*p*=0.3)(Figure 2).

Allergic sensitization to each of 5 staphylococcal superantigens was at least 2 to 3 times more likely to be associated with moderate AD than mild AD, although we found only IgE sensitization to SEA and SED was significantly associated with moderate AD, compared with mild AD (*p*=0.01 and 0.05, respectively)(Table II). It is known that SEA and SED are structurally similar and both may be co-expressed by certain strains of *S. aureus*.[13,14] One previous study indicated that SEA- and SED-producing *S. aureus* may be the predominant superantigen-producing strains in certain populations with AD.[15] These studies and ours support that SEA, SED and their specific IgE may play an important role in the pathogenesis of AD.

Skin barrier defects have been proposed as the primary defects in the pathogenesis of AD.[16] This concept is supported by the association of null mutations in filaggrin (*FLG*), a protein with important barrier functions, in moderate to severe AD.[17] More recently, association of null mutations in *FLG* also has been confirmed in patients with mild to moderate AD.[18] However, the external triggers of inflammation in these patients remain unclear. More than 90% of children with AD are colonized with *S. aureus*.[19] It has been shown that children with severe AD exhibited cutaneous T-lymphocyte inflammation consisting of T-lymphocyte receptor variable β repertoire that correspond to the staphylococcal superantigens found on their skin.[20] Staphylococcal superantigens also have been shown to induce a T helper 2 (Th2) ("allergic") inflammation, which is characteristic of the immune response found in acute AD lesions.[21,22] A consequence of a Th2 response is the production of IgE molecules, which may include superantigen-specific IgE in genetically-susceptible individuals. On re-encounter of staphylococcal superantigens, basophils bearing the relevant superantigen-specific IgE molecules release histamine or other inflammatory mediators, further aggravating the cutaneous inflammation of AD.[3] There may be other mechanisms by which *S. aureus* trigger AD inflammation that have yet to be defined.

Young children with mild to moderate AD constitute the majority of patients with AD.[23] Addressing any potential trigger in this population is an important clinical problem. An emphasis should be placed on the restoration of skin barrier functions.[24] This approach could minimize potential pathogen and allergen triggers including *S. aureus* and its superantigens. Routine use of antibiotics to reduce *S. aureus* colonization, in the absence of clinical signs of infection, is not recommended due to the concern of inducing bacterial resistance. In addition to their anti-inflammatory effects, both topical corticosteroids and topical calcineurin inhibitors have been shown to decrease *S. aureus* colonization and improve barrier functions in AD.[25,26] Timely use of these medications should be encouraged for symptomatic control.

Acknowledgements

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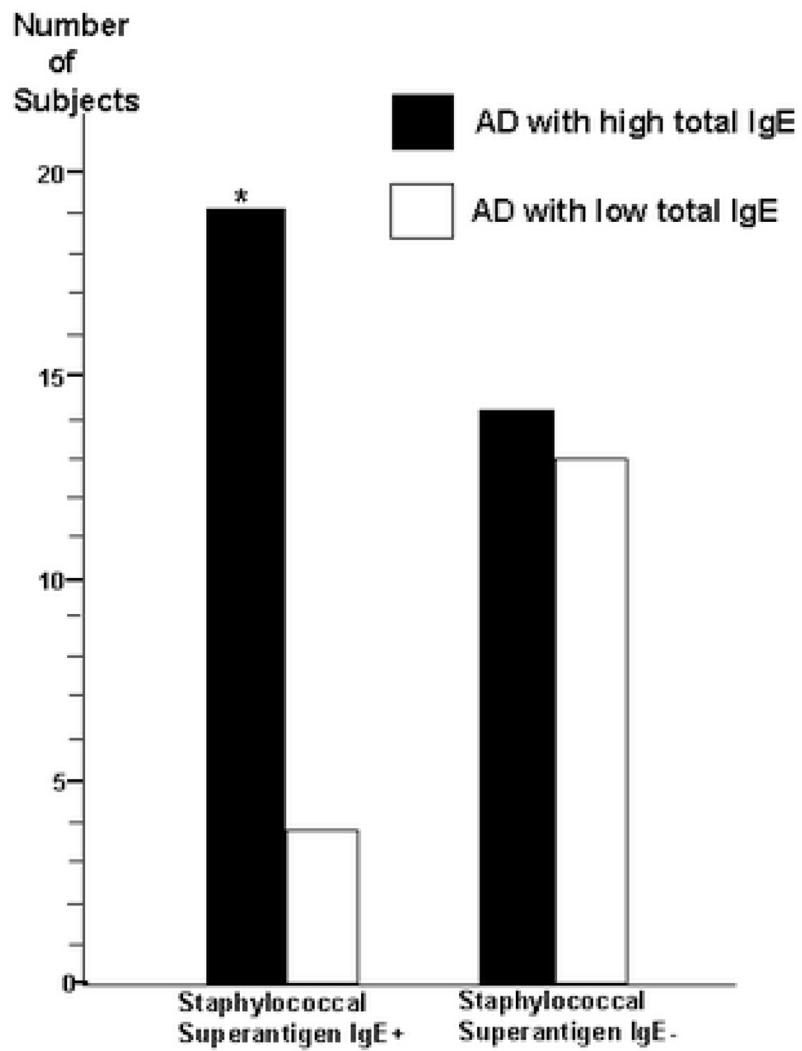
Figure 1.
Allergic sensitization of staphylococcal superantigens is significantly associated with patients with AD who have high total IgE (> 150 IU/mL)(*p<0.04)(Fisher exact test)
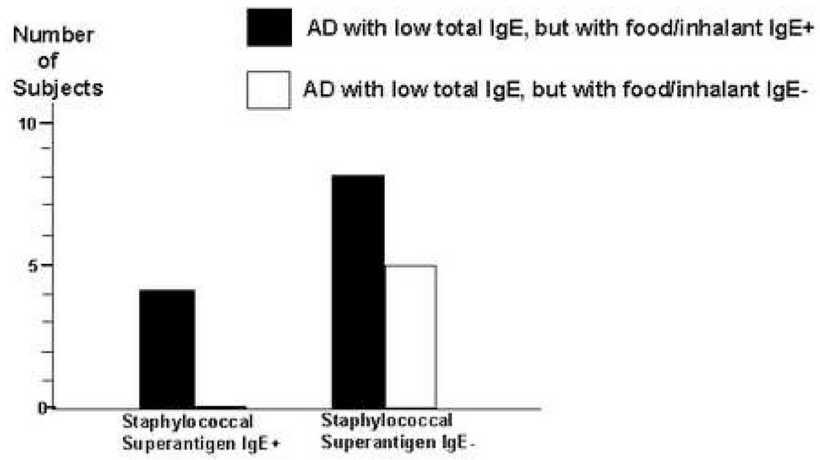
Figure 2.
No association between allergic sensitization to staphylococcal superantigens and that to common food/inhalant allergens in patients with AD with low total IgE (< 150 IU/mL)(*p*=0.3) (Fisher's exact test)

Table 1

The prevalence of allergic sensitization to staphylococcal superantigens among children with mild to moderate atopic dermatitis

	SEA IgE+	SEB IgE+	SEC IgE+	SED IgE+	TSST-1 IgE+	IgE+ to one or more staphylococcal superantigens
Mild AD (n = 34)	6 (18%)	4 (12%)	6 (18%)	1 (3%)	8 (24%)	13 (38%)
Moderate AD (n = 16)	9 (56%)	5 (31%)	5 (31%)	4 (25%)	6 (38%)	10 (63%)

Table 2

Odds ratios for mild vs moderate atopic dermatitis in relation to allergic sensitization to staphylococcal superantigens

	SEA IgE+	SEB IgE+	SEC IgE+	SED IgE+	TSST-1 IgE+	IgE+ to one or more staphylococcal superantigens
Mild AD (n = 34)	1.0	1.0	1.0	1.0	1.0	1.0
Moderate AD (n = 16)	6.3 * (1.4–27.4; *p*=**0.01**)	3.0 * (0.6–14.8; *p*=0.17)	2.0 * (0.4–7.9; *p*=0.50)	10.0 * (1.0–103.8; *p*=**0.05**)	2.0 * (0.5–6.6; *p*=0.40)	2.5 * (0.7–8.9; *p*=0.20)

*
95% confidence intervals with *p* values.