Association between egg and staphylococcal superantigen IgE sensitizations in atopic dermatitis

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ABSTRACT

Patients with moderately severe atopic dermatitis (AD) suffer from significant morbidity including secondary infections and psychosocial disturbances. However, there is currently no laboratory test for identifying these patients to implement early treatments. Because IgE sensitization to foods is frequently an early manifestation in infants with AD, this study aims to examine if food IgE levels may identify AD patients with more severe disease, and whether IgE sensitization to food may predict IgE sensitization to staphylococcal superantigens. Fifty-one young children with AD were included in the study. Eczema severity was measured by objective scoring AD. The levels of food and staphylococcal superantigen-specific IgE were measured by Phadia ImmunoCAP system. Of the five common food allergens (cow's milk, egg white, soybean, wheat, and peanut), only IgE levels to egg white correlated significantly with eczema severity in young children with AD. IgE sensitization to egg white was significantly associated with IgE sensitization to staphylococcal superantigens in older children.

(Allergy Asthma Proc 35:346–348, 2014; doi: 10.2500/aap.2014.35.3757)

Patients with increased atopic dermatitis (AD) severity have a higher risk of morbidity including infections and psychosocial disturbances.^{1,2} There is currently no laboratory test to identify this subgroup of AD patients. Thirty to 40% of children with AD have clinically significant food allergies.³ Ninety percent of infants with moderately severe AD have specific IgE sensitization to at least one food.⁴ This pilot study examines whether food-specific IgE levels correlate with eczema severity in young children with AD and whether IgE sensitization to foods is associated with IgE sensitization to staphylococcal superantigens in older children with AD.

METHODS

Fifty-one young children (31 subjects ≤ 3 years old and 20 subjects ≥ 4 years old) who fulfilled the U.K. Working Party's diagnostic criteria⁵ were included in the study. The ImmunoCAP system (Phadia, Portage, MI) was used to identify specific IgE sensitization (>0.35 kU/L). Food allergens included in the study were cow's milk, egg white, soybean, wheat, and peanut. Staphylococcal superantigens included in the study were staphylococcal enterotoxin A (SEA), SEB, SEC, SED, and toxic shock syndrome toxin 1. Eczema severity was

measured by objective scoring AD (SCORAD). Statistical analyses were performed using SPSS 16.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

The average age for the 31 subjects was 33 ± 10 months. Twenty-five subjects had at least one food IgE sensitization (81%). Among these 25 subjects, the number and percentage of subjects with specific food IgE sensitization are as follows: cow's milk (21/84%), egg white (20/80%), soybean (13/52%), wheat (14/56%), and peanut (15/60%). Specific IgE levels to cow's milk, egg white, soybean, wheat, and peanut in AD subjects ≤ 3 years old were plotted against objective SCORAD. As shown in Fig. 1, only specific IgE levels for egg white correlated significantly with objective SCORAD ($r = 0.5$; $p = 0.03$), whereas cow's milk-, soybean-, wheat-, and peanut-specific IgE levels did not correlate with objective SCORAD (data not shown). We have previously shown that the prevalence of specific IgE sensitization to staphylococcal superantigens increased with more severe AD and that sensitization tended to occur in older children.⁶ To evaluate if egg IgE sensitization predicts IgE sensitization to staphylococcal superantigens in older children with AD, logistic regression analysis was performed in the 20 AD subjects who were ≥ 4 years old. The average age for these subjects was 59 ± 8 months. The percentages of IgE sensitization to at least one food was 85% and to specific foods are as follows: cow's milk (70%), egg white (65%), soybean (65%), wheat (60%), and peanut (65%). Egg white IgE sensitization was found to be strongly associated with IgE sensitization to staphylococcal superantigens as a group (*i.e.*, one or more staphylococcal superantigens) in older children with AD (odds ratio = 33; $p = 0.008$) (Table 1).

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Funded by a CReFF award from the General Clinical Research Center, National Center for Research Resources at the University of Southern California (MO1 RR 00043)

The author has no conflicts of interest to declare pertaining to this article

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Figure 1. Egg white-specific IgE level correlates with eczema severity in young children with atopic dermatitis (AD).

Table 1 Association between food-specific IgE and staphylococcal superantigen IgE sensitization in older children (59 ± 8 mo)

	Egg White IgE ⁺	Cow's Milk IgE ⁺	Soybean IgE ⁺	Wheat IgE ⁺	Peanut IgE ⁺
No superantigen IgE ($n = 8$)	1.0	1.0	1.0	1.0	1.0
Superantigen IgE ⁺ ($n = 12$)	33.0* (2.5–443.6; $p = 0.008$)	5.0* (0.6–39.1; $p = 0.12$)	8.3* (1.0–67.1); $p = 0.05$)	5.0* (0.7–34.7; $p = 0.10$)	8.3* (1.0–67.1; $p = 0.05$)

*Ninety-five percent confidence intervals with p values.

DISCUSSION

In the recent years, the importance of skin barrier and innate immunity is thought to supersede that of cutaneous adaptive immunity in the pathogenesis of AD. The strong association between filaggrin mutations and AD has solidified the notion of skin barrier defects as a primary cause of AD. The innate components of the skin including keratinocytes and innate lymphoid cells have emerged as the primary cause of cutaneous inflammation in AD.⁷ Downstream interactions between Langerhans cells and T cells lead to amplification of cutaneous inflammation and chronic AD. *Staphylococcus aureus* is a well-established trigger of AD. The products of *S. aureus* interact with the cutaneous innate immune system in AD *via* skin barrier defects to increase inflammation. These events occur during early infancy and eventually shape the cutaneous adaptive immune responses in later childhood. This notion is supported by the late onset of staphylococcal superantigen-specific IgE in older chil-

dren with AD.⁶ Therefore, the interim between innate immune response and the development of cutaneous adaptive immunity may provide a window of opportunity for therapeutic intervention in young children with AD.

One of the earliest clinical manifestations of infants with AD is IgE sensitization to food. The increased prevalence of food allergy in children with AD, particularly in infants with AD of moderate severity, has been well established.⁴ Routine screening for food IgE sensitization and food allergy is recommended in this group of infants.⁴

In the current study, it is shown that specific IgE sensitization to egg white correlates with AD severity in young children ≤ 3 years old. The data suggest that increased specific IgE levels to egg white may potentially be applied to identify the subgroup of young children with AD of moderate severity. The current data are consistent with a previous study that showed a stronger correlation between AD severity and egg-

specific IgE, rather than cow's milk-specific IgE.⁸ There is currently no established laboratory test for clinical assessment of AD severity in infants. Physical assessment of AD severity using SCORAD or eczema area and severity index have been validated, but these measures are too time-consuming for routine clinical use. Another potential laboratory marker of AD severity includes serum thymus- and activation-regulated chemokine/CCL17.⁹ However, further studies are needed, especially in young children with AD.

Wolkerstorfer *et al.* further showed that infants with AD and IgE sensitization to egg or cow's milk, when compared with those without food IgE sensitization, are associated with a worse clinical outcome of AD at 18-month follow-up.⁸ In addition, Kawamoto *et al.* have more recently shown that egg white IgE sensitization at 6 months in infants with AD is significantly associated with more persistent AD.¹⁰ These observations are consistent with the notion that the subgroup of AD infants with food IgE sensitization may be predisposed to involve a more T helper 2-biased adaptive immunity in cutaneous inflammation. This is supported by the current observation that IgE sensitization to egg white is strongly associated with IgE sensitization to staphylococcal superantigens in older children with AD. However, whether IgE sensitization to egg white in infants with AD predicts the development of IgE sensitization to staphylococcal superantigens at a later age will require further confirmation by prospective studies.

Significant egg white-specific IgE levels based on ImmunoCAP have been established to correlate with clinically significant egg-allergic reaction (> 95% predictive value with a level of ≥ 2 kU/L for infants ≤ 2 years old, and ≥ 7 kU/L for children > 2 years old).^{3,4,11} Therefore, obtaining serum-specific IgE to egg white in infants with significant AD not only aids in the diagnosis of food allergy to egg, but may also identify those who are at risk for AD morbidity. Early identification in these infants may dictate more aggressive skin barrier repair and/or topical anti-inflammatory treatment; however, whether these treatments will lead to the prevention of staphylococcal superantigen IgE sensi-

zation, persistent AD, infections, and psychosocial disturbances in infants with AD remain to be proven in long-term therapeutic studies.

In summary, the current study showed that serum egg white-specific IgE level correlates with AD severity in young children and that IgE sensitization to egg white is associated with IgE sensitization to staphylococcal superantigens in older children with AD. However, the small sample size may be inadequate to draw any conclusion on the clinical use of egg-specific IgE in identifying at-risk AD children. Larger studies that include younger infants with more severe AD are needed to confirm these findings.

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