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Food-specific immunoglobulin E among children with atopic dermatitis: a retrospective study

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This retrospective study included 133 children aged between 2 and 16 years with elevated serum food-specific immunoglobulin E (IgE), including 59 children clinically diagnosed with atopic dermatitis (AD) and 74 children clinically diagnosed with atopic disease without AD (asthma, allergic rhinitis, or both). Six common serum food-specific IgEs were detected by the Pharmacia ImmunoCAP test, including: egg white, milk, peanut, soybean, shrimp and egg yolk. Serum total IgE was also measured. The results showed that both AD and non-AD atopic children had the highest sensitization rate to shrimp. AD children had significantly higher serum total IgE and average number of positive food sensitization items than atopic children without AD. Three serum food-specific IgEs, including peanut, soybean and egg yolk, were significantly higher in children with AD than in those without AD. Furthermore, 3 pairs of food-specific IgEs were correlated with each other in AD children: egg white IgE correlated with peanut IgE, egg white IgE correlated with egg yolk IgE, and peanut IgE correlated with soybean IgE. In logistic regression analysis of the serum of 6 food allergen-specific IgEs in AD children, we found that elevated peanut- and egg yolk-specific IgE were risk factors of AD in elevated serum food-specific IgE children whose serum total IgE was less than 1000 kU/L but not in those with total IgE greater than 1000 kU/L.

Key words: Atopic dermatitis, food hypersensitivity, immunoglobulin E, predictive value of tests, risk factors

Atopic dermatitis (AD) is a chronic inflammatory disease of the skin, characterized by erythematous and pruritic lesions, excoriations, papules and lichenification [1,2]. It has been shown that food allergies are a contributory factor in childhood AD [3]. Food allergens can penetrate the intestine after ingestion and can be transported in circulation, then binding to immunoglobulin E (IgE)-bearing mast cells in the skin, resulting in the release of mediator, causing cascades of immune responses, leading to skin inflammation of the AD [3].

For the physician, the general approach for food-induced AD patients includes noting the history of skin symptoms exacerbated by some foods, physical examination, prick skin tests to implicate suspicious foods, in vitro tests for serum food-specific IgE antibodies and oral challenges of food. Among these laboratory tests, detecting serum food-specific antibodies is a convenient way for a pediatrician to diagnose patients with food allergies [4]. The aim of this study is to investigate the characteristics of food allergens in AD patients whose serum food-specific IgE levels are elevated. Furthermore, we seek to evaluate the differences between each food allergen and attempt to search for the possible food risk factors in AD.

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Materials and Methods

Subjects

Serum samples were collected from patients aged between 2 and 16 years who had visited the allergy or dermatology outpatient departments of National Taiwan University Hospital from October 1, 2002 to September 30, 2003 with the diagnosis of asthma, allergic rhinitis (AR) or AD. Evaluation consisted of extensive history investigations and physical examinations. Food-specific IgE and total serum IgE were measured in all patients. Patients with elevated levels of at least 1 of the 6 common serum food-specific IgEs, including egg white, milk, peanut, soybean, shrimp, and egg yolk, were included in this study retrospectively.

Methods of measurement

Total and food-specific IgE were measured using the Pharmacia CAP® system (Sweden). The results were

Table 1. Clinical diagnosis of 133 patients with elevated food-specific immunoglobulin E

Diagnosis	Patient number (%)
Asthma only	4 (3.01)
AR only	29 (21.80)
Asthma + AR	41 (30.83)
AD only	5 (3.76)
Asthma + AD	4 (3.01)
AR + AD	29 (21.80)
Asthma + AR + AD	21 (15.79)
Total	133

Abbreviations: AR = allergic rhinitis; AD = atopic dermatitis

expressed in kU/L. The assay was calibrated against the World Health Organization standard for IgE, with 2-2000 kU/L for total IgE. Specific IgE titers were classified according to the Pharmacia system: class 1, 0.35-0.7 kU/L; class 2, 0.7-3.5 kU/L; class 3, 3.5-17.5 kU/L; class 4, 17.5-50 kU/L; class 5, 50-100kU/L; and class 6, >100kU/L. Specific IgE titers were considered positive at levels of 0.35kU/L or higher.

Statistical analysis

The rate of positive sensitization to food allergens, the average number of food-specific allergen sensitization items and average serum total IgE in elevated food-specific IgE children with or without AD was compared using a *t* test. The correlation index (r) between 6 food allergens in elevated food-specific IgE children with AD was assessed by Spearman's rank correlation with Bonferroni's adjustment according to the food-specific IgE levels. To assess possible risk factors of food allergens in AD, odds ratio estimates along with a corresponding 95% confidence interval for elevated serum IgE children with and without AD were obtained by logistic regression. The possible predictors were the 6 common food allergens: egg white, milk, peanut, soybean, shrimp and egg yolk.

Results

133 children with elevations in at least 1 serum food-specific IgE were enrolled in the study, which included 84 boys (63.2%) and 49 girls (36.8%). Disease distribution is summarized in Table 1. There were 59 children in this study who were diagnosed with AD: 5 of them had only been diagnosed with AD, 29 children had been diagnosed with AD and AR, 4 children had been diagnosed with AD and asthma, and 21 children had been diagnosed with AD, AR and asthma. Furthermore, 74 atopic children had been found without the diagnosis of AD. The mean age was 6.07 ± 3.40 years. There was no statistical difference in mean age between the AD and control groups (5.42 ± 3.33 vs 6.52 ± 3.45 years).

The patient number and percentage of elevated food-specific IgE children with and without AD who were positively sensitized to 6 common food allergens are summarized in Table 2. In our study, 29 (49.2%), 29 (49.2%), 21 (35.6%), 14 (23.7%), 37 (62.7%) and 17 (28.8%) children among 59 AD children had elevated specific IgE levels for serum egg white, milk, peanut, soybean, shrimp and egg yolk, respectively. AD patients had a significantly higher positive sensitization rate than patients without AD in 3 food allergens ($p<0.05$): peanut (35.6% vs 8.2%), soybean (23.7% vs 11%), and egg yolk (28.8% vs 8.22%), although there was no difference in the other 3 common food allergens (egg white, milk and shrimp).

We further analyzed the number of positive sensitization items of the food allergens and the serum total IgE of children with and without AD (Table 3). We found that AD children had a significantly larger mean positive sensitization to food allergens than children without AD (mean, 2.492 food allergens vs 1.703; $p<0.05$). AD children also had higher serum total IgE than atopic children without AD (mean serum total

Table 2. Patient number and percentage of positive sensitization to food allergens (≥0.35 kU/L) in elevated food-specific immunoglobulin E children with and without atopic dermatitis (AD)

Positive sensitization number	Children with AD (%) (n = 59)	Children without AD (%) (n = 74)	*p*
Egg white	29 (49.2)	25 (34.3)	0.0739
Milk	29 (49.2)	34 (46.6)	0.7154
Peanut	21 (35.6)	6 (8.2)	0.0001[a]
Soybean	14 (23.7)	8 (11.0)	0.0467[a]
Shrimp	37 (62.7)	47 (64.38)	0.9249
Egg yolk	17 (28.8)	6 (8.22)	0.0015[a]

[a]Significant difference ($p<0.05$) between children with and without AD (*t* test).

Table 3. Average number of positive food-specific allergen sensitization items and serum total immunoglobulin E (IgE) in children with and without atopic dermatitis (AD)

	Children with AD (%) (n = 59)	Children without AD (%) (n = 74)	*p*
Average food allergen positive sensitization items	2.492 ± 1.623	1.703 ± 0.989	0.0007[a]
Average serum total IgE (kU/L)	916.302 ± 658.213	645.302 ± 515.254	0.0240[a]

[a]Significant difference ($p<0.05$) between children with and without AD (*t* test).

IgE 916.302 kU/L vs 645.302 kU/L; $p<0.05$). Due to the fact that AD children had a higher positive sensitization rate than non-AD children in only 3 food allergens, we wanted to determine the correlation among these food allergens in AD children. Therefore, we analyzed the correlation among 6 serum food-specific allergens in 59 AD children (Table 4). Spearman's tests at a 5% level of significance were performed to qualify the correlations. There were 3 pairs of food allergens showing significant correlations: egg white to peanut (r = 0.411, $p=0.018$), egg white to egg yolk (r = 0.395, $p=0.03$), and peanut to soybean (r = 0.665, $p<0.001$). An example explanation for these results is as follows: if a child was noted with elevated serum soybean-specific IgE, we were also likely to detect elevated serum peanut-specific IgE.

Finally, multiple regression analysis was performed to study the effects of various food allergens as the predictor of AD. We separated all 133 cases into 2 groups: total serum IgE ≥1000 kU/L (31 children; 19 with AD, 12 without AD) [Table 5] and total serum IgE <1000 kU/L (102 children; 40 with AD, 62 without AD) [Table 6]. In the former group (total serum IgE ≥1000 kU/L), no food allergen could be considered as a risk factor of AD (Table 5). However, in the latter group (total IgE <1000 kU/L), sensitization to peanut and egg yolk demonstrated significance as potential factors for AD, while sensitization to egg white, milk, soybean and shrimp was not associated with AD in the lower total IgE group (Table 6).

Discussion

Serum food-specific IgE antibodies in AD children are usually associated with other respiratory atopic diseases, such as asthma [5-7], which is likely to become a life-threatening disease. Clinically, it is useful for a physician to check patient serum food-specific IgE in diagnosing food allergies, especially in children who cannot perform skin prick tests due to severe AD or the use of antihistamines [8,9]. Some studies have proven that it is possible to predict food allergies without oral challenge when serum food-specific IgE concentration is greater than the cut-off value [4].

Although about one-third of AD children have IgE-mediated food allergies [10,11], the incidence of AD in children with elevated food-specific IgE has not been well established. In our study, 59 of 133 elevated food-specific IgE children (44.3%) had a diagnosis of AD. We found that shrimp was the most frequent cause of food allergens in AD children (62.7%), followed by egg white and milk (both 49.2%), peanut (35.6%), egg yolk (28.8%), and soybean (23.7%). When making comparisons between the allergic patients with AD and those without AD in elevated food-specific IgE children, we found that the former had a significantly higher percentage of positive sensitization rates than the latter in peanut (35.6% vs 8.2%), soybean (23.7% vs 11.0%) and egg yolk (28.8% vs 8.22%). However, it made no difference with egg white (49.2% vs 34.3%), milk (49.2% vs 46.6%) and shrimp (62.7% vs 64.38%).

Table 4. Correlation among 6 serum food-specific antigens in 59 elevated food-specific immunoglobulin E children with atopic dermatitis [Spearman correlation with Bonferroni adjustment at 5% level of significance (n = 59)]

Rank	Egg white	Milk	Peanut	Soybean	Shrimp	Egg yolk
Egg white	1					
Milk	0.335	1				
Peanut	0.411[a]	0.165	1			
Soybean	0.221	0.054	0.665[b]	1		
Shrimp	0.026	–0.271	0.266	0.265	1	
Egg yolk	0.395[b]	0.102	0.318	0.337	–0.064	1

[a]$p<0.05$.
[b]$p<0.01$.

Table 5. Multivariable logistic regression analysis of 6 common food allergens as predictors of atopic dermatitis in 31 children with serum total immunoglobulin E ≥1000 kU/L[a]

	Odds ratio	95% Confidence interval		*p*
Egg white	1.406	0.498	3.967	0.520
Milk	0.924	0.315	2.717	0.886
Peanut	0.820	0.265	2.536	0.730
Soybean	1.616	0.201	13.02	0.652
Shrimp	1.361	0.638	2.901	0.425
Egg yolk	0.854	0.093	7.866	0.889

[a]Including 19 children with and 12 children without atopic dermatitis.

Cow milk sensitized about one-third of AD children [12]. However, in our study, as many as 49.2% of AD children were found to be sensitized to cow milk. The reason for this higher incidence of sensitization to cow milk in AD children in our study may be because we selected subjects with elevated food-specific IgE with AD. AD children without elevated food-specific IgE were excluded from our study, which resulted in a higher incidence of all food-specific sensitization rates to AD, including sensitization to cow milk.

Furthermore, the prevalence of sensitization to shrimp (62.7% in AD children, 64.38% in non-AD children) in our study is also higher than in other studies [13,14]. Reasons contributing to this phenomenon may be because older average ages and more AR children (90.2%) were selected in our study than in other studies. Evidence suggests that those with elevated serum IgE are prone to have AR [15], and older children with exposure to excessive shrimp diets will lead to higher shrimp-specific IgE. The other possible reason may be due to the cross sensitivity of shrimp with other allergens, which we will discuss later.

Some studies have proven that AD patients have a higher prevalence of food allergies and sera food-specific IgE antibodies than that in the general population and in non-food-allergic atopic children [4]. In our study, we also found atopic children with AD having higher average levels of serum total IgE than atopic children without AD (916.302 ± 658.213 vs 645.302 ± 515.254, $p<0.05$). In addition, the average number of positive food allergen sensitization items among children with AD was 2.492 ± 1.623, which is significantly higher than that of children without AD (1.703 ± 0.989, $p<0.05$). However, compared with non-AD children, it is of interest that AD children did not show increased sensitivity to all food allergens but only to 3 of them: peanut, soybean and egg yolk. The other 3 food allergens demonstrated no difference in the comparison (milk, egg white and shrimp). We wanted to clarify why only the former 3 food allergens had significantly increased sensitization rates in AD children. Therefore, we analyzed further the correlation among the 6 serum food-specific antigens. In Table 4, we note 3 meaningful pairs of food allergens, which show a significant positive food sensitized correlation in AD children. They are as follows: egg white to peanut (n = 21, r = 0.411, $p=0.018$), egg white to egg yolk (n = 17, r = 0.395, $p=0.03$), and peanut to soybean (n = 14, r = 0.665, $p<0.001$). That is, each of these 3 pairs of food allergens tends to sensitize AD children at the same time.

Table 6. Multivariable logistic regression analysis of 6 common food allergens as predictors of atopic dermatitis in 102 children with serum total immunoglobulin E <1000 kU/L[a]

	Odds ratio	95% Confidence interval		*p*
Egg white	1.194	0.697	2.046	0.518
Milk	0.985	0.588	1.650	0.955
Peanut	2.789	1.142	6.807	0.024[b]
Soybean	0.820	0.294	2.290	0.705
Shrimp	1.059	0.648	1.730	0.820
Egg yolk	2.447	1.118	5.358	0.025[b]

[a]Including 40 children with and 62 children without atopic dermatitis.
[b]$p<0.05$.

Sampson indicated that it is possible to measure levels of specific IgE without oral challenge for diagnosing food allergies [4]. In that study, the decision point (65 kUA/L) was relatively high in soybean with 86% positive predictive value and 99% specificity. The data suggest that the reason for the high decision point in soybean is probably the cross reaction between serum soybean antibody and peanut antibody [16]. Eigenmann et al indicated that soybean and peanut shared some common antigens and induced cross-reactive antibodies in a patient [17]. Furthermore, it has been shown that there is allergenic cross-reactivity in egg white and egg yolk protein [18]. In this study, we considered that possible correlations between the 3 pairs of food allergens (peanut to soybean, egg white to peanut, egg white to egg yolk) in AD patients might be due to cross-reaction. We suggest that cross-reaction of food allergens might be seen more frequently in AD than in non-AD patients. Whether patients who have antibody cross-reaction to these food allergens tend to have skin presentations is still unknown.

Finally, we used multivariable logistic regression to analyze whether these food allergens were related to AD in patients with elevated serum food-specific IgE. Surprisingly, we found peanut and egg yolk to be

significantly associated with AD in the group with total serum IgE <1000 kU/L. No other food allergens were significantly correlated with AD. In contrast to the lower serum total IgE group, none of the 6 food allergens were associated with the higher serum total IgE group. One of the possible explanations is that most children in the higher total serum IgE group were positively sensitized to more food allergen sensitization items but without higher titers of IgE in a single food allergen, which would decrease the significance during statistical calculations.

A lot of allergens demonstrated the same epitopes, causing cross-reactivity, for example, in previous cross-allergenicity tests among egg white and egg yolk protein [18]. In our study, the possible existence of cross-reactivity interfered with the statistical results in the higher serum total IgE group, especially the serum of patients with high elevations of IgE. This may represent a further reason why AD associated with egg yolk and peanut is only manifest in the lower serum total IgE group and not in the higher group. Furthermore, we cannot exclude the possibility that egg white and not egg yolk induced AD due to cross-reaction of the specific IgE in AD children with elevated serum egg yolk-specific IgE. Therefore, further prospective studies may be necessary, including oral challenge or skin prick tests, to confirm the possibility of peanut and egg yolk in the lower total serum IgE (<1000 kU/L) group.

In conclusion, among patients with elevated serum food-specific IgE, AD children are likely to have higher serum peanut-specific, soybean-specific, and egg yolk-specific IgE than atopic children without AD, but not serum egg white-specific, milk-specific, and shrimp-specific IgE. AD children also have higher serum total IgE and average number of positive food allergen sensitization items than atopic children without AD. Furthermore, elevated serum egg yolk-specific IgE and peanut-specific IgE potentially could be considered risk factors for AD. This should be considered in order to offer early diagnosis and early treatment to the patient.

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