Food Sensitization in Infants and Young Children with Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease. Children with AD tend to have a higher prevalence of food allergies. This study investigated the clinical significance of food sensitization in AD patients. A total of 266 AD patients participated in this study. The prevalence of food sensitization and clinically relevant sensitization were compared in the subjects according to their age and AD severity. Sera from all patients were analyzed for food-specific IgE levels using the Pharmacia CAP System FEIA. The serum specific IgE levels for egg, milk, peanut and soybean were measured. Patients were regarded as sensitized to the food if their food-specific IgE levels were above 0.35 kUA/L. Also the food-specific IgE levels, the so-called diagnostic decision point, which is recommended as the clinically relevant level, for clinical food allergy, as suggested by Sampson et al, was used as an alternative method. From the measurement of food-specific IgE antibodies of the four foods, egg was the most highly sensitized and the main causative allergenic food in children with AD. The positive rates of specific IgE to the four major food allergens, and the prevalences of clinically relevant food sensitization, were higher for all foods tested in the group less than 1 year of age, and were significantly higher in moderate to severe AD compared to mild AD in infants and young children. In summary, presence of food specific IgE is prevalent in infants and young children with AD, and clinically relevant food sensitization is important in Korean infants and children with moderate to severe AD.

Key Words: Atopic dermatitis, food sensitization, clinically relevant food sensitization

INTRODUCTION

Atopic dermatitis (AD) is a highly pruritic chronic inflammatory skin disease that commonly presents during early infancy and childhood, and frequently predates the development of allergic rhinitis or asthma. It is an important skin condition with significant costs and morbidity to patients and their families; the disease affects 10-20% of children and 1-3% of adults.[1] In Korea, Oh et al.[2] reported a 17% prevalence of AD in children aged from 6 to 12 years. AD is frequently associated with food allergies. A significant percentage (37%) of children with a history of a persistent eczematous rash, despite the use of topical corticosteroids, have symptomatic food allergies.[3] Up to 8% of children less than 3 years of age, and approximately 2% of the adult population, experience food-induced allergic disorders.[4] Although hundreds of different foods are included in the human diet, a relatively small number account for the vast majority of food-induced allergic reactions. Among the most commonly offending foods are egg, milk, peanut and soybean.[5,6]

AD is associated with increased serum IgE levels[7,8] and IgE-mediated food hypersensitivity has its greatest incidence in infancy and early childhood.[9] Patients with AD generally have elevated concentrations of total and food-specific IgE antibodies.[10] In a series of classic experiments, Walzer et al.[11,12] demonstrated that ingested food antigens penetrated the gastrointestinal barrier and were transported to IgE bearing mast cells in

the skin. Sampson et al.[13,14] performed studies relating to the strong association between IgE-mediated food hypersensitivity and AD in children.

With these considerations, the prevalence of clinically relevant food sensitization in AD patients was investigated by the measurement of food-specific IgE antibodies of egg, milk, peanut and soybean.

MATERIALS AND METHODS

Study Populations

A total 266 AD patients (168 males, 98 females) who visited the Ajou University Hospital and the Yonsei University College of Medicine between October 2001 and July 2003, and fulfilled the criteria of Hanifin and Rajka,[15] were enrolled in this study. The total clinical severity score of AD (range from 0 to 15) was defined as the sum of five individual scores - pruritus, erythema, edema/papulation, excoriation and scaling/dryness, and were graded as 0 (none), 1 (mild), 2 (moderate) and 3 (severe). Sixty-eight of mild AD patients having clinical severity scores from 1 to 5 and 198 moderate to severe AD patients having scores from 6 to 15, were enrolled in this study. Patients ranged in age from 2 months to 4 years (median, 1.9 years), and were divided into two groups according to age: one group was under the age of 1 year (infant), and the other was between the ages of 1 and 4 years (young children). The subjects were also divided into two groups according to their AD severity: one group included subjects with mild AD, and the other subjects with moderate to severe AD. The sera of the patients were obtained at the time of their initial visit for the quantification of food-specific IgE antibodies to the 4 major food allergens (egg, milk, peanut and soybean). The prevalence of clinically relevant food sensitization to the four foods was compared between less than 1 year (infant) and 1 - 4 years of age (young children), or between patients with mild AD and moderate to severe AD.

Laboratory studies

Serum samples from all patients were analyzed

for food-specific IgE antibodies using the Pharmacia CAP System FEIA (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).[16] Briefly, venous blood samples were obtained at the time of the initial evaluation and analyzed using the CAP System. The manufacturer recommends considering results of IgE levels greater than 0.35 kUA/L as positive. Therefore, children were regarded as sensitized if their food-specific IgE levels were above 0.35 kUA/L.

Recently Sampson et al.[17,18] reported diagnostic decision points of allergen-specific IgE levels to a number of foods using the CAP system, which had a high enough sensitivity and specificity that the results of double-blind placebo-controlled food challenges could be replaced. They found that a serum egg-specific IgE level of 7 kUA/L or greater was 98% predictive of clinical reactivity to egg, and infants under 2 years of age were 95% likely to react to egg if their serum egg-specific IgE levels were greater than 2 kUA/L. A serum milk-specific IgE level of 15 kUA/L or greater was 95% predictive of clinical reactivity to milk, and infants under 1 year of age were 95% likely to react to milk if their serum milk-specific IgE levels were greater than 5 kUA/L. A serum peanut-specific IgE level of 14 kUA/L or greater was 100% predictive of clinical reactivity to peanut. A serum soybean-specific IgE level of 30 kUA/L or greater was 73% predictive of clinical reactivity to soybean.[18] Therefore, using the diagnostic decision points, the prevalence of clinically relevant food sensitization of the subjects was analyzed.

Statistical analysis

The analyses were performed using the statistical package SPSS version 11.5. In order to evaluate the significance of the test, a statistical analysis was performed using Chi-squared test in this study. A p value of < 0.05 was considered to represent statistical significance.

RESULTS

The food-specific IgE levels, of which the detection limits to all four foods were above 0.35 kUA/L in 266 AD patients, were measured. Using

this positive cut-off value, the prevalences of food sensitization to egg, milk, peanut and soybean were 51.5, 31.2, 16.2 and 15.4%, respectively (Table 1). The positive rates of food sensitization were also measured using the diagnostic decision points suggested as clinically significant levels, and could be substituted with oral food challenges if the levels of specific IgE were the same or higher than the unique values for individual food allergens. As mentioned before, a clinically relevant food sensitization was defined as the specific IgE levels that were the same or more than the diagnostic decision point. Using this criterion, the positive rates of clinically relevant food sensitization to egg, milk, peanut and soybean were 32.7, 4.5, 3.0 and 1.1%, respectively. Therefore, in the present study, the sensitization to egg was found to be most prevalent and strong. Compared to egg sensitization, the positive rates of the specific IgE levels, using diagnostic decision points, were low for milk, peanut and soybean (Table 1).

Table 2 shows the positive rates of food sensitization to the four foods, using the cut-off value of 0.35 kU/L according to age and AD severity. The positive rates of food sensitization to egg, milk, peanut and soybean were significantly higher in infants compared with patients of 1 - 4 years of age. The positive rates of food sensitization to egg, milk, peanut and soybean were also significantly higher in patients with moderate to severe forms of AD compared to the mild form of AD.

Table 3 shows the positive rates of clinically relevant food sensitization to the four foods according to age and AD severity. As a result, the prevalence of food allergy to egg was the highest, with a positive rates of 44.7 and 8.0% in infants and young children (1 - 4 years of age), regardless of AD severity, respectively. The positive rates of clinically relevant food sensitization to milk, peanut and soybean were 8.6, 4.3 and 0.9%, respectively, and were remarkably lowered if the diagnostic decision points for food sensitization

Table 1. Positive Rates of Food Specific IgE Levels (N*=266)

Foods	> 0.35 kU/L		> DDP[†]	
	No. of Cases/N	Prevalence (%)	No. of Cases/N	Prevalence (%)
Egg	137/266	51.5	87/266	32.7
Milk	83/266	31.2	12/266	4.5
Peanut	43/266	16.2	8/266	3.0
Soybean	41/266	15.4	3/266	1.1

*Total number of AD patients enrolled in this study.
[†]DDP: Diagnostic decision point of specific IgE. For egg > 7 kU/L (2 or more than 2 years of age) and 2 kU/L (less than 2 years of age), for milk > 15 kU/L (1 or more than 1 year of age), 5 kU/L (less than 12 months of age), for peanut > 14 kU/L and for soybean > 30 kU/L.

Table 2. Positive Rates of Food Sensitization According to Age and AD Severity

Foods	Age		p-value*	AD severity		p-value[†]
	< 1 year (%)	1 - 4 years (%)		mild (%)	moderate-severe (%)	
Egg	62.9	42.7	$p<0.05$	30.9	58.6	$p<0.05$
Milk	36.2	27.3	$p<0.05$	27.9	32.3	$p=0.50$
Peanut	23.3	10.7	$p<0.05$	7.4	19.2	$p<0.05$
Soybean	21.6	10.7	$p<0.05$	5.9	18.7	$p<0.05$

Cut-off values for food sensitization: > 0.35 kU/L.
*Chi-squared test: comparison of the positive rate between patients less than 1 year of age and 1 - 4 years of age.
[†]Chi-squared test: comparison of the positive rate between patients with mild AD and moderate to severe AD.

Table 3. Positive Rates of Clinically Relevant Food Sensitization According to Age and AD Severity

Foods	Age		p-value*	AD severity		p-value[†]
	< 1 year (%)	1 - 4 years (%)		mild (%)	moderate-severe (%)	
Egg	44.7	8.0	$p<0.05$	13.2	39.4	$p<0.05$
Milk	8.6	1.3	$p<0.05$	1.5	5.6	$p=0.16$
Peanut	4.3	2.0	$p=0.28$	0.0	4.0	$p=0.09$
Soybean	0.9	1.3	$p=0.72$	0.0	1.5	$p=0.31$

Cut-off values for food sensitization: > diagnostic decision points for individual food allergen: for egg > 7 kU/L (2 or more than 2 years of age) and 2 kU/L (less than 2 years of age), for milk > 15 kU/L (1 or more than 1 year of age), 5 kU/L (less than 12 months of age), for peanut > 14 kU/L and for soybean > 30 kU/L.

*Chi-squared test: comparison of the positive rate between patients less than 1 year of age and 1 - 4 years of age.
[†] Chi-squared test: comparison of the positive rate between patients with mild AD and moderate to severe AD.

Table 4. Positive Rates of Food Sensitization and Clinically Relevant Sensitization According to Age and AD Severity

Cut off (kU/L)	Age		p-value*	AD severity		p-value[†]
	< 1 year (%)	1 - 4 years (%)		mild (%)	moderate-severe (%)	
> 0.35	72.4	48.0	$p<0.05$	39.7	65.2	$p<0.05$
DDP[‡]	56.9	15.3	$p<0.05$	13.2	40.4	$p<0.05$

*Chi-squared test: comparison of the positive rate between patients less than 1 year of age and 1 - 4 years of age.
[†] Chi-squared test: comparison of the positive rate between patients with mild AD and moderate to severe AD.
[‡] DDP: diagnostic decision points for individual food allergen; defined as the clinically relevant food sensitization if the specific IgE levels were the same or greater than the DDP, for egg > 7 kU/L (2 or more than 2 years of age) and 2 kU/L (less than 2 years of age), for milk > 15 kU/L (1 or more than 1 year of age), 5 kU/L (less than 12 months of age), for peanut > 14 kU/L and for soybean > 30 kU/L.

were used. The positive rates of clinically relevant food sensitization to egg and milk were significantly higher in infant compared to young children, while those to the peanut and soybean showed no significant difference between the two age groups. In the patients with mild AD, the positive rates to egg, milk, peanut and soybean were 13.2, 1.5, 0, and 0%, respectively, but were 39.4, 5.6, 4 and 1.5% in the patients with moderate to severe AD. Therefore, the positive rates of clinically relevant food sensitization to all four foods were higher in patients with moderate to severe AD than in mild AD, but a significant difference was only found in the case of egg sensitization.

Conversely, the positive rates of food sensitization in the subjects with IgE level, above 0.35 kU/L to at least one food allergen were also analyzed. As shown in Table 4, 72.4% of infants with AD (less than 12 months of age) and 48.0% of young children (1 - 4 years of age) were sensitized to one or more food allergens in this study. Of these, the prevalence of clinically relevant food sensitization was 56.9% in infants, but only 15.3% in young children. Also, 39.7% of patients with mild AD and 65.2% of patients with moderate to severe AD were sensitized to one or more food allergen, and the prevalence of clinically relevant food sensitization were 13.2 and 40.4%, respectively. Therefore, in the present study, positive rates of simple and clinically relevant food sensitizations to one or more food allergens were significantly higher in infants compared to young children ($p<0.05$), and higher in moderate to severe AD compared to mild AD patients ($p<0.05$).

DISCUSSION

AD is a form of eczema that usually begins in early infancy, and is characterized by a typical distribution, extreme pruritus, and a chronic and relapsing course. Children with AD tend to have a higher prevalence of food allergies. About 35% of children with moderate to severe AD have skin symptoms provoked by food hypersensitivity.[3] Although allergists and dermatologists have different opinions concerning the prevalence and importance of food allergies in AD, food hypersensitivity has been reported to play an important role in IgE-mediated mechanisms of AD pathogenesis.

Diagnostic procedures for food allergies in children with AD should rely on a good knowledge of the prevalence and most allergenic foods in a specific population. In the studies by Sampson et al.,[19,20] patients were mostly allergic to egg, milk and peanuts, and had moderate and severe AD. More recently, a prevalence of food allergy of 37% was reported by the same authors for a group of patients primarily referred to a dermatologist for AD.[3] A similar proportion (33%) was found earlier by Burks et al.[21] for a population of children with AD, who were predominantly allergic to egg, milk and peanuts. Further studies from the same group of investigators identified seven foods (milk, egg, peanut, soybean, wheat, fish and cashew) that were responsible for 89% of the positive diagnostic challenges.[6] In the UK, Atherton et al.[22] identified skin reactions in 14 out of 20 children with AD. Diagnostic exclusion diets in this study were only to egg and milk; and therefore, may not have detected other food sensitivities. Guillet & Guillet[23] found egg, milk, shellfish, cornstarch, peanut, fish and soybean allergies in French children diagnosed with moderate or severe AD. More recently, a group from Spain found egg and fish sensitizations in 65% of children with AD.[24] Kim et al.[25] found that of children with asthma, with clinical histories of food allergy, the ten most common foods implicated in allergic reactions were egg, pork, peach, mackerel, chicken, milk, buckwheat, crab, wheat and tomato, in that order of frequency, and that the children had past histories, such as urticaria, AD and drug allergies. In all these studies, egg

and milk allergies were common to AD patients, but the other food sensitivities were mostly population specific.

In this study, egg was the most highly sensitized food in infants and young children with AD. For the egg allergen, 137 (51.5%) of the 266 subjects showed food-specific IgE levels above 0.35 kUA/L, 83 (31.2%) for milk, 43 (16.2%) for peanut and 41 (15.4%) for soybean. The positive rates of food sensitization to the four major food allergens were significantly higher in the group of patients less than 1 year of age (infant) compared to young children aged 1-4 years. The positive rates of food sensitization were also significantly higher in patients with moderate to severe AD compared to mild AD. It was also found that egg was the most prevalent and potent allergen in our patients, regardless of age and AD severity.

For the correct diagnosis of food allergies, double-blind, placebo-controlled food challenge is still considered the standard method. For that reason, our study has a limitation for the diagnosis of real food allergies. Fortunately, however, Sampson et al.[17,18] recently reported valuable serologic diagnostic decision criteria, the so called 'diagnostic decision points' of allergen-specific IgE levels to a number of foods using the CAP system, which had a high enough sensitivity and specificity that it could replace the results of double-blind placebo-controlled food challenges. They found that a serum egg-specific IgE level of 7 kUA/L or greater was 98% predictive of clinical reactivity to egg, with infants under 2 years of age 95% likely to react to egg if the serum egg-specific IgE levels were greater than 2 kUA/L. A serum milk-specific IgE level of 15 kUA/L or greater was 95% predictive of clinical reactivity to milk, with infants under 1 year of age 95% likely to react to milk if the serum milk-specific IgE levels were greater than 5 kUA/L. A serum peanut-specific IgE level of 14 kUA/L or greater was 100% predictive of clinical reactivity to peanut. A serum soybean-specific IgE level of 30 kUA/L or greater was 73% predictive of clinical reactivity to soybean.[18] For evaluating the positive relations between AD and food allergies, unfortunately no 'double-blind, placebo-controlled food challenge' could be performed for the diagnosis of food allergies. Therefore, in this study, two analyzing system for

positive rates to food sensitization were used. If the cut-off values, the so called 'diagnostic decision point', were used, the positive cases could be defined as clinically relevant food sensitizations implying a roughly clinical food allergy. Using these values, the positive rates of the clinically relevant food sensitizations to the 4 foods were analyzed according to age and AD severity. As a result, the prevalence of a food allergy to egg was the highest, with positive rates of 44.7 and 8.0% in infants and young children (1 - 4 years of age), regardless of AD severity, respectively. The positive rates of clinically relevant food sensitization to milk, peanut and soybean were remarkably lowered if the diagnostic decision point for food sensitization was used. The positive rates of clinically relevant food sensitization to egg and milk were also significantly higher in infants compared to young children, while those to peanut and soybean were not significantly different between the two age groups. Furthermore, the positive rates of clinically relevant food sensitization to all four foods were higher in patients with moderate to severe AD compared to mild AD, but a significant difference was only found in the case of egg sensitization.

The positive rates of simple and clinically relevant food sensitizations to one or more food allergens were found to be significantly higher in infants compared to young children ($p < 0.05$), and higher in moderate to severe AD compared to mild AD patients ($p < 0.05$).

In conclusion, in this study the positive rates of food specific IgE levels (cut off > 0.35 kU/L) and the prevalence of clinically relevant food sensitization to egg, milk, peanut and soybean were significantly higher in infant and young children with AD. Furthermore, sensitization to egg was found to be most important and potent compared to milk, peanut and soybean regardless of age or AD severity.

Thus, it is proposed that for patients aged less than 1 year or with moderate to severe AD, the clinical food allergy should be considered as a cause of disease. The measurement of food specific IgE would provide a good guideline for evaluating clinical food allergies and for the further management for AD in infant and young children. However, to confirm the food allergies

in our patients, the clinical symptom relief still needs to be evaluated by food allergen elimination. Studies are underway to find the efficacy of food allergen elimination in the treatment of AD.

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