ABSTRACT. Objective. There is a growing body of clinical and laboratory evidence to support the notion that food allergy plays a role in the pathogenesis of atopic dermatitis (AD). However, the incidence of IgE-mediated food allergy in children with AD is not well established.

Design. A prospective study to determine the prevalence of IgE-mediated food hypersensitivity among patients referred to a university-based dermatologist for evaluation of AD.

Setting. University hospital pediatric dermatology clinic.

Patients. A total of 63 patients with AD were recruited (35 male; 22 white, 24 African-American, 7 Asian).

Methods. Patients were assigned an AD symptom score (SCORAD) and were screened for food-specific serum IgE antibodies to six foods (milk, egg, wheat, soy, peanut, fish) known to be the most allergenic in children. The levels of food-specific serum IgE were determined by the CAP System fluoroscin-enzyme immunoassay (CAP); patients with a value ≥0.7 kIU/L were invited for an additional allergy evaluation. Those with CAP values below the cutoff were considered not food allergic. Patients were considered to be allergic if they met one of the following criteria for at least one food: 1) reaction on food challenge; 2) CAP value more than the 95% confidence interval predictive for a reaction; 3) convincing history of an acute significant (hives, respiratory symptoms) reaction after the isolated ingestion of a food to which there was a positive CAP or prick skin test.

Results. A total of 63 patients (median age, 2.8 years; median SCORAD, 41.1) were recruited; 22 had negative CAP values (without a significant difference in age or SCORAD score, compared with the 41 with positive specific IgE values). Further allergy evaluation was offered to the 41 remaining patients; 10 were lost to follow-up and 31 were evaluated further. Of these, 19 underwent a total of 50 food challenges (36 double-blind, placebo-controlled, and 14 open), with 11 patients experiencing 18 positive challenges (94% with skin reactions). Additionally, 6 patients had a convincing history with a predictive level of IgE; 5 had a convincing history with positive, indeterminate levels of IgE; and 1 had predictive levels of IgE (to egg and peanut) without a history of an acute reaction. Overall, 23/63 (37%; 95% confidence interval, 25% to 50%) had clinically significant IgE-mediated food hypersensitivity without a significant difference in age or symptom score between those with or without food allergy.

Conclusions. Approximately one third of children with refractory, moderate–severe AD have IgE-mediated clinical reactivity to food proteins. The prevalence of food allergy in this population is significantly higher than that in the general population, and an evaluation for food allergy should be considered in these patients. Pediatrics 1998;101(3). URL: http://www.pediatrics.org/cgi/content/full/101/3/68; atopic dermatitis (eczema), food allergy, IgE-mediated, prevalence, hypersensitivity.

ABBREVIATIONS. AD, atopic dermatitis; DBPCFC, double-blind, placebo-controlled food challenge; RAST, radioallergosorbent test; CAP, CAP System FEIA (a quantitative antibody fluoroscein-enzyme immunoassay); CLA, cutaneous lymphocyte-associated.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects between 10% and 12% of the pediatric population. There is an increasing body of clinical and laboratory evidence suggesting that food hypersensitivity plays a pathogenic role in AD in a subset of patients. However, the prevalence of clinically relevant food hypersensitivity among children with AD remains an unanswered question. Sampson and McCaskill found that ~60% of a highly selected group of pediatric patients with AD evaluated by double-blind, placebo-controlled food challenge (DBPCFC) experienced a positive reaction to food. Burks and colleagues used DBPCFC to evaluate a group of 46 children with moderate to severe AD identified in an allergy-treatment clinic (31 patients) and a dermatology clinic (15 patients). Fifteen patients (33%) were determined to have clinically relevant food allergy, but the study has been criticized because a majority of the patients were recruited from the allergy clinic, introducing some selection bias.

Several lines of laboratory and clinical evidence suggest a role for IgE-mediated hypersensitivity in the pathogenesis of AD. Laboratory evaluations of children with AD reveal that ~80% to 90% have elevated total IgE levels, with ~80% having positive immediate skin tests and radioallergosorbent test (RAST) results to dietary and environmental allergens. More important, IgE has been implicated in the cutaneous late-phase response and in antigen-processing and T cell activation by cutaneous anti-
ige-presenting cells (eg, dendritic cells). Clinical studies have shown that associated atopic disorders, such as asthma and allergic rhinitis, develop in 50% to 80% of children with AD. In challenge studies, skin symptoms can be reproduced in some subjects challenged with foods to which they have specific IgE antibodies. When the incriminated foods are eliminated from the diet, patients typically have significant improvement in their symptoms, compared with children without food allergy or with those who do not adhere to the diet.

Because the true prevalence of food hypersensitivity in AD remains unknown, we undertook a study to determine the prevalence of clinically relevant food hypersensitivity in patients who were referred to a pediatric dermatologist (B.A.C.). These patients were referred to the dermatologist without selection for any adverse reaction to foods.

METHODS

All children between the ages of 6 months and 20 years with a history of a persistent eczematous rash in two or more predilection sites despite the use of topical corticosteroids and who presented to the dermatology clinic at the Johns Hopkins Hospital were eligible for the study. Patients were evaluated by the dermatologist (B.A.C.) at the initial visit, and an AD symptom score was assigned using the SCORAD index. Parents were informed by the dermatologist that children with eczema may have worsening of their symptoms triggered by foods to which they are allergic and were offered the opportunity to participate in the study. Participants had blood drawn for determination of specific IgE antibody concentrations to six foods, and patients with positive results to at least one food were contacted by an allergist to return for a full allergy evaluation. Informed consent was obtained for each subject, and the study was approved by the Joint Committee for Clinical Investigation of Johns Hopkins University.

Allergy Evaluation

All patients enrolled in the study were initially screened for food-specific serum IgE to a battery of six foods (milk, egg, wheat, soy, peanut, fish) that have been shown in DBPCFC to be the most common food allergens in children and to account for ~85% of documented food allergy in this group. The levels of food-specific serum IgE were determined using CAP System fluoroscein-enzyme immunoassay (Pharmacia Upjohn Diagnostics, Evansville, IL). This method provides greater sensitivity than the standard RAST. In a previous study of 196 patients with AD who underwent 494 DBPCFCs, this method was shown to provide useful positive and negative predictive values for clinical reactions to a number of foods, as shown in Table 1. Subjects with a value greater than the 95% predictive value predictive of a positive reaction and, therefore, were not challenged to foods to which they had a level of food antigen-specific IgE that exceeded the 95% predictive value. In some cases, open challenges were performed because of young age or parental request. DBPCFCs were performed as described previously. Patients were instructed to avoid the challenge food strictly for 2 weeks before the challenge and to discontinue antihistamine medications for the equivalent of at least five half-lives for the given medication. All challenges were performed in the Pediatric Clinical Research Unit of Johns Hopkins Hospital under physician supervision. Intravenous access was obtained, and emergency medications were available immediately. Up to 10 grams of dehydrated food were camouflaged in juice, infant formula, or a moist food (eg, cream of rice) and administered in graduated portions over 90 minutes. Two challenges separated by 4 hours were administered each day; one challenge contained the suspected food allergen, whereas the other contained only the camouflage food (placebo). Randomization and preparation of the challenges were performed by the dietitians on the Research Unit; thus, patients, parents, nursing staff, and investigators were unaware of the content of the challenges. All reactions were scored for type, time of onset, severity, and duration. Symptoms generally were not followed beyond a 4-hour observation period. Negative challenges were confirmed with open feeding with the quantity of the test food normally consumed in a meal.

Statistical Analysis

Statistical comparisons were performed using the Mann-Whitney U test, and a P value <.05 was considered significant.

RESULTS

A total of 63 patients were enrolled in the study (35 male; 32 white, 24 African-American, 7 Asian). The median age of these patients was 2.8 years (range, 0.4 to 19.4 years). The median SCORAD was 41.1 (range, 6.5 to 94.5), and the mean SCORAD was 41.8. Five patients had a SCORAD <20, and 7 had a SCORAD >60. Twenty-two of the 63 patients enrolled had CAP values to all six foods that were <0.7 kUA/L and were not evaluated further. Comparison of the 41 patients with at least one CAP value >0.7 kUA/L with the 22 patients without showed no significant difference in either the mean age (2.8 years vs 2.9 years; P = .33) or the mean SCORAD (43.5 vs 37.6; P = .47), respectively. Of the 41 patients, 10 did not undergo the allergy evaluation because of loss to follow-up or patient preference. None of these 10 patients had a CAP value more than the 95% cutoff value predictive of a positive reaction and, therefore, were considered not food allergic. The remaining 31 patients underwent additional allergy evaluation.

Of the 31 patients who underwent an allergy evalu-

| TABLE 1. Levels of Specific IgE-Yielding Predictive Values (kUA/L) for CAP–RAST Tests |
|-----------------|-----------------|
| Food       | 95% Positive Predictive Value | 95% Negative Predictive Value |
| Milk       | 32               | 0.8                      |
| Egg        | 6                | 90% at 0.6               |
| Peanut     | 15               | 85% at <0.35            |
| Soy        | 50% at 65        | 2                        |
| Wheat      | 75% at >100      | 5                        |
| Fish       | 20               | 0.9                      |

DBPCFC

DBPCFCs were performed on the basis of history and skin test and/or CAP results. Subjects with a convincing history of an immediate, severe reaction after the isolated ingestion of a food to which they had a positive prick skin test or CAP value were not challenged, but were considered allergic to that food. Patients also were not challenged to foods to which they had a level of food antigen-specific IgE that exceeded the 95% predictive value. In some cases, open challenges were performed because of young age or parental request.
Food Challenges

Although negative prick skin tests have an excellent predictive value for clinical reactivity to foods tested, it is well known that a positive prick skin test does not necessarily indicate clinical reactivity (false positive). Thus, 19 patients underwent 36 DBPCFCs and 14 open food challenges to a variety of foods as indicated by positive prick skin tests and/or indeterminate (positive but below 95% positive predictive value) CAP results in the absence of “convincing” histories of previous food reactions. The results of these challenges are shown in Table 2. There were 18 positive challenges in 11 patients. Symptoms elicited during positive challenges included cutaneous (erythema, hives, and/or maculopapular eruption) in 17 (94%), gastrointestinal (nausea, vomiting, diarrhea, and/or abdominal pain) in 1 (6%) and respiratory symptoms (wheezing, rhinitis, nasal congestion, and/or repetitive cough) in 2 (11%) of the challenges. Isolated cutaneous symptoms were seen in 15 (83%) of the positive challenges and 2 organ systems were involved in 2 (11%), and one patient experiencing an isolated respiratory reaction. There were no episodes of anaphylaxis and no false positive responses to placebo.

Characteristics of Patients With Food Allergy

Table 3 summarizes the foods to which the 23 patients were allergic based upon challenge results, a “convincing” history plus a predictive food-specific IgE antibody level as determined by CAP-System FEIA, a “convincing” history plus a positive food-specific IgE level and/or prick skin test, or a CAP-System FEIA value greater than the 95% predictive cut-off. Eight patients were allergic to one food, 4 to two, 5 to three, and 5 patients to four or more foods.

Overall, 23 of the 63 patients were allergic to at least one food (37%; 95% confidence interval, 25% to 50%). Comparison of these 23 food-allergic patients with the 40 with a negative or incomplete evaluation showed no significant difference in median SCORAD among those with (46.9) or without (39.6) food allergy (P = .92). The median ages of those with (2.3 years) and without (3.0 years) food allergy also were similar (P = .31).

DISCUSSION

AD is a form of eczema that usually begins in early infancy; is characterized by a typical distribution, extreme pruritus, and a chronic and relapsing course; and frequently is associated with asthma, allergic rhinitis, and a family history of allergic disorders. The rash is typically an erythematous, papulovesicular eruption, frequently with exudation early in infancy that progresses to a scaly, lichenified rash later in childhood. The distribution of the rash varies with age, involving the cheeks and extensor surfaces of the extremities in infants with a predilection for the flexor surfaces of the elbows, knees, hands, and feet of the older child and adult. The pathogenic role of allergy in AD has been the focus of much debate, but a number of clinical and laboratory observations have suggested a significant role for IgE-mediated mechanisms.

The pathogenic role of food allergy in AD was first suggested by clinical observations and uncontrolled studies performed >80 years ago and has been supported further by the results from large controlled studies using DBPCFC performed in the past 20 years. In a study in 1918, Talbot described a series of patients with eczema and positive skin tests to foods who experienced clearing of their skin with elimination of the incriminated foods from their diet. The issue of whether ingested food antigens could reach the skin and cause immune-mediated symptoms was addressed in studies by Walzer and colleagues. They passively sensitized healthy subjects by intracutaneous injection with serum from food-allergic subjects. When passively sensitized subjects ingested the relevant protein, they developed a wheal and flare reaction at the sensitized site within 1 to 2 hours, but not at the control site. Additional support for the relationship of AD to food allergy was demonstrated in 1936 by Engman and colleagues, who reported a patient with eczema in whom ingestion of wheat caused intense pruritus. The patient was admitted to the hospital on a wheat-elimination diet with clear skin, had his left arm and leg bandaged to prevent access for scratching, and was fed wheat, which led to itching and scratching. By the next morning, the patient had eczematous lesions only in exposed areas where rubbing and scratching occurred.

These studies gave way to larger, controlled studies of food allergy and AD. Sampson and colleagues have investigated the role of IgE-mediated food allergy in pediatric patients with AD using DBPCFC. In general, positive DBPCFCs elicit a variety of symptoms within minutes to 2 hours. Although a majority of reactions involve cu-
cutaneous symptoms, the upper and lower respiratory tract and gastrointestinal system are frequently involved. At first evaluation, skin symptoms provoked by DBPCFC generally consisted of a pruritic, erythematous, morbilliform rash that developed in predilection sites for AD; at follow-up evaluations years after the incriminated food was eliminated from the diet, skin reactions in children who remained sensitive generally consisted of urticarial lesions. Both immediate and late-phase effects of ingested food allergens have been described during DBPCFC, with some patients developing diffuse pruritus and, less frequently, an erythematous macular rash 4 to 8 hours after a positive challenge.2,15,31 When an appropriate elimination diet is undertaken in food-allergic children with AD, significant improvement has been documented in their skin symptoms, compared with food-allergic children with eczema who are not on an appropriate elimination diet or who have AD without evidence of food allergy.15 However, double-blind dietary intervention studies are needed to determine further the efficacy of elimination diets in the treatment of AD.

Laboratory evaluations of patients with AD have provided additional evidence for the role of IgE-mediated hypersensitivity in the pathogenesis of this illness. The immunohistochemical analysis of chronic lesions of AD reveals infiltration with predominantly CD4-positive T cells, Langerhans’ cells bearing high-affinity receptors for IgE, mast cells, eosinophils, and eosinophil granule products. One explanation for the development of this infiltrate is that it represents the chronic stages of a late-phase response after the IgE-mediated immediate-phase allergic response. However, other IgE-mediated mechanisms are likely to play a role, because cutaneous Langerhans’ cells also bear high-affinity IgE receptors and these cells can elaborate cytokines that activate T cells. Evidence supporting the immunopathogenic role of IgE-dependent, food-allergic reactions in the development of cutaneous symptoms that may exacerbate AD include the sharp rise in plasma histamine and the rise in serum levels of eosinophil granule products and eosinophil activation markers accompanying positive food challenges. Biopsies obtained at the site of the morbilliform eruption 10 to 14 hours after a positive DBPCFC revealed eosinophil infiltration and deposition of eosinophil major basic protein, cells, and cellular products capable of promoting the inflammatory response. Using skin blister chambers, it was shown that the T cells infiltrating the skin are enriched for the cutaneous lymphocyte-associated (CLA) antigen, whereas lung T cells were CLA-negative. Interestingly, when the peripheral blood lymphocytes of AD patients with cow’s milk sensitivity were stimulated in vitro with cow’s milk antigen, there was a marked increase in proliferation of CLA-positive T cells not seen in patients with milk allergy without AD. Another mechanism believed to play a role in AD involves the generation of a cytokine called histamine releasing factor from mononuclear cells that results, in vitro, in increased spontaneous basophil histamine release. The spontaneous release of this cytokine was documented in food-allergic children with AD who were not on elimination diets and was shown to decrease to baseline values when the children were maintained on appropriate elimination diets for 6 to 9 months.

Thus, both clinical and laboratory evidence support a role for IgE-mediated food hypersensitivity in some patients with AD. The population studied by Sampson and McCaskill2 had severe AD and was selected on the basis of possible food allergy. Burks and colleagues sought to overcome this selection bias by recruiting patients from both a dermatology clinic and an allergy clinic, but the 33% prevalence rate of food allergy found in that study has been questioned because two thirds of the patients were referred to a pediatric dermatologist for AD. Despite the elimination of the selection bias inherent in the study by Burks and colleagues, we found a similar prevalence rate (37%) of food allergy among children with AD.

A study by Guillet and Guillet suggested an increased prevalence of food allergy among patients with increasing severity of AD. However, we did not detect a difference in the prevalence of food allergy in relation to severity of AD in our population; patients with and without food allergy had similar SCORAD scores. We may not have been able to detect a correlation of food allergy because of the smaller population studied and the selection of patients predominantly with moderate to severe symptoms.

There were several factors in the current study that actually may have caused an underestimate of the prevalence of IgE-mediated food allergy in children with AD. First, screening patients with the CAP-System FEIA to six foods may have missed 10% to 15% of patients in whom some other food would have elicited a positive T cell response. Another factor is that some patients developing diffuse pruritus and, less frequently, an erythematous macular rash 4 to 8 hours after a positive challenge.

**TABLE 3.** Sensitivities of the 23 Food-allergic Children to Major Food Allergens

<table>
<thead>
<tr>
<th>Method of Determination</th>
<th>Peanut</th>
<th>Egg</th>
<th>Milk</th>
<th>Wheat</th>
<th>Soy</th>
<th>Fish</th>
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<tbody>
<tr>
<td>Challenge positive</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>History positive, IgE-positive</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>History positive, CAP-RAST more than 95% predictive</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CAP-RAST more than 95% predictive</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>16</td>
<td>14</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4 of 6  IgE-MEDIATED FOOD ALLERGY AMONG CHILDREN WITH ATOPIC DERMATITIS

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have been implicated. Second, 10 patients with indeterminate but positive CAP values were not evaluated fully and therefore considered not to be food-allergic. Third, 4 patients considered to have negative evaluations did not complete challenges to all of the foods to which they had food-specific IgE antibodies. Finally, we included children >5 years of age, a group that is likely to have a lower prevalence of food allergy than do infants and toddlers. Thus, a prevalence rate of 37% for food allergy in AD is conservative and probably represents an underestimate.

Considering that there are many triggers for AD, including both specific (aerallergens, food allergens, and staphylococcal enterotoxins) and nonspecific (heat, humidity, irritants, and stress) triggers, the question of which child should be evaluated for food hypersensitivity arises. Given a prevalence rate of 25% to 50%, an evaluation for food allergy may be warranted in any AD patient requiring chronic treatment or responding poorly to a regimen of hydrating baths, topical corticosteroids, lubricating ointments, antihistamines, and antibiotics. Certainly, if the patient has a history of an acute, life-threatening reaction to a food, appropriate measures should be taken to confirm the allergy and provide information on food-allergen avoidance and emergency management in case of accidental ingestion. Additionally, patients with associated atopic illnesses may require additional allergy evaluation.

In addition to studies suggested by information gleaned from history, a reasonable approach for screening children with poorly responsive AD for IgE-mediated food allergy would include prick skin testing to the major food allergens and any other suspected foods. Foods eliciting positive responses could be evaluated with open or single-blind challenges to exclude clinical reactivity, but must be performed in a setting where severe reactions, including anaphylaxis, can be treated. Alternatively, quantitation of food-specific IgE levels (CAP System FEIA) could be performed. Positive and negative predictive values for four foods have been established that can help determine who may ingest the food safely and who is likely to react. For those with indeterminate values, challenges should be performed. Open oral food challenges are less labor-intensive and resulted in a similar proportion of positive and negative results as the DBPCFC in this study. However, if a patient appears to be allergic to more than one major food (egg, milk, wheat, soy) or a large number of other foods, DBPCFC should be performed to confirm reactivity. Strict avoidance of the food is the only treatment currently available. The guidance of a dietitian often is required to ensure complete elimination of all hidden sources of food proteins and the nutritional adequacy of the diet. Studies suggest that strict avoidance results in improvement of skin symptoms and also may speed the acquisition of tolerance. Children typically outgrow their clinical reactivity to egg, milk, wheat, and soy (despite persistently positive skin tests), whereas clinical sensitivity to peanuts, tree nuts, fish, and shellfish is often life-long.

Ultimately one third of patients will outgrow their reactivity after 1 to 2 years of allergen avoidance, serial evaluations are an important part of follow-up.

In conclusion, a significant percentage (37%) of patients referred to a university-based pediatric dermatologist for AD have symptomatic food allergy. An evaluation for food allergy should be considered in patients with refractory, moderate to severe AD and in patients with a history of acute allergic reactions. Studies are underway to address further the efficacy of food allergen elimination in the treatment of AD.

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REFERENCES


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Philippe A. Eigenmann, Scott H. Sicherer, Teresa A. Borkowski, Bernard A. Cohen and Hugh A. Sampson

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