

Atopic dermatitis and food hypersensitivity reactions

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Objective: To determine the role of food hypersensitivity in atopic dermatitis and to determine whether patients with atopic dermatitis who had food hypersensitivity could be identified by screening prick skin tests using a limited number of food allergens.

Study design: Patients with atopic dermatitis attending the Arkansas Children's Hospital Pediatric Allergy Clinic underwent allergy prick skin testing to a battery of food antigens. Patients with positive prick skin tests underwent double-blind, placebo-controlled food challenges.

Results: One-hundred sixty-five patients were enrolled and completed the study. Patients ranged in age from 4 months to 21.9 years (mean 48.9 months). Ninety-eight (60%) patients had at least one positive prick skin test. A total of 266 double-blind, placebo-controlled food challenges were performed. Sixty-four patients (38.7% of total) were interpreted as having a positive challenge. Seven foods (milk, egg, peanut, soy, wheat, cod/catfish, cashew) accounted for 89% of the positive challenges. By use of screening prick skin tests for these seven foods we could identify 99% of the food allergic patients correctly.

Conclusions: This study confirms that most children with atopic dermatitis have food allergy that can be diagnosed by a prick skin test for the seven foods. (*J Pediatr* 1998;132:132-6)

Most investigators agree that atopic dermatitis is a complex multifactorial disease, but the role of allergy is controversial.¹ In particular, no consensus exists concerning the role of food allergy in the etiology of AD.² Several factors suggest a role for IgE-mediated hypersensitivity in the pathogenesis. Most patients have a history of atopic disease; 50% eventually have asthma, and 80% have asthma or allergic rhinitis.^{3,4} In addition, approximately two thirds of patients have a positive family history for atopy.⁵ Increased serum IgE concentrations

are found in 80% of these children, with most having positive immediate skin test reactions to various dietary and environmental allergens.^{5,6} Elucidation of the late-phase IgE response has provided further information linking abnormal production of IgE and AD.⁷⁻⁹

Sampson^{10,11} demonstrated that food hypersensitivity plays a pathogenic role in a significant number of children who have AD and that appropriate identification of food hypersensitivity and subsequent exclusion diets can lead to significant improvement. Because many of these patients were specifically referred for evaluation of suspected food allergy, the true prevalence of food hypersensitivity and AD continued to be debated.

To address this long-standing controversy we undertook an initial study¹² examining the prevalence of food hypersensitivity in patients who were evaluated in a pediatric allergist's office. This study

documented that approximately 30% of children with varying degrees of AD had food hypersensitivity. In general, these patients were not specifically referred for studies concerning adverse food reactions. This study further supports the previous evidence that food hypersensitivity can play a significant role in some patients with AD. An additional aim of this study was to determine whether we could identify any patient with AD who had food hypersensitivity by use of skin prick tests with a limited number of food allergens.

AD	Atopic dermatitis
DBPCFC	Double-blind placebo-controlled food challenges

METHODS

Patients

Patients who met the criteria¹³ for the diagnosis of AD were enrolled in the study. The dermatitis ranged from mild to severe. The patients were from the Pediatric Allergy Clinic at Arkansas Children's Hospital; approximately 50% of patients receive their medical care entirely at the hospital (inner-city population), and 50% are referred (for their AD or other allergic diseases) from primary care physicians in Little Rock and central Arkansas. Parents were informed about the study on their initial visit. All studies were approved by the University of Arkansas for Medical Sciences Human Research Advisory Committee. Only patients available for follow-up and food challenges were invited to participate (> 90% of available group).

Skin Tests

On entry into the study a detailed medical history and physical examination were obtained. All patients underwent al-

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lergy prick skin tests with a battery of at least 12 food antigens, plus other foods the parents thought caused symptoms. The antigens were standardized glycerinated extracts at a 1:20 (wt/vol) concentration (Greer Laboratories, Lenoir, N.C.). Mean diameters of erythema and wheal reactions were recorded. Wheal reactions 3 mm greater than the control reaction (glycerinated saline) were considered positive.¹⁴

Food Challenges

On the basis of prick skin test results, patients and their parents were asked to eliminate the suspected foods for 2 to 3 weeks before the double-blind, placebo-controlled food challenges. The challenges were done in the Arkansas Children's Hospital outpatient clinical research unit. Patients discontinued antihistamines for 7 days before the food challenge and β -agonists 12 hours before the challenge. No patients received oral corticosteroids within 1 month of the challenges.

The DBPCFCs were performed as outlined previously.^{10,14} Briefly, up to 10 gm of dehydrated food was administered in juice over 1 hour. Two challenges were performed each day, one at approximately 8:30 AM and the other at 12:30 PM. One of the challenges consisted of the suspected food, and the other of a placebo (sucrose or corn starch). All foods were obtained and prepared by the Clinical Nutrition Department of Arkansas Children's Hospital. The sequence of challenges was randomized so that patients, parents, nursing staff, and investigators were unaware of the contents of the challenges. The sequence code was broken after the challenge but before the patients left the research unit. The food was then fed to the patient in normal proportions. No child with a convincing history of a major anaphylactic reaction (i.e., major life-threatening systemic reaction) to a specific food was challenged with that food.

All reactions were recorded and scored as to type, time of onset, severity, and duration using a standardized scoring sheet as previously described.¹⁰

Statistical comparisons were performed with the Wilcoxon rank sum test.

Table I. Skin test and DBPCFC results in 165 patients

	Median age of onset (mo)	% Body involved	Symptom score
Skin test (+)	2*	15	8.5
DBPCFC (+) (n = 64)	(0.5-247)	(0-100)	(0-17)
Skin test (+)	3.5	13	8
DBPCFC (-) (n = 34)	(0.5-156)	(0-100)	(0-16)
Skin test (-) (n = 67)	7*	19	8
	(0.5-120)	(0-100)	(0-18)

DBPCFC, Double-blind, placebo-controlled food challenge.
Percent body involved and symptom score on initial presentation.
*p = 0.003 using Wilcoxon rank sum test.

RESULTS

Entire Group (Group 1)

One hundred sixty-five patients (91 males) were enrolled and completed the study from 1986 through 1995. Patients ranged in age from 4 months to 21.9 years (mean age 48.9 months). The mean age of onset of dermatitis was 16 months (range birth to 20.5 years). The family history was positive for atopic disorders (allergic rhinitis, asthma, or AD) in 92% of the patients. Forty-nine (30%) children had asthma, 84 (51%) had allergic rhinitis, and 37 (22%) had both allergic rhinitis and asthma. Before the food challenge, 25% of the patients or their families believed that foods contributed to the dermatitis.

Of the 2061 prick skin tests to foods performed, 323 (15.6%) yielded positive reactions. Ninety-eight (60%) patients had at least one positive food prick skin test and 67 (40%) patients had all negative food prick skin tests. One-hundred five (22 of the 105 were considered positive because of a history of anaphylaxis) of the 323 positive prick skin tests were considered to be clinically significant because of a positive food challenge. Compared with those patients without a clinically significant positive skin test reaction, the patients with positive prick skin tests to foods that were confirmed with a positive DBPCFC had a statistically significant lower age of onset, but the percent body involvement and symptom scores at initial presentation were not significantly different (Table I).

Double-blind Placebo-controlled Food Challenges

A total of 266 DBPCFCs were performed; 83 were interpreted as positive with 22 additional challenges considered positive because of a history of anaphylaxis in 64 patients (38.7% of total). Thirty-four patients (20.6%) with positive food skin test reactions had negative DBPCFCs. These results of the prick skin tests showed that a positive skin test had 100% sensitivity, 66% specificity, 65% positive predictive value, and 100% negative predictive value. The onset of symptoms occurred within 2 hours of ingesting the food antigen in all cases. No significant delayed food reactions were observed. Skin symptoms, which consisted of a diffuse erythematous macular or morbilliform rash and pruritus, were seen in 78% of positive challenges. Isolated cutaneous symptoms were seen in approximately half of the positive reactions. Gastrointestinal symptoms, which included nausea, abdominal pain, emesis, or diarrhea, occurred in 27% of the positive challenges; only six (7%) patients had isolated gastrointestinal symptoms. Respiratory symptoms, including wheezing, severe nasal congestion, coughing, or sneezing, developed in 13%.

Foods

Although multiple food allergens were used in the study, seven foods (or groups) (milk, egg, peanut, soy, wheat, cod/catfish, cashew) accounted for 89% of the positive challenges (Table II). Most children had multiple positive prick skin

Table II. Results of prick skin tests to foods and challenges

Food	Positive prick skin test	No. of challenges	Positive challenges
Peanut	55	44	27 (10)
Milk	31	28	14 (3)*
Egg	57	56	33 (0)
Wheat	13	13	5 (0)
Soy	21	19	3 (0)
Cod	11	9	3 (2)
Catfish	8	4	4 (3)
Cashew	16	9	4 (1)
Chicken	17	16	2 (0)
Kidney bean	6	5	2 (1)
Tomato	2	1	1 (1)
Beef	13	12	1 (0)
Black-eyed pea	13	9	1 (0)
Navy bean	9	5	1 (0)
Green pea	7	6	1 (0)
Shrimp	1	1	1 (0)
Green bean	5	4	0 (0)
Pork	11	7	0 (0)
Lima bean	8	5	0 (0)
Corn	9	7	0 (0)
Chocolate	6	3	0 (0)
Potato	2	1	0 (0)
Banana	1	1	0 (0)
Mustard	1	1	0 (0)

*Values in parentheses are numbers by history.

tests (mean 1.9, range 0 to 13). Of the children completing the challenges, 31 (48%) reacted to one food, 23 (36%) reacted to two foods, and 9 (14%) reacted to three foods (only 1 patient reacted to four foods). Despite some patients having positive prick skin test reactions within the same botanical family, there were few instances of patients reacting in DBPCFC to two related foods (one patient reacted to milk and beef, one patient reacted to chicken and egg, and three patients reacted to peanuts and another legume). There was only one false-positive response to placebo (skin symptoms).

Group of Seven Major Foods (Group 1a)

To further delineate the role of a specific, limited group of foods that may be involved in the pathogenesis of AD, we chose to examine patients as a subgroup that had prick skin tests and completed challenges to milk, egg, peanuts, soy,

wheat, cod/catfish, and cashew (tree nut). These specific foods represent most food allergens causing food hypersensitivity reactions. Our aim was to determine whether prick skin testing to a limited battery of food allergens would identify all patients that would eventually be diagnosed with a food hypersensitivity reaction. There were 163 patients in this defined subgroup of patients (Group 1a). Patients ranged in age from 4 months to 21.9 years (mean age 43.23 months). The mean age of onset of the dermatitis; the percentage of patients with a positive family history for asthma; and the percentage of patients with asthma, allergic rhinitis, or both were not different from the total group (Group 1) noted above. Ninety-six (59%) patients had at least one positive prick skin test to the battery of seven food allergens and 67 (41%) had all negative food prick skin tests. The skin test results showed that a positive skin test had 97% sensitivity, 61% specificity, 61% positive predictive

value, and 97% negative predictive value. Seventy-seven (20 by history) (35%) of the 219 positive prick skin tests were considered to be clinically significant because of a subsequent positive food challenge.

Sixty-three (six of those were considered positive because of an anaphylactic history) patients (38.6% of the total) had at least one positive DBPCFC. Thirty-nine patients (24% of total) with positive prick skin test reactions had negative DBPCFCs. The percentage of patients with skin symptoms (77%), gastrointestinal symptoms (25%), and respiratory symptoms (14%) were not different from Group 1.

Finally, we wanted to use these seven foods as a screen to, if a patient had negative prick skin tests to determine, if this screening battery of food allergens or a positive prick skin test to one of the seven foods but a negative food challenge, whether he or she would have any additional foods that would produce a positive challenge. Only two patients (1% of 163 total patients) had a positive prick skin test and positive food challenge to another food (not included in these seven foods). These two patients had a positive food challenge to chicken and kidney bean, respectively.

DISCUSSION

Despite recent evidence supporting the clinical significance of food allergy in children with AD, this issue continues to be debated. In the studies by Sampson,¹⁵ > 60% of children with moderate to severe AD had positive food challenges. The interpretation of these studies for the primary care practitioner, however, has been difficult because of the severity of the AD. Overall, ~75% of these patients had used systemic steroids on at least one occasion before entering their study. In our original study¹² and in this larger and more comprehensive study, we chose to study patients with varying degrees of AD in a pediatric allergy practice.

This study confirms that a significant number of children with AD do have positive food challenges. In our group of patients with mild to severe AD, 39% had

positive DBPCFCs. The patients who had positive food challenges were significantly younger at the time of onset of their AD, but they did not necessarily have a greater percentage of skin involvement or a higher symptom score. In addition, we could identify 99% of the patients with AD who would have positive food challenges by first screening with prick skin tests to a limited number of food allergens.

Several studies over the past 50 years have suggested that foods might play a role in exacerbations of AD.^{16,17} Because many of these reports were uncontrolled case studies, their application and clinical significance were questioned. Using more rigorous scientific methods, Bock et al.^{18,19} outlined the DBPCFC as the appropriate scientific method to evaluate and to confirm a suspected adverse food reaction. Their studies included several children with AD who experienced skin symptoms after positive food challenges. More recent studies in a subset of patients with AD have confirmed that food hypersensitivity reactions will cause an exacerbation in skin symptoms.¹⁵

The late-phase IgE response is the proposed mechanism by which adverse food reactions exacerbate skin symptoms in patients with AD. In the late-phase IgE response 2 to 4 hours after the ingestion of the offending antigen, a progressive accumulation of eosinophils and neutrophils reaches a maximum concentration at 6 to 8 hours.^{20,21} As the reaction continues 24 to 48 hours later, fibrin deposition and a mononuclear round cell infiltrate are present.^{8,9} A biopsy specimen of the experimental late-phase IgE response is indistinguishable from a biopsy specimen of involved skin in patients with AD.

A number of recent studies indicate that IgE-mediated mechanisms contribute to exacerbations of AD.^{15,22-25}

Although the exact cause of AD remains elusive, it is known that multiple factors exacerbate the disease.¹ Extreme heat or cold, staphylococcal skin infections, aeroallergens, and stress are known trigger factors.¹ With the proposed mechanism of adverse food reactions causing significant changes in skin symptoms in some patients with AD, it is certainly feasible that the clinical improvement in any

one child will vary depending on the degree that food hypersensitivity is present in that child. Sampson's natural history study following a group of children for 5 years clearly demonstrated that children with AD and food hypersensitivity on an appropriate elimination diet improved significantly.¹⁵

In most studies, the history of possible food sensitivity has been of little value in predicting whether a patient would have a positive reaction to a food challenge.¹⁴ This information underscores the fact that a food elimination diet based solely on the medical history will be inadequate. Studies have shown that elimination diets without guidance by prick skin testing are of no value in improving skin symptoms.^{26,27} Factors complicating the historical information include the fact that milk, egg, wheat, and soybean sensitivity are often outgrown in the first few years after diagnosis.¹

It appears reasonable to suggest that any child who has AD unresponsive to routine therapy of bathing followed by lubricating creams or ointments, topical corticosteroids, antihistamines, and antibiotics should be evaluated for food hypersensitivity. Children who respond to this routine therapy but continue to need daily treatment after several months should also be screened for food hypersensitivity.¹²

The best initial approach to screening is the use of an open or single-blind food challenge directed by prick skin tests.² In vitro techniques (RASTs) to determine which foods should be avoided are no better than prick skin tests, nor do they add anything to the diagnostic capabilities.²⁸ Patients with more than three positive food challenges may benefit from undergoing a DBPCFC to confirm the results. Screening for food hypersensitivity should include the following food allergens: milk, eggs, peanuts, wheat, soybeans, fish, and tree nuts. Although food challenges can easily be done in an office setting, the risk remains significant if patients are challenged at home. Because longitudinal studies demonstrate that approximately one third of patients lose their sensitivity, repeat challenges are a necessary part of clinical follow-up.^{2,15}

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