

Does food allergy cause atopic dermatitis? Food challenge testing to dissociate eczematous from immediate reactions

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ABSTRACT: The objective is to evaluate and diagnose, in a controlled setting, suspected food allergy causation in patients hospitalized for management of severe, unremitting atopic dermatitis (AD). Nineteen children were hospitalized at Oregon Health and Science University with atopic dermatitis from 1986 to 2003 for food restriction, then challenge, following standard recommendations. Challenges were prioritized by categories of (a) critical foods (e.g., milk, wheat, egg, soy); (b) important foods; and (c) other suspected foods. Patients were closely observed for evidence of pruritus, eczematous responses, or IgE-mediated reactions. If results were inconsistent, double-blind, placebo-controlled food challenge was performed. A total of 17 children with atopic dermatitis were assessed. Two could not be fully evaluated, thus were excluded from data tabulations. Only one positive eczematous food response was observed of 58 challenges. Three children had well-documented histories of food-induced IgE-mediated anaphylactoid or urticaria reactions to seafood and/or nuts and were not challenged with those foods. Atopic dermatitis, even in the highest-risk patients, is rarely induced by foods. Undocumented assumptions of food causation detract from proper anti-inflammatory management and should be discouraged. Immediate IgE-mediated food reactions are common in atopic dermatitis patients; such reactions are rapid onset, typically detected outside the clinic, and must be distinguished from eczematous reactions. Diagnosis of food-induced eczema cannot be made without food challenge testing. Such tests can be practical and useful for dispelling unrealistic assumptions about food allergy causation of atopic dermatitis.

Introduction

Atopic dermatitis (AD) is a common disease, especially in pediatric populations (1). It can cause severe morbidity in children and disrupt family dynamics. Several studies in recent years agree that the prevalence of AD has increased greatly in the past four decades and may exceed 10% in infants (2–4). Many children grow out of

their AD, although for the unfortunate ones, especially those with severe disease, the problems may be lifelong. There is considerable confusion and controversy in the literature over the role food allergy has to play in the etiology of AD. For nearly 90 years, concepts of food-induced eczema have been inferentially conditioned by amplification of rare case reports in children with AD (5,6). Further misapprehensions occurred from articles selectively citing positive effects of elimination diets (7,8), whereas failing to cite more convincing negative reports (9,10). A major aspect of the controversy-generating confusion centers on imprecise definitions of terms such as “atopy,” “allergy,” and “hypersensitivity.” Sampson and others have applied scientific techniques to diagnosing food

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hypersensitivity in children with AD using endpoints focused mainly on rapid IgE-mediated mast cell and basophil reactions (11–15). None have dealt specifically or convincingly with the eczematous responses that characterize AD.

Well-accepted concepts note the eczematous nature of lesions and emphasize the role of cellular immunity and T cells (16–19) challenging the long-held assumptions of mast cell involvement (20,21) in the pathogenesis of AD. This newer understanding requires better definition and precision when using terms such as “food allergy” and “food hypersensitivity,” both of which are used to imply food-induced AD, with no basis in fact. In AD, immune and inflammatory cells, including IgE-producing B cells and histamine-releasing cells, are functionally hyper-reactive (22). Such dysregulation, along with increased skin absorption of food allergens (23), helps to explain the high frequency of skin test responses and why IgE/mast cell-mediated food allergy reactions are frequently superimposed on the eczematous disease. This more comprehensive view of pathogenesis has not yet been translated to the clinical setting where food allergy is still inferred as causative of AD rather than a parallel occurrence.

Food allergy is considered to be more prevalent in children with severe disease, and the foods often implicated include milk, eggs, wheat, soy, peanut, and seafood (11,24). These foods are ubiquitous components in the majority of meals and important sources of essential nutrients for the growing child. Preventing further morbidity from AD demands that the present authors improve physician/patient understanding of eczematous flares, avoid unnecessary elimination of vital foods, and keep focused on proper skin therapy. Frequently the diagnosis of food allergy is questionable and therapeutic efforts are actually misdirected (10,25). The present report illustrates results of a practical approach to clinically evaluate food allergy concerns and to help clarify the distinction between food-induced AD and “food allergy.”

Method

The aim of this study was to evaluate and diagnose, in a controlled setting, suspected food allergy causation in patients hospitalized for AD. All patients had severe AD, refractory to multiple therapies, and had been referred to Oregon Health and Science University (OHSU) for evaluation and management. Some, especially those

from other states, were admitted directly, whereas others were initially managed with outpatient regimens and subsequently hospitalized because of recalcitrant skin disease. The inpatient regimen essentially followed recommendations developed by Sampson (12). Patients were asked to omit the foods most commonly associated with food allergy (eggs, milk, wheat, soy, peanut, fish), as well as personally suspected allergenic foods, for 1 week before hospitalization. All children (≤ 16 years of age) hospitalized for AD during the period 1986 and 2003 were enrolled in this study. AD was defined by standard criteria (26). The patients' inpatient and outpatient charts were reviewed to tabulate data.

Patients were also asked to withhold antihistamine treatment for 1 week prior to admission to preclude interference with any needed skin testing. Patients were admitted to an air-conditioned, low-allergen environment and put on a “rare foods” (i.e., foods rarely consumed and rarely allergenic) diet restriction consisting of lamb or turkey, rice, rare fruits, and rare vegetables. Inpatient management consisted of twice daily baths followed immediately by 0.1% triamcinolone ointment, emollients, and oral antibiotics (usually cephalosporin or dicloxacillin) if there were signs of skin infection.

After 24–48 hours, when skin inflammation had subsided, open food challenges were introduced daily at 8:00 a.m. and 1:00 p.m. Foods that, by history, had provoked urticaria or anaphylactic symptoms were not challenged. Hospitalizations were usually limited to 5 to 7 days. Thus, the foods selected for challenge were carefully prioritized by categories: (a) critical foods (milk, wheat, egg, soy), selected because they are ubiquitous dietary staples, present in most food preparations and thus difficult for patients to avoid; (b) other important foods (chicken, pork, beef, green vegetables, potatoes, citrus); and (c) other suspected allergens. Seafood and nuts, foods frequently associated with anaphylactic reactions and not essential for a balanced diet, were excluded from testing. At least 30 g of food was given at each challenge. Patients were observed during the 2-hour interval after challenge and a dermatologist evaluated for signs of increased itching or inflammation. A positive food challenge was defined as objective evidence of erythema, papulation, or wheal formation, or by evidence of increased and widespread pruritus within 2 hours of food ingestion (12). Gastrointestinal and respiratory reactions to food challenge were also sought. Foods associated with a positive skin response were withdrawn

and rechallenged 1 to 2 days later. If results were inconsistent, double-blind placebo-controlled food challenge was performed (12). If challenge tests were negative, the foods were added into the diet for subsequent meals, providing a continuous rechallenge. In some instances, serum IgE levels, radioallergosorbent tests (RAST), and skin prick tests (SPT) were performed. Generally these studies had been performed previously by allergy consultants and provided some guidance on food challenge priorities.

Results

Study populations

A total of 19 children with AD were hospitalized and food challenged between 1986 and 2003. Two children were eliminated from the study because they were not placed on the rare foods diet and food challenge (one child because of infectious isolation, and the other because the parent felt their allergist had previously evaluated for food allergy). This provided 17 children for study. The demographics and allergic features of study patients are summarized in Table 1.

Food challenge

A total of 91 food challenges were performed, of which 52 were to critical foods (egg, milk, wheat, soy) (Table 2A). All 17 patients were challenged to at least one of the critical foods (milk, wheat, egg, soy). Fifteen children received food challenge with eggs (Table 2A). All tolerated the egg challenges with no exacerbation of the AD or any other reaction. Seventeen children were challenged to milk (Table 2A). Within half an hour of taking milk,

Table 1. Demographic and allergic features among 17 children with atopic dermatitis

Age range/ median	Serum IgE (IU/mL)	No. of patients with positive RAST to foods	No. of patients with positive SPT to foods
1.5–16	<i>N</i> = 11 Mean = 2016 Range = 104–11,580	<i>N</i> = 5 3	<i>N</i> = 8 4

N, number of patients on which test was performed.
SPT, skin prick test.

Table 2a. Challenge tests to critical foods

Foods challenged	No. of patients challenged (<i>N</i> = 17)	No. of patients with positive challenge	No. of patients with positive rechallenge
Eggs	15	0	ND
Milk	17	1	1/1
Wheat	16	1	0/1
Soy	4	0	ND

N, number of patients in each study group.
ND, rechallenge not done.

Table 2b. Challenge tests to important foods

Foods challenged	No. of patients challenged (<i>N</i> = 17)	No. of patients with positive challenge	No. of patient with other reactions
Chicken	8	(1) ^a	0
Pork	4	0	0
Beef	8	0	0
Fish	1	0	0
Green vegetables	1	0	0
Potatoes	1	0	0
Citrus	2	0	0

N, number of patients in each study group.
^aPatient A, same patient reactive to milk.

patient A, an 18-month-old infant, developed pruritus and generalized papulation consistent with an eczematous reaction. These signs subsided within one and a half hours. Open rechallenge was difficult because the child refused milk, so double-blind placebo-controlled milk rechallenge was performed. The child again developed papulation and increased pruritus approximately 1 hour after the milk rechallenge; most symptoms subsided within 2 hours but increased evidence of dermatitis persisted. Interestingly, this patient had a negative SPT to milk, suggesting this may have been independent of IgE. All other patients challenged to milk experienced no reaction.

Sixteen children were challenged to wheat (Table 2a). Patient B developed a fine papular eruption over the trunk after wheat challenge, but on rechallenge, there was no reaction. He was able to continue eating wheat products and the skin remained clear. Previous SPT to wheat was negative. All the other patients challenged to wheat tolerated its introduction to the diet without any reactions. Four children were challenged to soy (Table 2a) and both tolerated it with no change in their condition.

Table 3. Challenge tests to other foods suspected by patients and parents

Foods challenged	No. of patients challenged (N = 17)	No. of patients with positive challenge 0–16 years
Corn	2	a
Green beans	4	0
Tomatoes	3	0
Banana	0	0
Cheese	1	0
Mayonnaise	0	0
Ketchup	0	0
Chocolate	4	0

N, number of patients in each study group.

^aIncreased pruritus occurred 5 to 6 hours following ingestion of corn; not deemed positive.

Table 2b shows the number of patients challenged to important foods, considered by the patients as necessary or desirable in their diet (chicken, pork, beef, fish, green vegetables, potatoes, and citrus). Patient A also experienced an exacerbation of symptoms following challenge to chicken (Table 2b). However, he had already started to flare (after the second positive milk challenge) before this challenge took place, and the reaction was considered uncertain. A rechallenge to chicken could not be performed during the time allowed in the hospital. The SPT was negative to chicken. All the other patients challenged to the important foods experienced no reactions.

Suspect foods that were challenged included corn, green beans, tomatoes, banana, cheese, mayonnaise, ketchup, chocolate, wine, and coffee (Table 3). There were no positive challenges, although one child developed worsening symptoms 6 hours after challenge to corn. This was not considered a positive reaction because so much time had elapsed, allowing for other flare factors and ingestions, and because the effect was fleeting with no eczematous exacerbation. Rechallenge was planned but the patient was discharged before the test could be performed. The SPT was negative to corn.

Allergy testing (SPT and/or RAST) was carried out on 13 of the 17 patients; mostly these had been performed previously by outside allergists and in some the present authors were unable to determine precisely the number of foods tested; thus, the present authors can report only the number of patients tested with either SPT or RAST and the number reported as having one or more positive responses (Table 1).

Table 4. Noneczematous food allergies in patients with atopic dermatitis

Case no.	Age of patient (in years)	Type of reaction	Allergens
1	5	Urticaria	Peanut
2	7	Urticaria	Egg, nuts, seafood
3	8	Urticaria	Nuts

Table 4. Food allergies in patients with atopic dermatitis

Case #	Age of patient (in years)	Type of Reaction	Allergens
1	5	Urticaria	Peanut
2	7	Urticaria	Egg, nuts, seafood
3	8	Urticaria	Nuts

Mean serum IgE levels were 2016 IU/mL in children, ranging as high as 11,580 IU. These values reflect the severity of AD in these patients.

IgE-mediated food allergy

Three of the 17 patients in this study had histories highly compatible with anaphylactic, IgE-mediated food allergy (Table 4). None were challenged with these foods and all patients had stringently avoided exposure, hence the foods could not be considered etiologically related to the dermatitis.

Discussion

Food allergy causation of AD is often assumed but seldom documented. It is easier and more socially acceptable for parents to say, "My child has allergies," rather than trying to explain eczema. Patients and parents readily accept an unsupported diagnosis of food allergy and are generally conditioned to associate foods with the frequent flares that are characteristic of AD (27). Allergy becomes a surrogate for blame and allows a tangible concept, which often directs therapeutic efforts against AD. The subject of food-induced AD is a longstanding nidus of controversy (11,28,29). Issues include vague, inconsistent definitions, imprecise diagnostic tests, selection bias, and insufficient scientific rigor, along with the inability to truly prevent and control exposure. There is general agreement that food allergy is not relevant in adult AD and the present authors' experience

supports this (19). The frequency of immediate, IgE-related food allergy reactions in children with severe AD is generally accepted as between 30% and 40% of patients with moderate to severe AD. In contrast, food-induced eczema is vanishingly rare, although allergists and pediatricians accept estimates of 30–80% in children (11,29). The reasons for the vast separation of opinion are apparently definitional, with dermatologists requiring evidence of eczematization following food challenge, whereas nondermatologists misinterpret urticarial and morbilliform eruptions.

The major finding in this study was the paucity of food exacerbations in a controlled hospital setting among a selected group of children most prone to food hypersensitivity. The present authors' results also highlight the crucial distinction between food-induced eczematous AD and anaphylaxis-related food allergy. Recognizing this distinction is central to ending controversy and making constructive progress in managing AD. Food allergy is common among young children with AD. They produce inappropriately high quantities and specificities of IgE and they have increased histamine releasability (22). These factors result in exaggerated and wide-ranging immediate hypersensitivity reactions to myriad antigens. Such reactions include positive skin tests, contact urticaria from immune and nonimmune stimuli, food-induced urticaria, gastrointestinal pain, vomiting or diarrhea, and even respiratory symptoms. All are rapid onset and attributable to IgE-mediated mast cell release of mediators (11).

Eczema responses are slower, T cell mediated, and mast-cell independent (16–21). Food-induced flaring of eczematous lesions is most uncommon (29), a fact borne out by the present study. Only 1 of 17 severely involved hospitalized children had worsening of dermatitis after food challenge. These were children with the type of widespread AD unresponsive to all forms of therapy, who are generally recommended and selected for food challenge studies. They would be expected to have the highest frequency of food allergy and all had considered that foods flared their AD. Most of these children had been evaluated by allergists and food causation had been suggested: They had avoided suspect foods, yet the dermatitis was continuous and undiminished. Although the short 5- to 7-day hospital stays did not allow challenge of the whole array of possible food allergens, 101 challenges in 17 children failed to confirm the most suspect food allergens except in a single case. These results are consistent with reports by others (10,25).

Table 5. Reaction patterns related to food allergy in patients with atopic dermatitis

Common:	Immediate reactions
	√ IgE-mediated, rapid onset, brief duration.
	Urticaria Asthma
	Gastroenteritis Rhinoconjunctivitis
	Anaphylaxis
Rare:	Eczematous reactions
	√ T-cell-mediated, subacute, slow onset, prolonged duration.
Uncertain/undocumented:	
	Late-phase reactions
	Delayed food reactions

The present authors' findings support the concept that there are two separate categories of allergic reactivity to foods that can be documented in patients with AD (Table 5). (a) Immediate reactions – common, but unrelated to dermatitis, these IgE-mediated reactions can cause contact urticaria, localized and systemic urticaria, anaphylaxis, gastrointestinal, and respiratory reactions. Thirty percent of the present authors' patients had histories of such reactions, a frequency similar to other estimates (11,13). (b) Eczematous reactions – these may directly worsen AD, but are extremely rare. The present authors avoided challenges with foods to which patients had a history of urticarial or anaphylactoid reactions because of safety considerations and because patients were invariably avoiding such foods. In all such cases, the foods were either nuts or seafood and they are not dietary staples. Most importantly, these foods were clearly not causing the eczema because they were not being ingested.

This is a key practical reality relating to food allergy in most patients with AD. Immediate allergic responses are easily recognized by patients and parents and they simply avoid those foods. Medical intervention and diagnostic studies are usually unnecessary, except to reinforce the need for avoidance. Selection of such patients for research studies guarantees positive results but adds little of practical value for the patient, unless there is a concern about compliance. This concern may be important where allergy to trace contaminants is suspected (especially for milk, wheat, and eggs) and then challenge testing can be helpful to provide proof of the need for careful, strict dietary avoidance (11). In too many instances, the opposite situation prevails and patients are misinformed, often as a result of allergy tests that have

an 80% rate of false-positivity (15). Irrational diet restrictions may ensue, sometimes sacrificing good nutrition, even to the point of obsessive-compulsive disorders such as Meadows syndrome/Munchausen by proxy (30).

In addition to eczematous and immediate food reactions, two other categories have been suggested: late-phase reactions and delayed food reactions. These remain undocumented (Table 5). Late-phase reactivity was long speculated to be a mechanism for food-induced AD but that lesion does not itch, is neutrophil-rich, and has little resemblance to eczema (31). Delayed food reactions likewise remain unconvincingly documented 20 years after Hammar's report, which suggested that AD could flare days after challenge (32). Interpretation of such results is difficult, even in hospitalized patients, because the disease is so labile, making it difficult to precisely assign causation after several days, multiple meals, and various stresses. Bouts of itching and erythema occur randomly each day in response to a variety of autonomic and emotional stresses (33). This interpretation is consistent with the present authors' experience. Some of the present authors' patients had random reactions but symptoms subsided and the patients were able to continue ingesting those foods. One report described delayed reactions in 27% of infants 1 to 2 days after challenge (34). Documentation was questionable, however, because the reactions occurred outside the hospital where AD is even more unstable. Certainly confirmatory studies, focused specifically on infants in a controlled setting, would be of interest. The present authors' patients developed no persistent delayed reactions despite continued food ingestion for 3 to 5 days after challenge in the hospital.

Currently, there are three methods commonly used for diagnosing food allergy: (a) parent/patient observation and history; (b) allergy tests (SPTs, RASTs); and (c) challenge tests. Some European groups have suggested use of the food patch test (34), but a comprehensive study has recently demonstrated this to be unreliable (35). A relevant, clearly described history of anaphylactic symptoms is highly supportive of the diagnosis of food allergy. Allergy tests are never diagnostic by themselves. They are imprecise indicators of IgE-mediated allergy with only about 20% positive predictive accuracy (15). Challenge test is the only objective means of documenting food hypersensitivity; when an open challenge response is considered questionable, double-blind challenge can be used, as in case A.

The present study illustrates the low likelihood of food-induced eczema, even in children with the most severe and suspect forms of AD. The present authors' results confirm the frequent occurrence of IgE-mediated clinical reactions that are not eczema associated (34). Physicians' recognition of the dichotomy between immediate reactions and eczematous lesions can greatly aid patient education, directing emphasis to the more relevant and effective skin care therapy, whereas reducing the risk of iatrogenic nutritional deficiency.

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