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Pediatric Atopic Dermatitis: The Importance of Food Allergens

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Food allergy and atopic dermatitis often occur in the same patients. Food-induced eczema may be perceived as a controversial topic because the immunologic mechanisms have yet to be fully elucidated. Nevertheless, published clinical studies have clearly demonstrated that foods can induce symptoms in a subset of patients with atopic dermatitis. Those at greatest risk are young children in whom eczematous lesions are severe or recalcitrant to therapy. Allergy testing can be helpful but must be applied judiciously. A medical history obtained by a skilled and knowledgeable health care provider is of paramount importance to interpret test results appropriately. Finally, the implementation of proper dietary avoidance can improve symptoms and provide safety from potentially fatal anaphylaxis. However, if inappropriate prescribed, elimination diets can have significant negative nutritional and social consequences.
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The relationship of atopic dermatitis (AD) and food allergy has been a source of controversy. Although most physicians would agree that an increased prevalence of food allergy exists in children with AD, some tend toward the view that food allergy occurs in parallel with AD rather than being a contributory factor.[1]

This is further complicated by the fact that parents often have very strongly held beliefs that various foods cause the eczema instead of other potential environmental factors known to exacerbate AD. Of note, patient history with regard to food allergy is notoriously inaccurate. In fact, when double-blind, placebo-controlled, food challenges (DBPCFCs) are used to establish the diagnosis of food allergy, only approximately 40% of patients' histories of food-induced allergic reactions can be verified.[2-5] Still, the role of food allergy in AD, although not pertinent to all patients, is an important consideration, particularly in children. The following is a review of the clinically relevant literature pertaining to the role of food allergy in AD.

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Atopy in AD

AD is often the first manifestation of the atopic march, as 80% of patients with AD will develop asthma or allergic rhinitis.[6,7] Moreover, approximately two-thirds of patients have a positive family history of atopy.[8] Approximately 80% of patients with AD have increased serum IgE levels (not uncommonly >10,000 IU/mL), and most demonstrate specific IgE antibodies (sIgE) to foods and aeroallergens.[9-11]

Epidemiology of Food Allergy in AD

Multiple studies have established that approximately 35% of children with moderate-to-severe AD have food allergy.[3,12-13] Although oral challenges have been used to demonstrate clinical reactivity to foods in patients with AD, DBPCFCs are considered to be the gold standard to identify causal food proteins. Sampson and coworkers[13-16] performed >2000 oral food challenges in >600 children with AD who were younger than 17 years of age, with 40% of challenges resulting in reactions.[17] Cutaneous reactions occurred in three-fourths of the positive challenges, but isolated skin symptoms were observed in only 30% of reactions. Cutaneous reactions generally consisted of pruritic, morbilliform, or macular eruptions in the predilection sites for AD. Gastrointestinal (50%) and respiratory (45%) symptoms also occurred. In fact, some patients required epinephrine. Reactions to egg, milk, wheat, and soy accounted for almost 75%

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of reactions.[11,12] Other common allergens included peanut, tree nuts, fish, and shellfish.[17] The most frequent cause of food-induced AD is attributed to egg protein, affecting two-thirds of children with AD in one series.[4] Egg allergy (over other food allergens) is also associated with a higher risk of asthma development.[18] Generally, the younger the patient and the more severe the AD, the more likely food allergy is to be a causative factor.[19] In contrast, food hypersensitivity has little, if any, role in adult AD.

Diagnosis

The diagnosis of food allergy in AD is complicated by several factors[14]:

1. Because the food allergen is being introduced repetitively (and unknowingly) into the child's diet, there is a downregulation of the immediate response. Therefore, acute reactions as typified by IgE-mediated hypersensitivity may not necessarily be observed from the causal food protein in patients.
2. Environmental factors, including infections, irritants, heat, and humidity, often play a role in disease flares. Families must be educated with regard to those factors which can obscure the effect of dietary changes, both positively and negatively.
3. Approximately 85% of patients with AD have sIgE to food and inhalant allergens,[6,8] which makes diagnosis based on laboratory testing alone inadvisable.

A complete history obtained should include a general medical history, dietary history, and history of any acute reactions to a particular ingestion. In addition, one should clarify whether the patient has been exposed to the food(s) after the acute reaction and whether there was an observable reaction or change in the skin. Foods not being ingested are unlikely to be playing a role in AD flares. For breastfed infants, a maternal dietary history must also be elicited.

Certainly, if there is a food that by history seems consistently to elicit AD flares, further testing may be warranted to that specific food allergen. If there can be no specific food trigger identified, a rational approach would be to screen for the most common allergens (egg, milk, soy, wheat, peanut and perhaps seafood or tree nuts if those have been introduced in the child's diet).

Before embarking on diagnostic testing for potential food allergy, topical therapy with antiinflammatory medications and emollients should be optimized. Often families of children with AD seek subspecialty care due to treatment failure but perceived failure is frequently due to use of a topical steroid of inappropriately low potency. Effective AD treatment has been shown to decrease significantly the level of parental concern about food reactions,[20] emphasizing the importance of adequately educating families with regard to appropriate therapy, the natural history of AD and trigger avoidance.

Evaluation for Immediate Hypersensitivity

Once it has been established that the child with moderate-to-severe AD is being treated with appropriate topical therapy, further testing may be warranted, particularly if the disease is recalcitrant. Skin prick tests (SPTs) are typically performed in an allergist's office. Antihistamines must be stopped before testing for a sufficient length of time. Different prick/puncture devices are available but the bifurcated needle and lancet have the lowest false positive rate.[21] Food extracts along with a positive (histamine) and negative (saline) control are applied to normal-appearing skin. A response of a 3 mm wheal or greater (associated with a flare or erythema) indicates the presence of sIgE, assuming there is a negative saline response. Larger wheal sizes (>8-10 mm) indicate an even greater likelihood of clinical reactivity.[22] Intradermal testing is contraindicated for food allergens due to its high false positive rate and risk of systemic reactions.

The ImmunoCAP assay (Phadia, Sweden) has been used in previous studies[23-26] to define diagnostic points for certain foods (Table 1).[27] These data curves have been generated for some of the more common food allergens, including egg, milk, peanut, and fish.[23] Greater levels of sIgE do not correlate with severity of reactions but rather with increased probability that the child will react to that food if ingested. Therefore, the 95% predictive values are helpful in determining which patients are at higher risk of developing a reaction with ingestion and in whom oral challenges may not be advisable (Table 1). On the other hand, there are limitations to this assay as patients (up to 20%) may clinically react to a food despite very low or undetectable levels of food sIgE as demonstrated by oral challenges.[23]

Simply establishing the presence of sIgE against allergens, whether measured *in vivo* (SPTs) or *in vitro* (ImmunoCAP assay), does not automatically designate the presence of clinical disease nor does it necessarily confer clinical relevance in a given patient. In general, properly performed SPTs to food allergens have a high negative predictive value (of >95%),[28,29] but the positive predictive value is 30% to 65%.[4,15,28-30] Therefore, a positive test indicates sensitization that may or may not be symptomatic. For example, 8.6% of the U.S. population have positive test responses to peanut,[31] but clinical peanut allergy is estimated to affect 0.4% of the population.[32] Therefore, testing, if undertaken, must be performed with regard to epidemiology and medical history. Screening for a

Table 1 Interpretation of Specific IgE levels (ImmunoCAP Assay): >95% Positive Predictive Value[27]

Allergen	kU_A/L
Egg	7
Infants <2 yrs	2
Milk	15
Infants <2 yrs	2
Peanut	14
Tree nuts	~15
Fish	20

wide panel of foods can result in unnecessary food avoidance for a prolonged period of time with potentially detrimental effects on childhood growth and development. Conversely, the absence of sIgE, in the setting of a highly suggestive history, does not necessarily confer the absence of allergy. Thus, the medical history must be considered before test selection and interpretation.

One may question the role in performing hypersensitivity testing for sIgE for a disease (AD) in which a variety of additional immunoregulatory abnormalities have been described.[33] Burks and coworkers[30] enrolled 165 patients with AD from a university hospital allergy clinic to undergo skin testing to a variety of food antigens. Sixty percent of patients (n = 98) had at least one positive SPT, and these children underwent DBPCFCs after a 2- to 3-week elimination diet. Nearly 40% of patients had at least one positive DBPCFC with onset of symptoms occurring within 2 hours of food ingestion. Interestingly, no delayed food reactions were observed. Among the 266 DBPCFCs performed, cutaneous symptoms (78%) were most commonly reported but gastrointestinal symptoms occurred in 27% and respiratory symptoms developed in 13%. In Sampson's studies,[17] as noted earlier, 59% of patients developed respiratory symptoms. Therefore, there is a risk of anaphylaxis after re-exposure,[34] particularly after a period of food antigen elimination.

Evaluation for Delayed Hypersensitivity

Atopy patch testing is still considered to be investigational for food allergy in patients with AD because there are no standardized reagents or methods of application or interpretation.

Treatment

Elimination of the food allergen is the only proven effective therapy at this time. Strict dietary avoidance is generally recommended once a food allergy is diagnosed. U.S. legislation has facilitated the ability to identify common allergens in foods; the Food Allergen Labeling and Consumer Protection Act (effective January 2006) mandated for "plain English" labeling with regard to ingredients derived from commonly allergenic sources (milk, egg, soybean, wheat, peanut, tree nuts, fish, and crustacean shellfish). If the mother is breastfeeding, she must also eliminate the causal foods from her diet. Educational materials are available through the Food Allergy and Anaphylaxis network (http://www.foodallergy.org) to help families cope with required dietary and lifestyle changes.

Indications for Autoinjectable Epinephrine

As demonstrated by previous studies outlined in this review, children with AD diagnosed with food allergy are at risk of an immediate reaction upon re-exposure to the allergenic food. Because of the difficulty in predicting which patients will develop anaphylaxis after allergenic exposure, it may be advisable to prescribe autoinjectable epinephrine to these patients as antihistamines do not block systemic reactions. Special consideration should be given to those at high risk of developing fatal-food anaphylaxis (Table 2),[35,36] specifically to those with concomitant asthma and/or peanut or tree nut allergy. EpiPen® (Dey, Napa, CA) and Twinject® (Verus, San Diego, CA) are both available in two doses: Jr. (0.15 mg) and regular (0.3 mg). The recommended dose for pediatric use is 0.01 mg/kg body weight. For patients near 30 kg (66 lbs) and greater, a dose of 0.3 mg is appropriate. For children around 15 kg (33 lbs), 0.15 mg is indicated. For very small children (<10 kg) and for those weighing between 15 and 30 kg, the physician must exercise clinical judgment.[37] Even when epinephrine is prescribed, it appears to be underused.[38] Demonstration or training is an important factor in encouraging use of epinephrine autoinjectors.[39] Physicians are advised to verbally counsel patients as well as demonstrate use (with a placebo device) of these autoinjectors.

Table 2 Risk Factors for Fatal Food-Induced Anaphylaxis[35,36]

Asthma, particularly if poorly controlled
Previous life-threatening reaction
Age groups at increased risk of fatality (teenagers, young adults)
Allergen associated with severe reaction (peanut, tree nuts, seeds, seafood)
Lack of immediate access to emergency care

Prognosis

Clinical tolerance can develop over time, more commonly to some foods (milk, egg, soy, wheat) over others (peanut, tree nuts, seafood). More recent retrospective studies from the Johns Hopkins Pediatric Allergy Clinic revealed that rates of resolution for cow milk allergy are 79% by 16 years[40] and for egg allergy 68% by 16 years.[41] In contrast, only about 20% of young children develop tolerance to peanut[42] and less than 10% outgrow allergy to tree nuts.[43]

Prevention of Atopy in Siblings or Offspring

Families often ask how AD or allergy can be prevented in future offspring. The American Academy of Pediatrics published a clinical report in 2008 with recommendations for those infants at high risk of developing atopy.[44] Children at high risk of developing allergy were defined as "infants with at least 1 first-degree relative (parent or sibling) with allergic disease." The following recommendations are evidence-based and specific to prevention of AD:

1. Exclusive breastfeeding for at least 4 months compared with feeding with intact cow milk protein formula decreases the incidence of AD and cow milk allergy in the first 2 years of life.
2. AD may be delayed or prevented by the use of extensively hydrolyzed [ie, Enfamil Nutramigen Lipil; (Mead Johnson Nutritionals, Evansville, IN) or Similac Ali-

mentum Advance; (Ross Products, Columbus, OH)] or partially hydrolyzed formulas [ie, Good Start Supreme; (Nestle USA, Glendale, CA) or Enfamil Gentlease Lipil; (Mead Johnson Nutritionals)], compared with cow milk formula, in early childhood. Extensively hydrolyzed formulas may be more effective in prevention than partially hydrolyzed but at a significantly higher economic cost.

3. There is no role of soy-based formula in allergy prevention. Amino acid formulas have not been studied with regard to atopy prevention.
4. Solid foods should not be introduced before 4 to 6 months of age. There is insufficient evidence to support dietary intervention beyond this age.

These recommendations do not apply to those patients who have already developed an atopic disease such as AD.

In conclusion, dermatologists are advised to refer children with AD in whom they suspect a potential role of food allergy. Approximately 35% of young children with AD have food allergy, particularly in infants and toddlers whose disease is more severe or recalcitrant to therapy. In addition, the stronger the test response (wheal size or sIgE concentration), the more likely there is clinical allergy. However, testing must be applied judiciously. Most importantly, the medical history must be considered to interpret test results appropriately.

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