

Manifestations of Food Allergy in Infants and Children



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Parents frequently report that their children have adverse reactions to foods.¹ Pediatricians must be familiar with the manifestations of food allergy in children to assess which children need further diagnostic evaluation, what evaluation is appropriate, and when a referral to an allergist is necessary.

Adverse food reactions include any abnormal reaction caused by ingestion of a food and can be either due to food intolerance (non-allergic reactions) or food allergy (immune based reactions).

History and knowledge of the manifestations of food allergy are crucial in distinguishing the two disorders.

Food intolerances are often confused with food allergy. Food intolerance is the result of an abnormal physiologic response to an ingested food but is not immunologic in nature. This includes adverse reactions due to unique host factors, such as bloating, abdominal pain and diarrhea with dairy products due to lactase deficiency, abdominal pain with fat ingestion due to gallblad-

der disease, and malabsorption caused by pancreatic insufficiency. Toxic and pharmacologic reactions to food can also cause food intolerances. For example, bacterial food poisoning may cause vomiting and diarrhea, tyramine in aged cheeses may cause headaches, and caffeine in coffee may cause tachycardia and nervousness. Food intolerances are thought to be responsible for most adverse reactions to foods.² In one prospective study of 480 children, 28% were believed to have symptoms produced by food ingestion, but in food challenges only 8% of the reactions were reproducible.¹

In contrast, food allergy is an immunologic reaction that occurs after the ingestion of food. The reaction is unrelated to any pharmacologic effects of the food and may occur even when a very small amount of the offending food is ingested. IgE-mediated food reactions are the best characterized type of food allergy. Still, non-IgE-mediated reactions and mixed IgE- and non-IgE-mediated reactions cause clinically important food allergic reactions that must be considered when a patient presents with an adverse reaction to food. Food allergy can be classified into three categories based on pathophysiology: IgE-mediated, mixed-IgE and non-IgE-mediated, and non-IgE-mediated reactions (see Sidebar 1, page 532). Such distinctions are important as they direct the appropriate testing and treatment.

IGE-MEDIATED REACTIONS

IgE-mediated food allergy occurs when a child fails to develop oral tolerance or there is a disruption in previously established oral tolerance.³ Food-specific IgE antibodies are formed and bind receptors on mast cells, basophils, and other immune cells.⁴ When the child is exposed to a food to which he or she is sensitized, the food aller-

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SIDEBAR 1.

Classification of Food Allergy

IgE-Mediated Reactions

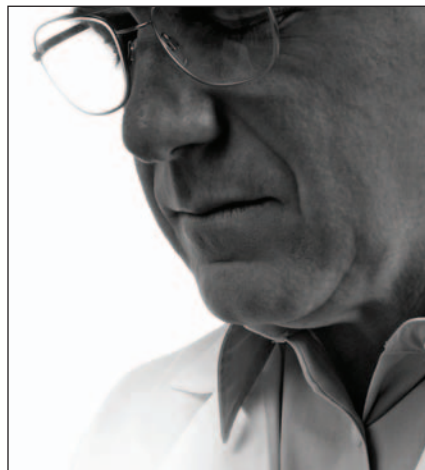
Oral allergy syndrome
(pollen-food allergy syndrome)
Gastrointestinal anaphylaxis
Acute urticaria and angioedema
Anaphylaxis

Mixed IgE/non-IgE-Mediated Reactions

Atopic dermatitis
Allergic eosinophilic esophagitis
Allergic eosinophilic gastroenteritis

Non-IgE-Mediated Reactions

Food protein-induced proctocolitis
Food protein-induced enterocolitis



Milk, egg, peanut, soy, wheat, and seafood are the most commonly implicated foods.

gen binds to the food specific antibodies on mast cells and basophils causing the release of mediators such as histamines, prostaglandins, leukotrienes, and cytokines. Mediator release results in the immediate symptoms of food allergy. In addition, cytokines released by activated mast cells help orchestrate a late-phase allergic response. A late-phase reaction occurs 2 to 8 hours after the immediate phase reaction, even without further exposure to the offending food allergen. Although any food can cause IgE-mediated food allergy, milk, egg, peanut, soy, and wheat account for 90% of reactions in young children, and peanut, fish, shellfish, and tree nut account for 85% of reactions in adolescents and adults.⁵ Virtually every organ system can be affected in an IgE-mediated food allergy (see Sidebar 2, page 533).

Oral Allergy Syndrome (Pollen-food Allergy Syndrome)

In oral allergy syndrome, patients develop pruritus, tingling, and swelling of the lips, palate, and tongue after ingesting fresh fruits and vegetables. Sym-

toms are immediate and usually limited to the mouth, but severe reactions may occur. One study found that 13% of patients experienced laryngeal edema and 2% experienced anaphylaxis.⁶ Allergens in inhalant pollens, typically ragweed and birch tree, share allergenic epitopes with proteins in fresh fruit and vegetables resulting in the symptoms of oral allergy syndrome.

Patients with birch sensitivity often have symptoms with raw carrots, celery, and apples, while patients sensitive to ragweed have symptoms with watermelon, cantaloupe, honeydew, and banana. The allergens responsible for oral allergy syndrome are heat-labile, so symptoms occur with the fresh fruit or vegetable, but not in cooked or processed forms. Thus, a patient with oral allergy syndrome to fresh apple can usually tolerate applesauce and apple pie. Individuals with this syndrome have a history of allergic rhinitis; therefore, onset is not in infancy but rather in childhood.

Gastrointestinal anaphylaxis

Patients with gastrointestinal anaphylaxis develop nausea, vomiting, and abdominal pain usually within minutes, but sometimes up to 1 to 2 hours after ingesting a food allergen. Diarrhea begins within 2 to 6 hours of ingestion. Typically, other organs, such as the skin or respiratory tract, are involved, but isolated gastrointestinal anaphylaxis can occur.^{7,8} Milk, egg, peanut, soy, wheat, and seafood are the most commonly implicated foods.⁹ Isolated gastrointestinal anaphylaxis presents in a similar manner to food protein-induced enterocolitis (FPIES), a non-IgE-mediated food allergy. However, the immediate time course of gastrointestinal anaphylaxis (as opposed to late onset of symptoms in FPIES), the frequent occurrence of other systemic symptoms in association with gastrointestinal anaphylaxis, and the presence of food-specific IgE antibodies in gastrointestinal anaphylaxis helps distinguish the two disorders.

Cutaneous Reactions

Cutaneous symptoms of food allergy include urticaria, angioedema, generalized pruritus, flushing, and an erythematous morbilliform rash. Cutaneous symptoms may be the sole manifestation of a food allergy or may be part of a constellation of symptoms in generalized anaphylaxis. These symptoms typically begin within minutes to 2 hours after ingestion of the offending food and tend to occur every time the food is ingested. (In some cases, baking or boiling the food reduces its ability to trigger reactions.) In children, egg, milk, peanut, and nuts are the foods most commonly implicated in acute urticaria and angioedema.² Chronic urticaria and angioedema (duration of > 6 weeks) are rarely associated with food allergy and more often are caused by autoantibodies to IgE receptors on mast cells and basophils.

Respiratory Symptoms

Allergic rhinoconjunctivitis with periocular pruritus, lacrimation, nasal

congestion, rhinorrhea, and sneezing often occur as part of a generalized allergic reaction, but are rarely the sole manifestation of food allergy. Unless there is a clear and consistent relationship between the ingestion of a specific food and rhinoconjunctivitis, screening for food allergy is not appropriate. In patients with chronic or seasonal allergic rhinoconjunctivitis inhalant environmental allergens, such as tree/grass pollen, mold, dust mites, and pet dander are the allergens most frequently implicated.

Laryngeal symptoms associated with food allergy include pruritus, throat tightness, dysphagia, dysphonia, hoarseness, stridor, and dry “staccato” cough. Bronchospasm with symptoms of shortness of breath, dyspnea, chest tightness, coughing, and wheezing also occurs as part of a generalized allergic reaction to food. Lower respiratory symptoms occur in a minority (15% to 25%) of reactions.^{10,11} In a study of 245 food challenges, wheezing as the sole manifestation of food allergy only occurred in four (2%) challenges.¹² Again, screening for food allergy in patients with persistent asthma with no clear relation of bronchospasm to specific food ingestion is not recommended, as inhalant environmental allergens are most often implicated in these disorders.

Anaphylaxis

Food allergy is the most common cause of anaphylaxis in the outpatient setting.¹³ Anaphylaxis is the most severe form of IgE-mediated food allergy and typically occurs in seconds to hours after ingestion of the offending food. Biphasic reactions have been reported in up to 20% to 25% of adult patients, although one pediatric study found only 6% of cases had a biphasic reaction.^{14,15} The late-phase reaction can be less severe, as severe, or more severe than the immediate-phase reac-



Food allergy is the most common cause of anaphylaxis in the outpatient setting.

tion. Although urticaria and angioedema are among the most common and most easily recognizable features of IgE-mediated food allergy, these manifestations are not universal. In fact, only 82% of children have cutaneous symptoms during an anaphylactic reaction.¹⁶ While any food can cause

anaphylaxis, most severe reactions are caused by peanut, tree nut, fish, and shellfish.¹⁷ In the United States, approximately 150 people die each year from food anaphylaxis.¹⁸

Surprisingly, universal agreement on the definition and diagnosis of anaphylaxis has been lacking until recently. The National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network convened the Second Symposium on the Definition and Management of Anaphylaxis in 2004 and defined anaphylaxis as “a severe, potentially fatal, systemic allergic reaction after contact with an allergen.”¹⁹

Anaphylaxis is considered likely if any one of the following criteria is fulfilled:

1. Acute onset of an illness (minutes to hours) with involvement of the skin and/or mucosal tissue and respiratory compromise and/or reduced blood pressure.
2. Symptoms involving two or more organ systems (skin/mucosal, respiratory, cardiovascular, gastrointestinal) that occur rapidly after exposure to a likely allergen for that patient.
3. Reduced blood pressure following exposure to a known allergen for that patient.

SIDEBAR 2.

Symptoms of IgE-mediated Food Allergy

Oral: pruritus, tingling and swelling of the lips, palate and tongue, metallic taste in mouth

Gastrointestinal: nausea, abdominal pain, cramps, vomiting, diarrhea

Cutaneous: urticaria, angioedema, generalized pruritus, flushing, morbilliform rash

Respiratory:

• Ocular/nasal: pruritus, tearing, nasal congestion, rhinorrhea, sneezing

• Laryngeal: throat pruritus, throat tightness, dysphagia, dysphonia, hoarseness, stridor, dry “staccato” cough

• Lungs: shortness of breath, dyspnea, chest tightness, cough, wheezing

Cardiovascular: feeling of faintness/light headedness, syncope, chest pain, dysrhythmia, hypotension, shock

Neurologic: anxiety, headache, seizure, loss of consciousness

Other: feeling of “impending doom,” uterine contractions

Food-dependent, Exercise-induced Anaphylaxis

There are two forms of food-dependent, exercise-induced anaphylaxis. In the first, anaphylaxis occurs only when exercise follows eating a specific food to which the patient has IgE. In the absence of exercise, the individual tolerates that food without a problem. In the second, anaphylaxis occurs 2 to 4 hours after eating any food if exercise occurs. The mechanism of these disorders is not known but they are often seen in athletic females in their late teens through mid-30s.¹⁴

NON-IGE-MEDIATED REACTIONS AND MIXED REACTIONS

The immune mechanism of non-IgE-mediated food allergy is not well elucidated but likely involves T cell responses to dietary antigens. Non-IgE-mediated responses typically begin several hours or longer after ingestion of offending foods. Some reactions have both IgE- and non-IgE-mediated mechanism (mixed reactions). Allergy skin testing and in vitro tests for IgE are not useful in the diagnosis of non-IgE-mediated food allergy.

MIXED REACTIONS

Atopic Dermatitis

Approximately 35% of children with moderate to severe atopic dermatitis have food allergy.^{20,21} In general, younger patients and those with severe atopic dermatitis that is refractory to medical treatment are more likely to have food allergy as a causative factor.²² Egg is the most frequent cause of food-induced atopic dermatitis, and egg, milk and peanut account for 75% of food allergy in children with atopic dermatitis.¹² Culprit foods can be difficult to identify in the presence of extensive chronic skin lesions. However, after elimination and reintroduction of a culprit food allergen, acute IgE-me-

diated reactions can occur. In a review of more than 2,000 oral food challenges, isolated skin symptoms were seen with food exposures in only 30% of reactions while concomitant gastrointes-

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tinal (50%) and respiratory symptoms (45%) occurred in many children.²³

Allergic Eosinophilic esophagitis and Gastroenteritis

Allergic eosinophilic esophagitis (EE) and gastroenteritis are disorders characterized by infiltration of the gastrointestinal tract with eosinophils. Symptoms depend on the site of involvement. In allergic EE, patients often present with chronic symptoms of gastroesophageal reflux, emesis, dysphagia, and abdominal pain. Symptoms of dysphagia and food impaction increase with age, but stricture is rare in children. In a retrospective study of 381 children with EE, only one child had a stricture.²⁴ Fifty-three percent of the children had other allergic disorders such as asthma, allergic rhinitis, and/or eczema. The pathogenesis of EE is not known, but food and aeroallergens likely play a role. Food allergy is suspected given the association of symptoms with specific foods, abnormal allergy skin tests, in vitro tests to foods, and clinical improvement with elimination and elemental diets in many patients.²⁵ Interestingly, although patients with EE commonly have food-specific IgE detectable by allergy skin tests or in vitro testing, food-induced anaphylaxis is not thought to occur in the majority of these patients.²⁶ Patients with allergic eosinophilic gastroenteritis often pres-

ent with abdominal pain, emesis, failure to thrive, weight loss, anemia, and protein-losing enteropathy. In both disorders, food aversions or refusal to eat may develop leading to poor growth.

NON-IGE-MEDIATED REACTIONS

Food Protein-induced Proctocolitis

Food protein-induced proctocolitis typically appears in the first 2 to 4 months of life with blood-tinged stools. Affected infants appear healthy and lack systemic symptoms. There is minimal blood loss and anemia is rare. Biopsies of the rectum and sigmoid colon reveal an eosinophilic infiltration of the mucosa and lamina propria. Symptoms usually occur secondary to milk or soy protein and most often occur in breastfed infants. It is common to react to both milk and soy protein. With dietary elimination of the offending protein from the diet (from the mother's diet in breastfed infants), resolution of bleeding occurs in 72 to 96 hours.²⁷ After 12 months of age, most infants tolerate an unrestricted diet.

Food Protein-induced Enterocolitis Syndrome (FPIES)

In contrast to infants with food protein-induced proctocolitis, infants with FPIES appear ill and may present with recurrent vomiting, severe bloody diarrhea leading to anemia, abdominal distention, and failure to thrive. Symptoms typically begin in the first month of life. FPIES is most frequently caused by milk and soy protein (50% of infants are allergic to both), but rice, oat, other cereal grains, and poultry have also been implicated.^{9,28} Most children tolerate breast milk and extensively hydrolyzed casein formula. Symptoms resolve when the offending food is removed from the diet. However, if the offending food is accidentally ingested there is usually a 2-hour delay before dramatic onset of symptoms of vomiting and diarrhea with

dehydration and, in some, hypotension. Shock occurs in 20% of cases.²⁹ Children with accidental exposure to offending allergens should undergo medical observation, as lethargy, dehydration, and shock may occur, requiring fluid resuscitation. By 36 months, 90% of children with sensitivity to cow's milk have become tolerant to the protein, but illness with soy is more persistent.⁴ Skin tests and in vitro tests for IgE are negative as the disorder is not IgE-mediated. Diagnosis is made based on history and, if necessary, a food challenge.

SUMMARY

Most adverse reactions to foods are the result of intolerances rather than food allergy. It is important to identify children with potential food allergy as life-threatening, and life-ending reactions can occur. A clear understanding of the manifestations of food allergy caused by both IgE- and non-IgE-related mechanisms will help the practitioner to identify children who likely have food allergy so that additional diagnostic evaluation can be performed and appropriate avoidance can be instituted.

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