

Diagnosis of Food Allergy

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Food allergies, as well as atopic disorders in general, have been increasing in pediatric populations during the past few decades. Underlying factors may include increased bottle feeding, early introduction of solid foods, and imbalance in T helper development in favor of Th2 over Th1 cells. Current estimates suggest that up to 6% of children in the United States have food allergy.¹⁻³

The most common food allergens in children are cow's milk, egg, soy, peanut, tree nut, shellfish, and fish. Milk and egg allergy are more common in very young children and often are "outgrown" with age,⁴ while peanut, fish, and shellfish allergy are more common in older children and adults and tend to persist for many years or for life.^{5,6} Multiple food allergies can co-exist in a child; one food may cause multiple symptoms, or multiple foods may result in a single manifestation, particularly in atopic dermatitis. Care must be taken to distinguish true allergy to multiple foods from hidden amounts of a known food allergen⁷ or food additives.⁸ Many commercial baby foods that appear to be a single vegetable or fruit actually may contain small amounts of egg or milk, sometimes listed under unfamiliar names.

Allergy or hypersensitivity is just one of several mechanisms of adverse reactions to food (Sidebar 1, see page 711). Food hypersensitivity is an immunologic reaction that can be mediated either by humoral (IgE), cellular, or both components of the immune system.⁹ Probably the most common condition misdiagnosed as allergy is lactose intolerance, where an enzyme (lactase) defect results in gastrointestinal symptoms shortly after the ingestion of dairy products.¹⁰



Aversion to certain foods is common in children, who may express physical complaints to avoid eating foods they dislike. Food–drug interactions also should be considered, such as tyramine-containing foods with monoamine oxidase inhibitors, or a skin rash in the area of topical tacrolimus application with the ingestion of alcohol.^{11,12} More detailed discussions about food allergy manifestations and their differential diagnoses are provided in the other articles in this issue.

DIAGNOSTIC APPROACH

In the process of considering a diagnosis of food allergy, a few questions need to be answered sequentially: Do the symptoms seem to be allergic in nature? Are they likely to be food related? If so, which food is the culprit? Accurate answers require use of the medical history, selected screening tests, and verification testing¹³ (Sidebar 2, see page 712).

Medical History

A detailed medical history is very useful in the diagnosis of food allergy.

In some cases, the history can be convincing either for or against the diagnosis of food allergy. In the vast majority of patients, however, the history is inconclusive, and appropriately chosen testing is required. His-



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torical information usually narrows down the list of potential culprits and often excludes some foods from further consideration. The history and nature of the reaction can also suggest the potential immunopathophysiology (ie, IgE-mediated versus non-IgE-mediated).

A food allergy history should include information regarding the age of the child, suspected foods, amount of food generating the reaction, route of exposure, onset of symptoms in relation to exposure, nature of the reaction, co-incident events (eg, intercurrent illness, exercise, ingestion of nonsteroidal anti-inflammatory drugs), time course, and response to any administered treatment. The history should be evaluated in the context of what is suggestive of a cause-and-effect relationship. Most IgE-mediated reactions occur within minutes to a few hours after exposure, whereas the manifestations of non-IgE-mediated reactions (mostly gastrointestinal) may be delayed for several hours or days.

Atypical reactions, although they do not eliminate the possibility of food allergy, make the diagnosis difficult to establish. Reproducibility of symptoms following eating a certain food is usually, but not always, in support of a causative relationship. If a history of rash with

milk ingestion is obtained, but on further questioning the child is found to tolerate yogurt, then the child is unlikely to be allergic to milk because the same allergenic milk proteins are found in yogurt.

A child with a personal or family history of atopic disease is more likely to

have a food allergy than a child with no such history. However, there is no strong evidence for inheritance of food allergy. Because there are no pathognomonic symptoms for food allergy, the medical history should also be used to eliminate other causes for observed symptoms. Special consideration should be given to the possibility of immunodeficiency, as the manifestations often are gastrointestinal, respiratory, or cutaneous.¹⁴

Physical Examination

No specific physical findings are diagnostic of food allergy. The presence of symptoms at the time of physical examination might, however, verify the diagnosis of an atopic disease such as eczema, urticaria, angioedema, allergic rhinitis, or asthma; these disorders may be triggered or aggravated by food allergy. Physical examination also may reveal findings more suggestive of another diagnosis that would require further investigation and testing.

Height and weight are essential elements to the physical examination. Food allergy may be associated with poor growth due to gastrointestinal symptoms, restricted diet, or food refusal. Growth curves should be kept in following children with food allergy to ensure appropriate growth.

CME EDUCATIONAL OBJECTIVES

1. Recognize patients with adverse reactions to food.
2. Differentiate between allergic and nonallergic causes of adverse reactions to food.
3. Evaluate patients suspected of having food allergy.

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Nonspecific Initial Tests

Initially, a total serum IgE level, circulating eosinophil count, or both may be needed to support the allergic nature of the symptoms. However, normal values do not exclude allergy, and elevated values can be secondary to other causes. While, or even before, evaluating the child for food allergy, diagnostic tests for other diseases may be needed depending on the differential diagnosis (eg, lactose intolerance, immunodeficiency, cystic fibrosis, celiac disease).

Specific Screening Tests

Trials of elimination diets. When only one or very few foods are suspected of causing a reaction, a strict trial of avoidance might be worthwhile. If significant improvement occurs, reintroduction of those foods one at a time could identify the culprit. This reintroduction must be done with caution, as children with an initial nonanaphylactic food allergy can react with anaphylaxis on subsequent challenge. This assessment requires close cooperation between the parents and the physician to obtain valid results. If severe symptoms are anticipated, the food should be reintroduced cautiously under supervision in a medical facility, preferably in a blinded fashion.

Food/symptoms diary. Keeping a chronological record of all foods and the appearance of symptoms might be

be enhanced markedly by limiting the recording to the several hours preceding the appearance of symptoms, in chronological order.¹⁵ Again, any suspected foods should be verified by medically supervised challenge testing.

results, and is significantly less expensive than blood tests for allergy. It is also more impressive visually to parents. The child must not take any medications with antihistaminic effects for a few to several days before testing, depending



helpful in identifying the culprit. This procedure can be time-consuming, and the accumulated information often is confusing. In patients with infrequent symptoms, the yield of using a diary can

Allergy skin testing. Skin-prick testing (SPT) is the most commonly performed procedure for the diagnosis of immediate-type (IgE-mediated) allergy. It is very sensitive, provides immediate

on the preparation (Sidebar 3, see page 713). Skin testing is generally avoided in patients with dermographism, generalized skin lesions, or severe reactions to foods by skin contact or inhalation.

SIDEBAR 1.

Examples of Adverse Reactions to Foods

Hypersensitivity

- IgE-mediated: anaphylaxis, urticaria, angioedema, acute wheezing, diarrhea, abdominal pain
- Non-IgE-mediated: contact dermatitis, chronic pulmonary disease (Heiner syndrome), celiac disease, food protein-induced enterocolitis or proctocolitis
- Mixed IgE- and non-IgE-mediated: atopic dermatitis, allergic eosinophilic esophagitis and gastroenteritis

Enzyme Deficiency

- Lactose intolerance
- Galactosemia
- Glucose-6-phosphate dehydrogenase deficiency

Pharmacologic

- Irritability from caffeine
- Headache from vasoactive amines in certain foods (eg, aged cheese, fermented sausage, pickled herring, red wine)

Toxicity

- Poisonous food
- Bacteria and bacterial toxins
- Chemical contamination
- Scromboid fish poisoning (histamine)

For some of the more common food allergies, such as milk, egg, and peanut, curves have been generated using the outcome of blinded oral food challenges to determine the likelihood of a child reacting to the food with a given food-specific immunoglobulin E level.

Diagnostic Approach to Food Allergy

Medical History

- Nature and course of symptoms
- Relationship to food or to other factors, or to a combination
- Response of symptoms to treatment
- Personal history of allergy, particularly of atopic dermatitis
- History of allergy in immediate family members
- Family history of nonallergic disease

Physical Examination

- Manifestations compatible with allergy
- Manifestations suggestive of nonallergic disease

Nonspecific Initial Laboratory tests

- Total serum IgE level
- Selected tests to exclude or verify nonallergic disease

Specific Screening Tests

- Trials of elimination diets
- Food/symptom diary
- Allergy skin testing
- Allergen-specific IgE antibodies in serum

Confirmation by Challenge Testing

- Oral (open or blind placebo-controlled)
- Food alone or concurrently with other suspected factors

Adapted from Bahna SL: Ann Allergy Asthma Immunol. 2003;90(Suppl 1):77-80.

Results of appropriately performed SPT merely indicate the presence or absence on the cutaneous mast cells of IgE antibodies specific to the food(s) tested. Therefore, positive results may be more likely if the allergic manifestation is in the skin instead of gastrointestinal or respiratory. In general, the reliability of a negative SPT result to exclude food allergy is better than a positive result in confirming it.⁴ Expertise is needed in performing and interpreting allergy skin testing, including knowledge about food cross-reactivities. In some patients, testing with fresh food can be more reliable than testing with extracts.

Intradermal skin testing for the diagnosis of food allergy has been abandoned

due to its high “false-positive” rate and increased risk of systemic reactions. Patch testing for food allergy has been studied recently, and the reported findings suggest that patch testing may provide additional information to SPT or specific IgE levels in eosinophilic gastrointestinal disorders and in atopic eczema.¹⁶ However, the test is not standardized and has not shown a sufficient level of reliability in diagnosing food allergy in general.¹⁷

Specific serum IgE testing. Food-specific serum IgE testing is the counterpart to skin testing; they depend on the presence of specific antibodies in the serum or on the cutaneous mast cells, respectively. Hence, their results may not correlate. In

fact, in some patients, both tests can be negative despite reactions to the suspect food under supervised blinded challenge. Serum testing can be especially useful when skin testing cannot be done or antihistamines cannot be discontinued. It can be very useful to evaluate children with a history of severe reactions, particularly when exposure was by skin contact or inhalation.⁷ Unless only a few allergens are tested, however, the cost of serum testing is far greater than skin testing. Also, specific IgE level originally was measured by the radioallergosorbent test (RAST), but subsequently, several modifications have been developed by various commercial laboratories. Hence, results from different laboratories generally are not comparable.

The medical history should be used as a guide to select appropriate foods to be tested. The majority of the clinical data correlating food-specific serum IgE levels to clinical reactivity have been determined using the ImmunoCAP assay; it is unclear how these levels correlate to those generated by other methods. There is not a standard cut-off that is considered positive for all foods. Undetectable (below 0.35 KIU/L) and low values generally indicate that a child is unlikely to have an allergy to that food. However, this varies by the food, total IgE level, allergy manifestations, and severity of reaction. Even with negative food-specific IgE, a small percentage of children will still react clinically when challenged.

Very high specific IgE levels are highly suggestive of clinical relevance. In general, intermediate levels require challenge testing to determine if a child is truly allergic to that food. For some of the more common food allergies, such as milk, egg, and peanut, curves have been generated using the outcome of blinded oral food challenges to determine the likelihood of a child reacting to the food with a given food-specific IgE level.² Such curves and cut-off levels were based on study patients and only provide the percentage of children ex-

pected to react based on a given specific IgE level.^{2,18,19} In general, as the level of specific IgE increases, its positive predictive value increases. However, in one study, specific IgE to peanut or tree nuts was “falsely negative” in 22% of patients with allergy and was “falsely positive” in 40% of those without allergy.²⁰

In interpreting the significance of the level of specific IgE antibody, the total IgE level should be taken into consideration. Highly elevated total IgE levels can be associated with numerous “positive” specific IgE levels that may not be clinically relevant. On the other hand, a low specific IgE level may have clinical relevance when total IgE level is low. Repeat measurements of specific IgE levels in a child with known food allergy can assist in determining if the child has become tolerant to that particular food, particularly when the level decreases markedly during a short period. However, a dramatic decrease in specific IgE level does not guarantee tolerance to the food. In one study, despite a 90% decrease in the specific IgE level within 1 year, milk was not tolerated in 34%, and egg in 22%, of children.²¹ Even when the specific IgE level dropped to 1% of the initial level, milk was still not tolerated in 6% and egg in 5% of children.

Unproven tests not recommended. Certain tests have been suggested or promoted for the diagnosis of food allergy, but they are either experimental or have no diagnostic validity.^{22,23} Examples include, but are not limited to, provocation neutralization, specific IgG or IgG4 antibody, immune complexes, cytotoxic tests, hair analysis, and kinesiology. It is worth noting that specific IgG and specific IgG4 antibodies merely reflect exposure¹³ to a food and not allergy.

Elimination Challenge Testing

The medical history, skin testing, or specific IgE tests for many foods that may

or may not be clinically relevant. Hence, verification requires a period of dietary elimination to document improvement of symptoms and their recurrence after reintroduction of the food(s).^{4,24} The elimination diet may require several weeks to see improvement in chronic symptoms such as atopic dermatitis or gastrointestinal complaints. All foods in question must be strictly avoided simultaneously. A young infant’s diet can be limited to a hypoallergenic formula, such as an extensively hydrolyzed casein or an elemental formula (synthesized amino acids). For exclusively breast-



fed infants, either the suspected food is eliminated from the mother’s diet or the baby is fed a hypoallergenic formula until the offending food is identified.

After documenting significant improvement on dietary elimination, the challenge test is carried out while the child is on minimal or no symptomatic medication. This should be designed and done under medical supervision to document the dose that provoked the reaction and to administer symptomatic

SIDEBAR 3.

Approximate Duration of Discontinuation of Common Medications with Antihistaminic Effects Before Allergy Skin Testing

- 3 to 6 days for most first generation anti-H1 (eg, chlorpheniramine, diphenhydramine, ebastine, promethazine, tripeleennamine)
- 7 to 10 days for azelastine, cetirizine, clemastine, cyproheptadine, desloratadine, doxepin, fexofenadine, hydroxyzine, ketotifen, loratadine, mequitazine, mizolastine
- 10 to 20 days for amitriptyline, desipramine, imipramine, nortriptyline

treatment, which may even require management of anaphylaxis. Experience is required to choose a safe initial dose; the dose is then gradually increased, while monitoring for any symptoms, until reaching a cumulative dose at least equal to the quantity usually eaten.

The challenge may be carried out in an open fashion in infants, but in older children, single-blind or double-blind, placebo-controlled challenges minimize bias.^{24,25} Several studies have shown through the use of double-blind, placebo-controlled challenges that only about one-third of the suspected foods are

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found to be truly offending.²⁴ In addition to verifying food allergy, challenge testing prevents unnecessary dietary avoidance and enhances compliance with the elimination diet. Nevertheless, in general, intentional challenge should be avoided in patients who have recently experienced a life-threatening reaction to a specific food, particularly if it occurred more than once. It is worth noting that in case of post-prandial exercise-induced reactions,²⁶ food intake should be

followed by exercise for the test to be valid. The interval between food intake and exercise is usually less than 2 hours, but in some cases anaphylaxis occurred several hours later.²⁷

POTENTIAL FUTURE TESTS

A variety of diagnostic tests for food allergy are under investigation. In the future, there may be tests that identify the specific part of the food protein (antigenic determinant or epitope) to which the patient is reacting.²⁸ This might allow prediction of the nature of the clinical reaction as well as the probability of outgrowing the food allergy. There are ongoing investigations to identify food allergy phenotypes through genotyping for single nucleotide polymorphisms, which would be useful for food allergy prevention strategies.

SUMMARY

The diagnosis of food allergy requires obtaining a detailed medical history and consideration of the differential diagnosis. The offending food(s) may be identified by the medical history, trials of elimination diets, SPT, food-specific IgE measurement, or some combination. However, the reliability of these methods is usually suboptimal, and confirmation of the offending food(s) requires well-designed challenge tests.

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