
Diagnosis of food allergy

Sami L. Bahna, MD, DrPH

Background: Food allergy is gaining substantial interest by both the public and health professionals. It is usually overdiagnosed by the public and misdiagnosed by physicians.

Objective: To provide an outline for appropriate evaluation of patients suspected of having food allergy.

Data Sources: Information was derived from selected review and original articles published in peer-reviewed journals and from authoritative textbook chapters, supplemented by the clinical experience of the author.

Results: Several approaches have been used for food allergy diagnosis, including the medical history, trials of elimination diets, food/symptom diary, skin testing, in vitro tests, and oral challenges. In most cases, the medical history is inconclusive and the reliability of the in vivo and in vitro tests is suboptimal. Appropriately designed challenge testing remains the gold standard, although it has a few limitations.

Conclusions: Appropriate selection, application, and interpretation of tests for food allergy are necessary for attaining a high degree of accuracy of diagnosis.

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INTRODUCTION

Allergy in general, and food allergy (FA) in particular, is probably the most commonly self-diagnosed health problem.¹ Whereas it is usually overdiagnosed by the public, FA is often underdiagnosed by physicians and is frequently misdiagnosed by allergists.

The primary objective of this presentation is to enhance the ability of physicians to appropriately evaluate patients suspected of having FA. In such a process, the physician needs to know when to suspect that the patient's symptoms might be related to food, what is the differential diagnosis of adverse reactions to food, to appropriately select and interpret tests for identification of the possible offending food(s), and to finally confirm the clinical relevance of each suspected food (Table 1).^{2,3}

MEDICAL HISTORY

In evaluating possible FA, a detailed history taking is of utmost importance, probably more so than in evaluating most other medical problems. Suspicion that food might be the underlying cause of the patient's symptoms might come from the patient or from the physician. In some instances, the medical history alone may be convincing enough to diagnose or to exclude FA. Often, however, the medical history is inconclusive, and selected screening tests would be needed.

Inquiry should cover the age at onset, the nature of symptoms, frequency, suspected food or other factors, time of onset in relation to food ingestion, response to avoidance or symptomatic allergy medications, and possible role of concurrent factors, eg, physical exercise, intercurrent illness, hormonal changes, or emotional stress. Latex-sensitive subjects are likely to develop allergy to avocado, banana, chestnut, fig, kiwi, and papaya.⁴

PHYSICAL EXAMINATION

The findings in physical examination, particularly while the patient is symptomatic, might support the diagnosis of allergy or suggest a nonallergic disorder. Because no symptoms or clinical signs are pathognomonic of FA, a differential diagnosis should be considered. The clinical problem may not be allergy at all, or it is allergy but not to food. Selected laboratory tests might be helpful in that regard. Elevated serum total IgE level would support allergy diagnosis, but normal values do not exclude allergy. Total IgE can be also elevated in several non-allergic conditions.⁵

TRIALS OF ELIMINATION DIETS

If the medical history points to only one or very few suspected foods, avoidance then re-introduction of those foods may be attempted. The avoidance period should be at least equal to the symptom-free periods the patient used to have. If the patient remains asymptomatic without taking medications, then the foods are reintroduced in appropriate quantities, each for a few days to identify the offending ones. When severe symptoms are anticipated, the procedure should be done under supervision in a medical facility. Foods that cause symptoms may need to be verified by blind challenge tests.

It is not uncommon that patients relate their symptoms to eating without suspecting any particular food. In such instances, trials of avoidance of certain food groups⁶ for 1 to 4 weeks each might be helpful. Members of the offending group then need to be tried individually. In addition to being time-consuming, this method has several inherent difficulties, particularly relevant to choosing the elimination diets and the patient's compliance.

FOOD/SYMPTOM DIARY

Keeping chronologic, accurate records of all ingested foods/beverages and any developed symptoms might focus the suspicion to one or a few foods.² Such foods should then be subjected to elimination and challenge trials. This method can

Allergy & Immunology Section, Louisiana State University, Health Sciences Center, Shreveport, Louisiana.

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Table 1. Diagnostic Approach to Food Allergy

Medical history
Nature and course of symptoms
Relationship to food or to other factors, or to a combination
Personal history of allergy, particularly of atopic dermatitis
Physical examination
Manifestations of allergy
Manifestations suggestive of nonallergic disease
Nonspecific initial laboratory tests
Total serum IgE concentration
Selected tests to exclude or verify nonallergic disease
Specific screening tests
Trials of elimination diets
Food/symptom diary
Allergy skin testing
Specific IgE antibodies in serum
Other selected in vitro tests
Confirmation by challenge testing
Oral (open or blind placebo-controlled)
Food alone or concurrently with other suspected factors

be time-consuming, and the findings are often confusing when symptoms are recorded frequently and in relation to a wide variety of foods. If diaries need to be kept for prolonged periods, the compliance with recording markedly drops.

In patients with infrequent symptoms, the yield of using a food/symptom diary can be markedly enhanced by using an as-needed recording.² Only when symptoms appear that recording is done and should include the place, time and nature of symptoms, as well as all foods and events during the preceding 6 to 12 hours, in a chronologic order.

SKIN TESTING

Percutaneous skin testing (ST) is the most commonly used screening method for FA, using glycerinated extracts, usually in concentration 1:10 or 1:20 wt/vol. Its reliability depends on several factors. (Table 2). In general, its negative predictive accuracy is much higher than its positive predictive accuracy.^{7,8} The reliability is enhanced by using fresh or native foods that are actually suspected of causing the symptoms, using the "prick-by-prick" technique.⁹ The currently available commercial extracts are not standardized, and their potency varies from one food to another as well as from one manufacturer to another. There is a definite need for standardization.¹⁰

Certain patients may react to a particular food only when processed in a certain way, eg, heated. Heat may denature heat-labile antigens but may reveal certain antigenic determinants (conformational epitopes) that were hidden in the molecular structure of fresh food.^{11,12}

Only a very few studies addressed the issue of potency of commercial food extracts.¹³ The potency of soybean extracts seemed to vary widely,¹⁴ whereas peanut extracts showed low variation despite a wide variation in protein content.¹⁵

Percutaneous allergy testing has a high record of safety, but it may carry a high risk in exquisitely sensitive patients who react on exposure to food by skin contact or inhalation.¹⁶

Table 2. Factors Influencing the Reliability of Skin Testing for Food Allergy

Technique; percutaneous has higher specificity and lower sensitivity than intradermal. The latter is becoming rarely used. Patch testing may add more information
Experience in its performing, reading and interpretation, particularly regarding cross-reactivity among foods or between certain foods and pollens
Food allergenicity; highest for peanuts, tree nuts, cottonseed, seafood, and fish
Quality of food extracts and variations from one manufacturer to another
Patient's degree of sensitivity
Manifestations; sensitivity and specificity are much higher in atopic dermatitis, anaphylaxis, and acute urticaria than in gastro-intestinal or respiratory allergies
Recent intake of medications that has antihistaminic effect

Such patients, if needed to be tested at all, may be subjected to an in vitro test or a cautious skin contact without pricking.

Intradermal testing with food extracts is becoming rarely used because its specificity is too low and its sensitivity is too high, ie, has high falsely positive rate.⁸ Dilute aqueous extracts should be used (usually 1:1000 wt/vol) to minimize the risk of systemic reaction. It may be used in instances where certain foods are suspected by the medical history yet showed a negative percutaneous test.

In infantile atopic dermatitis, where T cell plays a major role in the pathogenesis, combined skin prick and patch testing may enhance identification of the offending foods.¹⁷

SERUM IgE ANTIBODIES

Food-specific IgE antibodies in the serum can be measured by the classic radioallergosorbent test (RAST) or by one of its several analogs that use either isotope-labeled or enzyme-linked anti-IgE.² Even though the test procedure is more standardized than ST, its reliability can vary from one laboratory to another and from one method to another.^{18,19}

The Pharmacia-CAP assay (Pharmacia, Peapack, NJ) seems to be the most sensitive of the currently available methods.²⁰ Using the CAP-RAST fluorescent enzyme immunoassay assay, one study²¹ suggested that certain threshold levels of titers to individual foods predict the clinical relevance with a high degree of accuracy. For improved interpretation of the specific IgE antibody titer, it would be prudent to know the total IgE level. Allergens with low titers are less likely to be clinically relevant in the presence of highly elevated total IgE levels.

Serum IgE antibody testing is the counterpart of ST in that both depend on the presence of specific IgE antibodies in the serum or on the cutaneous mast cells, respectively. Thus, ST reflects also the releasability of mast cell mediators. However, their results may not correlate, which should not be surprising because the concentration of the IgE antibodies is highest on the mast cells of the shock organ. In fact, both tests can be negative in some patients with definite immediate-type

reactions.⁷ By the same token, both tests can be positive without clinical relevance.⁷

Testing for serum IgE antibodies can have advantage over ST in patients with dermatographism, generalized dermatitis, exquisite allergy by skin contact or inhalation, or inability to discontinue medications that have antihistaminic effect.

SERUM IgG ANTIBODIES

Certain, yet uncommon, food hypersensitivity reactions, eg, gastro-intestinal bleeding, protein-losing enteropathy, and milk-induced pulmonary disease (Heiner syndrome), are mediated totally or partially by IgG antibodies. The mere presence of IgG antibodies in the circulation, however, is a normal physiologic phenomenon and indicates exposure. Only in certain cases that high titers may explain the immunologic basis of a non—IgE-mediated reaction. When the combination of an antigen with its specific IgG antibody and complement form immune complexes that become impacted in small blood vessels, an Arthus-type reaction results in vasculitic inflammation and varying degrees of tissue damage.²²

Serum food-specific IgG antibody titers can be measured by radio-, enzyme-, or fluorescent-immunoassays that have better reproducibility than the previously used techniques of precipitation, hemagglutination, or complement fixation.²

Testing for food-specific IgG4 antibodies has no validated diagnostic value²³ and merely reflects exposure.^{24,25} Strongly positive results are common in allergic subjects who have high total IgE levels, regardless whether FA exists or not. High IgE concentrations can stimulate the production of IgG and IgG4 autoantibodies against IgE that can be mistakenly identified in immunoassays as food-specific.²⁶

Additional *in vitro* tests have been reported but either have no diagnostic validity at all or have limited research usefulness.^{7,27–29}

CHALLENGE TESTING

For a definite identification of the offending food(s), appropriately designed challenges need to be carried out. All foods that have been suspected (by history, diary, elimination trials, ST, or *in vitro* tests) should be simultaneously strictly avoided. If symptoms markedly improve, such foods would be individually re-introduced to identify the symptom-provoking one(s). Experience is needed in planning and administering the challenge test.

Double-blind, placebo-controlled challenge is ideal to avoid any possible bias on the part of the patient or the observer. Nevertheless, most cases in clinical practice can be reliably subjected to single-blind testing. Choosing a placebo that can completely mask the test food can be a difficult task.^{30,31} Open challenge can be suitable for young children with objective reactions. Details about each of these three procedures, including their advantages and limitations, are mentioned elsewhere.^{32–34} To avoid severe reactions, the challenge material should be administered in a few gradually increasing doses, starting with a “safe” dose for any particular patient, depending primarily on the medical history (severity

Table 3. Advantages of Food Challenge Testing

Verification of the diagnosis of food allergy
Identification of the truly offending food(s)
Limiting the dietary elimination, which would:
Improve the quality of life
Enhance the compliance with diet
Prevent potential malnutrition or undernutrition
Exclusion of food allergy would allow further investigation for other causes of the symptoms

of symptoms and provoking quantity of food) and to some extent on the degree of skin reactivity or RAST score. The dose can be increased every 20 to 30 minutes by 50 to 100% increments as long as no reaction develops. The cumulative dose should be at least equal to the quantity customarily ingested by the patient. Patients with a history of a severe reaction should be tested in a facility where resuscitation measures are available.

A meta-analysis³⁵ of 10 studies that used double-blind, placebo-controlled food challenges, revealed that only 50% (29 to 65%) of subjects suspected of having FA were truly allergic to any food, and only 28% (17 to 37%) of the suspected foods were truly offending. One study²¹ revealed that certain thresholds of specific IgE antibody concentrations can predict the positivity of food challenge with a high degree of reliability.

Challenge testing has several advantages (Table 3). Nevertheless, it would be prudent to avoid challenge testing in instances where a life-threatening reaction has occurred after exposure to a specific food, particularly if it happened more than once. However, if such a severe reaction followed eating a composite meal, it is necessary to identify the specific offending food item that might be incorporated in numerous other foods. In such instances, a careful challenge test should be conducted in the hospital, preferably in the intensive care unit.

CONCLUSION

Even though challenge testing is often referred to as the gold standard for FA diagnosis, it may yield a falsely negative result.³³ Every effort should be done to reproduce the natural exposure, particularly regarding the form and quantity of food suspected of provoking the reaction. In addition to food, concurrent other factors may be involved, eg, exercise, hormonal changes, gastro-intestinal disorder, intercurrent illness, and emotional stress. In one report,³⁶ food-induced systemic anaphylaxis occurred in some patients only when eating the offending food was combined with two other factors, namely exercise and menstruation. In some instances, the reaction occurs only when multiple foods are eaten simultaneously but not when eaten separately. Anaphylaxis has been reported to occur in a patient only when he exercises after eating a combination of two particular foods.³⁷ Only through a detailed history taking, a high degree of suspicion, and multiple trials of combinations may such additional factors be uncovered.

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Requests for reprints should be addressed to:

Sami L. Bahna, MD
Allergy & Immunology Section
Department of Pediatrics
LSU Health Sciences Center
1501 Kings Highway
Shreveport, LA 71130-3932
E-mail: sbahna@lsuhsc.edu