Immunoglobulin E–mediated food allergy diagnosis and differential diagnosis

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ABSTRACT

Food allergies consist of aberrant immunologic, typically immunoglobulin E mediated, reactions that involve food proteins. A clinical history with regard to the suspected food, temporal associations, the duration of symptoms, characteristic symptom complex, and reproducibility in some cases is the key to making an accurate diagnosis. The differential diagnosis includes, for example, other immunologic adverse food reactions, nonimmunologic adverse food reactions, and reactions that involve nonfood items. Skin and blood immunoglobulin E testing for the suspected food antigen can aid the diagnosis in the context of a supportive clinical history. Immunoglobulin E testing for food components may further enhance diagnostic accuracy. Novel testing modalities are under development but are not yet ready to replace the current paradigm. Thus, double-blinded placebo controlled oral food challenge is considered the criterion standard of testing, although unblinded oral food challenges are usually confirmatory.

(J Food Allergy 2:26–30, 2020; doi: 10.2500/jfa.2020.2.200019)

Food allergy (FA) is best defined as an inappropriate, reproducible immune response to food proteins. This is classically mediated by immunoglobulin E (IgE). Reactions are characterized by cutaneous, respiratory, gastrointestinal, and/or cardiovascular symptoms that typically occur within 30 minutes to 2 hours of ingestion (see Table 1 for details).[1,2] Because of the profound negative effects on growth and feeding associated with an FA diagnosis,[3] making an accurate diagnosis is critical, particularly in children.

HISTORY AND PHYSICAL EXAMINATION

As with many diseases, FA diagnosis requires an accurate history. Unfortunately, blind screening for FA, by testing for large panels of food allergens without a clear history, is often inaccurate, and there are also various FA diagnostic mimics.[2] The possible manifestations of an FA reaction are listed in Table 1. FA clinical manifestations, including additional history and physical examination factors, are also thoroughly described in the section of this issue entitled "Clinical Manifestations of IgE-Mediated Food Allergy."[4]

Although all these symptoms are possible in anaphylaxis, they occur with varying frequency in FA reactions and may vary with age. Cutaneous symptoms occur in 80–90% of food anaphylaxis episodes, although the frequency tends to be lower in children.[5] Hypotension has been rarely reported as the primary symptom of anaphylaxis, but, up to 39% of FA reactions may include cardiovascular compromise of some type.[5] Further, cardiovascular compromise need not lead to hypotension but rather may include symptoms of nausea, vomiting, light-headedness, or a "sense of impending doom." Populations at higher risk of FA include those individuals with another preexisting FA, atopic dermatitis, asthma, allergic rhinitis, or a strong family history of atopic disorders.[6] Factors that may exacerbate reaction severity include exercise, febrile illness, asthma exacerbation, menstruation, nonsteroidal anti-inflammatory drug use, and alcohol ingestion.[1,7]

Most patients experience symptoms within minutes to 1–2 hours after ingesting a food.[1] However, in the case of mammalian meat allergy, or "alpha-gal," there is a delay of 3–6 hours from ingestion to reaction.[8] This FA is triggered by the development of hypersensitivity to galactose-alpha-1,3-galactose in the saliva of a tick bite, classically, the lone star tick. This glycoprotein is also contained in mammalian meat. Although delayed, symptoms are usually similar to other FA reactions. This is further discussed in a later article in this primer, "Alpha-Gal Syndrome."[9] The physical examination can reveal evidence of other atopic diseases that might

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C.F. Schuler reports grant support from the Mary H. Weiser Food Allergy Center. M. Gupta and G.M. Sanders report clinical trials support from Regeneron Pharmaceuticals, Aimmune Inc., and DBV Technologies

Funded by Food Allergy Research & Education (FARE)

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make an FA diagnosis more likely by association. Evidence of eczema, asthma, and allergic rhinitis may suggest an individual who is atopic.[1] Caution should be used in patients with atopic dermatitis because indiscriminate screening by using large food allergen panels in the absence of a suggestive history in these patients may overestimate true FA diagnoses (see below).

DIFFERENTIAL DIAGNOSIS

Causes of food-related adverse events or conditions that might mimic FA are detailed in Table 2.[2,9,10] Of particular note are the various non–IgE-mediated food reactions, listed under "other immunologic adverse food reactions."[11–13] In addition, we note key differences that may distinguish some of these entities from typical FA.

Table 1 **Clinical manifestations of food allergy reactions***

Cutaneous
Redness
Pruritus
Hives
Angioedema
Ocular
Pruritus
Erythema
Tearing
Edema
Respiratory
Rhinorrhea
Sneezing
Laryngeal edema
Cough
Chest tightness
Dyspnea
Oral
Angioedema
Pruritus
Gastrointestinal
Nausea and vomiting
Diarrhea
Abdominal pain
Reflux
Cardiovascular
Tachycardia
Hypotension
Lightheadedness and syncope
Other
Uterine contractions
"Sense of impending doom"

*From Ref. 25.

Skin-Prick Testing

Skin-prick testing (SPT) involves the epicutaneous application of food extracts, many of which are available commercially. The resulting hive-like reaction includes a raised "wheal" and a surrounding "flare" reaction. The diameter of the wheal and flare is measured. Testing is considered reactive if the wheal is >3 mm greater than the negative control (saline solution). SPT possesses a high negative predictive value, except for fruit and vegetable commercial extracts; in this case, food proteins are destroyed during processing, which leads to false negatives. To address this, one can perform prick-to-prick testing, wherein the food tested is scratched with the device, which is then immediately used to scratch the skin.[1] Intradermal testing to foods, in which allergens are injected under the skin, is contraindicated in FA due to a high rate of false-positive reactions and serious, sometimes fatal, adverse reactions.[14]

There is an abundance of varied results with regard to the correlation of SPT wheal sizes and subsequent clinical outcomes adjudicated by oral food challenges. In general, a larger SPT wheal size cutoff gives greater specificity for reacting during food challenge but decreases sensitivity across all age groups. For example, a peanut SPT wheal cutoff size of 3 mm gives a sensitivity of 78.9–100% and a specificity of 29–98.1%; using a 6-mm cutoff leads to a reduced sensitivity, of 47.4–78%, and a higher specificity, of 94–99.8%. Similar trends hold across foods. Specific test characteristics vary by age. This has been extensively reviewed.[1,15,16] Skin and blood IgE testing to a particular food in a proper clinical context can provide valuable data with regard to the likelihood of an FA[15] but cannot currently address the likely severity of a future reaction.[1]

In Vitro IgE Testing

In vitro IgE tests for the presence of food specific IgE (sIgE) in the blood of patients with FA and is widely commercially available. The accuracy of this testing is highly dependent on pretest probability. A convincing history, young age, and a high rate of allergy in the population tested raises the probability of allergy at a specific IgE level.[17] Unfortunately, there is a notably high false-positive rate in atopic dermatitis; one must apply caution when interpreting both skin and *in vitro* IgE testing in this context.[2] Test characteristics for food sIgE levels have been extensively reviewed elsewhere; sensitivity and specificity and positive and negative predictive values for various foods can vary widely by food, study, age of the patient, and the cutoff used.[15,18] In general, using higher cutoffs for sIgE testing tends to reduce sensitivity while raising specificity, as with skin testing.

Table 2 **Differential diagnosis of IgE-mediated food allergy**

Food Allergic Reactions	Differentiating Symptoms
Typical IgE-mediated food allergy reactions	As described
"Alpha-gal" or mammalian meat allergy*	Anaphylaxis with typical symptoms, delayed by 3–6 hr; may involve cross-reactivity to multiple meats
Other immunologic adverse food reactions	
FPIES#	Delayed (1–3 hr after food ingestion) vomiting and diarrhea, cardiovascular compromise, lack of cutaneous symptoms; most often infants are affected but occasionally adult onset
FPIAP§	Bloody stools, classically associated with milk ingestion not anaphylaxis; often presents approximately age 3 mo
Pollen-food syndrome	Transient itching, tingling, or other oropharyngeal symptoms; anaphylaxis is rare
Celiac disease	Abdominal pain, diarrhea, potentially anemia, rash, joint symptoms but not anaphylaxis
Eosinophilic esophagitis and eosinophilic gastrointestinal diseases¶	Various gastrointestinal symptoms, associated with atopy, but anaphylaxis is not present
Other nonimmunologic adverse food reactions	
Food intolerances (such as lactose intolerance)	Symptoms quite variable, most commonly gastrointestinal
Food poisoning or toxic reactions (scombroid food poisoning)	Variable symptoms, most commonly gastrointestinal
Pharmacologic reactions (caffeine)	Quite variable
Auriculotemporal syndrome (Frey syndrome)	Redness and sweating of the cheek near the ear, stimulated by salivation
Gustatory rhinitis	Rhinitis induced by eating, often spicy foods
Nonfood reactions	
Allergic reactions to drug, venom, inhalants	Typical allergic reactions, including anaphylaxis but in response to a nonfood item
Panic, anorexia nervosa	Hyperventilation, numbness and/or tingling, globus sensation, tunnel vision, "sense of impending doom," typically hypertension

IgE = Immunoglobulin E; FPIES = food protein-induced enterocolitis syndrome; FPIAP = food protein-induced allergic proctocolitis.
**From Ref. 9.*
#From Ref. 11.
§From Ref. 12.
¶From Ref. 13.

A food component–resolved diagnosis (CRD), also known as molecular allergen analysis, takes the premise of food sIgE testing further by measuring IgE levels to specific individual food components. In some contexts, such as peanut CRD, sIgE levels for food components may be more predictive than traditional food sIgE testing. A summary of food component identities and qualitative assessments of utility is given in Table 3. However, the precise test characteristics of this testing are still being understood, so we have not included specific test characteristics here; test characteristics for CRD were recently reviewed elsewhere.[15,18]

A word of caution is needed with regard to the positive predictive value of SPT and food sIgE testing in patients without a history of a food reaction. Sensitization (a positive SPT or food sIgE value test result alone is insufficient to make an FA diagnosis; patients may have elevated food allergen sIgE levels despite tolerating food ingestion.[1] Indeed, when using food sIgE and dietary data from the National Health and Nutrition Examination Survey (NHANES) dataset, one group demonstrated that numerous members of the general population who eat a food may demonstrate very high levels of sIgE without reactions.[19] Further, patients in one study who were

Table 3 **Selected food component sIgE identities and clinical relevance***

Food	Component	Clinical Relevance
Peanut	Ara h 1 (7S globulin); Ara h 2 (2S albumin); Ara h 3 (11S globulin); Ara h 6 (2S albumin); Ara h 8 (PR-10)	Ara h 2 is associated with peanut anaphylaxis; Ara h 2 and 6 together are associated with severe peanut reactions; Ara h 8 is associated with Bet v 1 cross-reactivity and not clinical peanut allergy
Milk	Bos d 8 (casein); alpha lactalbumin; beta lactoglobulin	Casein is strongly associated with baked milk allergy
Egg	Gal d 1 (ovomucoid); Gal d 2 (ovalbumin)	Ovomucoid is associated with baked egg allergy; ovalbumin is associated with cooked and raw egg allergy
Hazelnut	Cor a 1 (PR-10); Cor a 8 (LTP); Cor a 9 (11S globulin); Cor a 14 (2S albumin)	Cor a 9 and 14 together are associated with hazelnut allergy and severe hazelnut reactions; Cor a 14 alone is predictive of hazelnut allergy
Cashew	Ana o 3 (2S albumin)	Ana o 3 is associated with cashew allergy
Walnut	Jug r 1 (2S albumin); Jug r 3 (LTP)	Jug r 1 is superior to crude extract in children but not adults for diagnosing walnut allergy
Sesame	Ses i 1 (2S albumin)	Ses i 1 is strongly associated with sesame allergy
Soy	Gly m 5 (7S globulin); Gly m 6 (11S globulin); Gly m 8 (2S albumin)	Gly m 5 and 6y together are somewhat predictive of severity of soy reactions; Gly m 8 is associated with soy allergy
Wheat	Tri a 19 (omega-5-gliadin); Gliadin; HMW-glutenin; LMW-glutenin	All four of the listed components are associated with wheat allergy and reaction severity; Tri a 19 is associated with wheat-dependent exercise anaphylaxis

LTP = Lipid transfer protein; PR-10 = pathogenesis-related protein 10; HMW = high molecular weight; LMW = low molecular weight.
**From Ref. 2, 17, 18, 26.*

placed on food avoidance based only positive food sIgE testing results tolerated the foods during food challenge at a rate of 84–93%.[20] Thus, current guidelines recommend against testing to large panels or multiple food allergens in the absence of a clinical history of a reaction to each of the foods tested. If this is done, then false-positive results may lead to an inappropriate dietary restriction of previously safe foods,[1] which potentially leads to "a disaster of misdiagnosis," with major potential impacts on growth and nutrition in children.[2,3]

OTHER TESTING

Basophil activation testing is an emerging FA diagnostic tool. This assay uses flow cytometry on living basophils from low volumes (1 mL) of whole blood. The test can detect the ability of food sIgE to cause basophil activation after allergen exposure. Basophils of patients with FA generally demonstrate a dose-dependent increased expression of basophil activation markers, including CD63 and CD203c. The basophils of sensitized but tolerant patients do not demonstrate activation markers after allergen exposure. This test has been applied most extensively for peanut allergy, with sensitivity ranges of 83–92% and specificity ranges of 77–100%.[17,21] This testing is limited somewhat by the need for fresh whole blood (<4 hours since the blood draw) and the lack of standardization across institutions in conducting the test and reporting the results. Thus far, insufficient evidence exists to determine how to apply this promising test outside of the research context.[17,21]

Epitope analysis, or mapping, is another emerging FA diagnostic tool, which involves mapping the specific sites of food protein–IgE binding (epitopes) for an individual patient. Sequential amino acids can form a sequential epitope, whereas a group of amino acids co-localized by protein folding can form a conformational epitope. The latter epitope type tends to be more labile when exposed to heat or digestion. For example, patients who produce IgE–recognizing sequential epitopes of egg proteins tend to have more persistent egg allergy than those whose IgE

recognizes conformational epitopes.[22] However, uncertainty remains on how to apply this technique, so it remains largely a research tool at this time. Other, unproven tests for FA are reviewed in detail in the subsequent section of this issue, "Food allergy: Unproven diagnostics and therapeutics."[23] Although new testing modalities are under development, these have yet to supplant the current criterion standard, the double-blinded, placebo controlled oral food challenge, which is reviewed in the article, "Oral food challenges."[24]

CONCLUSION

Although the future of FA diagnostics may ultimately lie beyond traditional testing, thus far, no test can replace the accuracy of a thorough history coupled with confirmatory testing and an oral food challenge if needed. Using current testing to "screen" for FA constitutes a potentially grave diagnostic error that can expose the patient to undue adverse effects and is not recommended. Indeed, a thoughtful, careful history can help the astute clinician sort through the differential diagnosis of FA and minimize unnecessary testing, reducing the patient's exposure to overdiagnosis.

CLINICAL PEARLS

- FA must be differentiated from other food reactions and nonfood reactions; the timing, reproducibility, and symptom complex are key.
- FA testing must be conducted in the context of the clinical history; skin and blood IgE testing to large panels of food allergens in the absence of a clear clinical history are not generally recommended as a screening mechanism.
- Other testing, including basophil activation testing, is currently under investigation.
- Double-blinded placebo controlled food challenge remains the criterion standard of an FA diagnosis, although open food challenges are usually sufficient.

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