REVIEW ARTICLE

Practical approach to the diagnosis of food allergy

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Abstract

Food allergy has become the first clinical expression of atopy, beginning with dermal or gastric manifestations to continue with asthma and rhinitis ("the atopic march"), a very severe health problem not only for many children and parents but also for the entire medical and paramedical community.

Food allergy is defined as an abnormal immunological reaction to food proteins, which causes an adverse clinical reaction. Most people become tolerant to many foods; however, these tolerances sometimes fail and become an immunological reaction. The evaluation of a child with a suspected food allergy includes a detailed medical history, physical examination, screening tests and response to elimination diet and to oral food challenge. None of the screening tests—alone or in combination—can definitely diagnose or exclude it.

Key words: diagnosis, food, allergy, atopy, antigen.

Introduction

We carried a review on food allergy diagnosis in pediatric population focusing on clinical approach and the use of diagnosis tools. Food allergy is a frequent pathology that may lead to confusion, misdiagnosis and therapeutic errors. As with other medical conditions, food allergy diagnosis begins with clinical history and physical examination. Patient management will be determined based on this information.[1-4]

The ability to identify patient's symptoms is essential to differentiate between food-associated disorders, non-immunological intolerance reactions and immunological reactions (Figure 1).

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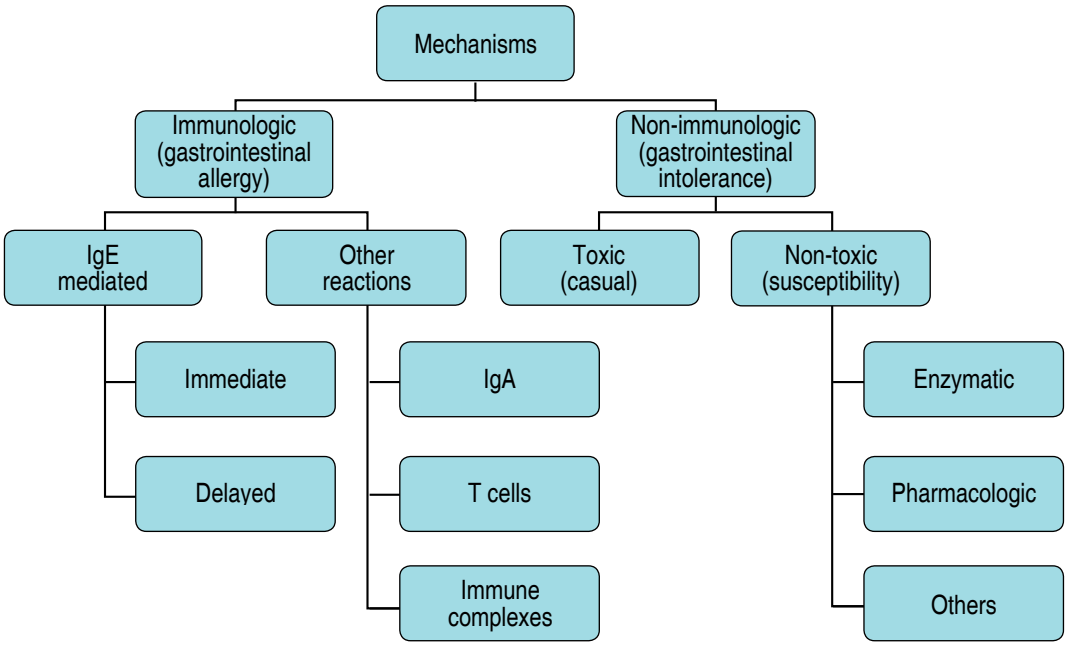
However, <50% food-allergies can be verified by the gold-standard for allergy diagnosis, the double-blind placebo-controlled food challenge (DBPCFC).[5,6]

Diagnosis

The following are required to establish the sequence of events during food-allergy reaction and proposed food challenge: 1) suspected food responsible for allergy, 2) type of food, 3) time elapsed between intake and symptom development, 4) history of similar symptoms developed in the past, 5) other associated factors (such as exercise) and 6) time elapsed since the last reaction (Table 1).

Any food can produce an allergic reaction; however, ~90% of allergies in adults are associated with peanuts, nuts, fish and shellfish, whereas in children they are associated with milk, eggs, soy and wheat. Nevertheless, clinical history is a not reliable marker when trying to identify the of-



Modified from Reference 44.

Figure 1. Classification of food adverse reactions.

Table 1. Clinical history for food allergies

Question	Possible meaning
Which is the suspected allergen?	Consider the typical allergen for patient's age and population.
Is the food allergen ingested, inhaled or by contact?	A portion of patients have reactions after inhalation or contact with the allergen.
Has the patient aversion to suspected allergen?	Patients usually reject the suspected allergenic food.
How frequently do symptoms occur after food allergen exposure?	IgE-mediated reactions usually occur within 20 min after exposure and definitely 120 min after exposure.
Which are specific symptoms and how severe are they?	If symptoms are non typical of allergy, then consider differential diagnosis. If symptoms are severe, an emergency plan should be in place.
How long do symptoms last?	Typical symptom resolution time after food reaction is 4-12 h.
Are symptoms experienced again after ingestion?	It is unlikely that a patient experiences food reactions only once. However, reactivity may vary depending on factors such as cooking (for instance eating raw or cooked egg) and the amount of antigen.
Does exercise trigger symptoms?	Excercise after allergen exposure may trigger symptoms (exercise-induced anaphylaxis)

fending allergen associated with chronic disorders (e.g., atopic dermatitis, asthma and urticaria, among others). Clinical history should include the nature of symptoms and the time elapsed between exposure and the first symptoms, consistency of allergic response and patient's response to treatment (Table 2).[7]

Daily records of symptoms are essential to study these conditions. Patient should be instructed to keep a chronological record of all food ingested during a specific period of time including those placed in his mouth only (such as a chewing gum) in order to report any symptom that helps determine the relationship between te ingested food and developed symptoms. In contrast with clinical history, this information is prospective and does not depend on the memory of the patient or family so it should be used selectively because the patient and family focus obsessively on food and not on other potential triggers.

Elimination diets are used both as a therapy and as a diagnostic tool because food suspected as being responsible for allergic reactions are completely removed from the diet. Their success depends on correct identification of allergens involved, the ability of the patient to ingest a complemental diet free of suspected allergens and assume other factors do not produce similar symptoms during the study period. Unfortunately, these conditions are seldom met. If parents of nursing infants who react to cow milk see their symptoms resolved after receiving soy formula, casein hydrolysate or elemental formula, this strongly suggests an allergic reaction, although it may also be associated with lactose intolerance. However, it is recommended to avoid suspected food allergens first before using a double-blind food challenge or extensive elimination diets.

Cutaneous allergy tests can be reproduced and are frequently used in patients with suspected food allergy through immunoglobulin E. Food extracts should be applied through the "prick test" technique, having an appropriate positive and nega-

Table 2. Differential diagnosis for adverse food reactions

Gastrointestinal disorders (vomiting or diarrhea)
Structure abnormalities
Hiatal hernia
Pyloric stenosis
Tracheoesophageal fistula
Enzymatic deficiency (primary *vs* secondary)
Disaccharidase deficiency (lactase, sucrase-isomaltase, glucose-galactose)
Galactosemia
Phenylketonuria
Malignancies
Pancreatic insufficiency (cystic fibrosis, Shwachman-Diamond syndrome)
Bladder disorders
Peptic ulcer
Other
Contaminants and additives
Flavonoids and preservatives
Sodium metabisulfite
Monosodium glutamate
Nitrites / nitrates
Dyes
Tartrazine, other azo-dyes
Toxins
Bacterial *(Clostridium botulinum, Staphyloccoccus aureus)*
Fungi
Associated with seafood
Scombroid food poisoning
Ciguatera fish poisoning
Saxitoxin (seafood)
Infecting organisms
Bacteria (Salmonella, Shigella, *Escherichia coli*, Yersinia, Campylobacter)
Parasites (Giardia, Trichinella)
Virus (hepatitis, rotavirus, enterovirus)
Fungal antigens (?)
Incidental contaminants
Heavy metals (mercury, copper)
Pesticides
Antibiotics (penicillin)
Dust/acari
Pharmacological agents
Caffeine (coffee and "diet" beverages)
Theobromine (chocolate, tea)
Histamine (fish)
Tryptamine (tomato, plum)
Serotonin (banana, tomato)
Phenylethylamine (chocolate)
Tyramine (cheese, pickled herring)
Solanine glycoside alkaloid (potatoes)
Alcohol
Physical reactions - aversions, phobias to food, etc.

Modified from Reference 7.

tive control. Bock established the criterion for its interpretation 30 years ago and affirmed the wheal should be >3 mm than positive control.[8] The usefulness of the mean diameter of the wheal as a reaction predictor has been recently evaluated, although this varies from one allergen to the next. Hill et al. reported that cutaneous tests that induce wheals with >8 mm diameter confirm allergy for milk, egg and peanuts with a clinical reaction prediction >95%[9]. In general, a wheal >3 mm diameter is regarded as a positive reaction when compared with negative control.[10,11]

In order to improve diagnosis, standardization of reagents and skin tests is required. If good quality food extracts are used, a positive result may be interpreted as a possibility that the patient has a reaction to a specific food. However, if the result is negative this confirms the absence of reaction through IgE (predictive negative value >95%).[5,8,12-15] There are certain exceptions to the above: 1) IgE regulates the sensitivity to several fruits and vegetables (e.g., apples, oranges, bananas, pears, melons, potatoes, carrots, celery) and is infrequently detected through commercial preparations perhaps because of lability of responsible allergens,[16] 2) commercial extracts sometimes lack the appropriate allergen as demonstrated with the use of fresh food for skin tests, 3) children <1 year of age may present IgE-regulated allergy in the absence of positive skin tests or when wheals are small, possibly because of poor skin reactivity,[17] 4) if a food has been clearly identified as the responsible agent for a serious anaphylactic response, a skin test should be avoided because of the implied risks.

The intrinsic predictive characteristics of the "prick test" can be affected by the quality of evaluated reagents and the technique used; therefore, these aspects should be considered during test interpretation. Sometimes it is best to use fresh food, particularly when testing fruits and vegetables subject to degradation. This is carried out through the "prick-prick test"[18,19] where a small sample is taken from the fresh food and the same instrument is used to puncture the skin, similar to the "prick test". Results are interpreted in the same way.

Intradermal tests are more sensitive than epidermal tests but less specific and increase the risk for inducing systemic reactions; therefore, they should be carried out under very special conditions.[8,12]

The interest in patch tests to diagnose non-IgE-mediated food allergy has increased in recent years.[20-22] Unfortunately, there are no standardized reagents or methods and their usefulness is limited. Recently, Mehl et al. concluded patch tests add a small diagnostic benefit when compared with standard diagnostic tests.[23]

The determination of *in vitro* allergen-specific IgE serum test has a lower sensitivity than skin tests[5] although some recent techniques reach a sensitivity up to 90%, such as the UniCAP system (detecting values >0.35 kU_A/L) and ImmunoCAP-Phadia (detecting values up to 0.1 kU_A/L).[24] Quantitative measurements have demonstrated having an important predictive value on IgE-mediated food allergy (Table 3).[25,26]

Levels exceeding "diagnostic values" indicate that the patient has >95% probability to experience an allergic reaction if he/she ingests a specific food. Also, IgE levels can be monitored and if they fall <2 kU_A/L for egg, milk or peanut, the patient should be reassessed to determine if he has "overcome" his food allergy.[27] Shek et al.[28] reported decreased percentages on specific IgE over time may predict the possibility to present tolerance to milk and egg. This helps physicians to provide a prognosis and evaluate the time required to carry out other food-challenges (Table 4).

Tests on basophil histamine release (BHR) are usually reserved for research purposes and use small blood quantities to search for multiple food allergens. These tests can avoid the problem of spontaneous histamine release in those individuals who continue allergen ingestion and show a good correlation with IgE-specific levels.[29] Intragastric-induced lower endoscopy has been used for more than 60 years[30] and relates positively with double-

Table 3. Food-specific IgE concentrations with high predictive clinical reactivity

Allergen/patient	IgE kU_A/L	Sensitivity	Specificity	PPV	NPV
Egg/ ≥2 years of age	7	61	95	98	38
≤2 years of age	2	–	–	95	–
Milk/ ≥1 year of age	15	57	94	95	53
≤1 year of age	5	–	–	95	–
Peanut	14	57	100	99	36
Fish	20	25	100	99	89
Soy	30	44	94	73	82
Wheat	26	61	92	74	87
Nuts	≈15			≈95	

PPV, positive predictive value.
NPV, negative predictive value.
Modified from reference 4.

blind placebo-controlled food challenges (DBPCFC),[31] although patients experienced systemic symptoms suggesting this procedure is not safer than oral challenges.

DBPCFC has been regarded as the "gold standard" to diagnose food allergy.[2] It has been used successfully both in children and adults. Selection of assessed foods is based on clinical history, skin tests or *in vitro* IgE results. Foods that are less likely to produce an allergic reaction should be evaluated in open or single-blind challenges. However, positive response should be confirmed through DBPCFC unless one or two "leading" allergens (egg, milk, soy, wheat) produce classic allergy symptoms or the patient is a breast-fed infant. Before carrying out a food-challenge it is necessary to eliminate the suspicious food 1-2 weeks prior and in case of a gastrointestinal disorder non-mediated by IgE this period should be longer. Antihistamine drugs should be withdrawn to avoid false negatives because of receptor blockage. Some asthmatic patients may require short steroid cycles to ensure the appropriate pulmonary reserve for evaluation [forced expiratory volume (FEV) >70% of predicted].[32-35] Food challenge is carried out in fasting state, starting with a quantity small enough that will unlikely produce symptoms (5-250 mg lyophilized food).[36] Dosage is doubled every 15-60 min depending on the expected reaction. Once the patient has tolerated the equivalent of a 10-g food dose, there are few chances he will present symptoms after that but this should be confirmed with free feeding under observation to discard a false negative challenge.

Table 4. Probability to develop egg and milk tolerance based on IgE-specific level reduction observed in 12 months

% of IgE level reduction in 12 months	Probability to develop tolerance	
	Egg	Milk
50	0.52	0.31
75	0.65	0.45
90	0.78	0.66
99	0.95	0.94

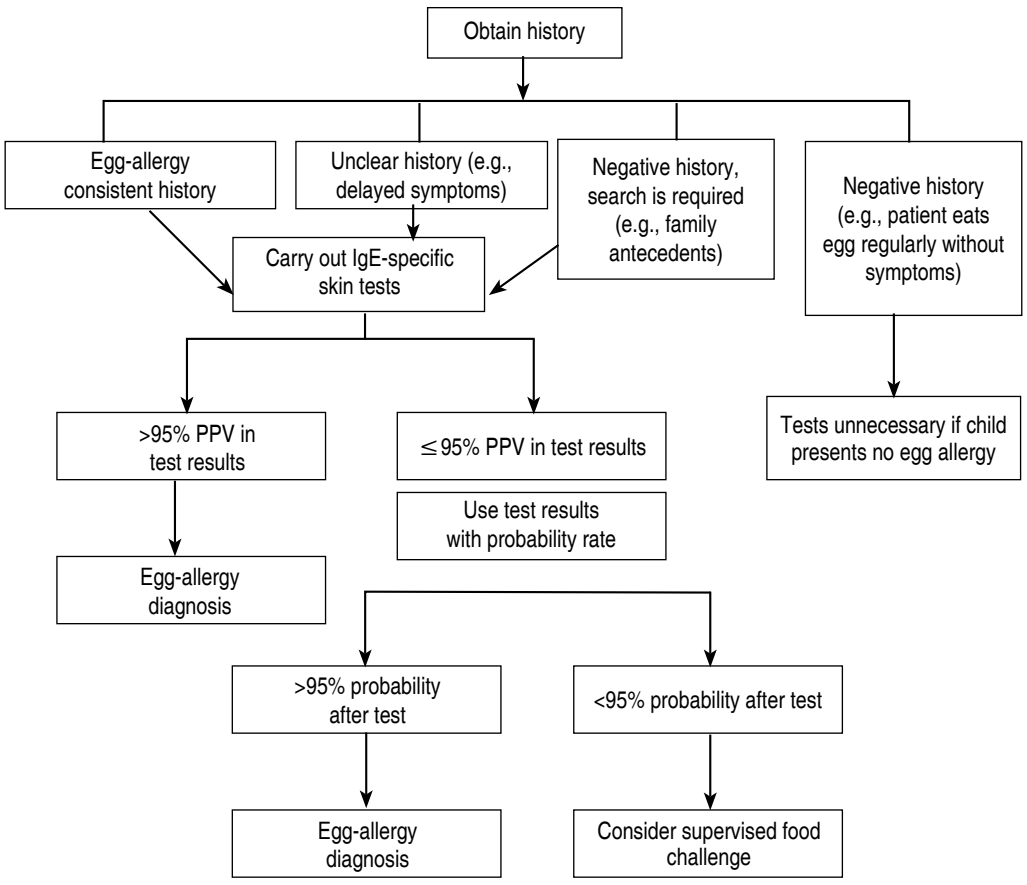
Modified from reference 27.

In order to avoid confusing factors, the same number of challenges should be carried out using alimentary antigen and placebo, administering them randomly by a third person.[37] Classification is made through a standardized system and observation time will depend on the expected reaction, e.g., 2 h for IgE-mediated reactions, >4-8 h for milk-induced enterocolitis, 3-4 days for eosinophilic allergic gastroenteritis, etc. Results shown by

blind challenges for expected signs and symptoms are seldom wrong but, in addition to clinical data, certain laboratory tests can be carried out such as histamine in plasma, pulmonary function tests and upper airway resistance.[38]

DBPCFC is the best method to control the large variability in chronic disorders (e.g., urticaria, atopic dermatitis) as well as any temporary effect and secondary acute reactions after reducing or withdrawing medication. Other triggering factors are controlled or at least neutralized; psychogenic factors, patient errors and observer errors are eliminated. False negative challenges are rare but may present when the patient does not receive the amount of food required to produce an allergic reaction or because the lyophilized sample is altered, changing relevant allergen epitopes (e.g., fish).

Food reactions non-mediated by IgE (e.g., food protein-induced enterocolitis) may require challenges with >0.3 g of food per body weight kilogram administered in one or two doses,[30,40] whereas allergic eosinophilic esophagitis/gastritis



Food allergy diagnosis using 95% PPV for IgE and skin tests

Food	IgE (kU_A/L)	Prick (mm)
Egg	6	7
Milk	32	8
Peanut	15	8
Fish	20	7
Nuts	15	8

PPV, positive predictive value.
Modified from Reference [45]

Figure 2. Egg-allergy diagnostic algorithm.

requires repeated administration over several days to produce symptoms. Most profiles mediated through IgE can be carried out every 1-2 days; however, non-mediated IgE reactions should be separated by at least 3-5 days.

Tests should be carried out in a hospital by trained personnel and with available equipment to treat a life-threatening anaphylactic reaction.[32,41] Assessment of several "delayed" reactions (e.g., most IgE-negative gastrointestinal allergies) can be carried out safely at the physician's office except for food protein-induced enterocolitis because IV access is required due to hypotension risk. When symptoms are unclear, the procedure should be repeated at least three times to conclude if there is any cause/effect relationship. When there is a history of life-threatening anaphylaxis, patients should only be challenged when the triggering antigen cannot be fully determined.

In conclusion, diagnosis of food-allergy is still a clinical procedure that depends on thorough clinical history, determination of specific IgE (either *in vivo* or *in vitro*), patch tests, an appropriate exclusion diet and blinded food challenges.

At the present time there is no evidence that supports the diagnostic value of IgG or IgG_4 antibody levels for specific foods,[42] the antigen-food complex, lymphocyte activation or intradermal or sublingual induction.[43] When there is a gastrointestinal problem, biopsies are required before and after food challenge.

When clinical profile is mediated by IgE, suitable treatment will require an elimination diet of all involved foods through clinical history or skin test, which should be carried out for at least 2 weeks. Food-induced enterocolitis and colitis require observation >12 weeks followed by suitable biopsies. If there are no improvements, it is unlikely to participate in food allergy.

As for atopic dermatitis and chronic asthma patients, other triggering factors may make difficult discrimination of food allergen effects from other triggering factors. Multiple allergies are more frequent, especially with minor allergens, so the physician should evaluate the benefit of identifying their clinical reactivity and the risk of food challenge. Elimination diets can lead to malnutrition or eating disorders, especially if they include a large amount of foods or are carried out for extended time periods.

Finally, we present an approach algorithm for patients with suspected food allergy, taking egg as an example (Figure 2).

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