Allergy 2005: 60 (Suppl. 79): 19–24

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ALLERGY

Original article

Food allergy – accurately identifying clinical reactivity

Up to 25% of adults believe that they or their children are afflicted with a food allergy. However, the actual prevalence of food allergy is much lower: approximately 6–8% of children suffer from food allergy during their first 3 years of life, and many children then develop clinical tolerance. Food allergy encompasses a whole spectrum of disorders, with symptoms that may be cutaneous, gastrointestinal or respiratory in nature. Food disorders also differ according to the extent that they are immunoglobulin E (IgE)-mediated. Skin-prick testing is often used to identify food sensitization, although double-blind, placebo-controlled food challenge (DBPCFC) tests remain the gold standard for diagnosis. Recent evidence suggests that quantitative IgE measurements can predict the outcome of DBPCFC tests and can replace about half of all oral food challenges. When an extensive medical history is obtained in combination with IgE quantification, even fewer patients may require formal food challenges. It has also become possible to map the IgE-binding regions of many major food allergens. This may help to identify children with persistent food allergy, as opposed to those who may develop clinical tolerance. In future, microarray technology may enable physicians to screen patients for a large number of food proteins and epitopes, using just a few drops of blood.

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Key words: diagnosis; food allergy; food challenge; immunoglobulin E; prevalence; skin prick test.

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Food allergies have become a major health concern in industrialized, westernized countries in the past two decades. Surveys suggest that between 5 and 25% of adults believe that they or their children are afflicted with a food allergy (1, 2). Although these questionnaire surveys undoubtedly overestimate the true prevalence of food allergy, validated studies indicate that food allergic disorders affect 6–8% of children in their first 3 years of life (3) and then decrease in prevalence over the first decade. It is estimated that about 4% of the American population is affected with food allergies (4). Table 1 presents the estimated prevalence of various food allergies in American children and adults. Of note, a recent study indicated that peanut allergy in children below 5 years of age has doubled in the past 5 years (5). Overall, about 80–85% of young children with milk and egg allergies have been shown to outgrow their allergy, i.e. develop clinical tolerance, in the first 5–10 years of life, whereas only about 20% of children with peanut allergy outgrow their response (6, 7). Children with atopy (atopic dermatitis, allergic rhinitis and/or asthma) are more likely to have a food allergy than nonatopic children; around 35% of children with moderate-to-severe atopic dermatitis have immunoglobulin E (IgE)-mediated food allergy (8), and around 6–8% of asthmatic children have food-induced wheezing (9).

Signs and symptoms of food allergy

Allergic reactions to foods may provoke characteristic responses in the gastrointestinal tract, skin and respiratory tract, regardless of the immunopathogenic mechanism responsible for the reaction. Gastrointestinal symptoms may consist of oral pruritus, swelling of the lips or tongue, pruritus and/or a sensation of tightness of the throat, nausea, crampy abdominal pain, vomiting, diarrhoea and melena. Cutaneous symptoms include generalized pruritus, an erythematous morbilliform rash or flushing, urticaria and angioedema. Respiratory symptoms may involve the larynx and the upper or lower respiratory tract. Typical symptoms include those of allergic rhinoconjunctivitis, i.e. periocular pruritus, conjunctival erythema and tearing, and nasal pruritus, congestion, rhinorrhoea and sneezing; laryngeal oedema, i.e. stridor, staccato cough, hoarseness and sensation of tightness; and asthma, i.e. dyspnoea, cough and wheezing. As reviewed elsewhere and depicted in Tables 2–4, a variety of food allergic disorders secondary to IgE-mediated and non-IgE-mediated mechanisms have been described (10).

Food-allergic disorders

The pollen-food allergy syndrome (oral allergy syndrome) is probably the most common food allergic disorder and

Table 1. Estimated prevalence of food allergies in the USA

Food	Children <5 years (%)	Adults (%)
Milk	2.5	0.3
Egg	1.3	0.2
Peanut	0.8	0.6
Tree nuts	0.2	0.5
Fish	0	0.4
Shellfish	0.1	2.0
Overall	6	3.7

is elicited by a variety of plant proteins that cross-react with airborne allergens, especially birch and ragweed pollens (11). It is estimated that up to 50% of patients with birch or ragweed-induced allergic rhinitis may suffer from this disorder. Birch-pollen-allergic patients may develop symptoms following the ingestion of raw potatoes, carrots, celery, apples, pears, hazelnuts and kiwi fruits, and ragweed, allergic patients may react to fresh melons and bananas. Grass-pollen-allergic patients may develop symptoms when ingesting raw tomatoes.

Allergic eosinophilic oesophagitis (AEE) appears to be increasing in prevalence and may be due to IgE- and/or non-IgE-mediated food allergy. The condition is characterized by infiltration of the oesophagus, stomach and/or intestinal walls with eosinophils (12, 13). AEE typically presents with symptoms of gastro-oesophageal reflux, i.e. nausea, dysphagia, vomiting and epigastric pain (14, 15). Some patients appear to have an association between pulmonary and oesophageal inflammation, with some patients reporting seasonal oesophageal symptoms (16). The long-term prognosis of AEE has not been clearly delineated, but there is concern that patients who are not appropriately treated may go on to develop Barrett's oesophagitis (16).

As depicted in Table 3, IgE-, non-IgE- and mixed reactions to foods can induce a variety of cutaneous hypersensitivity disorders. Acute urticaria and angioedema are believed to be among the most common symptoms of food allergic reactions, although the exact prevalence of these reactions is unknown. Acute contact urticaria because of food, e.g. meats, vegetables, fruits, is also common. Food allergies play a pathogenic role in

Table 2. Gastrointestinal food hypersensitivities (41), adapted with permission

Disorder	Mechanism	Symptoms	Diagnosis
Pollen-food allergy syndrome (oral allergy syndrome)	IgE-mediated	Mild pruritus, tingling and/or angioedema of the lips, palate, tongue or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms	Clinical history and positive SPT to relevant food proteins (prick-to-prick method); ± oral challenge (positive with fresh food, negative with cooked food)
Gastrointestinal anaphylaxis	IgE-mediated	Rapid onset of nausea, abdominal pain, cramps, vomiting, and/or diarrhoea; other target organ responses, i.e. skin, respiratory tract, often involved	Clinical history and positive SPTs or RASTs; ± oral challenge
Allergic eosinophilic oesophagitis	IgE- and/or cell-mediated	Gastro-oesophageal reflux or excessive spitting-up or emesis, dysphagia, intermittent abdominal pain, irritability, sleep disturbance, failure to respond to conventional reflux medications	Clinical history; SPTs; endoscopy and biopsy; elimination diet and challenge
Allergic eosinophilic gastroenteritis	IgE- and/or cell-mediated	Recurrent abdominal pain, irritability, early satiety, intermittent vomiting, failure to thrive and/or weight loss	Clinical history; SPTs; endoscopy and biopsy; elimination diet and challenge
Food protein-induced proctocolitis	Cell-mediated	Gross or occult blood in stool; typically thriving; usually presents in first few months of life	SPTs negative; elimination of food protein results in clearing of most bleeding within 72 h; ± endoscopy and biopsy; challenge induces bleeding within 72 h
Food protein-induced enterocolitis	Cell-mediated	Protracted vomiting and diarrhoea (± bloody) not infrequently with dehydration; abdominal distention, failure to thrive; vomiting typically delayed 1–3 h postfeeding	SPTs negative; elimination of food protein results in clearing of symptoms within 24–72 h; challenge induces recurrent vomiting within 1–2 h, ~15% develop hypotension
Food protein-induced enteropathy, e.g. coeliac disease (gluten-sensitive enteropathy)	Cell-mediated	Diarrhoea or steatorrhoea, abdominal distention and flatulence, weight loss or failure to thrive, ± nausea and vomiting, oral ulcers	Endoscopy and biopsy IgA; elimination diet with resolution of symptoms and food challenge; coeliac disease: IgA anti-gliadin and anti-transglutaminase antibodies

IgE, immunoglobulin E; SPT, skin prick test; RAST, radioallergosorbent test.

Table 3. Cutaneous food hypersensitivities (41), adapted with permission

Disorder	Mechanism	Symptoms	Diagnosis
Acute urticaria and angioedema	IgE-mediated	Pruritus, hives and/or swelling	Clinical history; positive SPTs or RASTs; ± challenge
Chronic urticaria and angioedema	IgE-mediated	Pruritus, hives, and/or swelling of >6 weeks duration	Clinical history; positive SPTs or RASTs; elimination diet; challenge
Atopic dermatitis (atopic eczema dermatitis syndrome)	IgE- and cell-mediated	Marked pruritus; eczematous rash in a classic distribution	Clinical history; positive SPTs; CAP-System® FEIA (i.e. quantitative IgE); elimination diet and food challenges
Contact dermatitis	Cell-mediated	Marked pruritus; eczematous rash	Clinical history; patch test
Dermatitis herpetiformis	Cell-mediated	Marked pruritus; papulovesicular rash over extensor surfaces and buttocks	Skin biopsy (IgA deposition); IgA anti-gliadin and anti-transglutaminase antibodies; ± endoscopy

IgE, immunoglobulin E; SPT, skin prick test; RAST, radioallergosorbent test; FEIA, fluorescent enzyme immunoassay; IgA, immunoglobulin A.

Table 4. Respiratory food hypersensitivities (41), adapted with permission

Disorder	Mechanism	Symptoms	Diagnosis
Allergic rhinoconjunctivitis	IgE-mediated	Periocular pruritus, tearing, and conjunctival erythema, nasal congestion, rhinorrhoea, sneezing	Clinical history, SPTs, elimination diet, food challenge
Asthma	IgE- and cell-mediated	Cough, dyspnoea, wheezing	Clinical history, SPTs, elimination diet, food challenge
Heiner's syndrome (food-induced pulmonary haemosiderosis)	Unknown	Recurrent pneumonia, pulmonary infiltrates, haemosiderosis, iron-deficiency anaemia, failure to thrive	Clinical history, peripheral eosinophilia, milk precipitins (if due to milk), ± lung biopsy, elimination diet

IgE, immunoglobulin E; SPT, skin prick test.

about 35% of children with moderate-to-severe atopic dermatitis (atopic eczema dermatitis syndrome), a form of eczema that generally begins in early infancy and is characterized by typical distribution, extreme pruritus and a chronically relapsing course (17). Allergen-specific IgE antibodies bound to Langerhans cells play a unique role as 'nontraditional' receptors (18). In one study, about 45% of adult patients with atopic dermatitis and birch-pollen allergy were reported to develop worsening of their eczema within 48 h of ingesting Bet v1-containing foods (e.g. raw apples, carrots, celery), even in the absence of noticeable immediate oral symptoms (19).

Symptoms of acute allergic rhinoconjunctivitis are rarely elicited as the sole manifestation of food allergy, although they commonly occur in conjunction with other allergic symptoms (see Table 4). Asthma is uncommonly provoked by food allergy, although acute bronchospasm is often seen with other food-induced symptoms (20). However, airway hyperreactivity and worsening of asthma may be induced in the absence of marked bronchospasm following the ingestion of small amounts of food allergens in sensitized subjects (21). In addition, food allergy was recently found to be a major risk factor for severe life-threatening asthma. Roberts et al. (22) reported that approximately 50% of asthmatic children requiring intubation for severe asthma had food allergy, compared with around 10% of asthmatics seen at the same hospital. Food-induced asthmatic symptoms should be suspected in patients with refractory asthma and a history of atopic dermatitis, gastro-oesophageal reflux, food allergy or feeding problems as an infant, or a history of positive skin tests or reactions to a food.

Food allergy is the most common single cause of anaphylaxis occurring outside of the hospital (10). Patients typically present with a variable expression of cutaneous, respiratory and gastrointestinal symptoms and may develop cardiovascular symptoms, including hypotension, vascular collapse and cardiac dysrhythmias (23, 24). At odds with our current understanding of anaphylaxis, serum β-tryptase, a marker of mast-cell activation, is rarely elevated in food-induced anaphylaxis (23, 25). Surveys of fatal food-induced anaphylactic cases have identified a number of common factors: most victims are adolescents or young adults, virtually all had a previous history of reacting to the implicated food (usually not life-threatening and often mild), virtually all of the victims had asthma, only 10% had self-injectable epinephrine available for use at the time of their reaction, and peanuts or tree nuts are responsible for the vast majority (94%) of the fatalities in the United States. Food-associated exercise-induced anaphylaxis is a form of anaphylaxis that occurs only when the patient exercises within 2–4 h of ingesting a food. It may account for up to 50% of the cases of exercise-induced anaphylaxis and is most common in females 15–35 years of age (26). In the absence of exercise, patients with this disorder can ingest the trigger food without any apparent reaction (27).

Diagnosing food allergy

The double-blind, placebo-controlled oral food challenge (DBPCFC) is the gold standard for diagnosing food allergy (10). However, medical histories, laboratory studies, elimination diets and, in some cases, supervised open food challenges are often used by practitioners to

diagnose food-allergic conditions. A thorough medical history should ascertain the following information:

- the food suspected of provoking the reaction and the quantity ingested,
- the length of time between ingestion and the development of symptoms,
- whether ingesting the suspected food produced similar symptoms on other occasions,
- whether other factors such as exercise or alcohol ingestion occurred around the time of ingestion and
- how long ago the patient experienced the last reaction to the food. Although the history is essential for planning the remainder of the evaluation, history alone corresponds to the outcome of a positive DBPCFC in about 30–40% of cases.

A number of laboratory studies are utilized to assist in the diagnosis of IgE-mediated food allergy. Skin-prick testing provides a rapid method to screen patients for sensitivity to specific foods. Food allergens eliciting a wheal at least 3 mm greater than the negative control are considered positive, indicating the possibility that the patient has symptomatic reactivity to the specific food, with strongly positive results, e.g. median wheal diameter >8–10 mm indicating a greater likelihood of clinical reactivity. In one study of infants above 2 years of age, skin-prick tests (SPTs) to milk or egg with wheal diameters ≥8 mm were reportedly >95% predictive of clinical reactivity (28). Negative skin tests essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy >95%) (29). In general, negative SPTs are extremely useful for excluding IgE-mediated food allergies, whereas positive skin tests, for the most part, suggest the presence of clinical food allergy. When evaluating allergic reactions to many fruits and vegetables (e.g. apples, oranges, peaches, potatoes, carrots, celery), commercially prepared extracts are less useful because of the lability of the responsible allergen, so fresh foods are used for prick-to-prick (i.e. prick the fruit and then prick the skin) skin testing (30).

The radioallergosorbent test and similar semi-quantitative *in vitro* assays also provide suggestive evidence of IgE-mediated food allergy, but these assays are being replaced by more quantitative measurements of food-specific IgE antibodies (e.g. CAP System® fluorescent enzyme immunoassay or UniCAP®; Pharmacia Diagnostics; Uppsala, Sweden), which have been shown to be more predictive of symptomatic IgE-mediated food allergy (31–34). Table 5 provides diagnostic levels of food-specific IgE antibodies for a variety of foods. When a patient has a food-specific IgE level exceeding any of these values, they are more than 95% likely to experience an allergic reaction if they ingest the specific food. As indicated in Fig. 1, there is a direct correlation between the food-specific IgE level and the probability that an individual will react to an ingested food. Consequently, when the medical history is taken into account, a clinician may conclude that an allergen-specific IgE level, which is 50% predictive of clinical reactivity, is sufficient to make the diagnosis of clinical food allergy. It should also be noted from Fig. 1 that a patient with an allergen-specific IgE < 0.35 kU/l may still experience an allergic reaction. Consequently, if there is any suspicion of possible allergic reactivity, a negative SPT and/or physician-supervised food challenge are necessary to confirm absence of clinical food allergy.

Table 5. Food-specific IgE concentrations predictive of clinical reactivity (41), adapted with permission

Allergen	95% predictive level (kU_A/l)	Positive predictive value (%)
Egg	7	98
Infants ≤ 2 years (34)	2	95
Milk	15	95
Infants ≤ 2 years (33)	5	95
Peanut	14	95
Fish	20	100
Tree nuts (42)	~15	~95
Soybean	30	73
Wheat	26	74

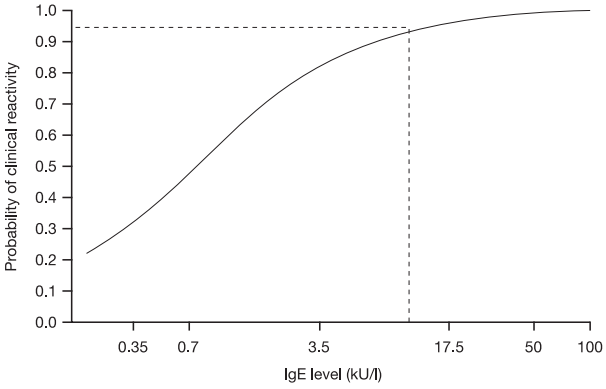


Figure 1. Peanut immunoglobulin E levels.

A number of recent advances in technology have enabled investigators to map the IgE-binding regions (allergenic epitopes) of many major food allergens and determine specifically where patients' IgE antibodies bind to these proteins (10). In mapping major food allergens such as egg and milk, it was found that both conformational and sequential epitopes are responsible for allergic reactions. Individuals who possess IgE antibodies primarily to conformational epitopes appear to tolerate small amounts of the food after extensive heating or partial hydrolysis because the tertiary structure of the protein is altered and the conformational epitopes are destroyed, whereas those with IgE antibodies to sequential epitopes react to the food in any form, i.e. extensively cooked, partially hydrolysed etc. (35, 36). In addition, it has been shown that egg- and milk-allergic patients with IgE antibodies directed at specific (informative)

sequential epitopes tend to have persistent allergy, whereas those with IgE antibodies primarily to conformational epitopes tend to develop clinical tolerance (37, 38). Further analysis revealed that determining epitope-specific binding may correlate better with clinical reactivity than determining quantitative IgE values to the whole food protein (39), and evaluating the number of allergenic epitopes bound by patients' IgE antibodies may be useful for predicting the clinical severity of food-allergic reactions (40). New miniaturized technology under development (protein and peptide microarrays) may, in the future, enable physicians to screen patients for a large number of food proteins and epitopes using just a few drops of blood, and tell whether they will react to specific foods, identify potential cross-reactivities to other foods based on homologous epitopes, and predict how severe the patients' reactions may be and whether they are likely to outgrow their food allergy.

Conclusions

While the DBPCFC still provides the definitive diagnosis of specific food allergies, a number of recent developments are improving the predictive value of laboratory tests. The use of quantitative food-specific IgE antibody levels has greatly increased the positive predictive value of these studies and eliminated the need to challenge around 50% of the patients who formerly would have required food challenges for diagnosis. When a careful, comprehensive medical history is obtained and used in conjunction with these IgE-antibody levels, even fewer patients may require formal food challenges. With the development of assays that analyse epitope-specific binding, future tests may further increase the positive predictive value of laboratory tests, provide information on the natural history of the allergy, i.e. whether the patient may outgrow their food allergy, suggest possible clinically relevant cross-reactivities with other foods, and perhaps provide information on the potential severity of their food-allergic reactions.

Key points

- The actual prevalence of food allergy is lower than that perceived by the general public.
- IgE tests predict the outcome of DBPCFC tests and can replace about half of all oral food challenges.

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