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Continuous Medical Education

Food allergy

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People eat approximately 2 to 3 tons of food in their lifetimes. Most people do not have an adverse reaction to foods. However, many people - approximately 25% of the United States population - believe that they have an allergic reaction to foods; but, the actual incidence confirmed by history and challenges suggests a prevalence rate closer to 2% to 8% in young infants and less than 2% in adults. The most common food allergens are milk, egg, peanut, soy, wheat, tree nuts, fish and shellfish[1].

Milk is the most common food allergen, with approximately 2% of infants having food intolerance or allergy compared with 1.3% for egg and 0.5% for peanuts and lesser rates for the other foods. Reactions to foods are not new and have been described for 2000 years. The ancient Greek physician Hippocrates described a reaction to milk in the first century. Anaphylactic reactions to egg and fish have been described as early as the sixteenth and seventeenth centuries[1].

It has 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[2].

PATHOGENESIS

For particles of food proteins to create an immune reaction, they must be absorbed, processed, and presented to an active immune system leading to an adverse reaction. The food protein first is processed in the mouth by salivary amylases and mastication and then is processed further down the gastrointestinal (GI) tract by gastric, pancreatic, and intestinal enzymes. After this processing, the food antigen penetrates the intestinal barrier, which consists of epithelial cells, glycocalyx, microvilli, tight junctions, and intestinal peristalsis. Food enters the systemic circulation by one of several mechanisms, including endocytosis or passage through the tight junctions[3]. Soluble IgA can block penetration of foods, and food antigen-specific IgA and IgG can clear the food antigen[4]. Therefore, only 2% of ingested food antigens are absorbed and transported throughout the body in an "immunologically" intact form or recognizable antigen. Food antigens then can cause three types of immune responses: (1) IgE mediated reaction, (2) non IgE mediated reaction, and (3) tolerance (i.e. , no reaction)[1].

Table 1. Immune-mediated adverse reactions involving the gastrointestinal (GI) tract

IgE mediated	
	Oral allergy syndrome
	Immediate GI hypersensitivity
Non IgE Mediated	
	Food protein-induced enterocolitis, proctitis, enteropathy
	Celiac disease
Mixed immune mechanisms (IgE and T-cell mechanism)	
	Eosinophilic esophagitis (EE), gastroenteritis, gastritis

(Quoted from Sampson, 1999)[1].

Table 2. Other food-induced immune disorders

Cutaneous	
	Acute uritcaria and angioedema
	Contact urticaria
	Chronic urticaria and angioedema
	Atopic eczema dermatitis syndrome (AEDS)
	Dermatitis herpetiformis
Respiratory	
	Allergic rhinitis
	Asthma
	Food-induced pulmonary hemosiderosis
Anaphylaxis	

(Quoted from Sampson, 1999)[1].

IgE-mediated reactions

The development of an IgE-mediated response to an allergen is the result of a series of interactions involving antigen-presenting cells (APCs), T Cells, and B cells. Once produced, antigen-specific IgE circulates by the bloodstream to the relevant mucosa and tissue sites and binds to the IgE receptor (FcεR) bearing cells. Food antigen then can bind to the specific IgE on the surface of mast cells, basophils, eosinophils, and macrophages, causing intracellular signaling and the production and release of histamine, prostaglandins, leukotrienes, and cytokines. For this IgE-mediated reaction to occur, the body must have been exposed to the antigen with priming of

the immune system. Interestingly, the first exposure can be in utero or through breast milk. Subsequent exposure in the sensitized host can lead to an immediate hypersensitivity reaction in varying target organs[5].

Non-IgE-mediated (T cell-mediated) reactions

The biology and documentation of food-specific T cell mediated reaction are currently not well understood. The strongest evidence comes from the identification of food-specific T cells in AEDS. The other clinical indications that T Cell-mediated food allergies exist arise from clinical experience. These patients have reactions to foods and are skin test negative[6].

Oral tolerance

A host is tolerant when food protein can enter the systemic circulation or contact any immune reactive cell and does not trigger an immune reaction. Three mechanisms have been associated with immune tolerance: (1) clonal anergy, (2) clonal deletion, and (3) active suppression.

In simplified terms, the T cells can be inhibited actively or passively. In the passive model, T cells are no longer stimulated by the respective food antigen. This lack of stimulation leads to decreased growth and eventually cell death. In the active model, clonal deletion, T cell death occurs after interaction with self-antigens and MHC cells that are developing within the thymus. The third mechanism for tolerance, active suppression, may be related to the mechanism of antigen presentation in the gut. M cells (i.e., specialized epithelial cells overlying the Peyer's patches) and intestinal epithelial cells (IECs) are the major sites of immune antigen sampling in the intestine[7]. Infants may have a higher incidence of food allergies because of how food is processed and presented to the immune system. Infants have immature systems, with decreased stomach pH, decreased enzyme activity and a low concentration of secretory IgA. These factors may lead to increased level of food antigen in the systemic circulation and to possible food allergy. As the intestinal tract matures, the T cell may be exposed to less antigen, leading to less stimulation of food-specific T cells[8].

CLINICAL MANIFESTATIONS

I- IgE-mediated gastrointestinal disorders

1) Oral allergy syndrome

The oral allergy syndrome is more prevalent in adults than in children. Symptoms are restricted essentially to the oropharynx and include rapid onset of itch or discomfort (e.g., "tingling"). Angioedema also may occur, and when accompanied by the sensation of throat tightness, it may be confused with a more severe systemic reactions. Symptoms are usually brief and triggered by various fruits and vegetables[1].

2) Immediate hypersensitivity reactions

Isolated immediate hypersensitivity reactions in the gastrointestinal tract (GIT) induced by food proteins can occur at any time in life. As expected from the mechanism, they usually develop within minutes of ingestion or as long as 2 hours later. Rapid onset within this time frame is an important diagnostic clue for the presence of an IgE-mediated or true immediate hypersensitivity process. Symptoms include vomiting, nausea, colic, abdominal pain, and diarrhea. Vomiting is the most explosive presentation, but this may be reduced in patients with long-standing exposure, possibly secondary to partial desensitization[9].

3) Constipation and IgE sensitization to cow's milk

A distinctive syndrome consisting of constipation and IgE sensitization to cow's milk has been described. After careful evaluation, most patients had symptoms and endoscopic evidence of proctitis. Constipation was relieved by milk protein elimination[9].

II- Non-IgE-Mediated Gastrointestinal Disorders

1) Food protein-induced enterocolitis syndrome

Enterocolitis induced in infants by cow's milk and/or soy protein has been recognized for decades. Symptomns typically begin in the first month of life in association with failure to thrive and may progress to acidemia and shock. Symptoms resolve after the causal protein is removed from the diet but recur with a characteristic symptom pattern on re-exposure. Approximately 2 hours after re-introduction of the protein, vomiting ensues, followed by an elevation of the peripheral blood polymorphonuclear leukocyte count, diarrhea and possibly lethargy and hypotension[10].

2) Food protein-induced proctitis

Food protein-induced proctitis is found early in infancy, presenting with blood-streaked stools in generally well-looking patients. Blood loss is rarely severe, and bowel lesions (eosinophil and neutrophil infiltration) are limited to the distal large bowel. Most common triggers are milk and soy formulas, but this syndrome also occurs in breast fed infants[9,11].

3) Food protein-induced enteropathy

Food protein-induced enteropathy is another disorder of infancy, presenting early with diarrhea and poor weight gain. Vomiting is common, together with malabsorption. Intestinal biopsy reveals villous atrophy and cellular infiltration which are likely responsible for the poor absorption of nutrients and protein loss leading to edema in some patients. Anemia is less common. Milk sensitivity is the most common trigger, but soy, egg, wheat, and other foods can be associated[9].

4) Celiac disease

Celiac disease is a specific food protein-induced enteropathy in which patients react to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley[12]. Diagnosis is made by documentation of typical abnormality (villous atrophy and cellular infiltrate), which is reversed by the elimination of gliadin from diet. Most patients produce IgA antigliadin and antiendomysial antibodies. GIT symptoms include weight loss, chronic diarrhea, steatorrhea, and associated abdominal distension. Extraintestinal features include oral ulcers[13].

III- Combined IgE-and T cell-mediated gastrointestinal disorders

1) Eosinophilic gastroenteritis

Eosinophilic gastroenteritis has been found in all age groups, with the predominance in early to mid adulthood.[14] Eosinophilic gastroenteritis presents with a variety of symptoms, including abdominal pain, diarrhea, melena, weight loss, and others. However, many other entities can present with eosinophils in the GI tract, including gastroesophageal reflux disease (GERD), parasitic infection, or inflammatory bowel disease. The diagnosis of eosinophilic gastroenteritis can be made only if other pathologic disorders have been eliminated. In this disorder, T-cell and IgE mechanisms may co-exist[9,15].

2) Eosinophilic esophagitis

Eosinophilic esophagitis (EE), primary EE, or idiopathic EE occurs in adults and children and may represent a disease subset or variant of eosinophilic gastroenteritis[15]. Patients with EE present with symptoms similar to those of GERD but are unresponsive to antireflux medications and have normal pH probe studies. Vomiting and abdominal pain are the most common symptoms, but other common symptoms include anemia (occult blood loss), weight loss, achalasia, and failure to thrive[9,16].

IV- Other food-induced immune disorders.

A) Cutaneous disorders

The skin is very much exposed to food contact, both in the occupational and non-occupational settings. Through such an exposure, adverse reactions can occur that may be irritant or immunologic. Both such types of reactions are particularly common in children with atopic dermatitis. Immunologic reactions can be IgE-mediated or delayed (cell-mediated), and can be localized or systemic. The latter can be life-threatening, even following trivial exposure. Clinical and experimental data are accumulating to indicate that epicutaneous exposure to food can induce de novo systemic immunoglobulin E sesitization[17].

1) Acute urticaria or angiodema

Here, the reactions are mediated by antigen-specific IgE triggered by absorbed food proteins delivered to the skin by the circulation. They often occur during severe systemic reactions, but cutaneous reactions can represent the sole systemic consequence of food allergen ingestion[18].

2) Topical urticarial reactions

Isolated topical utricarial reactions may also occur. The skin may react only from local contact without systemic absorption. Differentiation between cutaneous reactions caused by limited local contact versus systemic absorption can be difficult in infants who may ingest variable amounts of food or none but still cover their faces and other areas of the body with food. This type of clinical scenario obviously requires careful evaluation[18].

3) Chronic urticaria and angioedema

In contrast to acute skin reaction, chronic urticaria and angioedema (duration > 6 weeks) are rarely associated with food sensitivity, especially in children[18].

4) Atopic eczema dermatitis syndrome (AEDS)

It is a chronic inflammatory skin disorder. The role of food allergy in AEDS has been reviewed extensively[19]. Like other allergic diseases, the prevalence of AD seems to be increasing, changing from 3% to 4% in the 1960s to 10% in the 1980s. The major features include pruritus, typical morphology, and distribution of the lesions. The skin distribution varies with age. In infancy, the face and extensor surfaces of the arms and legs are most commonly affected. In older children and adults, a scaly and lichenified dermatitis on the flexor surfaces of the extremities, neck, and upper trunk is observed[20].

5) Dermatitis herpetiformis

Dermatitis herpetiformis is a non-IgE-mediated skin disorder that presents as a pruritic rash distributed over extensor surfaces and buttocks that may be mistaken for AEDS. It can be associated with celiac disease and sensitivity to gluten. Dermatopathology of the skin reveals IgA deposits in the dermoepidermal junctions, whereas GIT lesions resemble celiac disease[13].

B) Respiratory disorders

1) Nasal and bronchial.

Nasal and bronchial reactions to food are uncommon unless multiple target organs (e.g., skin and GI tract) are involved. The rarity of isolated nasal reactions has been documented in challenge studies. The rate of respiratory reactions documented in food challenge studies ranges from 6% to 25% of various populations, with the highest incidence among children with AEDS and asthma[1,18].

2) Food-induced pulmonary hemosiderosis.

The immune mechanisms underlying food-induced pulmonary hemosiderosis (Heiner's syndrome) are unknown. It is most often associated with sensitivity to milk or eggs. The syndrome is characterized by pulmonary infiltrates associated with hemosiderosis, GIT blood loss, anemia, and failure to thrive[21].

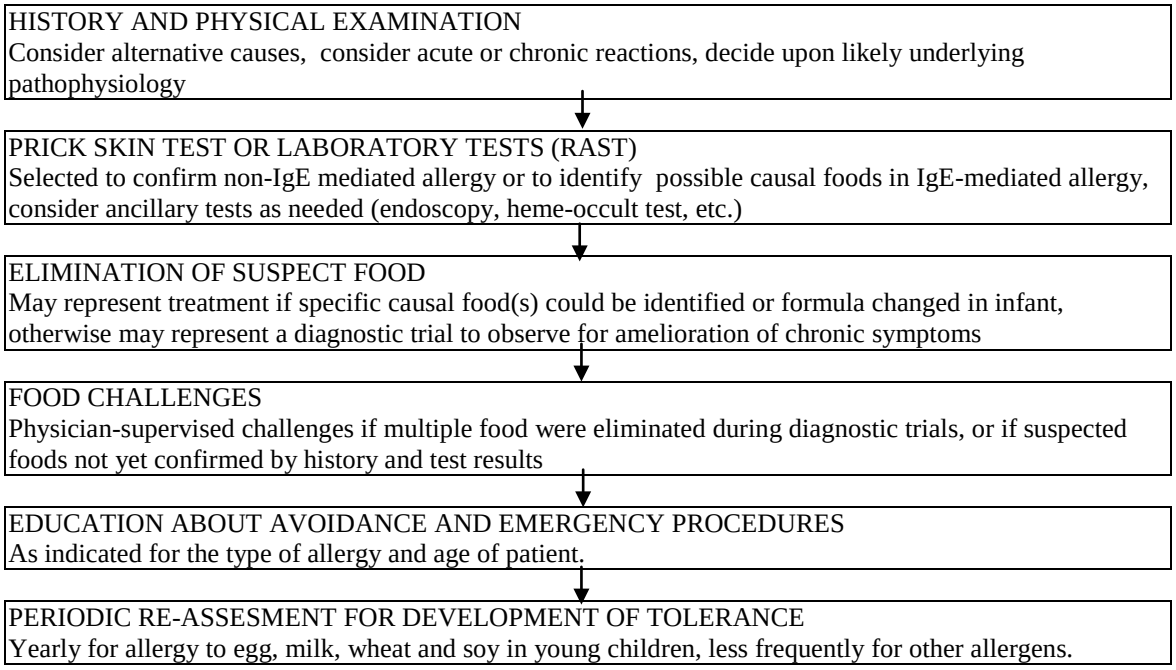
C) Anaphylaxis Syndromes

Here, an initial or "immediate" reaction, triggered by an IgE-mediated mechanism, is followed hours later by a "late-phase" reaction caused by a second wave of inflammation. The delayed resurgence of possible severe symptoms has obvious treatment implications[21]. Anaphylaxis can be associated with exercise, and, in an unusual form, the ingestion of a specific food(s) 2 to 4 hours before exercise is a necessary condition for anaphylaxis to occur. This rare condition usually occurs in teenagers and younger adults who are generally atopic and some of whom have a history of food sensitivity in earlier years[22,23].

DIAGNOSIS

Several approaches have been used for food allergy diagnosis including 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[24]. A suggested scheme is presented in Figure (1).

Figure 1. General scheme for the diagnosis of food allergy.



(Quoted from Ortolani et al., 1989)[25].

DIFFERENTIAL DIAGNOSIS

Non immune-mediated adverse reactions:

1- Metabolic
- Disaccharidase deficiency: lactase deficiency
- Glucose-6-phosphate dehydrogenase deficiency
- Pancreatic insufficiency: cystic fibrosis
- Galactosemia
- Phenylketonuria

2- Pharmacologic
- Caffeine
- Histamine
- Tyramine

3- Toxic
- Flavorings and preservatives: sodium metabisulfite
- Dyes: tartazine
- Bacterial and fungal toxins: C. botulinum, aflatoxin
- Seafood toxins: scromboid (tuna, mackerel)
- Contaminants: heavy metals, pesticides

4- Infectious
- Parasitic: Giardia
- Bacterial: Salmonella
- Viral hepatitis

5- GIT disorder: GERD, tracheo-esophageal fistula, malrotation, peptic ulcer.

6- Psychological : school phobia.

7- Functional: Irritable bowel syndrome, chronic non specific diarrhea of infancy.

(Quoted from Spergel & Pawlowski, 2002)[26]

GENERAL THERAPEUTIC CONSIDERATIONS

The only proved therapy for food allergy is food elimination, which may require an intensive learning process and work on the patient's and caregiver's parts because of pervasiveness or hidden allergens. For patients presenting with mild symptoms of an acute allergic reaction. Antihistamines may be the only required medication to reduce itching/rash caused by the release of histamine. The initial assessment of the patient suspected of acute anaphylaxis includes evaluation of the airway, breathing, and circulation. Emergency care includes the rapid administration of epinephrine and antihistamines with consideration for administering corticosteroids, oxygen, intravenous fluids, inhaled bronchodilators, and medications to support blood pressure and to stabilize the patient for transport for advanced care. Epinephrine is the drug of choice for treatment of anaphylaxis. Intramuscular injection allows for more immediate and efficient absorption compared with the subcutaneous route. The dose of 0.01 mL/kg of 1:1000 dilution of aqueous epinephrine (maximum dose, 0.3-0.5 mL, 0.3-0.5 mg) should be delivered promptly. Intravenous epinephrine carries the risk of dysrhythmias and should be reserved for refractory hypotension[27].

Dietary management of food allergy in infants is relatively straightforward for formula-fed infants. At least 86% of young children with IgE-mediated cow's milk allergy will tolerate soy, so for these disorders, evaluation for soy allergy and use of soy formula should be considered. For the breast-fed infant, maternal dietary restriction is advised, but the mother may require the aid of a dietitian for instruction and avoidance of malnutrition. Maternally ingested protein persists in the breast milk for several days following ingestion. New strategies for treatment are on the horizon. Although "standard immunotherapy" (analogous to that for pollen sensitivity) so far has been disappointing, anti-IgE therapy using injections of humanized anti-IgE monoclonal antibodies is promising and showed success in some of peanut allergy. Likewise, oligonucleotide immunostimulatory sequences may be useful adjuvants to sway systemic responses away from the T_H2 or allergic phenotype[18,28-30].

PREVENTION

There is no consensus as to whether food allergies can be prevented. However, several authorities recommend delayed introduction of major food allergens to infants from atopic families. Recommendations include promotion of breast feeding with maternal exclusion of peanut and nut products from the mother's diet and delay in introducing major allergenic foods: cow's milk until 1 year of age; egg until 18-24 months f age, and peanut, tree nuts, and seafood until 3 years of age[31].

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