

Pediatric Food Allergy Update

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Food allergy is mostly a childhood disease that differs from the adult-onset allergy in several aspects, including the prevalence, commonly offending foods, symptomatology, and prognosis. The prevalence is much overestimated by the public, but it probably affects up to 6% of children. In some cases, the diagnosis might be clearly evident, but in most cases an expert evaluation may be needed that usually includes verification by challenge testing. Currently, the management of food allergy is avoidance of the offending foods together with the availability of pharmacologic agents for symptomatic treatment, including self-administered epinephrine. The latter is of utmost importance in highly allergic subjects because accidental trivial exposure is not uncommon. Recent studies promise immunomodulatory agents that might be of potential use for prophylaxis. One such agent is anti-immunoglobulin E, which might be available in the near future.

Introduction

Food allergy (FA) is just one of the several mechanisms of adverse food reactions (Table 1). The terms “allergy” and “intolerance” are not synonymous; however, they are often used interchangeably. Food allergy should be limited to the immunologically mediated reactions that can be IgE or non-IgE mediated. Food intolerance, on the other hand, is a more generalized term that usually refers to nonimmunologic food reactions.

Prevalence

Food allergy is more common in children than in adults. Current estimates suggest that it affects approximately 6% of children [1,2•], with the highest prevalence during the first year of life. Cow’s milk (CM), egg, soy, wheat, and peanut are the most common offenders. As milk is the food most consumed by children, CM allergy alone affects 1% to 3% [3], followed by egg (1.5%), and peanut (0.05%) [2•]. Only a few studies addressed the prevalence of food-additive sensitivity. In a study in Denmark, the

prevalence was estimated to be 1% in children in general [4] and 2% in atopic children [5].

Predisposing Factors

Food-sensitive children have a high incidence of family history of allergy, not necessarily to food. Although there is no evidence of specific inheritance of FA, a familial tendency seems to occur in some cases, and a strong hereditability of peanut allergy in twins has been reported [6]. The highest incidence of FA is in atopic children, particularly those with atopic eczema (35%) [7], followed by asthma (6%–8%) [8]. Bottle-feeding [9,10] and early introduction of solid foods during the first 4 months of life [11] are among the risk factors, particularly to the development of FA and atopic eczema.

Pathogenesis

Probably the major factor for the higher incidence of FA in children is an immature gastrointestinal tract (GIT). The GIT mucosa is a major barrier against micro-organisms and food antigens. During infancy, the GIT mucosa is immature histologically, enzymatically, and immunologically, particularly in secretory IgA [12]. It is estimated that in a normal gut, approximately 2% of ingested food antigens are absorbed in an immunologically intact form. The latter rarely cause any symptoms because of the development of oral tolerance. Although the exact mechanism in the induction of oral tolerance is not fully understood, it seems that at a particular stage of development, the intestinal epithelial cells, dendritic cells, and regulatory T cells play a collaborative role [13]. Intestinal epithelial cells act as “nonprofessional” antigen-presenting cells by processing the antigen and presenting it on the major histocompatibility (MHC) complex to the T cell. The epithelial cells lack the secondary costimulatory signal, which leads to food tolerance [14].

It is conceivable that the immature GI mucosa of premature infants can be a predisposing factor to FA. However, prematurity is usually associated with frequent infections that enhance the development of naive T helper cells toward Th1 rather than Th2, with consequent lower incidence of atopy [15,16].

Food allergies can be caused by different immunologic mechanisms, and some reactions may involve more than one of the four classic mechanisms outlined by Gell and Coombs [17]. Type I, or immediate hypersensitivity

Table 1. Mechanisms of adverse reactions to foods and additives

Mechanism	Offending food
Hypersensitivity (allergy)	Various food proteins
Enzyme deficiency	
Lactase deficiency (lactose intolerance)	Lactose (most mammalian milks)
Sulfite oxidase (some cases)	Sulfites
Galactokinase (galactosemia)	Galactose
Phenylalanine hydroxylase (phenylketonuria)	Phenylalanine
G-6-PD (hemolysis)	Fava beans
Toxicity	
Non-edible food	Poisonous plants, mushrooms, fish
Histamine	Scombroid fish poisoning
Chemical	Chemical contaminant
Bacterial	Botulism
Gastrointestinal irritation	Spices
	Unripe fruits and vegetables
Pharmacologic	
CNS stimulation	Caffeine
Chinese restaurant syndrome	Monosodium glutamate
Hypertension	Licorice
Vasoactive amines (headaches)	Pickled herring, aged cheese, sausages, red wine
Unknown	
Celiac disease (gluten-induced enteropathy)	Wheat, barley, rye, oat
Hyperactivity (very rare)	Food colorings, additives
Psychologic (rare in young children)	Any food

reactions, are mediated by immunoglobulin E (IgE). They are the best understood and probably the most common. The symptoms can be in the form of urticaria/angioedema, vomiting, diarrhea, rhinitis, bronchospasm, or systemic anaphylaxis. Type II reactions involve complement activation by antibodies of the IgG, IgM, or IgA isotypes and seem to be responsible for the rare cases of immune thrombocytopenias. Type III reactions involve immune complexes of the antigen and antibody (IgA, IgG, or IgM isotypes) together with complement. They are probably the second most common, after type I reactions. Deposition of these complexes in the small blood vessels cause Arthus-type reactions that can manifest as gastrointestinal bleeding, cutaneous vasculitis, or chronic pulmonary disease (Heiner syndrome). Type IV, or delayed-type reactions, are mediated by T lymphocytes. This type is typically involved in contact dermatitis and some cases of atopic eczema and eosinophilic gastroenteropathies.

Manifestations

Various body systems can be affected by FA. Because type I reactions are the best understood, manifestations of FA are often classified as IgE-mediated and non-IgE-mediated (Table 2). Immediate reactions occur within minutes to a few hours after exposure, whereas late reactions occur after several hours or days. In children, the GIT seems to be the most common target organ, followed by the skin and the respiratory tract. Multiple systems can be involved, and the symptoms might progress rapidly and be severe enough to cause systemic anaphylaxis, which can be fatal.

In this review, certain manifestations of FA in children are worth describing in some detail.

Abdominal pain, vomiting, and diarrhea are the most common GI symptoms, occurring within a few minutes to hours after ingesting the offending food, whereas other symptoms are usually delayed. Food-induced gastroesophageal reflux [18,19] and constipation [20] have been reported. Occult GI bleeding may continue unnoticed for prolonged periods and results in microcytic hypochromic anemia that does not respond well to iron treatment unless CM is eliminated [21]. Gross GI bleeding from colitis is much less common, but can be alarming. Dietary protein-induced enterocolitis is usually present before 3 years of age and is mostly caused by CM and soy [22]. Presenting symptoms include recurrent vomiting and diarrhea that may lead to dehydration. Food-induced eosinophilic esophagitis and gastroenteritis are becoming more recognized and are more common in older children [23].

Of the cutaneous manifestations, atopic eczema is the most common, with FA being present in approximately one third of cases, and with egg being the most common, followed by CM and peanut [7,24]. Of the respiratory manifestations, rhinitis and chronic otitis media with effusion are thought to be the most common [25,26], but the least recognized. Asthma rarely occurs as a sole manifestation of FA, but is more common in infants with atopic eczema [27,28]. One study reported that half of the children who were intubated for life-threatening asthma had food sensitization compared with only 10% of controls [29].

Table 2. Clinical manifestations of food allergy

Target organ	IgE-mediated	Non-IgE-mediated
Gastrointestinal	Vomiting Colic Diarrhea Oropharyngeal irritation (Oral allergy syndrome)	Bleeding (occult, gross) Gastroesophageal reflux Eosinophilic GI diseases Protein-losing enteropathy Constipation
Skin	Atopic eczema Urticaria Angioedema	Atopic eczema Contact dermatitis Contact rash
Respiratory	Rhinoconjunctivitis Cough Asthma Otitis media with effusion	Chronic pulmonary disease (Heiner syndrome)
Systemic anaphylaxis	Most anaphylaxis	Food-dependent, exercise-induced anaphylaxis

Modified from Bahna [3].

Milk-induced chronic pulmonary disease (Heiner syndrome) seems to be rare, but most probably is underdiagnosed [30]. It should be suspected in infants and young children with unexplained chronic or recurrent pulmonary infiltrates who are being fed CM, although a few other foods have been implicated. Associated findings may include frequent upper respiratory symptoms, GI symptoms, poor appetite, failure to thrive, anemia, and eosinophilia. The serum contains high titers of precipitating antibodies to CM proteins. Symptoms usually begin to improve within a few days of milk elimination, but the pulmonary infiltrate may take several weeks to resolve. Confirmation of the diagnosis would require documentation of recurrence of symptoms and pulmonary infiltrates following milk challenge. However, most parents are so impressed by the improvement that they refuse the challenge test, which is understandable. In some patients, the reaction can be severe enough to cause vasculitis and alveolar bleeding leading to pulmonary hemosiderosis. There may be visible hemoptysis, and the diagnosis can be verified by the demonstration of iron-laden macrophages in smears of tracheal aspirates or the morning gastric washing stained with Prussian blue.

Over the years, there has been a debate whether food or food additives cause hyperactivity in children, as suggested in the old literature but mostly refuted by well-designed studies. A few well-designed studies showed that there is no effect of sugar, sucrose, or artificial sweeteners on the behavior or cognitive function of children [31,32]. We saw an 11-year-old boy with severe behavioral problems at home and school, whose mother reported that within 0.5 to 1 hour of ingesting red dye or artificial sweeteners, he becomes very agitated and dangerously aggressive. He was evaluated by double-blind, placebo-controlled challenge to each claimed substance, yet he did not exhibit any behavior change during 3 hours observation in the clinic or later at home. Recently, a double-blind, placebo-controlled study [33] showed that a 1-week trial of a diet

without dyes or benzoate in pre-school children was associated with reduced hyperactivity as reported by parents. The hyperactivity was reportedly increased during a 1-week challenge with a drink containing those substances. More well-designed studies are needed to settle this important but difficult issue.

Routes of Exposure

In addition to ingestion, FA may occur by inhalation or contact with mucous membranes or skin. Allergic reactions have been reported by inhalation of fumes, such as from cooking fish or boiling milk [34•]. In a report [35••] of 197 children allergic to fish by ingestion, 10% developed symptoms on exposure to fish odors or fumes. Symptoms were experienced while fish was being fried in 14 patients, boiled in six patients, and when it was served to other people in the vicinity in five patients. On the same series, 15% of patients showed symptoms upon skin contact with fish, some even through indirect contact [36••].

Symptoms ranging from contact urticaria to anaphylaxis have been reported through trivial direct or indirect skin contact, such as kissing by a person who just ate the offending food [37,38]. There are two case reports of CM-sensitive infants who developed systemic anaphylaxis following the application of an ointment that contained 5% calcium caseinate to an inflamed diaper area [39,40].

Several reports indicate that perinatal sensitization can occur, and young infants may react to the first exposure of a specific food [41–44]. Food antigens can also be excreted by the mammary gland and can sensitize or provoke reactions in exclusively breast-fed infants [45,46].

Diagnosis

The initial evaluation of suspected FA consists of detailed medical history, thorough physical examination, and screening tests. The medical history can be very valuable in

Table 3. Diagnosis of food allergy

Medical history
Age of onset
Nature of symptoms
Feeding history
Relationship of symptoms to food or to other factors
Personal and family history of allergy
Physical examination
Manifestations of allergy
Manifestations of nonallergic disease
Screening tests
Nonspecific tests
Total serum IgE
Eosinophilia
Trial of elimination diets
Specific tests
Food/symptom diary
Skin prick testing
Specific serum IgE
Skin patch testing
Verification of cause-and-effect relationship
Elimination-challenge testing

Modified from Bahna and Mayer [47].

suspecting FA and, in some cases, may be convincing enough to settle the diagnosis. However, the history is often inconclusive, and selected screening tests are necessary (Table 3) [47]. Elevated total serum IgE level and eosinophilia support atopy but normal values do not exclude allergy. Skin prick test or specific IgE antibodies in the serum are the most commonly used and support immediate-type hypersensitivity. However, neither of these tests, alone or in combination, can definitely diagnose or exclude FA. They merely indicate the presence of food-specific antibodies on the cutaneous mast cells or in the circulation. Verification depends on documentation of improvement of symptoms following elimination of the suspected food and recurrence of symptoms on its reintroduction.

Percutaneous skin testing is the most commonly used screening test. The negative predictive value of such tests is much higher than their positive predictive value, meaning that a negative skin test is more likely to be exclusive of IgE-mediated sensitivity [48,49]. The reliability of skin testing may be enhanced by using fresh food (prick-by-prick) because of the lability of some food allergens, particularly of fruits and vegetables [50]. Patch testing in addition to skin prick test may help in identifying foods that are involved in cell-mediated reactions such as contact dermatitis, atopic eczema, and eosinophilic esophagitis [51,52]. Intradermal skin testing with food extracts has been abandoned because of its high false-positive results and its risk for causing systemic reactions.

Food-specific serum IgE is the counterpart of skin testing. It can be measured by a variety of assays. The enzyme-linked ones are much more used than those using radioisotopes. Currently, the ImmunoCap assay (Pharmacia

Diagnostics, Kalamazoo, MI) seems to be the most sensitive and reproducible [53]. According to one study [54], the use of the ImmunoCap-FEIA assay suggested that certain thresholds of IgE antibody to a particular food can predict the clinical relevance with a high degree of accuracy. However, such predictive values vary according to the food allergen, the clinical manifestation, and the total IgE level. Measuring the total serum IgE might be very helpful, not only in determining the degree of atopy but also in the interpretation of the clinical relevance of a positive skin test or specific IgE level. The higher the total IgE level, the more are the positive specific IgE tests without clinical relevance [55].

Appropriately designed oral food challenges are usually required to make a definitive identification of the offending food [49,56]. If an elimination trial improves the symptoms, a challenge should be carried out while the patient has minimal symptoms and is on minimal or no symptomatic medications. It should be done under supervision to document the reaction and to administer appropriate symptomatic treatment that may require management of anaphylactic shock. Titrated doses should be administered, starting with a safe quantity and reaching a cumulative dose equal to or exceeding the quantity the patient usually consumes. In choosing the optimal challenge procedure with a minimal bias, the age of the patient and type of symptoms should be taken into consideration (Fig. 1). Open challenge can be appropriate in young children whose symptoms are objective and for whom a bias is unlikely. Single-blinded, placebo-controlled food challenge can be optimal for older children and adults with objective symptoms. However, if the symptoms are subjective or a psychologic factor is suspected, double-blind, placebo-controlled food challenge would be preferred, particularly in research studies. If the reaction was life-threatening and was caused by one particular food, particularly if it occurred more than once, it would be prudent to avoid challenge testing. In such situations, if verification is deemed necessary, a cautious skin or labial contact may be performed.

There are a number of other tests promoted by commercial laboratories or proposed by certain practitioners for diagnosis of FA, but their reliability has not been demonstrated. Such tests include, but are not limited to, food-specific IgG4 antibodies, cytotoxic testing, ALCAT (antigen leukocyte cellular antibody test), and kinesiology (muscle strength testing) [57].

Management

Once the diagnosis of FA is made and the offending foods have been identified, treatment is basically avoidance of that food. Reading labels of commercial food is important, particularly for highly allergic subjects. Patients should be provided with lists of foods that commonly incorporate the offending food as well as unfamiliar names. Commercial food labels may have allergenic proteins under unfamiliar

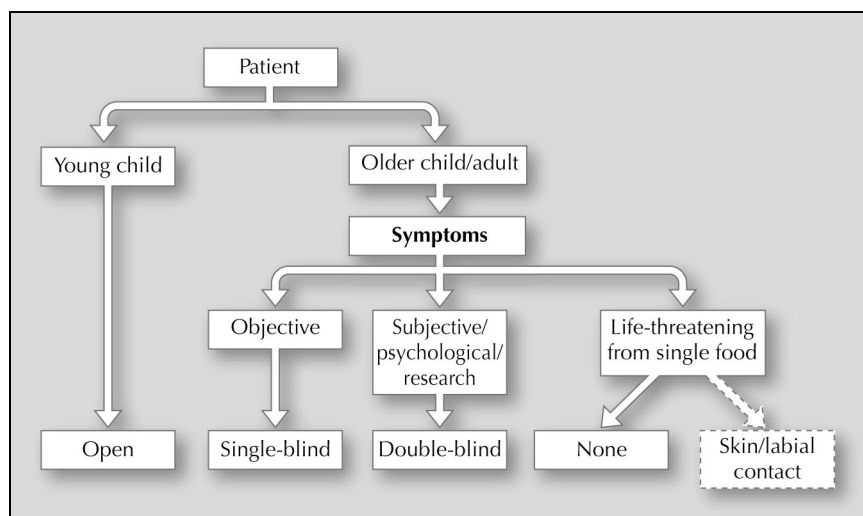


Figure 1. Selection of type of food challenge according to age and symptoms.

names such as casein, caseinate, or whey for milk, and ovalbumin, ovomucoid, or ovomucin for egg. Consultation with a dietitian familiar with food allergy might be needed, particularly in providing recipes that are devoid of the offending food but nutritionally adequate. Patients with history of anaphylaxis should wear MedicAlert identification and have self-injectable epinephrine for immediate administration when needed.

Soybean-based formulas, although not considered hypoallergenic, are tolerated by about three fourths of CM-sensitive subjects [58•]. They also have the advantage of being widely available, inexpensive, and palatable. Extensively hydrolyzed casein (Nutramigen, Mead Johnson; Pregestimil, Mead Johnson; Alimentum, Ross) and whey (Alfa-Ré, Nestlé) are considered hypoallergenic and are well-tolerated by most subjects [59,60]. Elemental formulas from synthesized amino acids (Neocate, SHS North America; EleCare, Ross; Vivonex, Novartis) are optimal for children with exquisite milk-sensitivity or with multiple food allergies.

Partially hydrolyzed whey formulas (Good Start, Beba HA, Nadina HA, Nan HA, Nestlé) are not considered hypoallergenic and are not recommended for milk-sensitive subjects [61,62]. Even extensively hydrolyzed formulas occasionally cause severe reactions in exquisitely milk-sensitive subjects [63–65]. Goat's milk is rarely (8%) tolerated by CM-allergic patients, as it shares several allergenic protein fractions with bovine milk [66]. In rare instances, a patient may be allergic to goat or sheep's milk and not to CM [67]. Mare's milk has a weak cross-reactivity with CM, and, in one study, it was well-tolerated by the majority (96%) of CM-allergic subjects [68]. Severe CM-sensitive subjects may not tolerate bovine meat. Werfel *et al.* [69] showed that milk allergy was associated with increased beef allergy (5 out of 25), and that most beef-sensitive patients were milk-sensitive (8 out of 11). Martelli *et al.* [70] noted that CM allergy occurred in 26 out of 28 (93%) beef-allergic children.

Several novel immunomodulatory approaches for the treatment of FA are under investigation. Studies on probiotics have shown potential benefit. The improvement in

atopic eczema in children with CM allergy was enhanced by adding *Lactobacillus* GG to the hydrolyzed formula [71]. Interaction of probiotics with the intestinal mucosa stimulates the T-cell differentiation in favor of Th1 over Th2, with consequent decreased production of IgE and increased secretion of IgA [72]. A preliminary study showed the potential use of anti-IgE (omalizumab) in FA, and might be useful in protection against accidental exposure to the offending food [73••]. Other potential immunomodulatory therapies include Chinese herbal formula and bacterial immunostimulatory sequence (eg, CpG oligodeoxynucleotide) covalently linked to allergen [2•].

Currently, there are no effective and safe methods of hyposensitization. However, future studies might lead to the development of immunogenic but nonallergenic peptides that may prove useful for hyposensitization.

Prognosis

The prognosis of FA depends on several factors, such as the age at onset, type of manifestations, degree of sensitivity, degree of avoidance, and the type and multiplicity of offending foods. Generally, the prognosis is better in young children, probably due to the beneficial role of immunologic maturity with age. In general, the prognosis is better for GI symptoms than for anaphylaxis or atopic eczema. Also milk, egg, and fruit tend to be tolerated faster than peanut, tree nut, and seafood. FA may persist for many years or even for life in patients who react by skin contact or by inhalation. Allergy to sequential epitopes tends to persist longer than allergy to conformational epitopes [74].

Periodic challenge testing under direct medical supervision may be carried out every 6 to 12 months. In most patients, accidental exposure occurs, and the outcome may obviate the need for intentional challenge. According to one study, favorable predictors of tolerance to CM included non-IgE-mediated reactions and low degree of skin reactivity or specific IgE antibody level [75]. Monitoring the drop

of specific IgE antibody level might be helpful. However, in some children, although specific IgE antibody level dropped by 99% over 12 months, food was not tolerated in 5% for egg and in 6% for milk [76••].

Prevention

Preventive measures for FA would be most recommended for infants of atopic families, including breast-feeding, exclusively until 4 to 6 months [60,77], preferably in association with maternal avoidance of the most allergenic foods (CM, peanut, egg, and seafood). Hypoallergenic formula may supplement or substitute breast-feeding [78,79]. Introduction of solid foods should be gradual and starting with the less allergenic foods. An optimal suggested age for introducing pasteurized CM is 1 year, egg 2 years, and fish, peanut, and tree nuts at 3 years [10].

Conclusions

Food allergy is more common, yet has better prognosis, in children than in adults. In addition to a detailed medical history, skin testing or specific IgE antibody are good screening procedures, but not definitive. Confirmation requires appropriately designed challenge testing. Currently, the best treatment for food allergy is strict elimination of the offending food. Education to the family is the key in dietary avoidance and management of acute reactions. A few novel approaches to the treatment of IgE-mediated reactions are underway (eg, anti-IgE and food vaccines) and might be valuable in the treatment or prevention of FA.

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