ASTIM ALLERJi iMMÜNOLOJi
ASTHMA ALLERGY IMMUNOLOGY

Asthma Allergy Immunol 2014;12:70-82

DERLEME REVIEW

Various clinical presentations of food allergy in children

Çocuklarda besin allerjisinin değişik klinik görünümleri

Öner ÖZDEMİR[1]

1 **Department of Pediatric Allergy and Immunology, Sakarya Training and Research Hospital, Sakarya, Turkey**
Sakarya Eğitim ve Araştırma Hastanesi, Çocuk Allerji İmmünoloji Kliniği, Sakarya, Türkiye

ABSTRACT

Food allergy is an important public health problem that affects adults and children and has been increasing in incidence. Despite the risk of severe allergic reactions and even death, there is still no certain treatment for food allergy at the moment. Moreover, the diagnosis of food allergy may be problematic as well, given that non-allergic food reactions, such as food intolerances and intoxications, are frequently confused with food allergy. Gastrointestinal system symptoms e.g. vomiting and diarrhea in consequence of food allergy include a spectrum of disorders such as proctocolitis and enterocolitis that result from adverse immunologic responses to dietary antigens. Cutaneous reactions to foods are some of the most common presentations of food allergy and include IgE-mediated (urticaria), cell-mediated (contact dermatitis), and mixed IgE/cell-mediated reactions (atopic dermatitis). Food-induced respiratory system manifestations such as asthma and Heiner's syndrome are also discussed in this review. Although any food might cause systemic symptoms such as anaphylaxis, the most commonly implicated foods in fatal cases are peanut, tree nuts, shellfish, and fish.

(Asthma Allergy Immunol 2014;12:70-82)

Key words: Food allergy, atopic dermatitis, eosinophilic gastroenteritis, Heiner's syndrome, enterocolitis

Received: 09/11/2013 • Accepted: 27/11/2013

ÖZ

Besin allerjisi, insidansı artan ve de çocuk ve erişkinleri etkileyen önemli bir halk sağlığı problemidir. Ciddi allerjik reaksiyon ve ölüm risklerine rağmen, besin allerjisinde hala kesin bir tedavi şekli yoktur. Ayrıca, besin allerjisi teşhisi, besin intolerans ve intoksikasyonları gibi allerjik olmayan besin reaksiyonlarının besin allerjisi ile karıştırılmasından dolayı zordur. Kusma ve ishal gibi besin allerjisine bağlı gastrointestinal sistem semptomları, diyet antijenlerine karşı gelişen ters immünolojik cevaptan kaynaklanan proktokolit ve enterokolit gibi bir grup hastalık sonucu oluşur. Besine bağlı cilt reaksiyonları, besin allerjisinin en sık görülen bulgularındandır. Bunlar IgE aracılı (ürtiker), hücre-aracılı (kontakt dermatit), ve miks IgE/hücre aracılı (atopik dermatit) reaksiyonlardır. Bu derlemede, besine bağlı solunum sistemi bulguları (astım ve Heiner sendromu gibi) da tartışılacaktır. Herhangi bir besin anafilaksi gibi sistemik semptomları meydana getirebilmesine rağmen, ölümcül olgulardan en sık fıstık, kabuklu kuruyemişler, kabuklu deniz ürünleri ve balık sorumludur.

(Asthma Allergy Immunol 2014;12:70-82)

Anahtar kelimeler: Besin allerjisi, atopik dermatit, eozinofilik gastroenterit, Heiner's sendromu, enterokolit

Geliş Tarihi: 09/11/2013 • Kabul Ediliş Tarihi: 27/11/2013

Yazışma Adresi/Address for Correspondence
Prof. Dr. Öner ÖZDEMİR
Sakarya Eğitim ve Araştırma Hastanesi, Çocuk Allerji İmmünoloji Kliniği, Sakarya, Türkiye
e-posta: ozdemir_oner@hotmail.com

INTRODUCTION

Food allergy is an important public health problem that affects adults and children and may be increasing in incidence. In spite of the risk of severe allergic reactions and even death, there is no certain treatment for food allergy at the moment: the disease can only be managed by allergen avoidance or symptomatic treatment. Moreover, the diagnosis of food allergy may be problematic as well, given that non-allergic food reactions, such as food intolerance and intoxication are frequently confused with food allergy (Table 1). There are additional concerns related to the differences in the diagnosis and therapy of food allergy in various clinical practice settings[1].

Recent epidemiological surveys reveal that swift increase in food allergy is a real phenomenon. It seems to involve interactions of various factors, such as changes in feeding habits and food processing, use of genetically modified foods, housing and environment[2]. According to the "hygiene hypothesis" low or no exposure to exogenous antigens in early life may increase the risk of allergic diseases by both delaying the development of the immune tolerance and limiting the Th2/Th1 switch. Different reports claim prevalence of food allergy at 13% for children and 7% for adults in the US, in Europe the claimed prevalence is at 0.3-7% for children and 2% for adults[3]. However, recent estimates suggest that 4% of the US populations are believed to have IgE-mediated food allergy[4]. Additionally, a new way of developing food allergy brought by the achievement of medical sciences is the transfer of food allergy to the recipient of a solid organ transplant such as liver that will be detected more frequently in the future[5].

In general adverse food reactions include any abnormal reaction resulting from the ingestion of a food. Although there are different classifications and adverse reactions to food can be caused by several mechanisms; two main types of reactions are widely accepted: food allergy (food hypersensitivity) and food "intolerance" (non-allergic food hypersensitivity)[6]. These two terms, however, differ from one another, both linguistically and scientifically[7]. And the popular classification of food allergy manifestations may be categorized into IgE- and non-IgE-mediated. Type I (immediate/IgE-mediated) reactions are the best understood and seem to be the most common (Table 1)[8,9]. The clinical symptoms elicited by food allergy involve different organs and systems, but those that correspond to the classic allergic symptoms are the only ones clearly identified with food allergy, i.e. systemic anaphylaxis, urticaria, angioedema, oral allergy syndrome, eczema, rhinitis and asthma (Table 2). Other manifestations such as eosinophilic gastroenteritis supposed to be associated with an immunological mechanism, but clear demonstration of this relationship is still missing. In this review, different manifestations besides common ones of food allergy in general during childhood will be discussed.

COMMON PRESENTATIONS of FOOD ALLERGY in CHILDREN

During infancy and early childhood, the gastrointestinal system (GIS) is the first organ to come in contact with food proteins and is probably the most affected system by food allergy.

Gastrointestinal System Symptoms

GIS symptoms in consequence of food allergy include a spectrum of disorders that result from adverse immunologic responses to dietary antigens. The most common GIS symptoms are vomiting and diarrhea. Also, infants with food allergy usually present with one or more of the following symptoms: blood or mucus in diarrhea, poor weight gain and infantile colic. GIS bleeding is usually occult, originating from the small intestine, and occasionally it may be gross due to colitis. However, constipation during infancy is also described as a manifestation of food allergy[10]. Although significant overlap may exist between these conditions, several specific syndromes have been described. Those are defined as follows:

Infantile colic is seen in 15% to 40% of infants up to 4 months of age and is characterized

Table 1. Differential diagnosis of adverse reactions to foods

A. Immunologic	**B. Non-toxic, non-immunologic**
1. IgE-mediated reactions (anaphylaxis)	1. Intolerance (Enzymatic or metabolic)
a. IgE-mediated cutaneous reactions	i) Lactose intolerance (Lactase deficiency)
i) Immediate onset reactions	ii) Carbohydrate malabsorption (G-6PD, Fructose-1-phosphate aldolase)
(a) Acute urticaria or angioedema	iii) Enzyme deficiencies (PKU, Wilson disease)
(b) Contact urticaria	**C. Food reactions of uncertain immunologic etiology**
ii) Late-onset reactions	1. Food-dependent exercise-induced anaphylaxis
(a) Atopic dermatitis	2. Eosinophilic esophago-gastroenteropathy
b. Systemic IgE-mediated reactions (anaphylaxis)	3. Food-additive reactions
i) Immediate-onset reactions (wheezing, bronchospasm)	**D. Toxic**
ii) Late-onset reaction	1. Bacterial (eg, food poisoning, ptomaine poisoning)
c. IgE-mediated gastrointestinal reactions	2. Pharmacologic (eg, scombroid poisoning, caffeine-causing jitteriness, licorice-induced hypertension)
i) Immediate gastrointestinal allergy	**E. Reactions not consistently related to food ingestion**
ii) Oral allergy syndrome	1. Irritable bowel syndrome
d. IgEmediated respiratory reactions	2. Inflammatory bowel disease
i) Allergic rhinitis	**F. Irritation**
ii) Asthma secondary to ingestion or to inhalation of food (e.g. occupational asthma)	1. Spices
2. Non-IgE-mediated (cellular or mixed) immunologic food reactions	2. Chemical contaminants
a. Gastrointestinal reactions	**G. Psychological reactions**
i) Infantile colic	1. Strongly held beliefs against any food
ii) Food-induced enterocolitis	**H. Unknown**
iii) Celiac disease	1. Behavior disorders
iv) Eosinophilic gastro-enteropathies	**İ. Idiosyncratic reactions**
b. Cutaneous reactions	
i) Dermatitis herpetiformis	
ii) Allergic contact dermatitis	
c. Pulmonary reactions	
i) Cow's milk-induced pulmonary hemosiderosis (Heiner's syndrome)	

by crying, irritability, abdominal distention, and excess flatus. Less than 50% of babies with problem crying have an identifiable organic cause such as food allergy, gastroesophageal reflux (GER) or food introlerance to cow's milk/lactose or soy protein. Only rarely has an allergic basis for infantile colic been implicated, although double-blind studies in bottle-fed and breastfed infants indicate that IgE-mediated hypersensitivity may be a pathogenic factor in some infants. GER may be a significant causative factor in infants with colic. GER in the first year of life has also been attributed, in a subset of infants, to cow's milk allergy or food introlerance. The prev-

Table 2. Symptoms of food-induced allergic reactions

Target organ	Immediate symptoms	Delayed symptoms
Skin	Erythema	Erythema
	Pruritus	Pruritus
	Urticaria	Flushing
	Angioedema	Morbilliform eruption
	Morbilliform eruption	Angioedema
		Eczematous rash
Eye	Pruritus	Pruritus
	Conjunctival erythema	Conjunctival erythema
	Tearing	Tearing
	Periorbital edema	Periorbital edema
Upper respiratory	Nasal congestion	
	Pruritus	
	Rhinorrhea	
	Sneezing	
	Laryngeal edema	
	Hoarseness	
	Dry staccato cough	
Lower respiratory	Cough	Cough, dyspnea, and wheezing
	Chest tightness	
	Dyspnea	
	Wheezing	
	Intercostal retractions	
	Accessory muscle use	
Gastrointestinal (upper)	Angioedema of the lips, tongue or palate	
	Oral pruritus	
	Tongue swelling	
Gastrointestinal (lower)	Nausea	Nausea
	Colicky abdominal pain	Abdominal pain
	Reflux	Reflux
	Vomiting	Vomiting
	Diarrhea	Diarrhea
		Hematochezia
		Irritability and food refusal (young children)
Cardiovascular	Tachycardia (infrequently bradycardia in anaphylaxis)	
	Hypotension	
	Fainting	
	Dizziness	
	Loss of consciousness	
Miscellaneous	Uterine contractions	
	Sense of "impending doom"	

alence of this association is controversial and has been estimated to be 16% to 42%. In a study of 70 infants with persistent crying, abnormally frequent or prolonged GER only occurred in babies who vomited more than five times a day. Silent GER becomes a more likely explanation for colic in infants as symptoms continue past 3-4 months of age[11]. In some irritable infants, food allergy may play a causal role. Food allergens commonly implicated include cow's milk protein and soy protein, both of which can be found in human breast milk. Intolerances or allergies to either cow's milk or soy protein are both temporary and result from intact protein being absorbed as a result of increased mucosal permeability in the infant's GIS. The intolerance gradually disappears over the first few months of life as the mucosal junctions tighten. The role of lactose intolerance as a cause of infant irritability remains debatable. It has been hypothesized that some babies have a transient underlying lactase deficiency, leading to a build-up of lactose derived from breast milk or formula. Gut bacteria break down the lactose, converting it to lactic acid and hydrogen. A clinical response to a lactose-free diet confirms the diagnosis. Whether the problem is an intolerance or an allergy to cow's milk or soy protein, it has been shown that complete removal of cow's milk or soy protein from the infant's or breast-feeding mother's diet will result in immediate improvement in 10–35% of colicky infants. In some infants allergic to both cow's milk and soy protein, changing to extensively hydrolyzed formulas or with amino acid formulas can be effective.

The pollen-food **(oral) allergy syndrome** is an interesting entity that occurs in some patients who have respiratory allergy to certain pollens. Oral allergy syndrome is a form of localized IgE-mediated allergy, usually to raw fruits or vegetables, with symptoms confined to the lips, mouth, and throat. The patients may have mild pruritus, tingling, and/or angioedema of the lips, palate, tongue, or oropharynx; occasional sensation of tightness in the throat and rarely systemic symptoms. Skin prick test responses to relevant food proteins (prick-to-prick method), positive oral challenge with fresh food but negative with cooked food could be confirmatory in the diagnosis[12].

Eosinophilic esophagitis (EoE) is a chronic remitting/relapsing condition that is commonly associated with sensitization to foods. EoE involves localized eosinophilic inflammation of the esophagus. Although EoE is commonly associated with the presence of food-specific IgE, the precise causal role of food allergy in its etiology is not well defined. Both IgE- and non-IgE-mediated mechanisms appear to be involved. In children, EoE presents with feeding disorders, vomiting, reflux symptoms, and abdominal pain. In adolescents and adults, EoE most often presents with dysphagia and esophageal food impactions[13-15]. In some patients, avoidance of specific foods will result in normalization of histopathology. Others can be managed successfully with medical therapy.

Eosinophilic gastroenteritis (EoG) also is both IgE- and non-IgE-mediated and commonly linked to food allergy. EoG describes a constellation of symptoms that vary depending on the portion of the GIS involved and a pathologic infiltration of the GIS by eosinophils, which may be localized or widespread. EoE is a common manifestation of EoG as well[16].

Food protein-induced allergic proctocolitis (FPIAP) typically presents in infants who seem generally healthy but have visible specks or streaks of blood mixed with mucus in the stool. IgE to specific foods is generally absent. The lack of systemic symptoms, vomiting, diarrhea, and growth failure helps differentiate this disorder from other disorders in GIS related to food allergy that present with similar stool patterns. Because there are no specific diagnostic laboratory tests, the causal role of food allergens such as those found in milk or soy is inferred from a characteristic history on exposure. Many infants present while being breast-fed, presumably as a result of maternally ingested proteins excreted in breast milk[17].

Food protein-induced enterocolitis syndrome (FPIES) is another non-IgE-mediated disorder that usually occurs in young infants and manifests as chronic emesis, diarrhea, and failure to thrive. Upon re-exposure to the offending food after a period of elimination, a subacute syndrome can present with repetitive emesis and dehydration. Milk and soy protein are the most common causes, although some studies also report reactions to other foods, including rice, oat, or other cereal grains. A similar condition also has been reported in adults, most often related to crustacean shellfish ingestion[18].

DERMATOLOGIC SYMPTOMS

Cutaneous reactions to foods are some of the most common presentations of food allergy and include IgE-mediated (urticaria-angioedema, flushing, pruritus), cell-mediated (contact dermatitis, dermatitis herpetiformis), and mixed IgE- and cell-mediated reactions such as atopic dermatitis (Table 1).

Foods are among the common causes of acute urticaria/angioedema related symptoms e.g. pruritus, hives, morbilliform rashes, flushing and swelling. Food-induced erythematous, papular, or urticarial contact rashes, primarily perioral, have been observed in some children. Immediate contact urticaria to food is relatively common and can be localized, generalized, or associated with other system involvement. **Contact urticaria** can be either non-immunologic (caused by direct histamine release) or immunologic (IgE-mediated reactions to proteins). The former does not require presensitization of the patient's immune system to an allergen, whereas the latter does. However, some contact urticaria reactions of unknown mechanism are unclassified and associated with generalized histamine-type reactions. Numerous reports of contact urticaria syndrome caused by a variety of compounds, such as foods, preservatives, fragrances, plant and animal products, and metals, have been made[19]. Although in chronic urticaria and angioedema may also be induced by immediate hypersensitivity, food or food additives are rarely implicated[20].

Allergic contact dermatitis (ACD) is a form of eczema caused by cell-mediated allergic reactions to chemical haptens that are additives to foods or occur naturally in foods, such as mango. Clinical features include marked pruritus, erythema, papules, vesicles, and edema[21,22].

Atopic dermatitis, also known as eczema, is linked to a complex interaction between skin barrier dysfunction and environmental factors such as irritants, microbes, and allergens. Eczema is mediated by IgE and cell-mediated and these patients have marked pruritus as well as eczematous rash. Null mutations of the skin barrier protein filaggrin have been suggested to increase the risk for transcutaneous allergen sensitization and the development of food allergy in subjects with atopic dermatitis. The role of food allergy in the pathogenesis and severity of this condition remains controversial. Several studies have demonstrated a role of food allergy in one-third to one-half of childhood atopic dermatitis. In some sensitized patients, particularly infants and young children, food allergens can induce urticarial lesions, itching, and eczematous flares, all of which may aggravate atopic dermatitis[23].

PULMONARY SYMPTOMS

Food-induced upper respiratory tract symptoms seem to be more common in infants and young children, but are probably markedly misdiagnosed. **Gustatory rhinitis** is mediated by a neurogenic reflex in individuals who experience profuse watery rhinorrhea while eating, particularly spicy foods. However, **allergic rhinitis** is IgE-mediated and may rarely be caused by food allergy. The role of food allergy in **serous otitis media** is controversial, probably uncommon, and further studies are needed. In a Spanish study, 25 patients with recurrent otitis media with effusion and food allergy demonstrated by positive skin testing. The most common food found to be associated was milk, egg, beans, citrus, and tomato. The elimination diet led to a significant amelioration of the otitis in 22/25 patients. The challenge diet with suspected offending food provoked a recurrence of the otitis problem.

This study results demonstrated the association between recurrent otitis media with effusion and food allergy[24].

Asthma and food allergy often coexist in pediatric and adult patients. **Food-induced** asthma is more common in young children, particularly in association with atopic dermatitis. The past three decades have seen a dramatic rise in the prevalence of allergic diseases, including asthma and food allergy. Asthma prevalence has mirrored this increase, and it is currently estimated that 8.5% of children suffer from asthma. Food allergy has been implicated as a risk factor for asthma development, a trigger for asthma exacerbations, and a factor determining asthma morbidity. Besides foods, some additives and preservatives can also trigger asthma in certain people[25].

New asthma development (incidence) occurs in about 5% of individuals who suffer from food allergy. The prevalence of asthma was found to be 46% in a food-allergic pediatric cohort[26]. This is markedly higher than the 29% prevalence of asthma in food-allergic children found by the US National Center for Health Services from data collected by national telephone survey in an unselected sample of the general population[27,28]. Early food sensitization has been previously identified as a predictor for asthma. Rhodes et al demonstrated positive skin prick test to egg or cow's milk in infancy to be predictive of adult asthma in a cohort at risk for asthma by virtue of family history of atopy. Similarly, hen's egg sensitization predicts later aeroallergen sensitization in infants with atopic dermatitis and, along with wheat sensitization, is associated with development of asthma in wheezy infants[29]. Up to 9% of children may have food-induced wheeze as their only allergic manifestation to a food allergen. The foods most often associated with food-induced wheeze in asthmatics are eggs, milk, and fish[25-29]. It has been suggested that the risk for asthma increases with the number of food allergies. Milk, egg, tree nut and wheat sensitizations are significantly associated with the development of asthma in very young children, independent of other risk factors. However, clinically relevant food allergy in children spanning all ages and the relationship to asthma has been less well described.

It has been shown that food allergy can elicit airway hyperreactivity and asthmatic responses[30]. Asthma may be triggered by foods up to 8% of children and 2% of adults[25]. Also, some studies evaluated the relationship between food allergy and asthma morbidity and mortality. Several conclusions could be withdrawn from those studies in the literature:

1. Children with asthma who are sensitized to foods, such as milk, wheat, peanut, or egg, have a higher rate of morbidity, emergency department visits and hospitalization than children with asthma who are not sensitized. They also require more steroid and bronchodilator use, independently of concurrent exposure to these allergens.
2. Patients with asthma with self-reported food allergy have significantly greater asthma severity and are more likely to be hospitalized and admitted to the intensive-care unit for asthma[31].
3. Some studies dealing with fatal or near-fatal anaphylaxis because of foods in US children reported that all or almost all patients who died also had asthma. Moreover, a high prevalence of asthma is reported among deaths from anaphylaxis due to food[32].

Non-IgE-mediated **Heiner's syndrome** is a chronic pulmonary disease caused by food hypersensitivity, primarily to cow's milk during infancy. Heiner's syndrome is an extremely rare condition in infants and toddlers that also may be related to egg or pork hypersensitivity. After first time described by Heiner in 1960, only a few reports have been published, which may be due to its misdiagnosis[33]. The immunopathogenesis of this disorder is not understood, but seems to combine cellular and immune-complex reactions, causing alveolar vasculitis. In severe cases, alveolar bleeding leads to pulmonary hemosiderosis. The Heiner syndrome should be suspected in young children with chronic pulmonary

disease of obscure cause. Caused primarily by the ingestion of milk, it is characterized by chronic or recurrent lower respiratory symptoms often associated with:

A. Upper respiratory symptoms (chronic cough, wheezing)

B. Pulmonary infiltrates (pneumonia)

C. GIS symptoms (anorexia, vomiting, colic, diarrhea, hematochezia)

D. Failure to thrive

The diagnosis is supported with a positive milk precipitin test (precipitating antibodies to milk protein fractions) and improvement on a trial of milk elimination. Milk elimination leads to marked improvement in symptoms within days and clearing of pulmonary infiltrates within weeks. Cow's milk-induced pulmonary hemosiderosis (Heiner syndrome) may also be related to egg or pork hypersensitivity. The presence of precipitating antibodies to the responsible antigen is necessary but not sufficient to make the diagnosis. Severe cases may be complicated with pulmonary hemosiderosis, which should be suspected in the presence of anemia or hemoptysis and be confirmed with the demonstration of iron-laden macrophages. Evidence often exists of peripheral eosinophilia, iron deficiency, and deposits of immunoglobulins and C3 in lung biopsies in some cases[33].

In a series, 8 cases of Heiner syndrome were reviewed. When first diagnosed, the patients were at 4-29 months of age. They were fed with cow's milk from birth and their chronic respiratory symptoms began at the age of 1-9 months. The symptoms were in the form of cough in seven, wheezing in three, hemoptysis in two, nasal congestion in three, dyspnea in one, and recurrent otitis media in three, recurrent fever in four, anorexia, vomiting, colic or diarrhea in five, hematochezia in one, and failure to thrive in two. All had radiologic evidence of pulmonary infiltrates. High titers of precipitating antibodies to cow's milk proteins were demonstrated in six of six and milk-specific immunoglobulin E was positive in one of two. Pulmonary hemosiderosis was confirmed in one patient who showed iron-laden macrophages in the bronchoalveolar lavage, gastric washing, and open lung biopsy. Additional findings, in a descending frequency, were eosinophilia, anemia, and elevated level of total IgM, IgE or IgA. Milk elimination resulted in remarkable improvement in symptoms within days and clearing of the pulmonary infiltrate within weeks. Parents consented to milk challenge in only three cases, all of whom developed recurrence of symptoms. After 2 year of milk avoidance in one patient, milk challenge was tolerated for 2 months, and then the patient developed symptoms, serum milk precipitins, pulmonary infiltrate, and iron-laden macrophages[34].

GENERALIZED (SYSTEMIC) SYMPTOMS

Although any food can cause systemic symptoms such as anaphylaxis, the most commonly implicated foods in fatal cases are peanut, tree nuts, shellfish, and fish. In an interesting some cases of food-induced anaphylaxis, the reaction occurred only when the person exercised within a few hours of eating the food [postprandial or food-dependent exercise-induced anaphylaxis (FDEIA)]. There is no specific diagnostic test, triggers are numerous, and possibly non-immunologic anaphylaxis can occur after a postprandial exercise[35].

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinct form of physical allergy that has been recently reported with increasing frequency. Although the majority of reports are described in trained athletes, it is not clear whether the magnitude or frequencies of exercise are independent risk factors. The gender distribution is equal and a family history is uncommon. At least half of the patients are atopic, and although some of them have symptoms only after ingesting specific foods, a definite co-precipitating factor can be identified only infrequently. Moreover, FDEIA linked to a food contaminant and multiple food intakes were also reported. Typical premonitory symptoms can include diffuse warmth, itching, erythema and large conventional (≥ 3 mm) urticaria, resulting in usually progression to confluence and often angioedema during exercise. Cutaneous

manifestations may be followed by gastrointestinal symptoms, laryngeal edema, and/or vascular collapse. Symptoms tend to occur variably with exposure to exercise and do not typically occur with passive warming. Also they can persist for 30 minutes to hours. Transient loss of consciousness occurs in about a third of patients because of vascular collapse, whereas symptoms of upper respiratory tract obstruction occur in almost two thirds of patients[36,37].

CO-MORBID CONDITIONS of FOOD ALLERGY

- Food allergy may co-exist with asthma, atopic dermatitis, EoE, FPIAP, FPIES and EIA.
- Children with food allergy may be especially likely to develop other allergic diseases. Several studies report on the co-occurrence of other allergic conditions in patients with food allergy, such as: 35% to 71% with evidence of atopic dermatitis; 33% to 40% with evidence of allergic rhinitis; and 34% to 49% with evidence of asthma[38]. Concomitantly, a retrospective review of the records of 201 children with an ICD-9 diagnosis of asthma found that 44% have concomitant food allergy[39].
- According to a recent CDC study, children with food allergy are about 2 to 4 times more likely to have other related conditions such as asthma (4.0 fold), atopic dermatitis (2.4 fold), and respiratory allergies (3.6 fold), compared with children without food allergy[40].
- One third of patients with EIA report reactions triggered by foods; EIA has natural history marked by frequent recurrence of episodes.

DIAGNOSIS of FOOD ALLERGY

- Food allergy should be suspected when typical symptoms (e.g., urticaria, edema, wheezing, mouth itch, cough, nausea/vomiting, anaphylaxis, etc.) occur within minutes to hours of ingesting a food. The medical history and examination are recommended to aid in diagnosis. A detailed history of the reaction to each incriminated food is essential for proper diagnosis.
- Tests for food-specific IgE are recommended to assist in diagnosis, but should not be relied upon as a sole means to diagnose food allergy. The medical history and exam are recommended to aid in diagnosis. A medically monitored feeding (food challenge-provocation) is considered the most specific test and gold standard for diagnosing food allergy[41].
- Food-specific IgE testing has numerous limitations, because positive tests are not intrinsically diagnostic and reactions sometimes occur with negative tests[42].
- Testing "food panels" using food-specific IgE and/or skin prick testing without considering history is often misleading and not recommended.
- Several tests are not recommended to show food allergy, including food-specific IgG/IgG4, total IgE, applied kinesiology, and electrodermal testing[43].

DIFFERENTIAL DIAGNOSIS of FOOD ALLERGY MANIFESTATIONS

The differential diagnosis of IgE-mediated food allergy should be done with entities that present similar symptoms but are not related to food: diseases with vomiting and diarrhea in children. Differential diagnosis should also include other reactions to food of possible immunological mechanism, but not mediated by IgE, such as eosinophilic GIS disorders. Furthermore, the differential diagnosis also needs to include non-immunological food intolerance syndromes (cow's milk intolerance) and reactions by toxic agents which contaminate or were generated during food processing (Table 1)[44,45].

RISKS of FOOD ALLERGY MANIFESTATIONS

- Fatal food allergic reactions are usually caused by peanut, tree nuts and seafood, but have also occurred from milk, egg, seeds and other foods.
- Fatalities have been associated with: age (teenagers and young adults), delayed treatment with epinephrine, and co-morbid asthma.

- Severity of future allergic reactions is not accurately predicted by past medical history. At this time there is no diagnostic testing to predict severity of future reactions.
- Therapy with beta-blockers may decrease effectiveness of epinephrine in anaphylaxis.

PREVENTION of FOOD ALLERGY MANIFESTATIONS

education about food avoidance is key to prevent reactions (Table 3). This includes information about label reading and cross contact of allergens (unintended contamination during food preparation).

Advice about influenza vaccination for persons with egg allergy is reviewed, with more options for administration to those with egg allergy, including vaccines with low dose of egg protein. Yellow fever and rabies vaccines are contraindicated in persons with history of urticaria, angioedema, allergic asthma or anaphylaxis due to egg proteins. Allergy evaluation and testing strategy before vaccine shot can provide insight into the potential risk for an individual[46].

The recommendations for infant diet substantially follow the 2008 AAP Clinical Report on this topic. Breast-feeding is encouraged for all, hydrolyzed infant formulas are suggested for infants "at risk", and complementary foods, including potential allergens, are not restricted after 4-6 months of age (not applicable for infants experiencing allergic reactions). Maternal diet during pregnancy should be healthy and balanced; avoidance of potential food allergens is not recommended[47].

Microbial agents such as probiotics may also have an important effect on atopic sensitization and induction of tolerance. Microbial exposure of infants during the neonatal period may influence postnatal maturation of the T-cell system toward the Th1 cell line and limiting the Th2/Th1 switch. For instance: infants with milk allergy and atopic dermatitis have exhibited milder symptoms and fewer markers of intestinal inflammation when milk formula was fortified with Lactobacilli, suggesting a salutary effect of adding probiotics into infant formulas. All of these observations have led to increasing efforts to prevent atopy, atopic dermatitis and food allergy through alteration of the gut microenvironment, usually directed to persons "at risk"[48].

MANAGEMENT APPROACHES of FOOD ALLERGY MANIFESTATIONS

The treatment of food allergy is avoiding the implicated food as long as necessary, until tolerance appears. Using alternate formulas including soy, elemental formula, and aminoacid formula is found to be helpful[49]. Also, few food diet consisting of a grain-rice or corn; a few vegetables; a few fruits; water (possibly apple juice and/or rice milk); salt, sugar, olive oil may also be useful. Immunotherapy is not yet well-

Table 3. Prevention and treatment strategies for food allergies

Increased supervision during meals and snacks (allergen-free table)
• No food, container, or utensil sharing
• Cleaning of tables, toys
Substitution of causal food during craft, cooking, science projects
Hand washing before and after food handling and eating
Avoidance of exposure to food during preparation and cooking
• Provision of safe substitute foods
• Foods brought in should have ingredient labels
Instruction of kitchen and family staff on issues of careful label reading and cross-contamination

documented[50]. Omalizumab (anti-IgE) trials are still experimental[51].

Management of anaphylaxis emphasizes prompt administration of epinephrine, observation for 4-6 hours or longer after treatment, education of the patient on avoidance, early recognition, treatment, medical identification jewelry, and follow up with a primary health care provider and consideration for consultation with an allergist-immunologist. Prescription of epinephrine auto-injectors and patient education advice includes having 2 doses available, switching from 0.15 to 0.30 mg fixed-dose auto-injectors at approximately 25 kg (55 lbs) in context of patient-specific circumstances, having a written emergency plan, and providing supporting educational material[52].

CONCLUSION

food allergy is an important public health problem that affects adults and children and has recently been increasing in incidence. Moreover, the diagnosis of food allergy may be problematic as well, given that non-allergic food reactions, such as food intolerances and intoxications, are frequently confused with food allergy. GIS symptoms in consequence of food allergy include a spectrum of disorders that result from adverse immunologic responses to dietary antigens. Cutaneous reactions to foods are some of the most common presentations of food allergy and include IgE-mediated (urticaria), cell-mediated (contact dermatitis), and mixed IgE-/cell-mediated reactions (atopic dermatitis). Food-induced asthma and Heiner's syndrome are other presentations of food allergy in respiratory system. Despite the risk of severe allergic reactions and even death, there is still no certain but only is managed by supportive treatment or allergen avoidance for food allergy. Microbial agents such as probiotics may also have an important effect on atopic sensitization and induction of food tolerance.

CONFLICT of INTEREST

The author declared that there was no conflict of interest.

REFERENCES

1. *Poulsen LK. Allergy assessment of foods or ingredients derived from biotechnology, gene-modified organisms, or novel foods. Mol Nutr Food Res 2004;48:413-23.*
2. *Boyce JA, Assa'a A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the vdiagnosis vand vmanagement of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. Nutrition 2011;27:253-67.*
3. *Crespo JF, Pascual C, Burks AW, Helm RM, Esteban MM. Frequency of food allergy in a pediatric population from Spain. Pediatr Allergy Immunol 1995;6:39-43.*
4. *Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2010;126:798-806. e13.*
5. *Özdemir Ö, Arrey-Mensah A, Sorensen RU. Development of multiple food allergies in children taking tacrolimus after heart and liver transplantation. Pediatr Transplant 2006;10:380-3.*
6. *Johansson S, Hourihane JO'B, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001;56:813-24.*
7. *Jansen SC, van Dusseldorp M, Bottema KC, Dubois AE. Intolerance to dietary biogenic amines: a review. Ann Allergy Asthma Immunol 2003;91:233-40.*
8. *Bahna SL. Clinical expressions of food allergy. Ann Allergy Asthma Immunol 2003;90(6 Suppl 3):41-4.*
9. *Sampson HA. Update on food allergy. J Allergy Clin Immunol 2004;113:805-19.*
10. *Heine RG. Gastroesophageal reflux disease, colic and constipation in infants with food allergy. Curr Opin Allergy Clin Immunol 2006;6:220-5.*
11. *Cirgin Ellett ML. What is known about infant colic? Gastroenterol Nurs 2003;26:60-5.*
12. *Mari A, Ballmer-Weber BK, Vieths S. The oral allergy syndrome: improved diagnostic and treatment methods. Curr Opin Allergy Clin Immunol 2005;5:267-73.*
13. *Uzuner N, Ölmez D, Babayiğit A. Gıda ile oluşan gastrointestinal sistem aşırı duyarlılık reaksiyonları. Türkiye Klinikleri J Pediatr 2009;18:214-21.*
14. *Ozdemir O, Mete E, Catal F, Ozol D. Food intolerances and eosinophilic esophagitis in childhood. Dig Dis Sci 2009;54:8-14.*
15. *Topal E, Bakırtaş A. Çocuklarda eozinofilik özefajit. Asthma Allergy Immunol 2012;10:1-9.*
16. *Kartal Ö, Çalışkaner ZA, Şener O. Eozinofilik gastrointestinal hastalıklar. Asthma Allergy Immunol 2010;8:139-49.*

17. *Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal vfood allergies: vdistinct differences in clinical phenotype between Western countries and Japan. Curr Allergy Asthma Rep 2012;12:297-303.*
18. *Özdemir Ö. Food protein-induced enterocolitis syndrome: review. Türkiye Klinikleri J Med Sci 2009;29: 1705-9.*
19. *Onesimo R, Giorgio V, Pill S, Monaco S, Sopo SM. Isolated contact urticaria caused by immunoglobulin E-mediated fish allergy. Isr Med Assoc J 2012;14:11-3.*
20. *Özdemir Ö. Idiopathic (autoimmune) chronic urticaria-pearls and pitfalls. Allergy and Asthma Proceedings 2006;27:431-4.*
21. *García-Gavín J, Parente J, Goossens A. Allergic contact dermatitis caused by sodium metabisulfite: a challenging allergen: a case series and literature review. Contact Dermatitis 2012;67:260-9.*
22. *Scheman A, Cha C, Jacob SE, Nedorost S. Food avoidance diets for systemic, lip, and oral contact allergy: an American contact alternatives group article. Dermatitis 2012;23:248-57.*
23. *Lee JM, Yoon JS, Jeon SA, Lee SY. Sensitization patterns of cow's milk and major components in young children with atopic dermatitis. Asia Pac Allergy 2013;3:179-85.*
24. *Arroyave CM. Recurrent otitis media with effusion and food allergy in pediatric patients. Rev Alerg Mex 2001;48:141-4.*
25. *Roberts G, Lack G. Food allergy and asthma--what is the link? Paediatr Respir Rev 2003;4:205-12.*
26. *Zicari AM, Indinnimeo L, De Castro G, Zappalà D, Tancredi G, Bonci E, et al. Food allergy and the development of asthma symptoms. Int J Immunopathol Pharmacol 2012;25:731-40.*
27. *Gaffin JM, Sheehan WJ, Morrill J, Cinar M, Borras Coughlin IM, Sawicki GS, et al. Tree nut allergy, egg allergy, and asthma in children. Clin Pediatr (Phila) 2011;50:133-9.*
28. *Liu AH, Jaramillo R, Sicherer SH, Wood RA, Bock SA, Burks AW, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005-2006. J Allergy Clin Immunol 2010;126:798-806 e13.*
29. *Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. J Allergy Clin Immunol 2001;108:720-5.*
30. *Krogulska A, Wasowska-Królikowska K, Dynowski J. Evaluation of bronchial hyperreactivity in children with asthma undergoing food challenges. Pol Merkur Lekarski 2007;23:30-5.*
31. *Vogel NM, Katz HT, Lopez R, Lang DM. Food allergy is associated with potentially fatal childhood asthma. J Asthma 2008;45:862-6.*
32. *Muñoz-Furlong A, Weiss CC. Characteristics of food-allergic patients placing them at risk for a fatal anaphylactic episode. Curr Allergy Asthma Rep 2009;9:57-63.*
33. *Heiner DC, Sears JW. Chronic respiratory disease associated with multiple circulating precipitins to cow's milk. Am J Dis Child 1960;100:500-2.*
34. *Moissidis I, Chaidaroon D, Vichyanond P, Bahna SL. Milk-induced pulmonary disease in infants (Heiner syndrome). Pediatr Allergy Immunol 2005;16:545-52.*
35. *Castells MC, Horan RF, Sheffer AL. Exercise-induced anaphylaxis. Curr Allergy Asthma Rep 2003;3:15-21.*
36. *Shadick NA, Liang MH, Partridge AJ, Bingham C, Wright E, Fossel AH, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. J Allergy Clin Immunol 1999;104:123-7.*
37. *Şener O, Kartal Ö, Güleç M, Baysan A, Muşabak U. Gıda ile ilişkili egzersiz anafilaksisi: olgu sunumu. Gülhane Tıp Derg 2012;54:320-2.*
38. *Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. J Allergy Clin Immunol 2001;108:128-32.*
39. *Simpson AB, Glutting J, Yousef E. Food allergy and asthma morbidity in children. Pediatr Pulmonol 2007;42:489-95.*
40. *Branum AM, Lukacs SL. Food allergy among children in the United States. Pediatrics 2009;124:1549-55.*
41. *Bahna SL. Diagnosis of food allergy. Ann Allergy Asthma Immunol 2003;90(6 Suppl 3):77-80.*
42. *Sicherer SH, Wood RA; American Academy of Pediatrics Section on Allergy and Immunology. Allergy testing in childhood: using allergen-specific IgE tests. Pediatrics 2012;129:193-7.*
43. *Eigenmann PA. Do we have suitable in-vitro diagnostic tests for the diagnosis of food allergy? Curr Opin Allergy Clin Immunol 2004;4:211-3.*
44. *Ortolani C, Bruijnzeel-Koomen C, Bengtsson U, Bindslev-Jensen C, Björkstén B, Høst A, et al. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) Reactions to Food Subcommittee. Allergy 1999;54:27-45.*
45. *Pascual CY, Crespo JF, Perez PG, Esteban MM. Food allergy and intolerance in children and adolescents, an update. Eur J Clin Nutr 2000;54(Suppl 1):75-8.*
46. *Watson JC, Hadler SC, Dykewicz CA, Reef S, Philips L. Measles, mumps, and rubella-vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998;47(RR-8):1-57.*
47. *Thygarajan A, Burks AW. American Academy of Pediatrics recommendations on the effects of early nutritional interventions on the development of atopic disease. Curr Opin Pediatr 2008;20:698-702.*

48. *Ozdemir O. Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. Clin Exp Immunol 2010;160:295-304.*
49. *Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91.*
50. *Greenhawt MJ. Oral and sublingual peanut immunotherapy is not ready for general use. Allergy Asthma Proc 2013;34:197-204.*
51. *Mankad VS, Burks AW. Omalizumab: other indications and unanswered questions. Clin Rev Allergy Immunol 2005;29:17-30.*
52. *Sicherer SH, Simons FE. Self-injectable epinephrine for first-aid management of anaphylaxis. Pediatrics 2007;119:638-46.*