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Gastrointestinal food hypersensitivity: Symptoms, diagnosis and provocation tests

Gastrointestinal gıda duyarlılığı: Semptomlar, tanı ve provokasyon testleri

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As many as 25% of the general population in Western countries believe that they suffer from adverse reactions to food. However, the actual prevalence of food allergy is much lower. Food-induced allergic reactions cause a variety of symptoms including cutaneous, gastrointestinal and respiratory tract. Food allergy might be caused by IgE-mediated, mixed (IgE and/or non-IgE) or non-IgE-mediated (cellular) mechanisms. The clinical diagnosis is based on a careful history, laboratory findings (total and specific IgE), skin prick test, elimination diet and food challenges. New intestinal provocation tests have also been applied to pick up the allergic response of the duodenal mucosa by endosonography and external ultrasound. The management of food allergy continues to be a strict avoidance of the offending food item.

Key words: Food allergy, food hypersensitivity, double-blind placebo-controlled food challenge, provocation tests

Batı ülkelerinde halkın %25`i gıdaya karşı duyarlı olduklarını ifade etmelerine rağmen, aslında gerçek gıda allerji insidansı çok daha düşüktür. Gıdaya bağlı allerji reaksiyonları deri, gastrointestinal ve solunum yollarını içeren birçok semptomlara neden olabilmektedir. Gıda allerjisi, IgE aracılığı, karma (IgE ve/veya non-IgE) veya IgE aracılığı olmayan (hücresel) mekanizmalar ile gerçekleşebilir. Klinik tanının konulması detaylı hastalık hikayesi, laboratuar bulguları (total ve spesifik IgE), deri prik testi, eliminasyon diyetleri ve gıda provokasyonlarına dayanmaktadır. Duodenum mukozasında gelişen allerjik reaksiyonu gözleyebilmek için endosonografi ve ultrason ile yapılan yeni intestinal provokasyon testlerine de başvurulmaktadır. Gıda allerjisinin tedavisi mutlak süratle duyarlılığa neden olan gıda maddesinden kaçınmaktır.

Anahtar kelimeler: Gıda allerjisi, gıda duyarlılığı, gıda provokasyon testleri

Food hypersensitivity affects nearly everyone at some point, either as an unpleasant reaction to something eaten or as a concern for a family member suspected of having food allergy. Increasing public and medical interest have also popularized claims that a variety of physical and psychological symptoms are the result of food hypersensitivity. Increasing numbers of patients are therefore requesting investigation. In Western countries, the rate of perceived food hypersensitivity is as high as approximately 25% in the general population (1). However, the prevalence of true food allergy is 8% in children under three years and 1-2% in adults. Therefore, it is very important to determine if the food really causes these symptoms or if there are other underlying factors. The increasing number of patients with problems attributed to food has thus resulted in growing tasks for clinicians, researchers and food chemists.

Definition of Food Hypersensitivity

In 1995 the European Academy of Allergology and Clinical Immunology (EAACI) Position Paper on Food Allergy established a classification of food allergy based on pathogenetic mechanisms. According to this classification, adverse reactions to food comprise two main groups, toxic and non-toxic reactions, the latter being subdivided into immune-mediated (food allergy) and non-immune-mediated based on the pathogenic mechanisms involved. The non-immunological reactions may depend on enzymatic, pharmacological and, although still unclear, include causes such as irritants and psychosomatic responses (2). This classification underwent revision by the EAACI in 2001. The term hypersensitivity is now being used as the "umbrella" term to cover all kinds of adverse reactions to food such as reactions to food additives, side-effects to drugs, psychological reactions blamed

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on environmental factors, behavioral disorders, and others (3). Food hypersensitivity can be subdivided into two groups as demonstrated in Figure 1.

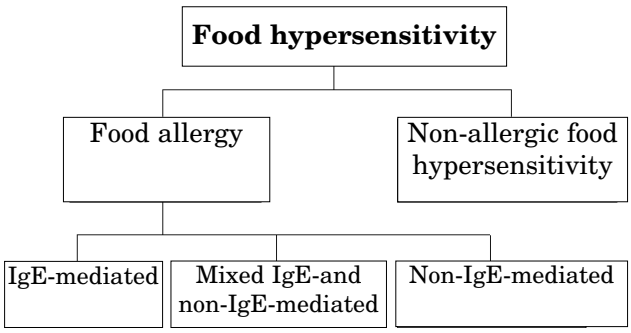

Figure 1. Nomenclature of food hypersensitivity

The term "food allergy" is often used non-specifically to include intolerances or psycho-emotional reactions, but should instead be restricted to reactions mediated by classical immune mechanisms (3). Food allergy is also divided into three groups, named IgE-mediated food allergy (type-I), mixed IgE and/or non-IgE-mediated, and non-IgE-mediated (cellular) food allergy (1, 4). Non-IgE-mediated food allergy (type III or IV) is supposed to be a cell-mediated immunologic reaction, which involves immune complex formation and complement deposition (5). Here, immunologically sensitized lymphocytes play a major role. Therefore, non-IgE-mediated allergic reactions are subdivided into those in which the reaction is initiated predominantly by mechanisms associated with allergen-specific antibodies other than IgE, and those in which a cellular response is predominant. A non-immunological reaction to food, previously called food intolerance, is now denoted as non-allergic food hypersensitivity (3).

"True" Food Allergy

Food allergy is a hypersensitivity reaction initiated by immunologic mechanisms. An overview of immune mechanisms in various "true" food allergy disorders is shown in Table 1.

IgE-Mediated Food Allergy

The symptoms in IgE-mediated food allergy are typical for immediate reactions. A positive skin prick test and specific IgE for a given food corroborate the IgE-mediated pathogenesis (6). This type of food allergy is most common in young children. Symptoms typically begin within minutes of food ingestion, and are short-lived, although onset may occasionally be delayed for up to two hours. The rapid onset correlates highly with positive skin prick test or IgE-radioallergosorbent test (RAST) to the offending antigen. Caution must be exercised because positive skin prick and RAST tests do not always predict clinically relevant reactions in blinded food challenges (7). Immediate gastrointestinal (GI) hypersensitivity, oral allergy syndrome, acute urticaria, angioedema, acute bronchospasm and allergic rhinitis are the main food allergic disorders, which occur by IgE-mediated mechanisms.

Mixed IgE- and Non-IgE-Mediated Food Allergy

Gastrointestinal eosinophilic infiltration is prominent in a number of disorders (eosinophilic esophagitis and gastroenteritis) for which food-induced hypersensitivity is the underlying cause (1). The mechanisms by which eosinophils mediate inflammatory effects are multiple and include the release of cytotoxic proteins and other lipid mediators together with the release of cytokines that deviate toward Th_2-type responses. Another possible mechanism is by acting as antigen-presenting cells (APCs). Allergic eosinophilic esophagitis, gastritis

Table 1. Overview of "true" food allergy

	IgE-mediated	**Mixed IgE / non-IgE-mediated**	**Non-IgE mediated**
GI	Immediate GI	Allergic eosinophilic esophagitis	Dietary protein enterocolitis
	hypersensitivity	Allergic eosinophilic gastritis	Dietary protein proctitis
	Oral allergy syndrome	Allergic eosinophilic gastroenteritis	Dietary protein enteropathy
			Celiac disease
Cutaneous	Acute urticaria		
	Angioedema	Atopic dermatitis	Dermatitis herpetiformis
	Acute contact urticaria		
	Chronic urticaria		
Respiratory	Allergic rhinitis	Asthma	Pulmonary hemosiderosis
	Acute bronchospasm		

and gastroenteritis are characterized by eosinophil infiltration of the esophagus and gastric and intestinal walls to varying depths and distribution, in the absence of other processes such as parasitic, collagen vascular disease, inflammatory bowel disease (IBD) and *Helicobacter pylori* infection (8-10). Peripheral eosinophilia is accompanying in about 50% of the patients (4). Although peripheral blood T cells from these patients have been shown to secrete excessive amounts of interleukin (IL)-4 and IL-5 compared with that found in normal control subjects, the underlying immunopathogenesis is poorly understood (11). Several investigations have demonstrated an association with atopy. For example, nearly half of the patients are atopic as defined by elevated levels of total IgE or food-specific IgE, and IgE-mediated mast cell degranulation has been demonstrated in patients with eosinophilic gastroenteritis (12, 13). The exact prevalence of the eosinophil disorders of the GI tract remains unknown.

Non-IgE-Mediated Food Allergy

Non-IgE-mediated food sensitivities are becoming increasingly recognized. Non-IgE antibody mediated or associated food allergies represent a spectrum of clinical diseases attributed to adverse immune responses to foods for which IgE antibodies to the causal food protein cannot be demonstrated, at least not by routine tests. Several clinically well-defined disorders that develop in infants are perhaps the best demonstration of this type of food allergy (14, 15). The onset of these reactions is slower than immediate IgE-mediated reactions, ranging from a few hours to more than a week after ingestion of the causative agent (16). In some cases, even more prolonged and repeated exposure is required for the development of clinically apparent abnormalities. Inflammatory cell infiltration of the GI wall is seen in many of these conditions, but most diagnoses are currently made on the basis of clinical presentation and response to dietary exclusion (1, 5). Identification of the causal foods for non-IgE-mediated disorders is a complicated undertaking. The symptoms are often subacute or chronic in nature and no simple tests are available to secure the diagnosis. Therefore, elimination diets and oral food challenges are the primary mode of diagnosis and ancillary tests are often needed (such as intestinal biopsy). The atopy patch test and in vitro lymphocyte studies may hold promise for future improved diagnosis of these disorders (17, 18).

Non-allergic Food Hypersensitivity

Non-allergic food hypersensitivity, previously called food intolerance, is a non-immune mediated food hypersensitivity. Mainly, two types of causes are responsible:

Intrinsic causes: Enzyme deficiency (lactase deficiency and phenylketonuria), malignancies and psychological factors.

Extrinsic causes: Infections (bacteria, virus and parasites), food additives (monosodium glutamate, aspartame, sulfites, nitrates and dyes) and pharmacological factors (alcohol, caffeine, histamine, tyramine, serotonin and metal contaminants) (2, 3, 19).

Clinical Features

Food hypersensitivity may affect many organs, thereby causing a perplexing variety of symptoms with different immunopathologic mechanisms. In IgE-mediated food allergy, anaphylactic shock, angioedema, urticaria, asthma, vomiting, diarrhea, atopic dermatitis, oral syndrome, rhinitis and conjunctivitis are classical manifestations (20, 21). Besides pure GI symptoms (nausea, vomiting, abdominal cramping or colic, diarrhea), there can be other allergic reactions in various target organs such as cutaneous (urticaria, flushing, erythematous pruritic rash, atopic dermatitis), respiratory (nasal congestion, rhinorrhea, sneezing, laryngeal edema, wheezing, asthma) and cardiovascular reactions (hypotension, shock, dizziness). In IgE-mediated food allergy, the response has a rapid onset soon after food ingestion, whereas in cell-mediated reactions, onset is slower following food ingestion. In mixed reactions, the features are overlapping to those seen in the other conditions.

Food items commonly cause rhinitis and atopic dermatitis in children, whereas in adults, they mainly cause GI symptoms (19). In children, 70-80% of atopic dermatitis is IgE-mediated and food items are responsible for 40% of those. Exercise, alcohol and drugs can be co-triggers for food allergy (22).

Food Allergens

An allergen may simply be defined as a substance which causes hypersensitivity by an immunologic mechanism. Food such as shrimp or peanut is an "allergen source" and might contain many allergens (Pen a 1 for shrimp and Ara h 1 for peanut). These allergens also have several epitopes, which can interact with many different primary targets.

Table 2. Most common major food allergens

Cow's milk		
Caseins	α_s-caseins	
	β-casein	
	κ-casein	
Whey	β-lactoglobulin	
	α-lactalbumin	
Chicken egg white	Ovomucoid	(Gal d 1)
	Ovalbumin	(Gal d 2)
	Ovotransferrin	(Gal d 3)
Peanut	Vicilin	(Ara h 1)
	Conglutin	(Ara h 2)
	Glycinin	(Ara h 3)
Fish	Parvalbumin	(Gad c 1; cod)
		(Sal s 1; salmon)
Shrimp	Tropomyosin	(Pen a 1; Pen i 1)
Rice	α-amylase inhibitor	(Ory s 1)
Celery	Pathogenesis-related protein	(Api g 1)
	Profilin	(Api g 2)
Apple	Pathogenesis-related protein (PRG)	(Mal d 1)
	Profilin	(Mal d 2)
Carrot	PRG	(Dau c 1)

The allergenic fraction of food is generally comprised of heat-stable, water-soluble glycoproteins ranging in size from 10 to 70 kd (4, 23). The major allergens in some food items are shown in Table 2.

The eight foods or food groups responsible for the vast majority of IgE-mediated food allergies are cow's milk, egg, fish, wheat, peanut, soybean, crustacea (shrimp, crab and lobster) and tree nuts (almond, hazel and walnut). However, there are regional and national variations reflecting dietary patterns. For example, fish allergy is common in Scandinavia, rice allergy in Asia and peanut allergy in the United States, while celery allergy appears to be fairly prevalent in Europe, sesame seed allergy in many parts of the world and buckwheat allergy in South Korea (24). In Mediterranean countries (Italy, Spain, Israel), fruit, especially peach, is a common allergen.

Pathophysiology

There is little information about the pathophysiology of intestinal hypersensitivity reactions. Whether reduced mucosal barrier function, hereditary elevated IgE responses or inflammation cells play the major role in pathogenesis is still unknown (2). Previous studies indicate that mast cells, eosinophils and intraepithelial T-cells are involved in the pathogenesis of intestinal food allergy (25-28).

Interaction between IgE on mast cell surfaces with food extracts has been well demonstrated in immediate reactions. GI mucosal reactions might be similar to those that follow mast cell degranulation as shown by intraluminal administration of food antigens in sensitive individuals, which leads to a rapid increase in histamine and tryptase (25). Mediators (histamine, tryptase, prostaglandins, leukotrienes and cytokines) which are released in response to Fc∈RI cross-linking from mast cells may contribute to the IgE-mediated late-phase response. Eosinophils may also accompany both the immediate and the late phase of allergic reaction and they might be activated by a direct (cross-linking surface-bound IgE or IgA on eosinophils) or an indirect effect (via mast cell mediators). It has been shown that patchy or diffuse lymphonodular hyperplasia with normal villous architecture is a typical endoscopic finding of food allergy in school-aged children. Increased densities of intraepithelial lymphocytes (IELs) have been observed in jejunal biopsy specimens from patients with cow's milk protein intolerance and latent milk allergy. However, the number of IELs in these patient groups has been lower than in celiac disease patients (27). This indicates that subjects with celiac disease and food allergy may have a similar type of immunological activation, but celiac disease patients have it in a far more advanced form.

In addition, several cytokines (IL-3, IL-4, IL-5, and IL-13) are important regulators of allergic inflammation, and an imbalance between Th_1 and Th_2 lymphocytes favors development of the allergic response (2, 11). The release of these mediators and cytokines by T cells, mast cells and eosinophils is presumably a relevant step in the pathogenesis of the late-phase reaction, characterized not only by increased vascular permeability and edema but by the infiltration of the tissue with inflammatory cells.

Diagnosis of Food Hypersensitivity

Case History

Most patients will describe a close connection between intake of specific food and development of symptoms. Therefore, a detailed history must be taken to identify whether or not the complaints are likely to be associated with food hypersensitivity. A careful history should focus on: the symp-

toms attributed to food ingestion (type, acute vs. chronic), which food are involved, consistency of reactions, the quantity of food required to elicit symptoms,

the timing between ingestion and onset of symptoms, the most recent reaction or patterns of reactivity, the manner in which the food was prepared (raw or cooked), potential contamination with known allergens and any ancillary associated activity that may play a role (e.g., exercise, alcohol or drug). Additionally, it is helpful if the patients keep a symptom diary and chart the foods they consume with and without symptoms, and to collect ingredient labels from the foods they eat. In this way, the physician may construct a priori assessments of chance that foods do play a role and which foods may be involved (19).

Diagnostic Tests

Skin prick test: Skin prick-puncture test is a commonly used method to detect food-specific IgE antibody. The foods selected for testing should be based on case history and the patients should stop taking any antihistamines for an appropriate length of time. The technique is simple. A device such as needle, bifurcated needle, probe or lancet is used to puncture the epidermis through an extract of food. Appropriate positive (histamine) and negative (saline-glycerin) controls are also placed. The test site is examined 10-20 minutes later. A local wheal and flare response indicates the presence of food-specific IgE antibody. A mean wheal diameter 3 mm or greater compared to a saline control is generally considered positive (29, 30).

Total and specific serum IgE levels: Total serum IgE does not add considerable insight into the diagnosis of food allergy because it may increase in other disorders than allergy such as parasitic infections. Therefore, specific serum IgE is more specific for food allergy. However, it cannot establish the diagnosis of a clinical food allergy. RAST allows the quantification of allergen-specific IgE in serum (25).

Atopy patch test: Atopy patch tests are classically used to evaluate cell-mediated (type IV, late phase reaction) responses to various chemical sensitizers. The test is generally performed by applying the suspected allergen to the surface of the skin in a metal cup under an occlusive dressing and leaving it in place for 24 hours (31). The test site is evaluated at the time of removal and 1-2 days later for evidence of inflammation that can be scored by severity. Controls are applied to determine possible irritant reactions. The atopy patch test can hypothetically induce T cell responses reflecting those that occur in subacute and chronic atopic dermatitis or perhaps in GI food hypersensitivity (32, 33). In several studies, positive atopy patch test was associated with delayed reactions and it may perhaps help to distinguish between non-IgE-mediated food allergy and non-allergic food hypersensitivity (34). Atopy patch test requires two to three physician visits and a fairly large area of intact, rash-free skin, and the test is more cumbersome and more costly than the skin prick test. Clearly, atopy patch test shows some promise as a diagnostic tool, but the method needs to be further studied.

Elimination Diet

An elimination diet is often warranted before undertaking food challenges. This can be done by eliminating one or several food items from the diet, and would also represent a therapeutic intervention. The length of trial depends on the type of symptoms, but the time interval required is usually 1-6 weeks. If there is no improvement with elimination, then the foods eliminated are not likely to be a cause of the complaints. However, if resolution of symptoms is achieved, food challenges may be warranted as a next step in identifying the offending foods among those eliminated (35).

Food Challenges

The food challenges ultimately either confirm or refute specific foods as causing clinical disease. Indication for challenge, challenge type (open, single or double-blind) and challenge location (home, office or hospital) should be decided before undertaking a food challenge. Severe anaphylaxis after ingestion, with a positive test for specific IgE antibody to the causal food, is a relative contraindication for food challenge. Patients should avoid the suspected foods for at least two weeks, antihistamines should be discontinued according to their elimination half-life, and chronic asthma medications should be reduced as much as possible prior to undertaking the challenge.

There are several methods for food challenge such as open, single-blind and double-blind placebo-controlled food challenge (DBPCFC). Labial food challenge was performed in children with food allergy (36, 37). Some researchers begin challenges with labial food challenge by placing the food extract on the lower lip for two minutes observing

local or systemic reactions in the ensuing 30 minutes. The development of contiguous rash of the cheek and chin, edema of the lip with conjunctivitis or rhinitis, or a systemic reaction is considered a positive test (38). Negative labial challenges are generally followed by an oral food challenge.

During open provocation, both the patient and the physician know the food item, whereas in DBPCFC, neither the patient nor the physician knows the food item being tested. In single-blind test, the food item is only unknown to the patient. In the latter two formats, the food must be hidden in some way, such as in another food or in opaque capsules. DBPCFC is least prone to bias by patients and/or physician. Although the open food challenge is most prone to bias, it is often preferred because no special preparation is needed to mask the food.

In all challenges, the food is given in gradually increasing amounts. For most IgE-mediated reactions, the researcher gives a total of 8-10 g of the dry food or 100 ml of wet food (double amount for meat and fish) in gradually increasing doses at 10-15-minute intervals over about 90 minutes followed by a larger, meal size portion of food a few hours later (39, 40). However, a variety of other challenge regimens have been used with successful results (lower starting doses, variations in the degree of dosing increases, different time intervals) (38,41). The challenge data for 513 positive challenges to six common allergenic foods in children with atopic dermatitis showed that starting dose were usually 500 mg, but at the physician‘s discretion, this was sometimes 100-250 mg. Usually, starting doses of 100 mg or less were recommended (42). The dose that elicited a reaction was not predictable from the skin prick test response or IgE antibody concentration. DBPCFC also applies graded doses, but in this case either a placebo or a challenge food is administered. The order of administration should be randomized.

Even though there is dissatisfaction and doubt about DBPCFC, this method is still considered the "gold standard" for diagnosing food allergy (25). However, false positive and false negative results should be taken into consideration. To help exclude false negatives, it has long been suggested to include an open feeding under supervision of a meal-size portion of the tested food prepared in its usual manner, as a follow-up to any negative DBPCFC (43).

Other Provocation Tests

Jejunal perfusion: An alternative food challenge was performed by collecting jejunal perfusion samples. The investigators isolated an approximately 10 cm long segment in the proximal part of the jejunum by a two-balloon, six-channel tube and perfused it with an allergen solution. Samples of the perfusate were collected after 20 minutes. Bengtsson et al. (44) indicated increased intestinal secretion of eosinophil cationic protein (ECP) and histamine after intestinal challenge in patients with cow's milk intolerance. Intraluminal administration of food antigens may induce intestinal release of mast cells tryptase, histamine, prostaglandin D2 and eosinophils peroxidase activity within 30 minutes after challenge (45). A disadvantage of this procedure is that the mucosal changes are not visible and biopsies cannot be taken. So far, this technique has been reserved to research settings.

Gastroscopic provocation test: In previous studies, attempts have been made to challenge gastric mucosa with food allergens during gastroscopy. In the intragastral allergen provocation test under endoscopic control (IPEC), mucosal changes with edema, reddening and bleeding of the stimulated area were reported in cases of positive challenges with food allergen (46, 47).

Colonoscopic allergen provocation test: During the colonoscopic allergen provocation (COLAP) test, liquid (food) antigen extracts, a buffer control and a positive control containing histamine are injected into the mucosa of the cecum with a fine needle. The antigen extracts are selected according to patient’s history and/or RAST results. After 20 min, the wheal and flare reaction of the provoked mucosa is registered semiquantitatively using a score from 0 to 4, and biopsies are taken from the provocation areas as well as from unprovoked cecal mucosa (48, 49).

New provocation tests with ultrasound: In previous studies we applied endosonography and external ultrasound to pick up the allergic response of the duodenal mucosa to provocation (50, 51). Patients were challenged with the suspected food item through a nasoduodenal tube. Using external ultrasound, the sonographic features (wall thickness and diameter of the duodenal bulb and jejunum, peristalsis activity, and luminal fluid) were recorded before and during one hour after challenge. GI symptoms were registered using a Visual Analo-

gue Scale (VAS). Sonographic changes in response to challenge were observed in 44% of patients. The sonographic response was significantly related to the response of the skin prick test and of the DBPCFC. Interestingly, the degree of provocation-induced symptoms was significantly correlated to the increase in intestinal wall thickness. Hence, responses of the proximal small intestine to direct provocation (swelling of the wall and exudation of fluid into the lumen) could be visualized by transabdominal ultrasound, and this new provocation test may become helpful in the evaluation of patients with food hypersensitivity. However, further validation studies are required.

Laboratory Tests

Histamine, Tryptase and Eosinophil Cationic Protein (ECP): Several mediators are released from 1) mast cells: histamine, tryptase, prostaglandins and leukotrienes, 2) eosinophils: ECP, eosinophil protein X (EPX), eosinophil peroxidase (EPO), major basic protein (MBP), prostaglandins and leukotrienes, 3) basophils: histamine and leukotrienes, and 4) neutrophils: myeloperoxidase (MPO), human neutrophil lipocalin (HNL), lactoferrin, calprotectin and lysozyme (52). In various studies, some of these mediators have been measured in serum, urine and stool, and have been shown to be elevated in patients with food allergy (44, 48, 53-55). The notion that mast cells, eosinophils and basophils become activated after food allergen exposure (provocation test) to skin, lung or intestine is further emphasized by histological studies showing degranulation and cytokine production in these cell types and by the measurement of enhanced levels of proinflammatory mediators after allergen provocation tests. In addition, methylhistamine, which is a metabolite of histamine, can be determined in urine in patients with food allergy (56, 57). However, none of these measurements are well established as clinical diagnostic methods.

Leukotrienes: Leukotrienes (LT) and prostaglandins (PG) have been used to monitor inflammation in allergic disorders, mostly in patients with airway allergy, asthma and drug allergy. Both LTE_4 and PGD_2 metabolite 9α, 11b-PGF_2 can be determined in the urine, although there is rather limited information on this in relation to food allergic reactions (58). A specific test, CAST-ELISA, has been developed to measure the LTB_4, LTC_4 and LTE_4 released from peripheral cells (59). However, all these methods need further documentation before they are applied within a clinical routine.

Cytokines: Serum cytokines have not yet proven useful for clinical information. Some studies have reported an imbalance of IL-4 and interferon-γ (INF-γ) in children and adults (60, 61). Furthermore, INF-γ and IL-2 have been reported to be elevated in food allergic reactions (62). However, much more information is needed before use in clinical routine.

Differential Diagnosis

GI disorders (functional GI disorders, IBD, celiac disease and eosinophilic gastroenteritis), enzyme deficiency (disaccharidase deficiency, galactosemia, phenylketonuria), malignancy, contaminants and food additives (dyes, toxins, infectious organisms, seafood-associated disorders), pharmacologic agents (caffeine, histamine, serotonin, tyramine, alcohol) and psychologic reactions should be considered in the differential diagnosis of food hypersensitivity (19, 25).

Management

The mainstream treatment of food allergy continues to be a strict avoidance of the offending food item. The practicability of such an elimination diet is, however, limited by the number of allergens and quite often also by the frequency of the allergen within normal nutrition. A spontaneous desensitization may occur in 19-44% of patients following an elimination diet, but this process usually takes years (1, 19). If an elimination diet cannot be performed properly, or if the responsible foods could not be identified, antiallergic medication is required. In any patient with signs and symptoms of anaphylaxis, epinephrine should immediately be administered by intramuscular injection. Oral cromolyn sodium is effective in treating IgE-mediated food allergies and allergic eosinophilic gastroenteritis. Due to a low side-effect rate, oral cromoglycate can be used in children as well. Other medications such as H_1 and H_2 antihistamines, ketotifen, corticosteroids and leukotriene inhibitors have been used in an attempt to modify symptoms of food-induced allergic disorders. Antihistamines may partially mask symptoms of oral allergy syndrome and IgE-mediated skin symptoms. Oral corticosteroids are generally effective in treating chronic IgE-mediated disorders (atopic dermatitis or asthma) or non-IgE-mediated GI disorders (allergic eosinophilic esophagitis or gastroenteritis and dietary food induced enteropathy) (19). At present, several other antiallergic drugs are under development, such as anti-CD4,

anti-IgE, anti-IL-5 or anti-IL-4 strategies (25). The results on the use of anti-IgE antibodies are promising (63, 64). However, it is unclear whether these therapeutic approaches are effective in the GI tract.

REFERENCES

1. O'Leary PF, Shanahan F. Food allergies. Curr Gastroenterol Rep 2002; 4: 373-82.
2. Brandtzaeg P. Mechanisms of gastrointestinal reactions to food. Environ Toxicol Pharmacol 1997; 4: 9-24.
3. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. Allergy 2001; 56: 813-24.
4. Sampson HA. Food allergy. Part 1: immunopathogenesis and clinical disorders. J Allergy Clin Immunol 1999; 103: 717-28.
5. Sicherer SH, Munoz-Furlong A, Murphy R, et al. Symposium: Pediatric food allergy. Pediatrics 2004; 111: 1591-4.
6. Ortolani C, Vighi G. Definition of adverse reactions to food. Allergy 1995; 50: 8-13.
7. Justinich CJ. Update in gastrointestinal allergic diseases. Curr Opin Pediatr 2000; 12: 456-9.
8. Behm CA, Ovington KS. The role of eosinophils in parasitic helminth infections: insight from genetically modified mice. Parasitol Today 2000; 16: 202-9.
9. Torpier G, Colombel JF, Mathieu-Chandelier C, et al. Eosinophilic gastroenteritis: ultrastructural evidence for a selective release of eosinophil major basic protein. Clin Exp Immunol 1988; 74: 404-8.
10. Walsh RE, Gaginella TS. The eosinophil in inflammatory bowel disease. Scand J Gastroenterol 1991; 26: 1217-24.
11. Jaffe JS, James SP, Mullins GE, et al. Evidence for an abnormal profile of interleukin-4 (IL-4), IL-5, and gamma-interferon (gamma-IFN) in peripheral blood T cells from patients with allergic eosinophilic gastroenteritis. J Clin Immunol 1994; 14: 299-309.
12. Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. J Allergy Clin Immunol 1996; 97: 822-7.
13. Sampson HA. Food allergy. JAMA 1997; 278: 1888-94.
14. Sampson HA, Anderson JA. Summary and recommendations: classification of gastrointestinal manifestations due to immunologic reactions to foods in infants and young children. J Pediatr Gastroenterol Nutr 2000; 30: 87-94.
15. Sampson HA, Sicherer SH, Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. American Gastroenterological Association. Gastroenterology 2001; 120: 1026-40.
16. Ring J, Brockow K, Behrendt H. Adverse reactions to foods. J Chromatogr B Biomed Sci Appl 2001; 756: 3-10.
17. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. J Allergy Clin Immunol 1996; 97: 9-15.
18. Roehr CC, Reibel S, Ziegert M, et al. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2001; 107: 548-53.
19. Sampson HA. Food allergy. Part 2: diagnosis and management. J Allergy Clin Immunol 1999; 103: 981-9.
20. Ferguson A. Symptoms and manifestations of food allergy, with particular relevance to the gut. Environ Toxicol Pharmacol 1997; 4: 33-8.
21. Vatn MH. Symptoms and manifestations of food intolerance. Environ Toxicol Pharmacol 1997; 4: 51-3.
22. Dohi M, Suko M, Sugiyama H, et al. Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. J Allergy Clin Immunol 1991; 87: 34-40.
23. Aalberse RC. Food allergens. Environ Toxicol Pharmacol 1997; 4: 55-60.
24. Park JW, Kang DB, Kim CW, et al. Identification and characterization of the major allergens of buckwheat. Allergy 2000; 55: 1035-41.
25. Bischoff SC, Mayer JH, Manns MP. Allergy and the gut. Int Arch Allergy Immunol 2000; 121: 270-83.
26. Crowe SE, Perdue MH. Gastrointestinal food hypersensitivity: basic mechanisms of pathophysiology. Gastroenterology 1992; 103: 1075-95.
27. Kokkonen J, Holm K, Karttunen TJ, et al. Children with untreated food allergy express a relative increment in the density of duodenal gammadelta+ T cells. Scand J Gastroenterol 2000; 35: 1137-42.
28. Schade RP, Van Ieperen-Van Dijk AG, Versluis C, et al. Cell-surface expression of CD25, CD26, and CD30 by allergen-specific T cells is intrinsically different in cow's milk allergy. J Allergy Clin Immunol 2002; 109: 357-62.
29. Dreborg S. Skin tests used in type I allergy testing, methods for skin testing. Allergy 1998; 44: 22-30.
30. Eigenmann PA, Sampson HA. Interpreting skin prick tests in the evaluation of food allergy in children. Pediatr Allergy Immunol 1998; 9: 186-91.
31. Niggemann B, Reibel S, Wahn U. The atopy patch test (APT) -- a useful tool for the diagnosis of food allergy in children with atopic dermatitis. Allergy 2000; 55: 281-5.
32. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. J Allergy Clin Immunol 2002; 109: 363-8.
33. Wistokat-Wulfing A, Schmidt P, Darsow U, et al. Atopy patch test reactions are associated with T lymphocyte-mediated allergen-specific immune responses in atopic dermatitis. Clin Exp Allergy 1999; 29: 513-21.
34. Niggemann B. Atopy Patch Test (APT)--its role in diagnosis of food allergy in atopic dermatitis. Indian J Pediatr 2002; 69: 57-9.
35. Sicherer SH. Food allergy: when and how to perform oral food challenges. Pediatr Allergy Immunol 1999; 10: 226-34.
36. Lee S, Noh GW, Lee KY. Clinical application of histamine prick test for food challenge in atopic dermatitis. J Korean Med Sci 2001; 16: 276-82.
37. Rance F, Dutau G. Labial food challenge in children with food allergy. Pediatr Allergy Immunol 1997; 8: 41-4.
38. Rance F, Kanny G, Dutau G, et al. Food hypersensitivity in children: clinical aspects and distribution of allergens. Pediatr Allergy Immunol 1999; 10: 33-8.
39. Eigenmann PA, Sicherer SH, Borkowski TA, et al. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics 1998; 101: E8.
40. Sicherer SH, Sampson HA. Cow's milk protein-specific IgE concentrations in two age groups of milk-allergic children and in children achieving clinical tolerance. Clin Exp Allergy 1999; 29: 507-12.
41. Niggemann B, Sielaff B, Beyer K, et al. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. Clin Exp Allergy 1999; 29: 91-6.

42. Sicherer SH, Morrow EH, Sampson HA. Dose-response in double-blind, placebo-controlled oral food challenges in children with atopic dermatitis. J Allergy Clin Immunol 2000; 105: 582-6.
43. Niggemann B, Wahn U, Sampson HA. Proposals for standardization of oral food challenge tests in infants and children. Pediatr Allergy Immunol 1994; 5: 11-3.
44. Bengtsson U, Knutson TW, Knutson L, et al. Eosinophil cationic protein and histamine after intestinal challenge in patients with cow's milk intolerance. J Allergy Clin Immunol 1997; 100: 216-21.
45. Santos J, Bayarri C, Saperas E, et al. Characterisation of immune mediator release during the immediate response to segmental mucosal challenge in the jejunum of patients with food allergy. Gut 1999; 45: 553-8.
46. Bagnato GF, Di Cesare E, Caruso RA, et al. Gastric mucosal mast cells in atopic subjects. Allergy 1995; 50: 322-7.
47. Reimann HJ, Lewin J. Gastric mucosal reactions in patients with food allergy. Am J Gastroenterol 1988; 83: 1212-9.
48. Bischoff SC, Mayer J, Wedemeyer J, et al. Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. Gut 1997; 40: 745-53.
49. Bischoff SC, Mayer J, Meier PN, et al. Clinical significance of the colonoscopic allergen provocation test. Int Arch Allergy Immunol 1997; 113: 348-51.
50. Arslan G, Ødegaard S, Elsayed S, et al. Food allergy and intolerance: response to intestinal provocation monitored by endosonography. European J Ultrasound 2002; 15: 29-36.
51. Arslan G, Gilja OH, Lind R, et al. Response to intestinal provocation monitored by transabdominal ultrasound in patients with food hypersensitivity. Scand J Gastroenterol 2005; 40: 386-94.
52. Ahlstedt S. Mediators in allergy diagnosis. ACI International 1998; 10: 37-44.
53. Bischoff SC, Grabowsky J, Manns MP. Quantification of inflammatory mediators in stool samples of patients with inflammatory bowel disorders and controls. Dig Dis Sci 1997; 42: 394-403.
54. Bischoff SC, Mayer J, Nguyen QT, et al. Immunnohistological assessment of intestinal eosinophil activation in patients with eosinophilic gastroenteritis and inflammatory bowel disease. Am J Gastroenterol 1999; 94: 3521-9.
55. Kosa L, Kereki E, Borzsonyl L. Copro-eosinophil cationic protein (ECP) in food allergy. Allergy 1996; 51: 964-6.
56. Weidenhiller M, Trankner A, Schwab D, et al. Different kinetics of mediator release can be detected during allergic reactions after oral provocation (double blind placebo-controlled food challenge). Inflamm Res 2002; 51: 29-30.
57. Winterkamp S, Weidenhiller M, Wilken V, et al. Standardised evaluation of urinary excretion of N-tele-methylhistamine in different periods of age in a healthy population. Inflamm Res 2003; 52: 57-58.
58. Kumlin M. Measurement of leukotrienes in humans. Am J Respir Crit Care Med 2000; 161: 102-6.
59. Moneret-Vautrin DA, Sainte-Laudy J, Kanny G, et al. Human basophil activation measured by CD63 expression and LTC4 release in IgE-mediated food allergy. Ann Allergy Asthma Immunol 1999; 82: 33-40.
60. Andre F, Pene J, Andre C. Interleukin-4 and interferon-gamma production by peripheral blood mononuclear cells from food-allergic patients. Allergy 1996; 51: 350-5.
61. Hauer AC, Breese EJ, Walker-Smith JA, et al. The frequency of cells secreting interferon-gamma and interleukin-4, -5, and -10 in the blood and duodenal mucosa of children with cow's milk hypersensitivity. Pediatr Res 1997; 42: 629-38.
62. Kondo N, Fukutomi O, Agata H, et al. The role of T lymphocytes in patients with food-sensitive atopic dermatitis. J Allergy Clin Immunol 1993; 91: 658-68.
63. Borish LC, Nelson HS, Lanz M, et al. Phase I/II study of interleukin-4 receptor (IL-4R) in moderate asthma. J Allergy Clin Immunol 1998; 101: S8.
64. Corne J, Djukanovic R, Thomas L, et al. The effect of intravenous administration of a chimeric anti-IgE antibody on serum IgE levels in atopic subjects: efficacy, safety, and pharmacokinetics. J Clin Invest 1997; 99: 879-87.