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Review

Adverse reactions to foods

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Abstract

Allergic reactions to foods represent a prominent, actual and increasing problem in clinical medicine. Symptoms of food allergy comprise skin reactions (urticaria, angioedema, eczema) respiratory (bronchoconstriction, rhinitis), gastrointestinal (cramping, diarrhea) and cardiovascular symptoms with the maximal manifestation of anaphylactic shock. They can be elicited by minute amounts of allergens. The diagnosis of food allergy is done by history, skin test, in vitro allergy diagnosis and — if necessary — oral provocation tests, if possible placebo-controlled. Avoidance of respective allergens for the allergic patient, however, is often complicated or impossible due to deficits in declaration regulations in many countries. Increasing numbers of cases including fatalities, due to inadvertent intake of food allergens are reported. It is therefore necessary to improve declaration laws and develop methods for allergen detection in foods. Allergens can be detected by serological methods (enzyme immunoassays, in vitro basophil histamine release or in vivo skin test procedures in sensitized individuals). The problem of diagnosis of food allergy is further complicated by cross-reactivity between allergens in foods and aeroallergens (pollen, animal epithelia, latex etc.). Elicitors of pseudo-allergic reactions with similar clinical symptomatology comprise low-molecular-mass chemicals (preservatives, colorings, flavor substances etc.). For some of them (e.g. sulfites) detection assays are available. In some patients classic allergic contact eczema can be elicited systemically after oral intake of low-molecular-mass contact allergens such as nickel sulfate or flavorings such as vanillin in foods. The role of xenobiotic components in foods (e.g. pesticides) is not known at the moment. In order to improve the situation of the food allergic patient, research programs to elucidate the pathophysiology and improve allergen detection strategies have to be implemented together with reinforced declaration regulations on a quantitative basis.

Keywords: Reviews; Adverse reactions; Food allergy; Anaphylaxis; Hidden allergy

Contents

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1. Epidemiology

Allergic reactions to foods represent an increasing problem in clinical medicine. There are few well controlled epidemiological studies on the prevalence of food allergy available [1]. The prevalence has been estimated to be at least 2–5% in infancy and childhood [2–4]. Breast-feeding and delayed introduction of solid foods in infant diets prevent some food allergies and atopic dermatitis infants and young children [5]. Infants with food allergies often outgrow their food sensitivities, in particular those to cow's milk and hen's eggs. In adult populations the prevalence of food hypersensitivity is lower, it has been estimated to be 2.4% in a Dutch population employing questionnaires and confirming the clinical reactions by double-blind placebo-controlled food challenge [6]. Patients who experience immediate allergic reactions to foods are often atopic or are from an atopic family. The prevalence of adverse reactions to food additives has been estimated at 0.01–2% [7,8].

2. Clinical symptoms of adverse reactions to food

The majority of allergic reactions to food occur within minutes of consuming a food to which a given individual is sensitive. Immediate reactions to foods affect all age groups and involve multiple target organs. The clinical symptomatology ranges from localized symptoms at the site of direct contact (e.g. oral allergy syndrome with itching and swelling of the pharynx, and pruritus, and angiodema of lips and tongue immediately after intake of fresh fruits, vegetables, and other foods), contact urticaria (e.g. of the hands after contact with food proteins), localized gastrointestinal allergy with nausea, cramping, pain, vomiting, flatulence and diarrhea) to systemic symptoms occurring in different organs after ingestion of food such as skin symptoms (urticaria, angioedema, eczematous skin eruptions, atopic and classic contact eczema), respiratory symptoms (bronchoconstriction, rhinitis) or the maximal variant of an immediate type allergic reaction (anaphylaxis with cardiovascular and gastrointestinal symptoms sometimes leading to shock). Systemic anaphylaxis after ingestion of a food allergen generally occurs within 1–30 min, however, in rare cases it has also been described hours after ingestion. Fatal reactions may progress rapidly or begin with mild symptoms and progress to shock and cardiorespiratory arrest.

Food additives (e.g. tartrazine) may also induce urticaria, wheezing and anaphylactoid symptoms (e.g. potassium metabisulfite). A syndrome consisting of a burning sensation, weakness, headache, tingling and gastric discomfort is caused by monosodium glutamate.

3. Classification of adverse reactions to food

Adverse reactions to food can be elicited by different pathomechanisms [9]. The term 'food allergy' is often used unspecifically to include psychoemotional reactions or intolerances, but should rather be restricted to reactions mediated by classical immune mechanisms.

The vast majority of food allergies are due to the presence of specific IgE antibodies to food constituents. Food antigens seem to penetrate the normal gastrointestinal tract. In a passive anaphylaxis test, patients were sensitized intracutaneously with serum from a fish allergic individual [10]. They all developed a wheal-and-flare reaction at the sensitized site within 15–60 min of being fed raw fish. Specific IgE antibodies to food allergens are produced by the immune system and bound on the surface of mast cells and basophils. The higher prevalence of food allergic reactions in infancy may, in part, be the result of immunologic immaturity and immaturity of the gastrointestinal barrier. Cross-linking of the IgE antibodies after subsequent exposure to the offending

food leads to release of chemical mediators in the involved organs. Preformed mast cell mediators being stored in the mast cell granules, such as histamine are released and lead to the acute phase of the allergic immediate-type reaction. In some cases, mediators that are produced more slowly, such as leukotrienes, prostaglandins and cytokines may lead to recruitment of inflammatory cells and finally result in a subsequent reaction after several hours, termed late-phase reaction. Only a few reports and examples of non-IgE-mediated food allergy exist, such as gluten-sensitive enteropathy (celiac disease), allergic eosinophilic gastroenteritis, hemorrhagic gastroenteritis of childhood, food induced colitis, food-induced pulmonary hemosiderosis (Heiner's syndrome), or dermatitis herpetiformis.

Toxic phenomena have to be differentiated from hypersensitivity reactions. Other non-immunological hypersensitivity reactions include food intolerance (e.g. lactose intolerance on the basis of lactase deficiency) and idiosyncrasy, also called pseudo-allergy, when mimicking allergic diseases. Pseudo-allergy is distinguished from allergy by failure to detect immunological sensitization in skin tests or in vitro tests, such as the radio allergosorbent test (RAST). Clinically it may be impossible to determine if a reaction is caused by an allergic or pseudo-allergic reaction, as both may release the same chemical mediators of inflammation. However, examining the history of an adverse reaction to food to compare the offending food with well known allergens and elicitors of pseudo-allergic reactions gives a first hint on the underlying pathomechanism. (Fig. 1).

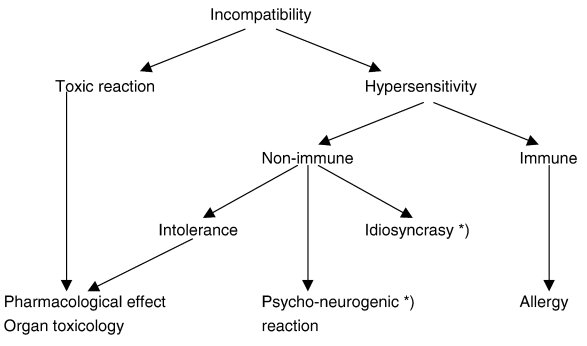

Fig. 1. Classification of adverse food reactions. *, If symptoms mimic allergic reaction, the term 'pseudo-allergy' is used.

4. Allergens and elicitors of pseudo-allergic reactions

The most common elicitors of food allergy vary according to nutritional habits and sociocultural background. In central Europe and USA the most common food allergens comprise cow's milk, hen's eggs, fish, seafood, nuts, peanuts, fruits, soy, vegetables, and wheat [11].

Food antigens are derived from animal or plant origin. Most allergenic foods contain several allergenic structures, which are divided into major and minor allergens. In most cases they consist of proteins or glycoproteins with a molecular mass between 10 000 and 40 000 [12]. The great majority of food allergic subjects are sensitive to the major allergens. In childhood, allergens of animal origin, cow's milk and hen's eggs are the foods most frequently reported to cause food allergies in infants and children [2,13]. Cow's milk contains 3.6% protein. Heat stable caseins and β-lactoglobulin are the most important allergens in cow's milk, whereas α-lactalbumin is less heat stable. The major allergens in hen's eggs have been identified as ovomucoid as well as ovalbumin and conalbumin [14]. In adults, allergy to cow's milk and hen's eggs are untypical. Allergic reactions to tree nuts and fruits, such as apple, cherry or pear are most often found in adult patients with concomitant allergic rhinoconjunctivitis and allergy to pollens.

Eight foods, cow's milk, hen's eggs, together with peanut, soybean, tree nuts, fish, crustaceae and wheat account for more than 90% of the documented food allergies worldwide [15]. Severe and sometimes life threatening reactions most often occur after ingestion of peanuts, nuts, fish and crustaceae. Peanuts are one of the most allergenic foods [16]. They are extensively consumed in the form of peanut butter, especially in the US and UK, but are also included as a protein supplement in processed foods. Peanuts are the most common cause of fatal food anaphylaxis [17–21]. Allergy, sometimes in the form of anaphylaxis, is common to fish and crustaceae, such

as shrimps, crabs, prawns and lobsters in countries where fish consumption is high.

Many IgE-inducing food allergens from plant sources are proteins belonging to pathogenesis-related (PR) protein families (see Table 1). These proteins are increasingly or newly synthesized after contact of the plant with bacteria, but may also be induced by other pathogenic factors (chemicals, osmotic stress or air pollution) [22,23]. PR proteins are constitutively present in low amounts in seeds of many plants. Other important allergens are profilins, which are found to play an important role in plant cell growth and pollen germination. They are actin-binding proteins found in all eukaryotic cells [24,25]. Profilin has been demonstrated to be one of the birch pollen allergens, Bet v 2, and has been identified in a variety of foods, such as celery, tomato, orange, soy, wheat and natural rubber latex [26]. Also a considerable number of allergens belong to other protein families, such as seed storage proteins, lipid transfer proteins or tropomyosins [27] (Table 1). Allergy to plants is often associated to allergy to pollens. Pollen-related food allergy is caused by binding of IgE antibodies to cross-reacting homologous molecules on foods and pollens such as profilin or PR proteins. In natural rubber latex allergic patients, allergies to bananas, avocado, and chestnuts are often found.

Many foods also contain additives such as preservatives, flavorings, colorings, antioxidants etc.

Table 1
Common food allergens

Protein classification	Property	Allergen source (allergen)
PR 2	β1–3-Glucanase	Fruits
PR 3	Type I (basic) and Type II (acidic) chitinases	Avocado (Pers a 1), banana, chestnut
PR 5	Thaumatin and osmotin like proteins (antifungal)	Cherry (Pru av 2), apple (Mal d 2), paprika
PR 6	Protease and amylase inhibitors	Soy, wheat, barley, rye, rice
PR 9	Peroxidase	Wheat, barley
PR 10	Bet v 1 homologue similar to ribonuclease	Apple (Mal d 1), cherry (Pru av 1) carrot (Dau c 1), celery (Api g 1), pear (Pyr c 1), hazelnut (Cor a 1), apricot (Pru ar 1)
Profilin	Actin binding, signal transduction	Celery, potato, hazelnut, apple, pear, tomato, cherry, soybean, peanut
Parvalbumin	Ca^{2+}-binding proteins	e.g. Salmon (Sal s 1)
Tropomyosin	Ca^{2+}-binding proteins	e.g. Shrimp (Met e 1, Pen a 1, Pen i 1), lobster (Hom a 1), squid (Tod p 1), abalone (Hal m 1), scallop, crab (Cha f 1)
Seed storage proteins	2 S albumins, vicilins, conglutins	Mustard (Sin a 1, Bra j 1), castor bean (Ric c 1), rapeseed (Bu III), brazil nut (Ber e 1), walnut (Jug r 1, Jug r 2), peanut (Ara h 1, Ara h 2, Ara h 3, Ara h 4) soy
Lipid transfer proteins	Lipid metabolism	Plum (Pru p 3), rapeseed, apple, apricot, maize, peach, broccoli, carrot
Protease	Proteolysis	Papaya (papain), pineapple (bromelain), fig (ficin), kiwi (Act c 1), soy (Gly m 1)
Lectins	Carbohydrate binding	Peanut agglutinin

Table 2
Common elicitors of pseudo-allergic food reactions

Colorings
Azo dyes (e.g. yellow orange S, tartrazine, amaranth)
Other synthetic colorings (e.g. erythrosin, patent blue, chinolin yellow)
Natural dyes (iron III oxide, cochenille red)
Preservatives
Sorbic acid
Benzoates
Sulfites
Nitrites
Antioxidants
Propyl gallate
Tocopherol
Butyl hydroxyanisol
Taste enhancers
Glutamate
Sweeteners
Cyclamate, aspartame
Naturally occurring ingredients
Salicylates, biogenic amines, benzoates

(see Table 2). Some of these additives like salicylates, benzoates. sulfites may naturally occur in certain foods. Many of these additives of low molecular mass can induce allergy-like diseases and symptoms which mimic allergic reactions and are called pseudo-allergic reactions.

In some patients with classic contact allergy, eczematous skin lesions can be elicited by oral intake of contact allergens such as nickel sulfate or flavorings (e.g. vanillin) in foods. Veien et al. have reported the effect of a nickel-restricted diet in patients with contact dermatitis to nickel and a benefit of a diet low in flavors in patients with exacerbation of dermatitis after challenge with balsam of peru [28].

The role of xenobiotic food components (e.g. pesticides) is, at the moment, not fully known. There is evidence that some pesticides in commercially available foods can alter allergy relevant reactions in vitro and in vivo [29].

On the basis of increasing use of genetically modified foods, the evaluation of risk of allergenicity of these products becomes increasingly important. It is possible that by gene technological modification allergy relevant changes in food proteins may occur as has been shown by the introduction of the major Brazil nut allergen into soy. A Brazil nut 2S albumin protein had been genetically engineered into soybean and initially the gene was perceived as an ideal candidate for enhancement of nutritional seed quality. However, Brazil nut is known to cause allergic reactions and RAST and immunoblot assays from sera of eight of nine Brazil nut allergic patients reacted to genetically modified soybeans containing the Brazil nut gene [30,31]

5. Diagnosis and management of food allergy

The diagnosis of adverse food reactions is based on the four columns of allergy diagnosis, namely history, skin test, in vitro diagnostics and provocation tests.

The diagnostic approach begins with a careful case history and clinical examination. Reactions or diseases that may mimic food allergy, such as lactase deficiency, presenting with abdominal cramping, bloating and diarrhea after the ingestion of milk and milk products have to be considered in the differential diagnosis. The information required includes the food and quantity of the food suspected to have caused the reaction, the time-course of events and symptoms provoked as well as other potentially coexisting and triggering factors. Diet diaries are helpful in chronic conditions, such as urticaria and atopic eczema, when history is generally less reliable. Elimination diets based on rice, potatoes and mineral water are utilized in the diagnosis of adverse food reactions in chronic conditions, when hidden allergens, spices or additives are suspected. Although improvement of symptoms under the diet is rarely diagnostic, the role of food is excluded when no improvement occurs.

Skin tests are frequently utilized to screen patients with suspected allergy for IgE-mediated food allergy. Various techniques can be performed ranging from the application of commercial glycerol extracts, prick-to-prick tests with raw food to intracutaneous application of aqueous extracts [32,33]. Important aspects are appropriate positive (histamine) and negative (saline) controls and the quality of the extracts. Commercial food extracts are often unable to detect sensitisation, especially to some fruits and

vegetables, presumably because of the lability of the responsible allergen [33]. Using fresh food increases the sensitivity of the skin prick test.

Determination of specific serum immunoglobulin E (IgE) antibodies to food is possible employing RAST or similar in vitro assays, such as enzyme-linked immunosorbent assay (ELISA) or fluoro-enzyme immunoassay (FEIA), etc. Generally determination of specific serum IgE is considered to be less sensitive than skin prick tests. The results are expressed in six classes or in kU/l. Sensitivity and specificity may differ from assay to assay, reflecting different cut-off values and quality of standardized food extracts. Whereas a negative skin test and RAST confirms the absence of IgE-mediated reactions to food with a high negative predictive accuracy of up to 95%, positive test results indicate sensitisation, which alone is not sufficient to diagnose food allergy. A typical case history supported by a clear positive skin test and/or demonstration of specific IgE antibodies to the suspected food can usually confirm the diagnosis of food allergy. However, in many cases, to confirm or refute the patient's history, oral provocation tests are necessary. After an elimination diet to achieve symptom free or baseline conditions, the incriminated food is carefully introduced to see if the symptoms recur. Oral provocation tests are potentially dangerous and should only be performed under observation. In doubtful cases, in clinical practice open oral provocation or diagnostic diets are often given to patients. These are sufficient to exclude food allergy when yielding negative results. At present, double-blind placebo-controlled food challenges (DBPCFC) are considered the 'gold standard' for diagnosis of adverse reactions to food [9]. They have been designed to minimize the subjective bias of the patient. This test is hampered by the heavy demands for resources and time. Other potential problems of oral provocation tests with foods include differences in the amount and nature of the tested food, development of tolerance, influence of triggering factors and bypass of potential sites of reaction (e.g. pharynx when using capsules).

Acute symptoms of food allergy are treated according to the relevant pathophysiology using antihistamines, glucocorticosteroids, bronchodilators or epinephrine according to the consensus treatment of anaphylaxis. Some patients being allergic to 'hidden allergens', such as peanuts or celery, have a high risk of inadvertently consuming these proteins which are widely used in food preparations. They should be equipped with a rescue medication consisting of an antihistamine, glucocorticosteroid and epinephrine at all times.

The only management of food allergy at the moment is strict allergen avoidance [34]. For many food allergic individuals, however, this is not easily achieved in daily life. Elimination diets may lead to malnutrition or eating disorders. Whenever a large number of foods is excluded from the diet, a dietitian should instruct the patient. Patients must be taught how to read food labels to avoid sources of hidden food allergens.

In some patients oral hyposensitisation against specific food allergens has been successfully reported, however, this is not a routine therapeutic procedure.

The use of mast cell blockers, e.g. cromoglycates has been proven effective in prevention of mild food induced allergic symptoms in some studies [35].

6. Conclusions

In the field of food allergy and other food induced hypersensitivity reactions there is a need for increased research especially with regard to the

- detection of allergens
- quantitative dose–response relationships in certain risk groups
- development of methods for predictive testing of possibly sensitizing food constituents
- improved methods for diagnosis (especially in vivo)
- new concepts of therapy.

Furthermore, declaration regulations have to be improved considerably in order to protect highly sensitized individuals. Increased education of the public and of health care, industry and political

authorities is crucial to gain a better understanding for the many people suffering from food allergy.

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