Clinical aspects of food allergy

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Abstract

Food allergy affects 2.5% of adults and 6–8% of children, and is a leading cause of life-threatening anaphylactic episodes. Food allergy is defined as an adverse reaction to foods that is mediated immunologically and involves specific IgE or non-IgE mechanisms. In this review only IgE-related food allergy will be considered. Many food allergens are glycoproteins, but they do not share any striking biochemical similarities. The definition of many food proteins at the molecular level has tremendously facilitated our understanding of clinical syndromes and seemingly bizarre observations. Clinical manifestations of food allergy include symptoms of the gastrointestinal, cutaneous and respiratory systems, as well as systemic anaphylaxis. The diagnosis of food allergy involves a stepwise approach, including medical history taking, demonstration of specific IgE and confirmation by oral food challenge. The management of the food-allergic patient at present consists of avoidance of the culprit food and education, while future advances may include specific immunotherapy with modified allergens or DNA vaccination.

Introduction

In most cases a person’s digestive system can tolerate a tremendous diversity of biological macromolecules, introduced by food intake, mounting a defensive reaction only to pathogens. However, in certain individuals, untoward reactions to foods occur, including food allergy.

Although young children are the main victims of food allergy, no age group is spared, and the disease involves many organs. Food allergy affects up to 2.5% of the adult population and 6–8% of children less than 3 years of age, with an enormous impact on quality of life [1,2]. It is the leading cause of life-threatening anaphylactic episodes, accounting for 100–125 deaths/year in the U.S.A. [3,4]. In the U.K., anaphylaxis in general has doubled during the last decade, with a major increase in the subcategory of food-induced anaphylaxis [5].

Food is frequently implicated in a variety of maladies, causing many diseases in individuals who believe they are afflicted with food allergy. The plethora of articles in newspapers and magazines and news stories on radio/television/websites on the subject bespeak the importance and concern our society places on the topic of food allergy. This publicity, however, has led to an overestimation of food allergy, especially in Western societies.

Since much of the problem derives from the indiscriminate use of terms, the subcommittee on Adverse Reactions to Food of the European Academy of Allergy and Clinical Immunology (EAACI) proposed a classification of these disorders in 1995 [6]. Adverse reactions to food are defined as any aberrant reaction after the ingestion of a food or food additive. Adverse food reactions are divided into toxic reactions, that can occur in anyone provided that a sufficient dose is ingested (e.g. histamine in scombroid fish poisoning), and non-toxic, which depend on individual susceptibility. Non-toxic reactions may be the result of immunological mechanisms (allergy or hyper-
sensitivity) or non-immunological mechanisms (intolerance). Among allergic reactions, IgE-mediated food allergies are the most clearly delineated, although non-IgE-mediated immune reactions are being increasingly recognized. Food intolerance accounts for the majority of adverse reactions to food, and may be due to pharmacological properties of the food or metabolic disorders of the host, or be undefined. This article will address IgE-mediated food allergy.

**Pathogenetic aspects of IgE-mediated food allergy as the basis of clinical reactions**

**Mechanisms**

Although sensitization to food allergens can occur transplacentally in newborns or by inhalation in adults, IgE-mediated food allergy reactions arise most commonly when food allergens penetrate the gastrointestinal (GI) barrier, initiating the classical immediate hypersensitivity chain of events by sensitizing genetically predisposed individuals. Atopic individuals are most predisposed to food allergy. Even in the mature gut, about 2% of ingested food antigens are absorbed and transported throughout the body in an ‘immunologically intact’ form but, due to tolerance, do not normally cause adverse reactions [7]. However, in the sensitized host they can provoke hypersensitivity responses to foods at any age, although more frequently in infants. Food allergies are notably more common during the first 2 years of life, when the gut barrier is immature and the immune system is still refining its ability to tolerate foods. Many children outgrow a food allergy, especially to milk and eggs, and by the end of the first decade of life the prevalence of food allergy is at the adult level. Food allergy is typically the first manifestation of the atopic syndrome (atopic dermatitis, asthma and rhinitis). The development of an IgE-mediated response to an allergen is the result of a series of molecular and cellular interactions, leading first to Th2-type cell activation, and then to immunoglobulin isotype switching and the generation of antigen-specific IgE [8]. The antigen-specific IgE then binds to surface receptors of mast cells, basophils and other cells, arming the immune system for an allergic reaction upon re-introduction of the specific antigen, giving rise to a state of sensitization.

In the sensitized individual, the allergen reacts with IgE attached to the cell surfaces, mainly mast cells and basophils, leading to the release of biologically potent chemical substances called mediators of immediate-type hypersensitivity, which have profound effects on smooth muscle, capillary vessels, sensory fibres and inflammatory cells (e.g. eosinophils). The mediators are responsible for the clinical symptoms of food allergy. The best known mediator is histamine, which affects the surrounding tissues, resulting in intense swelling, muscle spasm of the walls of involved organs and the production of mucus. These reactions may occur in any part of the body, even those distant from the GI tract, since the food allergens are absorbed in the intestine and carried to all areas of the body [7].

**Structural features of food allergens**

Although any food may provoke an allergic reaction, a relatively small number of foods account for the vast majority of food-induced allergic reactions. In adults, fish, shellfish, peanuts, tree nuts, fruits, vegetables and seeds account for approx. 85% of reactions, while in young children eggs, milk, peanuts, soy and wheat account for almost 90% of such reactions. Food allergens are mostly heat-stable, water-soluble glycoproteins, ranging in size from 10 to 70 kDa. The allergenic proteins in many foods have been identified, isolated, sequenced and cloned. Furthermore, IgE and IgG epitopes, as well as T-cell epitopes, have been mapped on many of these protein fractions [9–12]. A given food may contain 10–30 glycoproteins, of which a few may be important in triggering allergic reactions, regardless of their proportion in the particular food. Among the egg glycoproteins, for instance, ovomucoid, which accounts for only approx. 10% of egg-white protein, appears to be the major allergen.

The elucidation of many food proteins at the molecular level has tremendously facilitated our understanding of clinical syndromes and seemingly bizarre observations. These include the oral allergy syndrome [13,14] and the curious property of certain food allergens of provoking a reaction either only if the food is eaten raw or only after processing. The effect of food processing on the allergenicity of food proteins is based on the type of amino acid sequence of their IgE-binding epitope (linear compared with conformational) that is capable of triggering a reaction.

The oral allergy syndrome is due to the presence of similarities between amino acid sequences (cross-reactivity) of food allergens (e.g. apple, carrot or hazelnut) and pollen proteins (e.g. birch pollen). Over 70% identity in primary
Plant Food Allergens

sequence is generally needed for cross-reactivity. Hence patients allergic to birch pollen report mouth itching and tongue and lip swelling following ingestion of fresh apple, raw carrot or hazelnut. Other syndromes due to cross-reactivity between respiratory allergens and foods include the latex/food syndrome, the house-mite/seafood syndrome, and the bird/egg syndrome [15]. There are indications that the severity of an allergic reaction to a food depends on the allergen responsible for the sensitization [16]. More recently, Pastorello et al. [17], by studying the IgE reactivity profiles against hazelnut extract of patients with severe anaphylactic reactions, demonstrated that anaphylactic patients reacted only to an allergenic hazelnut lipid transfer protein. On the other hand, patients sensitized to the major hazelnut allergen (Cor a1), which is 70% similar to birch pollen (Bet v1), presented only oral allergy syndrome [18].

Plant-derived proteins that are responsible for allergies include various families of pathogenesis-related proteins, protease and α-amylase inhibitors, peroxidases, profilins, seed storage proteins, thiol proteases and lectins [15]. Different properties of these groups of plant-derived proteins may account for differences observed in the clinical presentation of food-allergic patients. Lipid transfer proteins, which are extremely resistant to digestion by pepsin, are correlated with severe symptoms of food allergy [19]. Classification of allergens into groups with structural similarities may help to predict cross-reactivities, thus providing useful information to food-allergic patients.

Clinical manifestations of IgE-mediated food allergy

Food allergy presents as a broad spectrum of symptoms, many of which are not hives, the classic reaction to food. Indeed, most patients who experience only hives do not consult a physician. Furthermore, many non-immunological adverse reactions to food (false food allergy or intolerance) present with symptoms indistinguishable from those of classical IgE-mediated allergy. These facts may explain the difficulties in appreciating the prevalence of true IgE-mediated food allergy, and also indicate the need for accurate diagnosis if proper management is to be delivered to the patient. Table 1 summarizes food-induced symptoms and syndromes that are mediated through the various mechanisms.

GI reactions

The most common clinical manifestations of IgE-mediated food allergy include reactions of the GI tract, skin and respiratory system, and sometimes also life-threatening systemic anaphylaxis [2]. The most common GI symptoms of food allergy are nausea, vomiting, abdominal pain and diarrhoea, which can appear within minutes or up to 2 h following the ingestion of the responsible food. Often GI symptoms accompany allergic manifestations in other organs, mainly skin and lung.

Oral allergy syndrome is also an IgE-related GI food-induced reaction, which occurs mainly in adults, affecting up to 40% of patients with pollen allergy, especially to birch, ragweed or magword [13,14,20,21]. Patients with oral allergy syndrome present oropharyngeal itch and/or lip and tongue swelling, less often pruritus in the ears and/or tightness in the throat, and rarely a systemic reaction, following ingestion of fresh fruit and raw vegetables. The symptoms are generally mild and short lived. As mentioned above, oral allergy syndrome is a consequence of allergic sensitization to pollens cross-reacting with certain plant foods. This is called class 2 food allergy, in contrast with class 1 food allergy, where the sensitization process occurs in the GI tract, usually leading to more severe reactions.

Skin disorders

The ingestion of food allergens may provoke the rapid onset of cutaneous symptoms, or may aggravate various chronic skin conditions. The most common cutaneous symptoms are acute urticaria and angioedema, which appear within minutes following ingestion of the food. Acute contrast urticaria in response to food is also quite common. The foods most often incriminated in these reactions are raw meats, fish, vegetables and fruits [22,23]. Food allergy is rarely a causative factor in chronic urticaria. In contrast, up to 40% of children with atopic dermatitis (a form of eczema) have been shown to have food allergies, as shown by appropriate challenges [2].

Respiratory IgE-mediated food allergy

Respiratory symptoms of rhinconjunctivitis, bronchospasm and asthma appear to be rare as a solid manifestation of food allergy. They usually occur in association with cutaneous or GI symptoms, or as part of systemic anaphylaxis. However, food-induced respiratory reactions were
Table I
Clinical manifestations of non-toxic adverse food reactions according to mechanism

<table>
<thead>
<tr>
<th>Non-immune</th>
<th>IgE-mediated</th>
<th>Mixed or non-IgE-mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine shock</td>
<td>Systemic anaphylaxis</td>
<td>Atopic dermatitis</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Acute urticaria and angioedema</td>
<td>Asthma</td>
</tr>
<tr>
<td>GI</td>
<td>GI</td>
<td>Allergic eosinophilic gastroenteritis</td>
</tr>
<tr>
<td>Rhinitis, asthma</td>
<td>Oral allergy syndrome</td>
<td>Protein-induced enteropathy, enterocolitis, proctitis</td>
</tr>
<tr>
<td>Exacerbation of atopic dermatitis</td>
<td>Acute bronchospasm (wheezing)</td>
<td>Food-induced pulmonary hemosiderosis</td>
</tr>
<tr>
<td>Vasomotor headaches</td>
<td></td>
<td>Dermatitis herpetiformis</td>
</tr>
</tbody>
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demonstrated in about 6–8% of asthmatic children [24]. Asthmatic reactions have been also reported in instances where susceptible individuals were exposed to vapours or steam emitted from cooking food containing airborne allergens (e.g. fish, crustaceans, eggs and garbanzo beans) [25].

**Systemic anaphylaxis**

Food allergy is the leading cause of cases of generalized anaphylaxis referred to hospital emergency departments [4,5]. Clinical symptoms include, in addition to the respiratory, cutaneous and GI symptoms described above, cardiovascular symptoms including hypotension, vascular collapse and cardiac arrhythmias [26,27]. In life-threatening or fatal reactions, the most common presenting symptom is severe respiratory distress, which is followed by nausea and vomiting and, less commonly, skin symptoms [3]. Factors predisposing patients to severe reactions include concomitant asthma, a history of a previous severe reaction, denial of symptoms and treatment delays. In certain patients, anaphylaxis occurs only when the patient exercises within 2–4 h of ingesting the food; this is termed food-associated exercise-induced anaphylaxis [28].

**Diagnostic aspects of IgE-mediated food allergy**

The general principles that apply to the diagnosis of IgE-mediated food allergy include the following. The case history of the patient should support the diagnosis, accompanied by the presence of specific IgE antibodies to the suspected food. Furthermore, allergen exposure should be sufficient to cause sensitization and disease elicitation, with the appearance of allergic symptoms upon exposure to the offending allergen. Diagnostic procedures for IgE-mediated food allergy therefore include case history and clinical examination, tests for sensitization (specific IgE determination) and tests for symptoms (clinical tests) to investigate the contribution of allergen exposure to the symptoms [6,29].

Establishment of the diagnosis of allergy to a suspected food requires the presence of food-specific IgE antibodies in combination with a positive challenge test, because sensitization to a food is not synonymous with a clinically relevant food allergy.

An accurate clinical history is very important in diagnosing food allergy, yet less than 50% of reported food-allergic reactions could be verified by the double-blind placebo-controlled food challenge (DBPCFC), which is considered the ‘gold standard’ in the diagnosis of food allergy. However, medical history has a much higher positive predictive value in cases of food-induced systemic anaphylaxis.

**Tests for sensitization**

The most commonly applied methods for specific IgE identification in clinical practice are skin tests and the in vitro measurement of serum-specific IgE antibody. The major limiting factors for the usefulness of these methods are the lack of standardized reagents and their limited clinical relevance. It must be remembered that a positive skin test or in vitro IgE immunoassay does not confirm food allergy. They merely establish the presence of allergen-specific IgE.

The most widely used test for sensitization is the skin prick test (SPT). Correlation of the SPT with other diagnostic tests by using standardized extracts showed agreement with in vitro IgE tests ranging from 74% to 95% (with SPT as the gold standard) and agreement with in vivo challenge (with DBPCFC as the gold standard) of between...
< 50% and 88% [29]. A positive SPT to a food ingested in isolation which provokes a serious systemic anaphylactic reaction may be considered diagnostic. The thyglycerol in commercial skin-test reagents can make glycoproteins non-allergenic, and hence a negative SPT with a commercial extract in the face of a strong case history should be repeated with fresh food [20,21].

With the increasing sensitivity of in vitro methods for the determination of food-specific IgE, skin tests and immunoassays tend to be interchangeable [30]. Recently, quantitative IgE antibody assays have been shown to be clinically useful in predicting reactions to food challenge and monitoring dietary avoidance [30–32].

**Tests for symptoms**

These include oral challenge procedures (specific provocation) and elimination/re-introduction diets. According to the EAACI Position Paper [6], the DBPCFC is the only accepted test for confirmation of the diagnosis of food allergy, although it does not confirm an IgE-mediated mechanism. The diagnostic accuracy of the DBPCFC was evaluated in two studies [29], and was found to be very high. Provocation tests are potentially dangerous and should be performed by a specialist. They are not recommended for life-threatening anaphylactic reactions. Elimination/re-introduction diets are used to test whether symptoms abate with the elimination of a suspected food from the diet. They are most useful in patients with chronic symptoms and positive sensitization, and/or where there are strongly suspected foods.

**Management of the patient with food allergy**

Although there is no specific therapy for any food allergy, and strict avoidance of the foods to which the patient is sensitive is the only proven therapy, diagnosis of food allergy, education and follow-up of the patient is imperative [29,33]. Most importantly, patients should be made aware of the danger of anaphylaxis and of the factors that heighten the probability of such a reaction. Food-allergic patients at high risk should be equipped with self-injectable adrenaline (epinephrine) [27]. Successful allergen avoidance also requires patient education, since small amounts of allergens or allergens with concealed names (‘hidden’ allergens) exist in widely consumed food supplies. These hidden allergens are mostly responsible for severe or even fatal food-allergic reactions, especially in children. Patients should be encouraged to read labels, although inadequate food labelling and inadvertent cross-contamination of meals remains a major risk [34].

Pharmacological management of food-allergic patients and administration of hypoallergenic milk formulae are useful in certain situations, while specific immunotherapy for food allergy has not been proven safe in its present form.

New approaches to food allergy therapy are under investigation. Administration of allergens with amino acid substitutions in their IgE-binding epitopes is being investigated. The rationale is that exposure to the allergens’ T-cell epitopes may mediate desensitization, whereas the IgE-binding epitopes have been rendered incapable of triggering anaphylaxis [35]. Current murine models are promising. Polysaccharide vaccination has also been considered as an alternative desensitization strategy in murine models [36].

**References**

Plant protein families and their relationships to food allergy

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Abstract

The analysis of plant proteins has a long and distinguished history, with work dating back over 250 years. Much of the work has focused on seed proteins, which are important in animal nutrition and food processing. Early studies classified plant proteins into groups based on solubility (‘Osborne fractions’) or protein function. More recently, families have been defined based on structural and evolutionary relationships. One of the most widespread groups of plant proteins is the prolaminin superfamily, which comprises cereal seed storage proteins, a range of low-molecular-mass sulphur-rich proteins (many of which are located in seeds) and some cell wall glycoproteins. This superfamily includes several major types of plant allergen: non-specific lipid transfer proteins, cereal seed inhibitors of α-amylase and/or trypsin, and 2 S albumin storage proteins of dicotyledonous seeds.

Introduction

Plant protein chemistry has a long and distinguished history, with the isolation of the gluten proteins of wheat being reported over 250 years ago (in 1745) by Jacopo Beccari at the University of Bologna. The rich stores of proteins in seeds have since proved to be attractive to other chemists, particularly T. B. Osborne, who published studies of seed proteins from over 30 plant species over the period 1886–1928 [1]. Similarly, globulins were among the first proteins to be crystallized (edestin from hemp in 1881 and several others in the 1880s and 1890s), while a range of protein toxins, including ricin from castor bean, were isolated and characterized over the same period [1]. Seed globulins were also among the first proteins to be characterized by ultracentrifugation [2,3].

Although convenience of preparation is clearly an advantage, much of the interest in