

Adult Food Allergy

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Current Allergy and Asthma Reports 2005, 5:80–85

Current Science Inc. ISSN 1529-7322

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Adult food allergy is estimated at approximately 3.2% worldwide. The persistence of childhood food allergy is unusual, peanut allergies excepted. Once established in adults, food allergy is rarely cured. Factors favoring the acquisition of allergy could be sensitization to pollens, occupational sensitization by inhalation, drugs (such as tacrolimus), and sudden dietary changes. Severe anaphylaxis and oral allergy syndrome are frequent. The fatality risk is estimated at 1% in severe anaphylaxis. Risk factors for severe anaphylaxis are agents causing increased intestinal permeability, such as alcohol and aspirin. β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and exercise are other factors. Gastrointestinal food allergy remains, to a large extent, undiagnosed in adults. Food allergens are mainly fruit and vegetable, related to pollen sensitizations, or to latex allergy. Wheat flour allergy is increasing. The diagnosis relies on prick skin tests, detection of specific IgEs, and standardized oral challenges. Strict avoidance diets are necessary. Specific immunotherapy to pollens may be efficient for cross-reactive food allergies.

Introduction

During the past 20 years, many studies have projected food allergy into the limelight as one of the multiple clinical aspects of allergic disease.

Most clinical manifestations are related to an IgE-dependent mechanism. Diagnosis uses the same tests for children and adults through a two-step procedure: skin tests and laboratory tests are required to demonstrate the sensitization, and then positive, standardized oral challenges are the hallmark of food allergy [1]. However, the clinical characteristics, the process of diagnosis, and the therapy for food allergy are not as well documented in adults as they are in children [2]. This article summarizes the current clinical data and considers the similarities and differences between food allergy in children and adults with particular regard to prevalence, natural history, pathogenesis, and relative frequency of food allergens. It does not deal with progress in the immunochemistry of food

allergens now studied extensively with recombinant allergens. Nor does it consider mechanisms of hypersensitivity to food proteins [2,3–5].

Prevalence

Adult food allergy is estimated at approximately 3.7% in the United States, 3.2% in France, and 3.7% in Germany [1,6•,7]. Data from the Circle of Clinical and Biological Investigations in Food Allergy (CICBAA) indicate that there is one adult with food allergy for every 3.6 children. Male dominance in children (62%) is replaced by female dominance in adults (60%) [6•]. Several studies have tested the relative prevalence of particular food allergies in the general population: there is a 0.48% prevalence of peanut allergy in the British population [8]. An Australian study reported a prevalence of 0.61% for peanuts, 0.53% for shrimp, 0.27% for wheat flour, and 0.09% for milk and for eggs [9].

Natural History of Food Allergy in Adults

No specific data are available. The CICBAA data bank shows that in adults younger than 30 years, one third of the cases present as a persisting childhood allergy, most often related to peanuts, supporting the assertion that more than 80% of peanut allergies persist into adulthood [1]. Childhood allergy to other food allergens unusually persists after 30 years of age, except rare cases of allergy to fish or eggs.

On the contrary, when the onset of food allergy arises in adults, it resolves less often than in children; allergy to sesame or fish has not been known to have a favorable outcome [10].

Several factors that favor the acquisition of allergy by adults have been identified. Food allergy to fruits and vegetables clearly results from sensitization to pollens. *Betulaceae* and *Artemisia* pollens are often involved. Another factor is the occupational sensitization by inhalation of food proteins in food industries. Food allergy could represent 20% of the patients with occupational asthma related to food proteins when the latter are resistant to cooking, such as egg proteins. Bakers who wheeze upon exposure to wheat are sensitized to hydrosoluble proteins (albumins and globulins) and can safely ingest bread and cookies because wheat allergy is related to the non-hydrosoluble, thermoresistant gluten fractions [11]. The role of drugs must not be overlooked. In the event of liver transplantation, orally administered tacrolimus substantially increases the risk for food sensitization and for clinical reactions [12]. Recently, attention has been drawn to the possible risk related to exten-

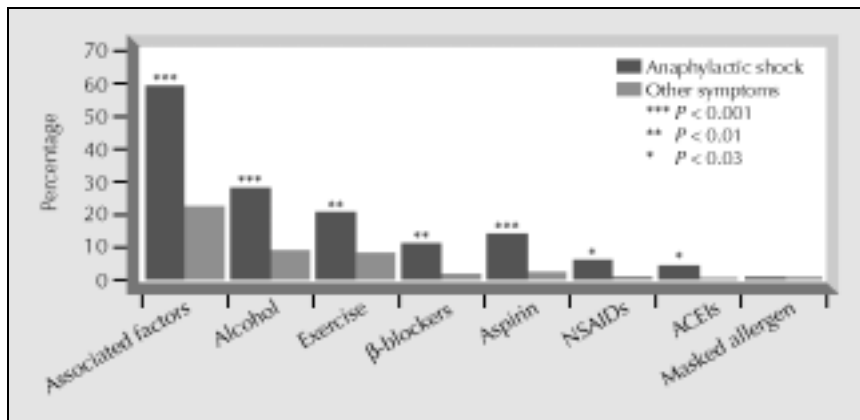


Figure 1. Associated factors involved in severe anaphylaxis (64 cases) and in other symptoms (192 cases) of food allergy in adults. ACEIs—angiotensin-converting enzyme inhibitors; NSAIDs—nonsteroidal anti-inflammatory drugs.

sively prescribed anti-ulcer drugs [13]. Sudden diet changes for slimming have been noted in the months preceding onset of food allergy (personal cases). The role of viral gastrointestinal infection is not documented.

Clinical Features

Food allergies to animal allergens in adults are mono-allergies, whereas a child may suffer allergy to eggs, milk, meat, and fish (multiple food allergy syndrome). However, allergies to fruit and vegetables are often multiple, reflecting cross-sensitizations with pollen allergens. Clinical manifestations in adults are as varied as in children, but severe anaphylaxis and oral allergy syndrome are more frequent: 69% of cases of severe anaphylaxis reported to the French Allergovigilance Network occurred in adults [14]. Anaphylaxis included cardiovascular collapse (60%), systemic reactions affecting several organs (18.7%), laryngeal angioedema (15.9%), and serious acute asthma (5.6%) [14]. In 2004, this network reported three deaths out of 226 cases, one in a young adult.

Food anaphylaxis is not uncommon, involving 17% to 37% of patients admitted to hospital emergency units [15–17]. There is a 1% fatality risk with severe anaphylaxis [14,18], food allergy being the most frequent cause [19,20]. Thirty-seven percent of the fatalities occurred in adults [21]. Death due to serious acute asthma usually occurs within 30 minutes in young adults or adolescents, as opposed to drug or venom anaphylaxis, which usually manifests as a cardiovascular collapse within a shorter period [20,21,22]. In the United States, 90% of fatal cases of anaphylaxis are caused by peanuts and hard-shelled fruit [21].

Exercise-induced anaphylaxis typically affects young adults and adolescents. The activity is usually jogging or dancing. The period between food intake and the clinical reaction, like the effort period, varies from 30 minutes to 3 hours. All foods are involved, with a marked predominance of wheat flour [23,24].

Certain risk factors for severe anaphylaxis in adults have been identified by a first multicenter study [25]. Agents causing increased intestinal permeability, such as alcohol, are very obviously involved [6,14,25]. Aspirin and non-steroidal anti-inflammatory drugs also modify intestinal permeability and favor abnormal metabolism of arachidonic acid,

leading to enhanced leukotriene synthesis [26–28]. β-blockers have unfavorable effects by antagonizing the physiologic role of catecholamines counteracting the decreased peripheral resistance following histamine release. The role of angiotensin-converting enzyme (ACE) inhibitors in the prevention of bradykinin degradation is not as well documented. Isolated observations have lead to the suspicion of their possible involvement [29]. A comparison of the incidence of association of these factors to food allergy, either in patients experiencing severe anaphylaxis or in patients with other clinical features, shows a significant difference for alcohol, exercise, treatment by β-blockers, or simultaneous intake of aspirin (Fig. 1). Attention is particularly drawn to the possibility of cumulative effects in sensitized patients, such as the simultaneous intake of several food allergens before exercise or the ingestion of fruit or vegetable allergens added to the exercise-induced polypneic inhalation of cross-reactive pollens. When food allergy is suspected, but the identification of exposure to a single causative allergen remains negative, more complex testing using a combination of exposures to several food allergens and to other factors clearly confirms this phenomenon [30,31].

Additionally, tacrolimus may increase the severity of allergy. Deaths related to food allergy have been reported in transplant patients treated with tacrolimus [32].

Among other clinical manifestations to be noted in adults, the frequent occurrence of oral allergy syndrome associated with vegetable allergens and of angioedema and asthma in those allergic to pollens has been underlined [6,9].

Food allergy as a cause of chronic urticaria has rarely been recognized. However, a careful screening for food allergy with skin tests, detection of specific IgEs, and double-blind oral challenge tests, followed by an avoidance diet in a single study, have demonstrated allergy to daily ingested foods (wheat flour, dairy products, or meat) in 4.3% of adults with chronic urticaria. However, recovery was observed in only 50% of these patients [33].

Gastrointestinal food allergy remains, to a large extent, underestimated in adults. In Australia, the frequency of eosinophilic esophagitis appears to be increasing in parallel with that of asthma and allergic rhinitis and is seen in 46% of those with respiratory allergy, 25% of whom have a food

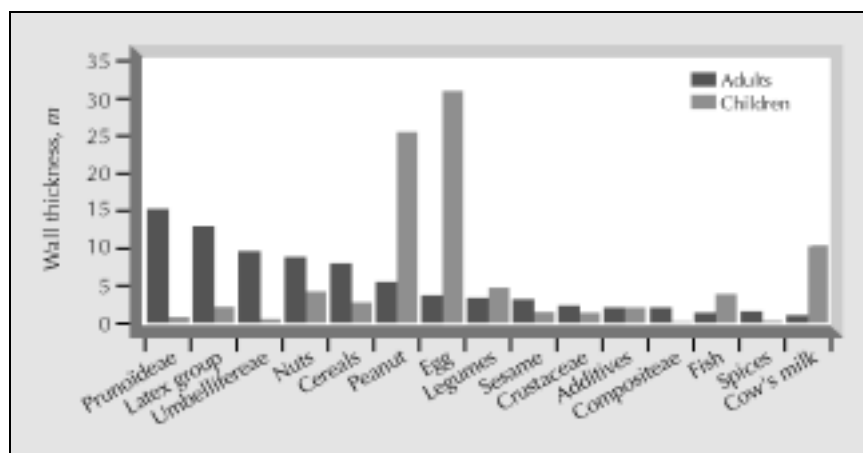


Figure 2. The 15 most frequent allergenic foods in 256 food-allergic adults, compared with 571 food-allergic children.

allergy [34]. The study of gastrointestinal mucosa revealed tissue eosinophilia during the pollen season in people allergic to birch pollen and with cross-reactive food allergies, expressing oral syndrome and gastrointestinal complaints [35]. This tissue eosinophilia appears to be frequent [36]. It is still rare to obtain biopsies from people presenting with functional symptoms (bloating, nausea, irregular transit with a tendency to diarrhea). In many cases, a diagnosis of irritable bowel syndrome (IBS) could overshadow that of gastrointestinal allergy to wheat flour, milk proteins, or meat. The difficulty of attributing these symptoms to allergy is due to the fact that skin prick tests and specific IgE assays are negative, indicating the lack of a systemic IgE-dependent allergy. The IgE mechanism could be located in the gastrointestinal mucosa, and its identification would require biopsy and immunohistologic analysis. Such a study in patients presenting with gastrointestinal symptoms has demonstrated the predominance of interleukin (IL)-4-secreting T lymphocytes and of activated eosinophils in the duodenal mucosa [37]. Another possibility may be allergen sensitization restricted to food proteins denatured by digestion. This could be the case for wheat flour proteins [38]. In wheat flour allergy (WFA), delayed-type hypersensitivity might be hypothesized, on the basis of positive lymphocyte activation tests. Gluten is the major allergenic fraction of wheat in WFA [39]. In chronic digestive disorders often linked to fatigue, differentiation between wheat flour allergy and celiac disease may be difficult [40]. Atypical clinical manifestations (*eg*, arthralgia, headache, epilepsy, cerebellar ataxia), usually evolving in the context of gluten intolerance, have been reported recently [41–43].

Nephrotic syndrome and eosinophilic cystitis, reported infrequently in the past, would merit further investigation [44,45].

Sensitization Routes and Clinical Reactions to Food Allergens

The gastrointestinal route is involved in the ingestion of foods as well as in the swallowing of pollens, and the respiratory route is involved in the occupational inhalation of

food proteins [11,27]. The injectable route has been identified in regard to gelatin allergy after exposure to gelatin-containing vaccines [46]. In babies with atopic dermatitis, the cutaneous route is implicated with protein-containing skin creams [47]. According to Lack *et al.* [48], this could also apply to babies with normal skin; there is an odds ratio of 4 for peanut allergy when a child has previously received topical drugs containing peanut oil. No data are available for adults having a less permeable skin.

Transfer of IgE-mediated sensitization after liver transplant remains a special case [49]. Numerous routes of sensitization leading to the clinical reactions have been observed, rectal as well as oral and cutaneous routes [50–52]. Five percent of food-allergic reactions may be triggered through the respiratory tract [53].

Food Allergens Implicated in Adult Food Allergies

These are mainly fruit and vegetable allergens. The first three classes are Prunoideae (*eg*, hazelnut, apple, peach, apricot, pear, plum), latex group (*eg*, avocado, kiwi, banana, chestnut), and Umbellifereae (*eg*, celery, carrot) [2,54] (Fig. 2) related to pollen sensitization [4,55]. It has been shown that many families of proteins that are essential for the development of plants share a variable but often marked homology with pollens, fruit, and vegetables, and account for many cross reactivities. Pathogenesis-related (PR) and lipid transfer (LT) proteins often cause clinically relevant cross reactions [5]. This is not the case of cross sensitization between profilins [4,5]. The risk for food allergy to plant allergens is directly related to the polysensitization to pollens. The association of allergies with birch and *Artemisia* pollens particularly favors allergies to spices [56,57]. Widespread pollen polysensitization suggests sensitization to ubiquitous carbohydrate determinants. Their clinical relevance is challenged, as demonstrated in some cases, such as tomatoes [4,58]. Cumulative effects could affect the risk for clinical reaction.

The other vector for fruit and vegetable allergy is latex allergy. Twenty percent of patients with latex allergy later

develop avocado, banana, chestnut, or buckwheat allergy [6•,59,60].

In France, the increase of wheat flour allergy is highlighted [39], whereas in Australia, the emphasis is on fish and shellfish [9]. Allergy to milk and egg is rare [61].

Allergy to industrially processed foods, either from new allergens, or from high concentrations of allergenic proteins in the case of isolates, should be mentioned because these are commonly used ingredients [62–64].

Diagnosis of Food Allergy in Adults

The diagnostic techniques are similar to those used for children. Sensitization is readily established from prick skin tests and identification of specific IgE [1].

The quality of commercial food-allergen extracts varies greatly, depending on their origin. Efforts are being made to standardize these extracts, showing that the concentration of proteins required for extract efficacy varies greatly between different foods—from 0.01 mg/mL for cod to 5.4 mg/mL for wheat flour [65]. Extracts for fruit and vegetables not dealing with special procedures to eradicate phenolic compounds are moderately sensitive [66,67]. Therefore, it is particularly important to carry out prick-in-prick tests with natural foods [68]. Atopy patch tests have not been studied in any detail but would appear to be less useful in adults ([69]; Moneret-Vautrin, Unpublished data).

The basophil activation test using flow cytometry for membrane expression of CD 63 or CD 203c is highly sensitive and specific [70,71]. It could be particularly interesting for detecting membrane-bound IgE, by confirming the cellular activity due to the bridging of IgE that generates histamine release. This test could be more clinically relevant than the determination of the presence of food-specific IgEs.

However, in most situations (except oral allergy syndrome to fruit and vegetables in people sensitized to pollens), the existence of allergy must be confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) [1,66,67,72,73]. The diagnosis of gastrointestinal allergies is often problematic and cannot be easily diagnosed by DBPCFC because the amounts of food required are very high. A two-step procedure comprises first a DBPCFC, then an open test for higher doses. If results are negative, it is necessary to complete the test with a fixed, sufficient amount of food for seven to 10 consecutive days. When a cow's milk allergy is suspected, the use of a milk without lactose is necessary.

Challenge with a rectal intramucosal injection has been proposed, and its validity confirmed by a histologic study [74]. Coupling an oral challenge to food with a wireless video capsule endoscopy may be a promising technique.

Therapy

As with children, the therapeutic strategy is based on strict avoidance diets (accessible on www.cicbaa.org). The utiliza-

tion of a specialized dietician is essential. Injectable immunotherapy (IT) has very limited indications but has been used successfully in some cases of egg, fish, and hazelnut allergies (Moneret-Vautrin, Unpublished data). Good results have been observed with injectable IT to birch pollen in a birch pollen-Prunoideae cross-reactive allergy [75,76•]. Conversely, IT to house dust mites may have caused severe cross allergy to snails [77]. A fatal risk with peanuts was reported in an IT study [78]. There are high hopes for treatment with anti-IgE because it has been confirmed that the clinical reactivity for peanut was clearly decreased after a 3-month treatment. The duration of the relative protection is not yet known [79••]. Rather than being definitive treatment, anti-IgE could provide transient protection while implementing immunotherapy with recombinant major allergens. Interesting results for efficacy have been seen in animal models [80].

Conclusions

Adult food allergy clearly differs from food allergy in infancy and childhood. Oral allergy syndrome to fruit and vegetables is common in adults already sensitized to pollens, albeit mild. Severe anaphylaxis is also more often observed in adults, linked to the association of risk factors, such as alcohol and various drugs. Another hypothesis could indicate a role for sex hormones. This theory has not yet been studied.

Gastrointestinal allergies are underestimated in adults and remain difficult to diagnose. The frequency of new cases of peanut allergy in children will increase, as will peanut allergy in older adults, together with a certain risk for increased death. Allergy to wheat flour, particularly exercise-induced anaphylaxis, is on the increase. The developing practice of leisure sports, together with the advice of dieticians to increase the daily intake of starchy foods, are factors contributing to this increase. The consumption of industrially processed foods including wheat isolates is a new risk factor.

A future topic for research is the expansion of peanut allergy that occurred 20 years ago in the pediatric population. The persistence of peanut allergy is going to be observed more and more often in young adults. Currently, only avoidance diets can protect patients. Their efficacy depends, to a certain extent, on suitable labeling. The growing amount of industrially processed food on the market, resulting in the daily ingestion of many ingredients, is an etiologic factor that to date has escaped all scientific control. It is now essential that the food industry be made aware of these problems [62]. Additionally, we cannot disregard the challenging problem of the increasing frequency of sensitizations to all environmental allergens (food allergens included), suggesting important changes in immune reactivity. Therapeutic advances might be aimed at the modification of immune reactivity through the use of vaccines.

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