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SMALL INTESTINE (D SACHAR, SECTION EDITOR)

Food Allergy

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Abstract

Purpose of Review The goal of this review is to present an updated summary of the natural history of major childhood and adult food allergies and report recent advances in potential treatments for food allergy.

Recent Findings The most common childhood food allergies are typically outgrown by adolescence or adulthood. However, peanut/tree nut allergies appear to more commonly persist into adulthood. Adults can develop new IgE-mediated food allergies; the most common is oral allergy syndrome. There are multiple different approaches being tried as possible treatments for food allergy.

Summary The prevalence of food allergy appears to be increasing but the varied approaches to treatment are being actively pursued such that an approved modality may not be too far in the future.

Keywords Food allergy · Specific IgE · Peanut allergy · Adult food allergy · Food immunotherapy

Introduction

Food allergy is an abnormal response to a food caused by immunoglobulin E (IgE) antibody. In children, the foods that most often trigger allergic reactions include egg, cow's milk, peanut, tree nuts, soy, and wheat [1]. For adults, this list includes fish and shellfish in addition to peanut and tree nuts. Allergic reactions can be life-threatening when these involve respiratory and/or cardiovascular distress; however, most reactions are not severe. There is no current FDA-approved therapy, so avoidance of relevant foods and access to epinephrine are recommended. Fortunately, several potential therapies are under study. Many reviews exist for food allergy and food intolerance and this one is focused on several of the more common IgE-mediated food allergies in children and adults.

This article is part of the Topical Collection on *Small Intestine*

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Natural History of Childhood Food Allergies

Understanding the natural history of food allergy is essential in managing patients with these disorders. Food allergy typically begins in the first 2 years of life [1]. While some food allergies, such as cow's milk and egg, are often outgrown, peanut and tree nut allergies are more likely to persist into adulthood. Although more than one third of parents will report adverse food reactions in their young children, the rates of verifiable IgE-mediated food allergy are much lower—in the range of 6–8% at 1 year of age (peak prevalence). Most childhood food allergy is acquired in the first or second year of life and then falls progressively until late childhood, after which the prevalence remains stable at approximately 3 to 4% [1–4]. The prevalence of food allergy in children (aged 0 to 17 years) has slowly increased in the USA, from 3.4% in 1997 to 1999 to 5.1% in 2009 to 2011 [5]. The factors that may make an IgE-mediated reaction to food more severe are shown in Table 1.

Cow's milk allergy is the most common food allergy among infants and young children, affecting approximately 2.5% of children during the first 2 years of life [1]. Resolution is gradual throughout childhood and adolescence with resolution occurring in 19, 42, 64, and 79% of children at ages 4, 8, 12, and 16 years, respectively [6]. Clinical features associated with persistent cow's milk allergy include the presence of concomitant allergic rhinitis, asthma, or moderate to

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Table 1 Factors associated with more severe allergic reactions

Concomitant asthma: Patients with asthma are at higher risk for food-induced anaphylaxis
Agents that increase intestinal permeability, such as alcohol and aspirin
Certain medications, such as angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, which can impair the body's compensatory responses to hypotension and interfere with the actions of epinephrine, respectively
Exercise, exertion, or stress
Concomitant illness (viral infections, etc)
High dose of triggering antigen
Menstruation

severe atopic dermatitis and onset of the allergy in the first month of life [6]. In general, the higher the cow's milk-specific IgE (sIgE), the less likely the child will become tolerant over time [6].

Egg allergy (hen's egg) is one of the most common food allergies of childhood, and, like cow's milk allergy, it is frequently outgrown during childhood or adolescence [7]. The presence of egg allergy is a marker for subsequent sensitization to aeroallergens, as well as the later development of asthma [8]. Egg allergy affects 1 to 2% of young children [1, 7]. The estimated overall prevalence in the USA in a national survey was 0.2%, based upon sIgE blood testing [3]. Allergy to egg has been found to resolve in 4, 26, 48, and 68% of children at ages 4, 8, 12, and 16 years, respectively [7]. Tolerance to egg in baked goods is common and typically occurs at an earlier age than tolerance to lightly cooked or raw egg [7, 9].

Peanut and tree nut allergies are frequently studied together as they coexist in up to 30 to 40% of patients [10–12]. Allergy to peanut appears to resolve in approximately 20% of patients but it is unclear if a similar rate is true for tree nut allergy [12–14]. The prevalence of peanut and tree nut allergies is estimated to be slightly greater than 1.0% in children [12, 14]. Interestingly, studies have suggested that the reported prevalence of peanut allergy appears to be increasing over time from 0.4 in 1997 to 0.8% in 2002 and 1.4% in 2008 [11, 12]. When it comes to resolution, patients who had outgrown peanut allergy were more likely to outgrow tree nut allergy. In contrast to cow's milk and egg allergies, there have been reports of recurrent reactions in patients thought to have outgrown peanut allergy [12, 14]. Although the number of reported patients is small, it appears that "resensitization" may be more common among those who continue to avoid peanut or eat it infrequently [12, 14].

Wheat allergy is also a common childhood food allergy that is usually outgrown by adolescence [15]. IgE-mediated wheat allergy, which is separate from celiac disease (gluten-sensitive enteropathy), has been reported to affect 0.4 to 1% of children in the USA and the UK, where wheat is pervasive in the diet [15–17]. Childhood wheat allergy resolves in approximately 80% of patients by 5 years of age [16], but this rate appears to be lower and occur more slowly in children with food allergy and atopic dermatitis [17]. Overall, tolerance was achieved by 29, 56, and 70% at 4, 8, and 14 years of age, respectively [15].

Natural History of Adult Food Allergies

Food allergy has been estimated to affect nearly 2 to 5% of adults, compared with 6–8% of children [1, 18–20]. In a retrospective chart review, approximately 15% of patients with an initial food allergy diagnosis developed the problem as an adult [21]. The same study found that age at first reaction peaked during the early 30s, although there was a wide range. There are several factors that may lead to the development of sIgE and subsequent food allergy in an adult (Table 2). In many cases, however, no predisposing exposures can be identified.

Although any food can cause IgE-mediated allergy, a few foods account for most of the reactions: fish/seafood and peanuts/tree nuts. These two food groups are both estimated to affect up to 2% of the US population. The other foods that cause allergy in adults vary around the world, probably reflecting the prominence of that food in a particular cultural diet.

Despite the predominance of fish/seafood and peanuts/tree nuts causing the most reactions in adults, the most common form of IgE-mediated food allergy in adults is oral allergy syndrome (OAS), or pollen-food allergy syndrome. OAS affects up to 5% of the general population in some studies [22]. It is a generally mild form of food allergy that is caused by contact of the mouth and throat with raw fruits and vegetables and sometimes nuts. The most frequent symptoms of OAS are itchiness or mild swelling of the mouth, face, lip, tongue, and throat, generally developing within minutes after eating raw fruits or vegetables. Since these reactions typically do not progress to cause a systemic issue, the number of reported reactions remains fewer than fish/seafood and peanuts/tree nuts. The conformational cross-reactive epitopes are denatured with heating, so cooked fruits and vegetables typically do not elicit the symptoms, and this can be an important question in the clinical history. Although tree nuts and peanuts (raw and cooked) can also cause isolated oral symptoms, these foods can also cause more serious systemic reactions; therefore, it is appropriate to refer all nut reactions to an allergy specialist.

Of reported food allergy among adults, seafood (i.e., fish, shellfish, and mollusks) allergy is the next most common, with an estimated prevalence of 1 to 2% both in the USA and internationally. One study suggested that 40 to 60% of seafood allergies developed in adulthood, rather than in childhood

Table 2 Factors leading to development of specific IgE associated with food allergy

Pollen exposure and sensitization in patients with oral allergy syndrome
Occupational exposures can lead to sensitization and subsequent reactions to food
Repeated tick bites or jellyfish stings can cause sensitization to red meats and certain soybean products (natto), respectively
Cutaneous exposure to hydrolyzed wheat protein in face soaps has been linked to wheat-dependent, exercise-induced anaphylaxis in Japanese women
The use of acid-suppressive medications has been suggested to predispose toward food sensitization, although this has been called into question—so, the role of acid suppression remains unclear

[23]. Most seafood-allergic patients are allergic to either one or more finned fish or one or more shellfish/mollusks. Only 10% of allergic patients are reactive to foods in both groups. Thus, a person with allergy to one specific type (e.g., shrimp) can often safely continue to eat other types of seafood (e.g., fish and possibly some mollusks). Seafood allergy is unrelated to radiocontrast allergy. Individuals with allergic disease (i.e., those with asthma, allergic rhinitis, atopic dermatitis, or food allergies) as a group are three times more likely than individuals without these conditions to have a severe adverse reaction to intravenous iodinated contrast media. Most of this increased risk is believed to be related to asthma. There is no additional risk associated with seafood allergy specifically, despite this not uncommon misconception.

Peanuts and tree nuts are also commonly implicated in adults with food allergy. In most cases, the nut allergy developed in childhood and persisted into adulthood, unlike what is found with seafood allergies.

Uncommon Food Allergies

Food-dependent, exercise-induced anaphylaxis is a form of food allergy in which the patient only develops symptoms when ingestion of the culprit food is followed within a few hours by exertion or exercise. Symptoms do not develop if the food is eaten at rest or if the patient exercises without first eating the food. Thus, the connection between the food and exertion may not be recognized for some time. In addition, the reactions are unpredictable, which further complicates recognition.

Occupational food allergy most often develops in patients who work in food processing. Common causes include fish, shellfish, wheat, other grains, fruits, and vegetables. Patients may present with respiratory allergy (i.e., asthma, allergic rhinitis), anaphylaxis [24, 25], and/or contact urticaria [26, 27]. A history of symptoms occurring predominantly in the work environment is suggestive.

Latex allergy peaked in the 1990s in the USA and Europe due to the introduction of "universal precautions," then declined again as hospitals and other work environments switched to non-latex alternatives. However, rates of latex glove use and associated latex allergy remain high in some countries and in certain occupations, such as health-care workers, food handlers/restaurant workers, and housekeeping staff. Among patients with latex allergy, 30 to 50% of individuals who are allergic to latex show an associated hypersensitivity to some plant-derived foods, such as avocado, banana, kiwi, chestnut, peach, tomato, white potato, and bell pepper.

One unusual form of IgE-mediated food allergy is caused by sensitization to the allergen galactose-alpha-1,3-galactose (alpha-gal), which is present in tissues from most lower mammals. This form of meat allergy is distinguished by a delayed onset, with symptoms appearing 3 to 6 h after ingestion (sometimes in the middle of the night, if meat was eaten for dinner) [28]. The symptoms are otherwise typical of IgE-mediated reactions, such as urticaria, angioedema, or anaphylaxis, sometimes with gastrointestinal symptoms or hypotension. Allergy due to sensitization to alpha-gal is described in an increasing number of countries, including the USA, Australia, Spain, Germany, Japan, and Sweden. Patients may become sensitized to alpha-gal through tick bites [28–33].

Potential Food Allergy Treatments

The aim of allergen-specific immunotherapy is to alter the allergic response to a food allergen so that the patient becomes desensitized or, possibly, tolerant to the specific food. Alternatively, some patients may receive benefit simply from an increase in the threshold dose of food required to trigger an allergic reaction. In these instances, patients would have some protection from accidental exposures and this enhanced safety often also improves quality of life.

Food allergen-specific therapies under investigation include oral, sublingual, and epicutaneous immunotherapy. Oral immunotherapy is under investigation as a potential approach to the treatment of food allergy [34]. A high rate of desensitization has been demonstrated in both randomized trials and observational studies of oral immunotherapy. The rationale for using the oral route is that ingestion of a food antigen preferentially results in oral tolerance, which is an active immune response [35•, 36••]. Patients are generally started on a very small daily dose of the food (e.g., 3 to 6 mg of food protein) and advanced every 2 weeks until a maintenance dose is reached—a process that typically takes several months. The initial dose and dose increases are given under clinical supervision, whereas the remainder of the daily doses during the dose advancement phase and maintenance therapy are administered at home. The majority of oral immunotherapy-treated patients become desensitized, which

provides protection from reactions to unintentional ingestion of small amounts of food allergen. However, this initial desensitization is dependent upon regular intake of the dose [37•]. Allergic reactions are common, particularly during the build-up phase of oral immunotherapy, and this may be due to the higher dose than is used in other approaches outlined below. Nevertheless, many who have allergic side effects still continue the therapy. A small percentage of patients develop eosinophilic esophagitis on oral immunotherapy with a larger number reporting GI-related symptoms after dosing [38].

In sublingual immunotherapy, food extracts are placed under the tongue—where there are few effector cells [39]. Allergen extracts given sublingually are not systemically absorbed. Rather, they are taken up by dendritic cells in the mucosa and presented to T cells in the draining lymph nodes. The sublingual approach has been attempted for peanut [40–42, 43•], hazelnut [44, 45], cow's milk [46, 47], and kiwi [48, 49] allergies. One of the favorable aspects to sublingual immunotherapy is that it appears to be safer than oral administration with only one reported reaction that required treatment with epinephrine [40, 42–45, 48]. The more common issue is allergic symptoms isolated to the oropharynx, occurring in 33 to 40% of doses. Unfortunately, the lower dose of sublingual therapy has been associated with reduced effectiveness in the amount of food challenge doses tolerated compared to oral immunotherapy [41, 45]. Overall, the approach for sublingual immunotherapy is to begin with a very low dose of allergen and advance the dose every week or two until the maintenance dose is achieved over several months [40–42, 46].

The epicutaneous delivery of protein for immunotherapy is under investigation in patients with cow's milk and peanut allergies [50–53, 54••]. The epicutaneous delivery system solubilizes the allergen by perspiration and disseminates it into the thickness of the stratum corneum [55]. Epicutaneous delivery is non-invasive and may pose a lower risk for systemic reactions than other food allergen delivery approaches under study. Preliminary reports suggest that the epicutaneous antigen delivery for food allergy immunotherapy can lead to desensitization and appears to be more effective in children 6 to 11 years old than in older children and adults [53, 54••]. One important difference between the epicutaneous protocol and oral or sublingual approaches is that there is no dose escalation phase: the initial dose is the maintenance dose. Doses are also lower than those used for other investigational therapies and, thus far, none of the trials reported serious adverse events [50–53]. The most frequent adverse events were localized erythema, eczema, pruritus, and/or urticaria at the site of application. Adherence was high, and dropout for adverse events was generally low.

Subcutaneous immunotherapy is under investigation in various forms, including chemically modified food extracts, peptide immunotherapy, intradermal/intramuscular immunotherapy with lysosome-associated membrane protein-DNA vaccine, and intradermal synthetic immunostimulatory oligodeoxynucleotides containing unmethylated CpG. Alternatively, a non-specific approach to target IgE using the monoclonal anti-IgE, omalizumab, may be effective for allergy to any food and has already been shown to decrease the rate of adverse events during oral immunotherapy. Overall, these varied approaches provide hope that a much-needed treatment for food allergy is on the horizon.

Conclusion

Food allergy affects children, adolescents, and adults—each with unique foods and distinct natural history. Despite these differences, management of food allergy at any age consists of strict avoidance of the food allergen and treatment of accidental exposures with medications. Novel therapeutic approaches to food allergy may offer a reduction in the risk of allergic reactions with an ultimate goal of allowing avoided food to be fully reintroduced into the diet.

Compliance with Ethical Standards

Conflict of Interest Scott Commins reports personal fees as a member of the speaker's bureau from Genentech and from Boehringer Ingelheim, and grants from NIH, outside the submitted work. Onyinye Iweala and Shailesh Coudhary declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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