

Food allergy prevalence: new possibilities for therapy and prevention

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Prävalenz von Nahrungsmittelallergien – Neue Möglichkeiten für Therapie und Prävention

Zusammenfassung Nahrungsmittelallergien sind ein wichtiges klinisches Problem mit weltweit zunehmender Verbreitung. IgE-vermittelte allergische Reaktionen sind die am meisten anerkannte Form der Nahrungsmittelallergie. Die Häufigkeit von Nahrungsmittelallergien wird von Land, Alter, Kultur und Ernährungsgewohnheiten beeinflusst. Strategien zur Prävention von Nahrungsmittelallergien wurden ausgiebig untersucht. Derzeit gibt es keine anerkannte Standardbehandlung für Nahrungsmittelallergien, und Allergen-spezifische Immuntherapien wurden in der Vergangenheit oft von schweren Nebenwirkungen begleitet. Ein mutiertes rekombinantes Apfel-Hauptallergen erwies sich klinisch als hypoallergen und öffnet damit die Tür zu einer sichereren Immuntherapie für die Behandlung von Nahrungsmittelallergien.

Die Traditionelle Chinesische Medizin (TCM) ist eine der ältesten medizinischen Praktiken in der Welt. Eine chinesische Kräuterrezeptur (Food Allergy Herbal Formula-2, FAHF-2) wurde zur Therapie von Patienten mit Nahrungsmittelallergie getestet. FAHF-2 erwies sich sowohl im Tiermodell als auch in einer humanen klinischen Studie als bemerkenswert effektiv gegen Nahrungsmittelallergie und hat das Potenzial als dauerhafte Therapie eingesetzt werden zu können.

Schlüsselwörter: Nahrungsmittelallergie, Prävalenz, Komplementäre und alternative Medizin, Traditionelle Chinesische Medizin

Summary Food allergy is an important clinical problem of increasing prevalence worldwide. Immunoglobulin E

(IgE)-mediated allergic responses are the most widely recognized form of food allergy. The prevalence of food allergy is influenced by country, age, culture, and dietary habits. Strategies for the prevention of food allergy have been extensively studied. There is currently no standard treatment for food allergy and allergen-specific immunotherapy has been hindered by severe side effects in the past. A mutated recombinant major apple allergen is clinically hypoallergenic, which paves the way toward safer immunotherapy for the treatment of food-allergic patients.

Traditional Chinese medicine (TCM) is one of the oldest medical practices in the world. A Chinese Food Allergy Herbal Formula-2 (FAHF-2) has been used as a therapy for food allergy patients. FAHF-2 was shown to be remarkably effective against food anaphylaxis in an animal model and in human clinical trial with the potential to be a long-lasting therapy.

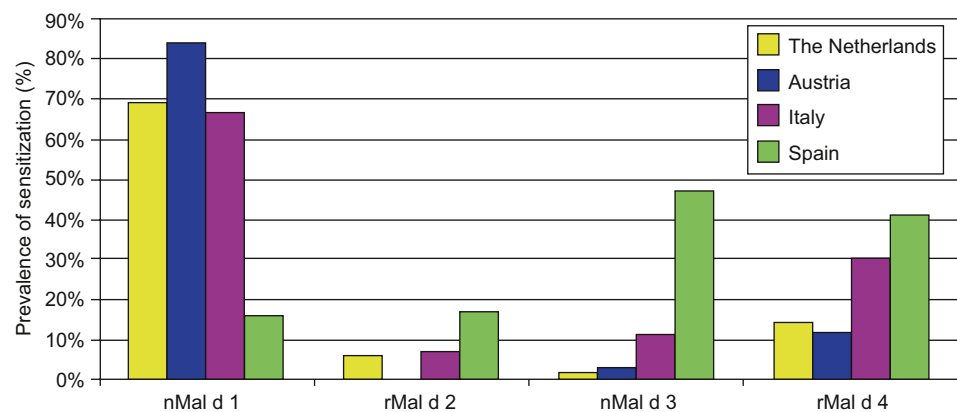
Keywords: Food allergy, Prevalence, Complementary and alternative medicine, Traditional Chinese medicine

Introduction

Food allergy is increasing in Western countries as well as in many developing countries constantly in the recent past. Food allergy is becoming an important public health problem that affects children and adults worldwide. Approximately one in five is believed to be suffering from a food allergy. In fact, 1–3 % of adults and 6–8 % of children have a true, immunoglobulin E (IgE)-mediated allergy. The extent of its importance is highlighted by the volume of publications on this topic, which has exceeded 10,000 articles over the past 10 years alone [1]. The National Institute of Allergy and Infectious Diseases (NIAID) USA has recently published food allergy guidelines, including a consensus definition for food allergy, a discussion of comorbid conditions often associated with food allergy, and information on the epidemiology, natural history, diagnosis, and management of food

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Fig. 1 Regional differences in allergen recognition pattern



allergy, including recommendations for treatment of severe symptoms and anaphylaxis. The European Academy of Allergy and Clinical Immunology has also created a task force to develop guidelines for the diagnosis and management of food allergy [2].

Approximately 15–20 % of the population in Central Europe suffers from pollen allergies, and 50–93 % of birch pollen allergy patients develop an allergy to pollen-associated food allergens [3]. Many food allergies, particularly allergies to milk, egg, soy, and wheat, are usually outgrown within the first 10 years of life [4]. In contrast, allergies to peanut, tree nuts, fish, and shellfish are often lifelong, although 20 % of individuals may outgrow peanut allergy [5]. Peanut and tree nuts are responsible for the most serious allergic reactions and food allergy-related fatalities [6]. There are approximately 200 deaths every year in the USA attributed to food allergy [7].

Although food allergy can arise from any food, the allergens responsible for more than 85 % of food allergy are: milk, egg, peanut, tree nuts, shellfish, fish, wheat, sesame seed, and soy [5, 8]. Food-induced allergic disorders are broadly categorized into those mediated by IgE antibodies or by non-IgE-mediated mechanisms. IgE-mediated allergic responses are the most widely recognized form of food allergy and are characterized by the rapid onset of symptoms after ingestion [9]. It is also necessary to note that sensitization can be present without clinical reactivity, meaning that specific IgE to a food is present, but no reaction occurs with exposure [9–14].

Prevalence

The prevalence of food allergy is influenced by country, age, culture, and dietary habits. Age is one of the most important factors determining the type of food allergy. Children with atopic disorders tend to have a higher prevalence of food allergy; approximately 35 % of children with moderate-to-severe atopic dermatitis have IgE-mediated food allergy [15]. Studies have shown that children with atopic dermatitis and food allergy have a higher prevalence of allergic rhinitis and asthma. Approximately 75 % of children with atopic dermatitis develop allergic rhinitis and 80 % develop asthma [16].

The order of importance of specific allergens varies by country, reflecting the interaction of culture and dietary habits. Peanut allergy is a good example of this. Despite similar levels of peanut consumption, there is a difference in the prevalence of peanut allergy between the USA and China, and it is generally agreed that this discrepancy stems from the effects of different cooking methods on the allergenicity of peanuts; i.e., roasting using higher temperatures apparently increases the allergenic properties of peanut proteins [17].

European Union (EU) granted projects like “SAFE” (Plant food allergies: field to table strategies for reducing their incidence in Europe, 2011–2014) demonstrated that geographic differences in the sensitization to allergens may be related to genetic factors, differences in dietary habits and pollen exposure, or both. This study has analyzed the relation between sensitization to individual apple allergens (nMal d 1, rMal d 2, nMal d 3, and rMal d 4) and the resulting clinical presentation of apple allergy in a comprehensive multicenter approach across Europe (Fig. 1) [18].

The analysis of individual apple allergens in a clinical context has provided valuable information about the sensitization pathway and about the intrinsic risk an allergen bears to induce severe or mild food allergy. Information on the sensitization pathway is essential to develop preventive strategies in food allergy.

Clinical manifestations

The mildest IgE-mediated reaction is the oral allergy syndrome, which causes tingling and itching of the mouth and pharynx. This is typically triggered after consumption of fresh fruits and vegetables in pollen-allergic individuals. It is caused by cross reactivity of IgE antibodies to certain pollens with proteins in some fresh fruits and vegetables (see Table 1) [19].

Fortunately, these proteins are heat labile, enabling allergic individuals to eat these foods when cooked. Allergy skin tests are usually negative to commercial food extracts in individuals with oral allergy syndrome, but are positive to the fresh food. Also, progression to systemic

Table 1. Oral allergy syndrome: cross reaction between proteins in pollen and fresh fruits and vegetables [19]

Pollen	Fresh fruit/vegetable/nuts	
Birch	Almon	Kiwi
	Apple	Nectarine
	Apricot	Peach
	Brazil nut	Peanut
	Carrot	Pear
	Celery	Plum
	Cherry	Potato
	Coconut	Swede
	Fennel	Tomato
	Hazelnut	Walnut
Ragweed	Banana	Honeydew
	Cantaloupe	Watermelon
	Cucumber	Zucchini
Grass	Cherry	Peach
	Kiwi	Potato
	Orange	Tomato
	Melon	Watermelon

symptoms is rare, but may occur in a small proportion of patients with the condition [9–12, 20].

The most severe reaction is anaphylaxis, which is defined as a serious allergic reaction that is rapid in onset and may cause death [7]. There are numerous signs and symptoms of anaphylaxis which usually develop within minutes and up to 2 h of food exposure. Early symptoms should not be ignored because reactions can be highly unpredictable. This is especially true if there is a history of a previous anaphylactic reaction. Although peanut, tree nuts, and shellfish are typically the most responsible culprits, anaphylaxis can be triggered by any of the common food allergens [6, 9].

Diagnosis

The diagnosis of a food allergy requires a detailed history and physical examination, and diagnostic tests, such as skin prick tests (SPT) and/or serum-specific IgE testing to foods (ImmunoCAP). In some cases, oral food challenges may also be required [9–12]. It is important to inquire about all suspect foods and to discuss the manner of food preparation (e.g., cooked, raw, added spices or other ingredients). The primary purpose of the physical examination is to look for supporting evidence of atopic and other allergic diseases (e.g., atopic dermatitis, asthma, and allergic rhinitis) and to rule out the presence of other conditions that may mimic food allergy [9]. Current food allergy guidelines have focused on tools for better diagnosis of food allergy and treatment of reactions.

Skin prick tests (SPT)

The SPT is a rapid, safe and sensitive method for diagnosing suspected IgE-mediated food allergy. A positive SPT has a sensitivity of approximately 90 %; however, its specificity is only around 50 %. Therefore, a positive SPT alone is not sufficient for diagnosing food allergy; the patient must also have a supportive history [9]. SPT should only be done for those foods that are relevant to the patient's history. The negative predictive value of a SPT is greater than 95 % and, therefore, a negative SPT generally confirms the absence of IgE-mediated reactions [10, 21].

Serum-specific IgE tests

Although less sensitive and more costly than SPTs, serum-specific IgE tests can also be used for diagnosing food allergy, particularly if SPTs cannot be performed or are not available [12]. If there is still clinical suspicion of food allergy, but the diagnosis is uncertain based on the results of SPT and/or serum-specific IgE testing, then an oral food challenge may be appropriate.

Oral food challenge

Oral food challenges involve gradual feeding of the suspected food with careful, medically supervised assessment for any symptoms. In the event of symptoms, feeding is discontinued and the patient is treated where appropriate [22]. The oral food challenge is believed to be the gold standard for the diagnosis of a food allergy [1].

Microchip diagnosis

Microchip diagnosis (ImmunoCAP ISAC[®]) is an innovative in vitro diagnostic test based on biochip technology. It allows simultaneous measurement of allergen-specific antibodies to many allergen components in a single test and requires only a few microliter serum or plasma. The specific IgE-chip provides the results for more than 100 allergen components from more than 50 allergen sources. The allergens are preselected and include the most relevant species-specific and cross-reactive markers. Microchip diagnosis is a useful tool, especially for difficult cases such as patients with an unclear history, polysensitized patients, or patients with no response to the treatment. This method is being applied in many allergy clinics extensively in European countries.

Prevention

Strategies for the prevention of food allergy have been extensively studied [9]. Currently, the way to prevent and manage food allergy is avoidance of the allergen and prompt treatment of symptoms when they arise. The

preventive treatment of food allergy is clearly a desired clinical target. The early exposure to an allergen, for example, may prevent the development of IgE-mediated food allergy [23–25].

It is well known that cooking substantially reduces the allergenicity of fresh fruit and vegetables such as apples and carrots and that cooked fruits and vegetables can be consumed by many allergic subjects without any symptoms. Allergenicity of other foods such as peanuts, however, is hardly influenced by heat [26]. It is only rare that a patient is allergic to fruits and vegetables and also allergic to cooked fruits or vegetables [27].

In other pollen-associated allergenic foods, such as celery or hazelnut, however, this situation is more complex. Celery contains both heat-stable and thermolabile allergens. The thermal processing is not suitable to deplete the allergenicity of celery completely. There has been no information about the tolerability of cooked celery in celery-allergic patients [27, 28]. The allergenicity of hazelnut is greatly reduced by roasting. However, a part of the hazelnut allergy is still present on roasted hazelnuts [27, 29].

Because even trace amounts of food allergens may trigger severe reactions in highly sensitive food-allergic individuals, strict avoidance is very important in these individuals. It is essential to educate patients and families regarding cross-contamination and label reading, because many patients and their caregivers do not recognize the risk of exposure to trace amounts of food allergen [2]. For families of patients in the USA with food allergy who need practical information and a comprehensive curriculum regarding food allergy management, the websites www.foodallergy.org provides advice on dietary avoidance, along with survival strategies for schools, restaurants, and camps, manufacturers' updates, and special support programs for teenagers and food allergy experts [30].

Treatment

There is currently no standard treatment for food allergy. Once a food allergy is diagnosed, strict elimination of the offending food allergen from the diet is necessary. In the case of accidental exposure, the treatment of choice is epinephrine administered by intramuscular injection into the lateral thigh [10–12]. All individuals receiving emergency epinephrine must be transported to hospital immediately (ideally by ambulance) for evaluation and observation [31].

Allergen-specific immunotherapy for food allergy has been hindered by severe side-effects in the past. A well-characterized recombinant major food allergen from apple, Mal d 1 was demonstrated as a hypoallergenic allergen by in vitro methods, i.e., RAST (inhibition), immunoblotting and basophil histamine release (BHR) and by in vivo methods, i.e., skin-prick test and double-blind placebo-controlled food challenge (DBPCFC) [23]. This is the first study that confirms by DBPCFC that a

mutated recombinant major food allergen is clinically hypoallergenic. This paves the way toward safer immunotherapy for the treatment of food-allergic patients [23, 24]. Recent research has also shown that children allergic to peanut can be desensitized to peanut by feeding them increasing amounts of peanut under close supervision as an oral immunotherapy [25]. Similar studies have been conducted for egg and milk allergy. Results of these studies are promising; however, they have involved only small numbers of subjects, side effects have been noted, and protocols are still evolving. Therefore, further confirmatory studies in this area are needed.

Treatment of complementary and alternative medicine (CAM)

Currently, there is no effective treatment for food allergy. Food allergy is often associated with other disorders, for example severe and recalcitrant eczema. Therefore, novel approaches for treatment of food allergy and comorbid conditions are urgently needed [35, 36].

Traditional Chinese medicine (TCM) is one of the oldest medical practices in the world, and has a unique system of theory, diagnosis, and treatment [36], in which acupuncture and Chinese herbal medicines are the major modalities of treatment. TCM is the major component of CAM therapies used in the USA and many Western countries, and is beginning to play a role in Western healthcare [35–37]. A National Institutes of Health/National Center for Complementary and Alternative Medicine survey reported that more than 50 % of Americans have used some form of CAM treatment. In Europe the interests of the applications of CAM as well as TCM are rapidly increasing in recent last years by patients and medical doctors [37–40].

Scientific publications indicate that TCM has potential for treating asthma [43], managing allergic rhinitis [44], and improving quality of life of atopic dermatitis patients [45]. Since 2005, there have been a number of scientific studies reporting well-designed double-blind, placebo-controlled clinical trials investigating the acupuncture and its related therapies and the efficacy and safety of herbal medicine, as well as basic studies aimed at understanding the mechanism of actions at the immunological and molecular levels [39–42]. Li et al. [35–38, 43] have investigated a Food Allergy Herbal Formula-2 (FAHF-2) containing nine TCM herbs (*Prunus mume*, *Zanthoxylum schinifolium*, *Angelica sinensis*, *Zingiber officinalis*, *Cinnamomum cassiae*, *Phellodendron chinense*, *Coptis chinensis*, *Panax ginseng*, and *Ganoderma lucidum*) as a multiple therapy for food allergy patients at the Hospital of Pediatrics, Mount Sinai School of Medicine, New York. The pharmacological and immunological actions and mechanisms of FAHF-2 were tested in both in vivo and in vitro models. Many studies focused on recent advances in TCM for food allergy, including acupuncture, herbal medicine, probiotics, and alternative approaches to allergen immunotherapy. FAHF-2 is the only investiga-

tional herbal formulation currently validated for use in human clinical trials in Western countries.

The Austrian Government (Austrian Federal Ministry of Health and Austrian Federal Ministry of Science and Research) has granted a joint research project of the TCM Research Cluster Austria (2008–2011) including nine partners across Austria together with the Sino-Austrian Collaborating Centre for Chinese Medical Sciences since 2008. The topic of investigation is “Prevention and early intervention of chronic diseases by TCM: Evaluation of immunomodulatory, anti-inflammatory and neuroprotective effects” (2012–2015), which will provide continuous support and guidance for the scientific investigation of TCM in Austria. This effort will lead to better health-care and patient outcomes and improved therapies including food allergy in Austria. The Medical University of Vienna has started a Master degree university course of TCM (<http://www.meduniwien.ac.at/studienabteilung/content/studium-lehre/weiterbildung/universitaetslehrgaenge/tcm/>; www.meduniwien.ac.at/ulg-tcm/) since 2010 for promoting the use of TCM in Austria with evidence-based knowledge.

Conclusions

Food allergy is an important clinical problem of increasing prevalence worldwide. Assessment by an allergist is very important for appropriate diagnosis and treatment. Diagnosis currently relies on a careful history and diagnostic tests, such as SPT, serum-specific IgE testing (where appropriate) and, if indicated, oral food challenges. The mainstay of treatment is avoidance of the responsible food(s) and appropriate, prompt response to allergic reactions with epinephrine. Further insight into the pathophysiology of food allergy will lead to the development of improved methods for prevention, diagnosis, and management of the disorder.

Traditional Chinese Medicine (acupuncture, herbs and formulas) is now attracting significant interest in the West. The evaluation of efficacy and safety of TCM is being approached with methodologies and clinical trial protocols that are standard in Western medicine. Published English-language studies investigating TCM herbs and formulas for their anti-allergic effects have been increasing. Controlled clinical trials highlight the potential of TCM formulas to be efficacious and safe alternatives or complements to standard western therapy for asthma and allergy. FAHF-2, a potential TCM herbal treatment for food allergy, was shown to be remarkably effective against food anaphylaxis in an animal model and in human clinical trial with the potential to be a long-lasting therapy. Some TCM herbal remedies may be available in the near future as botanical drugs for the treatment of food allergy in Western countries.

Conflict of interest

The author has declared that she has no conflict of interest.

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