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Review Article

The Progress of Food Allergy Concept, Classifications and Diagnosis

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Abstract: Food allergies, defined as an immune response to food proteins, affect as many as 8% of young children and 5% of adults in most countries, and their prevalence appears to be rising like all allergic diseases, In addition to well-recognized urticaria and anaphylaxis triggered by IgE antibody-mediated immune responses. Food allergy is a rapidly growing public health concern because of its increasing prevalence and life-threatening potential. Food allergic reaction can be further subdivided into IgE mediated and non IgE mediated. The diagnosis of food allergy is made from the history, supported by investigations and by responses to avoidance of specific food triggers. So in this work we want to introduce some concepts in food allergy such as classification of allergic and diagnosis of food triggers and finally how to manage this problem and minimize the prevalence of food allergy.

Keywords: Allergy, IgE, Diagnosis, Application in Food Industries

1. Introduction

Food allergy is defined as an immunological reaction resulting from consumption or other contact with food. It only affects susceptible people who are sensitive, or sensitized to the specific food allergen, which would otherwise normally be well tolerated by the rest of the population [1]. Food hypersensitivity symptoms only appear, or are 'elicited', when you consume or have contact with the food to which you are sensitized [2]. Typical symptoms of IgE-mediated food allergy can be subjective symptoms such as purities or itching [3]. Food-allergic reactions can be triggered by consuming even very small amounts of food in the range of 10–100 mg [4]. The most common food allergies in the United States are milk, egg, peanut, soy, wheat, tree nuts, fish and shellfish. The individual food allergy does vary by culture and population [5]. The type of food allergies can even vary across regions of Northern Europe. In Russia, Estonia, and Lithuania; citrus fruits, apple, hazelnut, strawberry, fish, tomato, egg, and milk were common self-reported allergy. But, in Sweden and Denmark; tree nuts, apple, pear, kiwi, stone fruits, and carrot were the most common self-reported food allergy [6] For reasons that are not yet clear, 90% of hypersensitivity reactions are attributable to only eight major types of food: milk, eggs, shellfish (particularly crustaceans), peanuts, soybeans, tree nuts, and wheat [8]. [9]. Allergic responses to milk, soybeans, eggs, and wheat are typically transient and restricted to childhood; while peanuts, tree nuts, and shellfish are more likely to induce life-long anaphylactic hyperreactivity [7] [10].

2. Classification

Food intolerance refers to an adverse physiologic response to a food and may be due to inherent properties of the food (i.e. toxic contaminant, pharmacologic active component) or to characteristics of the host (i.e. metabolic disorders, idiosyncratic responses, psychological disorder) [11-12].

Food-induced anaphylaxis is a serious allergic reaction that is rapid in onset and can cause death. 10 IgE-mediated food-induced anaphylaxis involves systemic mediator release from sensitized mast cells and basophils. In patients with food-dependent, exercise-induced anaphylaxis, whether a reaction occurs depends on the amount of time between food consumption and exercise, usually within 2 hours not included under food intolerance reactions, the reason being that they do not depend on individual susceptibility [14].

2.1. Mixed IgE-and Non– IgE-Mediated or Non– IgE Mediated Food Allergy

Diagnosing mixed IgE- and non–IgE-mediated or non–IgE mediated food allergies is more challenging than diagnosing IgE mediated food allergy. The approach begins with the clinical history. A clear cause and effect between food ingestion and symptoms might not be clear because the symptoms of these types of food allergy are typically chronic versus immediate but on toxic effects. Non that are immune whereas non immune [15]. Intradermal tests, total serum IgE measure, and atopy patch tests were not recommended for use in diagnosing food allergy in the NIAID-sponsored guidelines and in the Diagnosis and Rationale for Action against Cow's Milk Allergy guidelines sponsored by the World Allergy Organization mediated react. [16-17]. the guidelines for specific immunotherapies for IgE mediated food allergies face several specific issues. [18]

2.2. Diagnosis of IgE-Mediated Food Allergy

The diagnosis of IgE-mediated food allergy, Allergen-specific IgE can be detected by SPTs or immunoassays of serums IgE levels. These tests identify foods that might provoke IgE-mediated reactions, but neither can be considered diagnostic of food allergy and must be combined with the history. [47-48] Serums IgE levels can be measured by using immunoassays (Immuno CAP, Immunlite), which provide reliable and reproducible measurements, although results can take hours to days. SPTs are quick and simple to perform. The SPT wheal size is correlated with the likelihood of clinical allergy,[49-50] and 95% positive predictive thresholds (wheal size above which there is a >95% chance of clinical allergy) have been described for the common allergens. [51-52].

3. Epidemiology

The most common food allergens in the pediatric population include cow's milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish, whereas peanuts, tree nuts, fish, and shellfish predominate in adults in the United States (US). [19-20-21]. The prevalence of sensitization to the specific food allergens varies based on the age and characteristics of the population, but studies incorporating diagnostic food challenges currently estimate that the prevalence of cow's milk allergy in infants is 2.5%, egg hypersensitivity prevalence in young children is 1.6% and peanut allergy is estimated to be between 0.8 and 1.5% in young children in US and England. [22-23].

Most infants with non-IgE mediated cow's milk allergy "outgrow" their sensitivity by the third year of life, but about 10- 25% of infant with IgE mediated cow's milk allergy retain their sensitivity and about 50% develop sensitivity to other foods. [24-25] most children with egg allergy are also likely to develop egg tolerance by late childhood, with the exception of patients with an egg IgE greater than 50 kU L, who are unlikely to develop egg tolerance. [26] Peanut, sesame seeds and tree nuts allergies are more persistent with a chance of becoming tolerant is about 20% for peanut and sesame seeds and about 10% for tree nuts. [27-28]. There has been a significant increase in the incidence of food allergies including a rise of Emergency Department visits for food allergic reactions. [29-30], moreover peanut allergy prevalence in children in US and England doubled in the last few years in identical telephone surveys. [31-32]. the reasons for the increase in food allergy prevalence are not known, but, the short period of time over which the increase occurred, suggests that environmental factors are more likely to be relevant than genetic factors as part of the hygiene hypothesis. [33-34]. the introduction of food later in the infant diet has been postulated to play a role in the increase of food allergy [35]. As food allergy is more common in infants [36], higher permeability of the intestinal mucosa in infants and early exposure to allergenic antigens have been proposed as a possible cause of sensitization in infant. However, it has been shown that the gastrointestinal mucosa reaches its maturity in terms of permeability at day 2-3 of life and the increased permeability observed in some children with food allergy is a consequence rather than a cause of the allergic inflammation [36-37-38].

4. Microbiota Regulation of Tolerance and Allergy

Alterations in the microbiota have now been implicated in the pathogenesis of AD, asthma, and food allergy. [39] Intestinal microbiota influences the network of the immune system and result in impaired regulatory functions and TH2 skewing. While germ-free (GF) conditions are almost impossible in human studies, limiting the types of analysis that can be performed, a role for commensal microbiota in promoting oral tolerance has been clearly defined by using gnotobiotic mice, in which reconstitution of GF mice with well-characterized communities of microbiota or defined bacteria has been performed. Numbers of CD41Foxp31 Treg cells are reduced in antibiotic-treated mice or GF mice, [40-41] which exhibit a prides position toward allergic sensitization.

[41-42] Administration of defined commensal microbiota, such as Clostridia species and Bactericides fragilis, or short-chain fatty acids (microbiota-derived products) to GF mice induced Treg cells [40, 43-44] and reduced allergic sensitization, [40] supporting the notion that intestinal commensal microbiota promote Treg cells and limit allergic responses to foods. Il4raF709 mice carrying a gain-of-function mutation in IL-4 receptor a-chain, which are susceptible to allergic sensitization and anaphylaxis, [45-46] exhibit an altered gut Microbiota signature from that seen in control mice.

5. Studies of OIT for Peanut and Tree Nut Allergies

It is important to develop therapeutics that target the causes of peanut and tree nut allergies. Fewer patients have natural tolerance to these allergens than to other food allergens; most children who are allergic to peanuts remain allergic as

Teenagers and adults and have more severe reactions. [53]. Peanuts and tree nuts are responsible for most food-induced anaphylactic reactions among children. [54]. However, subcutaneous immunotherapy for peanut allergy has many side effects. [55]. OIT for peanut allergy has only recently been investigated, and there have been no studies for tree nut allergy. The first studies of OIT for peanut allergy were uncontrolled and performed in the United States [56-57] and Europe, [58-59] and these studies showed promising results. A systematic review of OIT for peanut allergy by Sheikhet [60] discussed findings from these studies and 3 abstract articles. Most recently, 1 controlled study was performed in the United States and another uncontrolled one in Europe. [61-62] the details of all uncontrolled and controlled studies are summarized in Table 1. [56-58-59-61-62].

OIT and sublingual immunotherapy seem to be the most promising approaches for treating food allergies. OIT was initially described decades ago in case reports and small uncontrolled trials. The first controlled studies reported high levels of efficacy, but the safety and side effects of the therapy were debated. [64-65]. several studies have been conducted since, but it has been difficult to compare their results because different protocols and allergens were used. [63].

Table 1. *Characteristics of OIT and peanut allergy.*

Year publish	**2009**	**2009**	**2010**	**2011**
Countries	**Europe**	**united states**	**Europe**	**Europe**
Type immunotherapy	OAT	OAT	OAT	OAT
Randomized controlled trial	NO	NO	NO	NO
NO. of patients	4	39	23	22
Ages of patients	9-13	1-9	3-14	4-18
Exclusion criteria	not given	severe life Anaphylaxis	unstable asthma	major immuno deficiency

Characteristics of OIT and sublingual immunotherapy for peanut allergy [56-58-59-61-62]

6. Diagnosis

The importance of a thorough clinical history of the patient, taking in as many relevant details as possible, cannot be over emphasized. In the case of IgE mediated food allergy, the acute onset of the response is normally a useful indicator of the diagnosis. The clinical history will normally indicate the causative food (s) allowing for more defined investigation. The detection of allergen-specific IgE is also a useful laboratory test to help confirm diagnosis and identify the triggering food. This may be done either by looking for specific IgE in a blood sample or by using the skin prick test. The skin prick test involves placing a small drop of allergen solution on the skin and gently breaking the skin below the drop. The allergen in the solution will make contact with any IgE bound to mast cells in the skin. If the IgE is specific for the allergen, the bound IgE will be cross-linked by the allergen causing mast cell degranulation, histamine release and a wheal and flare reaction. [66]. In general, the history can be more helpful in IgE-mediated disorders, because these reactions occur so soon after food ingestion and because multiple target organs are affected. History is harder for food-protein induced enterocolitis, where symptoms occur hours later or days later in eosinophilic esophagitis. What is the time frame for the reaction? Immediate hypersensitivity reactions generally occur rapidly, often within minutes and virtually always within 2½hours. [67]. Mixed and T-cell mediated reactions have a characteristically delayed onset. Therefore patients with FPIEC begin to have symptoms later than 1 ½ hours after ingestion Additional clinical history elements can be helpful.

7. Diagnosis in Laboratory

Immediate hypersensitivity skin tests (prick skin tests) examine for the presence of food protein specific IgE. In general, skin tests have positive predictive accuracies of about 50%; but their negative predictive values are in excess of 95%. [68]. the larger the size of wheal on skin test, the more likely a patient will react to the food [68-69].

An alternative method to detect food protein specific IgE is by in vitro methods, (FEIA-CAP or "RAST test"). Some investigators may prefer to use in vitro testing when there is persistent dermatographism (rare), severe eczema, or when families are reluctant either to discontinue H1 blockers. Similar to prick skin tests, a "cut-off" value can be developed for predicting 95% [70-71] or even 50% predictive values [72] on food challenges (Table 1). However, similar to prick skin test, the predictive values changes for the food, age of the

patient or the history of previous reaction. Predictive values can only be developed for milk, egg, peanut, tree nuts, sesame seed and fish. 95% predictive values cannot be developed for soy and wheat. The younger patients have a lower "cut-off" value for 95% predictive value, while no previous exposure to the food or clear history has a higher predictive value (Table 1). For non-IgE-mediated disorders, fewer laboratory diagnostic tools exist. Atopy patch test have been used for eosinophilic esophagitis, food protein induced enterocolitis and atopic dermatitis. [73-74] Compared to prick skin test, atopy patch test is more specific, but less sensitive. [75-76-77]. the negative predictive value is close to 90% except for milk, where it is close to 60%. Therefore, atopy patch test can be provide guidance but not absolute for dietary advice for nonIgE mediated food allergy. Eosinophils in the blood or stool may point to an ongoing enteropathy, but these findings are certainly nonspecific. Serum levels of allergen-specific IgG are not helpful. Endoscopy followed by examination of biopsy specimens are the most important tools in non-IgE-mediated disorders and critical for the diagnosis of eosinophilic esophagitis. Challenges are needed to identify specific food triggers in all cases. There are no tests that indicate the severity or what patients are at high risk for severe allergic reaction or anaphylaxis. However, recent work by Vadas and colleagues examining patients with experienced fatal and nonfatal peanut-induced anaphylaxis compared to normal controls, patients with food allergy and patients with mild peanut reactions. The patients with peanut anaphylaxis had elevated factor (PAF) and decreased PAF acetyl hydrolase suggesting failure of PAF acetyl hydrolase to inactivate PAF contributes to anaphylaxis. [78].

8. Application of Existing Therapies to Food Allergy

The global suppression of immune responses is a common therapeutic strategy applied to inflammatory diseases, such as allergic asthma, autoimmune diseases, or post-transplantation. For allergic asthma, glucocorticoids have become a mainstay, and yet they are generally considered ineffective for food allergy. Work with a murine model of food allergy examined the potential effects of rapamycin in altering food-induced allergic responses. [79] Perhaps not surprisingly, given its potent abilities to suppress T-cell responses, rapamycin was able to diminish the generation of food allergy associated pathology when administered during the sensitization window. In addition, treatment of fully sensitized mice was also sufficient to reduce the severity of diarrhea, symptoms, and core body temperature decreases seen on antigen challenge. Interestingly, the immediate responses to passive immunization with antigen-specific IgE or in cultured mast cells were unaffected, but instead, the IL-9–mediated survival of mast cells was diminished. Increasing evidence from animal models has supported the critical role for mast cells and the IL-9 pathway in the severity of food-induced allergic responses, [80-81] including the beneficial effects of mast cell stabilization in IL-9 transgenic mice with systemic cromolyn sodium treatment. [81] Interestingly, several case reports have shown therapeutic benefit from oral cromolyn sodium treatment for food dependent exercise-induced anaphylaxis [82] and, taken together, the results suggest that existing therapies that limit mast cell numbers or enhance mast cell stability might be clinically effective for food allergy.

Similarly, recent work has demonstrated the potential efficacy of the tyrosine kinase inhibitor compound sunitinib malate (Sutent; Pfizer, New York, NY) [83] in food allergy models. Several receptor systems, including that of the stem cell factor receptor, which is highly expressed on mast cells, and has been successfully used in the treatment of renal carcinoma and resistant gastrointestinal tumors. [84]. although high doses were used, the findings demonstrated a clear diminishment of oral antigen–triggered anaphylactic responses in mice previously sensitized to ovalbumin. Importantly, inhibition of passively immunized mice, as well as primed in vitro mast cells, was shown, suggesting that the efficacy of this approach lies with inhibition of the immediate mast cell response to antigen.

9. Conclusion

Food allergy is of increasing importance to public health, with a growing emphasis on provision of accurate, reliable allergen information for foods and urgent need for capable analytical tools to support and assure food industry risk management programs, allergen labeling and claims, and regulatory authority monitoring and control.

Increased understanding for the pathogenesis of both IgE and non-IgE mediated reactions have been done with the use of new techniques and murine models. These advances are creating the opportunities for novel therapies for food allergy. There is still a need to validate the methods for the use of new diagnostic tools and to evaluate their use in the management of food allergic disorders. More information is required to clarify precipitating factors.

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