FOOD ALLERGY DIAGNOSTICS:
IMMUNOLOGIC REACTIONS TO FOODS AND FOOD ADDITIVES

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Abstract

Food allergies affects approximately 5% of adults and 8% of the children population and has severe effects on the daily life of patients. These manifestations occur not only in the digestive system but also affect other organs or systems.

Bibliographical searches were performed in available studies and reports using the following terms: “food allergy”, “allergy mediators”, “allergies and IgE”, “food intolerance” and “allergy related diseases”. Possible mechanisms of pathogenesis in food allergy, include cross-linking of mast cell– and basophil-bound immunoglobulin E (IgE) and immediate release of inflammatory mediators, as well as chronic allergic inflammation, resulting from T-cell, basophil, and eosinophil activation. The diagnosis of food allergy has traditionally been based on clinical history and food specific IgE testing, including skin prick testing (SPT), serum tests, or both. Routine testing modalities and an oral food challenge is often required to make a definitive diagnosis, with a risk to induce an allergic reaction.

The molecular era offers several alternative diagnostic modalities that have been investigated where testing for IgE antibodies to particular protein components in foods, has shown promise to improve diagnostics and has entered clinical practice.

Accurate diagnosis of food allergy is necessary not only to provide appropriate and potentially life-saving preventive measures but also to prevent unwarranted dietary restrictions. The introduction of routine SPT to pan-allergens can be a simple and feasible way of improving diagnostic and therapeutic efficacy.

Key words: Food allergy, IgE, Skin prick testing, Dietary restrictions.

1. Introduction

Food allergy is phenotypically an extremely heterogeneous group of diseases affecting multiple organs, sometimes in an isolated way, sometimes simultaneously, with the severity of reactions ranging from mild and local to full-blown anaphylaxis. Food allergy, which is the theme of this paper, is often confused with other adverse reactions to food of both an-immune (e.g., celiac disease) and non-immune (e.g., lactose intolerance) nature. To reliably diagnose food allergy, a careful history (immediate-type reactions) needs to be complemented with demonstration of specific immunoglobulin E - IgE (immune mechanism) and confirmed by an oral challenge [1].

Symptoms of a classic IgE-mediated food allergy vary in severity and can include any combination of: laryngeal edema, wheezing, nausea, vomiting, diarrhea, urticaria, angioedema, and hypotension. Many foods can induce an allergic reaction, but the most commonly implicated foods include: cow’s milk, egg, peanut, tree nut, soy, wheat, fish, and shellfish. Milk and egg allergy generally develop and are outgrown in childhood [1, 2]. Peanut and tree nut allergy can occur during childhood or adulthood, are less likely to be outgrown, and tend to cause more fatal reactions.

Given the possibility of life-threatening reactions, it is important to recognize the potential for cross-reactivity among food groups. Diagnosis of food allergy includes skin prick testing, specific serum IgE testing, and oral food challenges. Management is centered on avoidance of allergenic and cross-reacting foods and early recognition and immediate treatment of reactions [2]. Treatment protocols to desensitize patients to food are currently under investigation.
2. Pathophysiology of food allergy

One of the major problems in management of the food allergies is understanding the pathophysiology of allergic reaction. It is a complex pathway involving the subset of T and B lymphocytes, dendritic cells, mast cells and eosinophilic granulocytes [3]. The gastrointestinal tract, which is the largest immunologic organ in the body, is constantly exposed to an enormous array of exogenous antigens including commensal bacteria and ingested proteins [4].

A single epithelial layer separates this antigenic load from the lymphocytes, antigen presenting cells (APC), stromal cells and other immune cells in the lamina propria, which together comprise the mucosal-associated lymphoid tissue (MALT). Within the MALT, unique populations of dendritic cells (DCs) interact with dietary antigens, and determine the fate of the resulting adaptive response, i.e. immunity versus tolerance [5]. In this context, immune tolerance is defined as the antigen-specific suppression of cellular or humoral immune responses. When the initial antigen exposure is mediated through the GI tract, a robust T cell-mediated suppression develops called oral tolerance [6]. However, in the 4 - 6% of children and 2% of adults with food allergies, this mechanism appears to fail, and the ensuing immune response proceeds through two phases: allergic sensitization, and elicitation. Allergic sensitization involves T cell priming after DC activation, and the resultant T-helper-2 (T₂) response is characterized by the production of interleukin-4 (IL-4), IL-5, and IL-13 from CD4+ T cells. This T₂ response leads to B-cell immunoglobulin E (IgE) production, and this IgE binds to its high-affinity receptor on the surface of mast cells in the skin, gut, respiratory, and cardiovascular systems, arming them for reactivity upon re-exposure to allergen. The elicitation of classic allergic symptoms occurs within minutes after allergen exposure, when IgE-bound mast cells recognize the allergen and become activated [7].

The “first-line” features of mucosal defense serve to prevent luminal antigens from interacting with the Mucosa associated lymphoid tissue (MALT) entirely. These include a hydrophobic layer of mucin oligosaccharides which trap antigen, and both constitutive and inducible antimicrobial peptides. Secretory IgA has generally been considered to provide important tolerogenic function by binding to luminal antigens and preventing absorption (i.e., “immune exclusion”), although its specific importance has been controversial [8]. A recent studies showed that mice deficient in the receptor which secretes IgA and IgM into the intestinal lumen are hypersensitive to IgG-mediated anaphylaxis; nonetheless they can be tolerated by an oral feed prior to systemic priming. In this model, tolerance was transferrable by CD4+CD25+ splenic cells, suggesting that cellular mechanisms can compensate for an impaired immune exclusion mechanism [9]. However, a recent case-control study from a larger placebo-controlled trial examining probiotics for allergy prevention in high risk infants showed that the risk of atopy was inversely correlated with fecal IgA levels [10]. These data serve as one example of the complex and complementary forces which act to suppress immunity in the gut.

Another critical influence on the gastrointestinal mucosal immune response is the microbial stimulation provided by the enteric flora, which by adulthood number approximately 100 trillion in the large intestine, providing essential nutritional and immunologic benefits [11]. These bacteria colonize the neonatal GI tract and begin interacting with the MALT within hours of birth. This interaction probably represents the primary stimulus for proper postnatal immune development, since germ-free mice, which are not colonized with bacteria at birth, have disorganized and poorly developed mucosal and secondary lymphoid structures. In the absence of a microbial flora, these animals have impaired antibody responses and do not develop oral tolerance [12]. In humans, specific differences have been identified in the flora of allergic and non-allergic children [13]. This suggests that although intestinal microbial colonization is required for proper immune development, certain microbes may play a significant role in skewing the immune response towards allergic sensitization. Exactly how this may occur is almost completely unknown [14].

2.1 Food allergy

Every food can be potential allergen depending on geographical site or personal constitution. While any food can cause an adverse reaction, eight types of food account for about 90 percent of all reactions.

2.1.1 Peanuts

Peanut allergy is one of the most common food allergies. Peanuts can cause a severe, potentially fatal, allergic reaction called anaphylaxis. To prevent a reaction, strict avoidance of peanut and peanut products is essential. Allergy to peanuts appears to be on the rise in children. According to a FARE funded study, the number of children in the U.S. with peanut allergy more than tripled between 1997 and 2008 [15]. Studies in the United Kingdom and Canada also showed a high prevalence of peanut allergy in schoolchildren. Peanut allergies tend to be lifelong, although studies indicate that approximately 20 percent of children with peanut allergy do eventually outgrow their allergy. Younger siblings of children allergic to peanuts may be at increased risk for allergy to peanuts.
Peanuts are not the same as tree nuts (almonds, cashews, walnuts, etc.), which grow on trees. Peanuts grow underground and are part of a different plant family, the legumes. Other examples of legumes include beans, peas, lentils and soybeans. The allergy to peanuts, does not imply a greater chance of being allergic to another legume (including soy) than to any other food.

Trace amounts of peanut can cause an allergic reaction. Casual contact with peanuts, such as touching peanuts or peanut butter residue, is less likely to trigger a severe reaction. Casual contact becomes a concern if the area that comes into contact with peanuts then comes into contact with the eyes, nose or mouth (for example, a child with peanut allergy gets peanut butter on his/her fingers, and then rubs his/her eyes).

Based on recent studies, an estimated 25 – 40 percent of people who have peanut allergy also are allergic to tree nuts [16]. In addition, peanuts and tree nuts often come into contact with one another during manufacturing and serving processes. For these reasons, patients with peanut allergy should have to avoid tree nuts as well.

2.1.2 Tree nuts

Tree nut allergy is one of the most common food allergies in children and adults that can cause a severe, potentially fatal, anaphylactic reaction. To prevent a reaction, strict avoidance of tree nuts and tree nut products is essential. An allergy to tree nuts tends to be lifelong; recent studies have shown that approximately 9 percent of children with a tree nut allergy eventually outgrow their allergy. Younger siblings of children who are allergic to tree nuts may be at increased risk for allergy to tree nuts.

Tree nuts include, but are not limited to: walnut, almond, hazelnut, cashew, pistachio, and Brazil nuts. These are not to be confused or grouped together with peanut, which is a legume, or seeds, such as sunflower or sesame. A person with an allergy to one type of tree nut has a higher chance of being allergic to other types.

Therefore, many experts advise patients with allergy to tree nuts to avoid all nuts. Patients may also be advised to also avoid peanuts because of the higher likelihood of cross-contact with tree nuts during manufacturing and processing [17].

2.1.3 Milk

Allergy to cow’s milk is the most common food allergy in infants and young children. Symptoms of a milk allergy reaction can range from mild, such as hives, to severe, such as anaphylaxis [18].

Approximately 2.5 percent of children younger than three years of age are allergic to milk. Nearly all infants who develop an allergy to milk do so in their first year of life. Most children eventually outgrow a milk allergy. The allergy is most likely to persist in children who have high levels of cow’s milk antibodies in their blood, usually of Immunoglobulin E type (IgE). Blood tests that measure these antibodies can help to determine whether or not a child is likely to outgrow a milk allergy [18, 19].

Sensitivity to cow’s milk varies from person to person. Some people have a severe reaction after ingesting a tiny amount of milk. Others have only a mild reaction after ingesting a moderate amount of milk. Reactions to milk can be severe and life-threatening.

Milk allergy should not be confused with lactose intolerance. A food allergy is an overreaction of the immune system to a specific food protein. When the food protein is ingested, it can trigger an allergic reaction that may include a range of symptoms from mild symptoms (rashes, hives, itching, swelling, etc.) to severe symptoms (trouble breathing, wheezing, loss of consciousness, etc.). A food allergy can be potentially fatal [19].

Unlike food allergies, food intolerances do not involve the immune system. People who are lactose intolerant are missing the enzyme lactase, which breaks down lactose, a sugar found in milk and dairy products. As a result, lactose-intolerant patients are unable to digest these foods, and may experience symptoms such as nausea, cramps, gas, bloating and diarrhea. While lactose intolerance can cause great discomfort, it is not life-threatening.

It is recommended that formula-fed infants who are allergic to milk use an extensively hydrolyzed, casein-based formula. This type of formula contains protein that has been extensively broken down so it is different than milk protein and not as likely to cause an allergic reaction. For the practical purpose, if the child is not allergic to soy, a soy-based formula may be recommended.

A milk-free formula is an excellent source of necessary nutrients, so many doctors recommend continuing its use well past the age of one year for children on restricted diets due to food allergy [20].

2.1.4 Eggs

Egg allergy is also one of the most common food allergies in children, second only to milk allergy. Symptoms of an egg allergy reaction can range from mild to severe. While the whites of an egg contain the allergenic proteins, patients with an egg allergy must avoid all eggs completely (the egg white and the egg yolk). This is because it is impossible to separate the egg white completely from the yolk, causing a cross-contact issue [21].
Some vaccines contain egg protein. The recommendations of the American Academy of Pediatrics (AAP) acknowledge that the MMR (measles-mumps-rubella) vaccine can be safely administered to all patients with egg allergy. These recommendations have been based, in part, on scientific evidence that supports the routine use of one-dose administration of the MMR vaccine to patients with an egg allergy.

Influenza vaccines usually contain a small amount of egg protein. According to the American Academy of Allergy, Asthma & Immunology (AAAAI), "Studies show that flu vaccines can be safely administered to egg allergic individuals, wither in the primary care provider's office or allergist's office depending on the severity of the allergic reaction to eating eggs" [22].

2.1.5 Soybeans

Soybean allergy is common food allergy, especially among babies and children, and approximately 0.4 percent of children are allergic to soy. Studies indicate that an allergy to soy generally occurs early in childhood and often is outgrown by age three. Research indicates that the majority of children with soy allergy will outgrow the allergy by the age of 10 [23].

Allergic reactions to soy are typically mild; however, although rare, severe reactions can occur. Soybeans are a member of the legume family, which include plant species that bear seed pods that split upon ripening. Some examples of other legumes include beans, peas, lentils and peanut. People with a soy allergy are not necessarily allergic to other legumes.

In the United States, soybeans are widely used in processed food products. Soybeans alone are not a major food in the diet, but because soy is used in so many products, eliminating all those foods can result in an unbalanced diet. Therefore, consultation with a dietitian is essential in planning proper nutrition [23].

2.1.6 Sea food

Finned fish and shellfish can cause severe allergic reactions and this allergies usually are lifelong. Approximately 40 percent of people with fish allergy experienced their first allergic reaction as adults [24]. To prevent a reaction, strict avoidance of fish and fish products is essential.

Salmon, tuna and halibut are the most common kinds of finned fish to which people are allergic. More than half of all people who are allergic to one type of fish also are allergic to other fish, so allergists often advise their fish-allergic patients to avoid all fish [25]. Finned fish and shellfish do not come from related families of foods, so being allergic to one does not necessarily mean that you must avoid both.

There are two kinds of shellfish: crustacea (such as shrimp, crab and lobster) and mollusks (such as clams, mussels, oysters and scallops). Reactions to crustacean shellfish tend to be particularly severe [26]. The allergy to one group of shellfish, usually imply allergy to other types, so all the varieties should have to be avoided. In addition, touching shellfish, going to the fish market, and being in an area where sea foods are being cooked (the protein in the steam may present a risk) should be avoided [27].

2.1.7 Sesame

A 2010 survey showed that hundreds of thousands of Americans and Europeans are affected by sesame allergy [28]. Although the exact prevalence of sesame allergy is unknown, several reports have shown that sesame allergy prevalence has increased significantly in the worldwide population over the past two decades. Sesame is not currently included in the list of major allergens that must be declared by food manufacturers as part of the Food Allergen Labeling Consumer Protection Act (FALCPA), although FARE supports the addition of sesame to the list of "major food allergens" that are required to be identified on ingredient labels of processed foods. In the meantime, FARE continues to expand its educational resources to support individuals with sesame allergy in avoiding their allergen [29].

2.2 Food additives

For centuries, food additives have been used for flavoring, coloring and extension of the useful shelf life of food, as well as the promotion of food safety. During the last 20 years, the studies implicating the additives contained in foods and medicine as a causative factor of allergic reactions have been proliferated considerably [30]. There are thousands of substances added to various foods and they are usually only a very small component of foods, but have been suspected of causing various reactions. Food additives include the following groups:

- Food dyes and colorings (such as tartrazine, annatto and carmine).
- Antioxidants (such as BHA and BHT).
- Emulsifiers and stabilizers (such as gums and lecithin).
- Flavorings and taste enhancers (such as MSG, spices and sweeteners).
- Preservatives (such as benzoates, nitrates and sulfites).

Since it is probable that many reactions to food additives are not diagnosed, the exact rate of reactions is not known. However, various studies estimate that the rate is probably less than 1% of adults, and up to 2% of children. A diagnosis of allergy to food additives is suspected when a person experiences various reactions to prepared foods or when eating at restaurants, but
not from foods prepared at home. Various seemingly unrelated foods might in fact have common ingredients, such as food colorings or preservatives [31]. Once a food or food additive is suspected, allergy testing (using skin testing or RAST) may be possible to certain natural substances such as annatto, carmine, and saffron. Testing for synthetic substances is not possible or reliable, and therefore a trial of a preservative-free diet may support a diagnosis of food additive reactions [32].

In many instances, the only way to truly diagnose an adverse reaction to food additives is for the person to undergo an oral challenge with the suspected additive under close supervision of an allergist [32].

2.2.1 Allergy to Tartrazine

Also known as FD&C Yellow #5, tartrazine has been suspected as the cause of many reactions, including urticaria (hives), asthma and other illness [33]. Recent studies have disproven the thought that aspirin-allergic asthmatics were especially sensitive to tartrazine [33, 34]. Other studies suggest a role of tartrazine as worsening atopic dermatitis [35].

2.2.2 Carmine

Carmine is a red food coloring made from a dried insect called Dactylopus coccus - Costa, which can be found on prickly pear cactus plants. This coloring is also found in various cosmetics, drinks, red yogurt and popsicles. Reactions to carmine are probably due to allergic antibodies [36].

2.2.3 Annatto

Annatto is a yellow food coloring made from the seeds of a South American tree, Bixia orellana. This additive has been found to cause allergic reactions, including anaphylaxis and urticaria/angioedema [37].

2.2.4 Saffron

This yellow food coloring, obtained from the flower of the Crocus sativa plant, has been reported as a cause of anaphylaxis. Many other food colorings are less common, but possible, causes of adverse reactions. These include sunset yellow (yellow #6), amaranth (red #2), erythrosine (red #3), and quinoline yellow, among others [38].

2.2.5 Allergy to Antioxidants

Antioxidants such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are added to prevent the spoilage of fats and oils. Both BHA and BHT are suspected of causing urticaria and angioedema [39, 40].

2.2.6 Lecithin

Lecithin in an emulsifier made from soybeans and eggs, and may contain soybean proteins. Reactions to soy lecithin are rare, even in soy-allergic people, since the level of this additive is usually very low in most foods [41].

2.2.7 Monosodium Glutamate Allergy

Monosodium glutamate is a flavor enhancer added to various foods, and also occurs naturally. Reactions to MSG have been called the “Chinese Restaurant Syndrome,” and symptoms include numbness on the back of the neck, shoulders and arms, weakness and palpitations. Other symptoms include facial pressure/tightness, headaches, nausea, chest pain and drowsiness. MSG is also suspected of worsening asthma symptoms [42].

2.2.8 Allergy to Gums

Various gums are used as food additives and function as emulsifiers and stabilizers. Major gums include guar, tragacanth, xanthan, carrageenan, acacia (Arabic) and locust bean. Many of these gums are known to worsen asthma, particularly in the occupational setting, when airborne. Others are known to cause allergic reactions when present in foods [43].

2.2.9 Allergy to Spices

Spices are the aromatic part of various weeds, flowers, roots, barks and trees. Because they are derived from plants, spices have the ability to cause allergic reactions, just like pollens, fruits and vegetables. The most common spices used include chili peppers, celery, caraway, cinnamon, coriander, garlic, mace, onion, paprika, parsley and pepper [44, 45].

2.2.10 Allergy to Aspartame

Aspartame is a sweetener used in many sugar-free foods and drinks. This food additive has been suspected of causing such symptoms as headaches, seizures and urticaria [46].

2.2.11 Allergy to Sulfites

Sulfites or sulfate agents (in the forms of: sodium sulfate, sodium bisulfite, sodium metabisulfite, potassium bisulfite and potassium metabisulfite) are common preservatives used in various foods and medications. Sulfites cause little to no problems in most people without allergies and asthma, even when large amounts are consumed. Sulfites are known to increase asthma symptoms in approximately 5% of asthmatics, particularly in adults with severe disease [47, 48].

2.2.12 Allergy to Benzoates

Benzoates are used in foods as antimicrobial preservatives, and have been responsible for worsening asthma, allergic rhinitis, chronic urticaria, and flushing in some people [47, 48].
2.2.13 Allergy to Sorbates and Sorbic Acid
Sorbates are added to foods as antimicrobial preservatives. Reactions to sorbates are rare, but have included reports of urticaria and contact dermatitis [47, 48].

2.2.14 Allergy to Nitrates and Nitrites
These additives are used as curing agents in meat products. Few reports of reactions to nitrates and nitrites exist, and include urticaria, itching and anaphylaxis [49, 50].

2.3 Diagnosis & testing of food allergies
Suspected food allergies should always be evaluated, diagnosed, and treated by a qualified medical professional, such as a board-certified allergist. The primary care doctor may refer the patients to an allergist. Self-diagnosis can lead to unnecessary dietary restrictions and inadequate nutrition, especially in children. Additionally, some people think they are allergic to a food when they actually have another type of food disorder, and treatment may differ [51].

Some methods of food allergy testing are unproven and are considered controversial, since no definitive studies have shown that they can effectively diagnose food allergies [52]. Some may even increase the risk of an allergic reaction. The first step to diagnose a food allergy is a thorough medical history.

Next, the allergist may conduct tests to help identify a food allergy. While these tests alone do not always provide clear-cut answers, the allergist will combine the test results with the information given in the medical history to provide a diagnosis [53]. These tests may include: Skin prick test, Blood test, Oral food challenge and Trial elimination diet [54]. These tests are all proven diagnostic methods. Depending on the medical history and initial test results, the patients may have to take more than one test before receiving their diagnosis [55].

2.3.1 Treatment & managing of allergies
For all allergic reactions to food it is advised a quick access to an epinephrine auto-injector (such as an EpiPen®, Auvi-Q™ or Adrenaclick®) at all times, and reading the ingredient labels to products is strictly recommended [56 - 58]. Once epinephrine is administered, other medications also may be used to control the reaction:

- Steroids (e.g., cortisone) may be given, typically in the emergency room, to help reduce inflammation after an anaphylactic attack. Although steroids do not work fast enough for emergency treatment, they may help prevent a recurrence after the initial reaction has been treated [56].

- Antihistamines, known as H1 blockers, are prescribed to relieve mild allergy symptoms, although they cannot control a severe reaction. Medications in this class include diphenydramine (Benadryl®) and cetirizine (Zyrtec®). An antihistamine should never be given as a substitute for epinephrine [57].

- Asthma Medications. Short-acting bronchodilators (known as “rescue” inhalers), such as albuterol (Alupent®, Proventil®, Ventolin®), may be used to help relieve breathing problems once epinephrine has been given, particularly if you are experiencing asthma symptoms. They should not be depended upon to treat the breathing problems that can occur during anaphylaxis - use the epinephrine [58].

3. Conclusions
- FA is a complex, multifactorial disease with increasing prevalence worldwide. Research into the mechanisms and risk factors underlying FA has elucidated some of the features of this disease and have suggested potential avenues for treatment, although much remains unknown.

- Further understanding of FA mechanisms will likely come from studies of genetics and epigenetic factors, as well as enhanced demographic studies; new guidelines regarding maternal diet will likely be generated on the basis of early exposure studies. Although there has been an increase in the report of FA, diagnostics are currently imprecise, and must be refined in order to determine disease severity and the possibility of developing spontaneous tolerance, as well as to better understand the global impact of FA.

- Accurate diagnosis of food allergy is necessary not only to provide appropriate and potentially life-saving preventive measures but also to prevent unwarranted dietary restrictions. The introduction of routine SPT to pan-allergens can be a simple and feasible way of improving diagnostic and therapeutic efficacy.

4. References


