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REVIEW ARTICLE

AN UPDATED REVIEW OF FOOD ALLERGY AND ASSOCIATED RISK FACTORS

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ABSTRACT

A large body of medical literature has indicated that hidden food allergy is a frequent cause of a wide range of physical and mental conditions. The immune system protects our body against pathogens and other foreign substances by producing a kind of glycoprotein known as immunoglobulin or antibodies from plasma cells or B-cells. Surveys show that about one-third of all adults believe they have food allergies. About 4-8% percent of young children are diagnosed with food allergies, most of which are evident in the first years of life and are often outgrown. A food allergy is any adverse reaction to an otherwise harmless food or food component that involves Theresa word, body's a food allergy is iman**m**mune system response to a food In that the body mistakenly believes is harmful. Components of a food that trigger the immune system are called food allergens. Cow's milk allergy appears to be among the more prevalent food allergies in infants. Eggs and peanuts are also common allergenic foods for infants, along with soybeans, tree nuts, fish, and wheat. Seafood allergies, especially to crustaceans (shrimp, crab, lobster) are also rather common among adults. The present review provides brief information about food allergy and allergic reactions, their types, symptoms and approaches for reduction.

KEYWORDS: food allergy, adverse reactions, immune system, top allergens.

INTRODUCTION:

Food allergy is well recognized in clinical medicine as a cause of acute attacks of asthma, angioedema and urticaria, and as a contributing factor in some cases of eczema and rhinitis.Allergy is one of the most widespread diseases of the modern world. More than 25% of the population in industrialized countries suffers from allergies.1 The immune system protects our body against pathogens and other foreign substances by producing a kind of glycoprotein known as immunoglobulin (Ig) or antibodies from plasma cells or B-cells (a type of lymphocyte). Antibodies are mainly of five types, each one having a different function; the type involved in allergy is immunoglobulin E (IgE). Immunoglobulin E (IgE) is overproduced during an allergic response. On the very first exposure to an allergen, an allergic person becomes sensitized by producing allergen specific IgE that binds with IgE receptors on mast cells (in tissues) and basophils (in circulation). Binding of two or more IgE molecules to mast cells (cross linking) is required to activate the mast cells. These activated cells result in the release of certain chemicals, such as histamine, serotonin, proteoglycans, serine protease, leukotriene C4 and heparin, which will further bind with their receptors present in other cells (e.g., histamine receptors of blood vessels) and lead to inflammation, irritation, redness and other allergic symptoms.2These types of allergic reactions are considered to be mediated by IgE antibodies, and usually can be diagnosed by medical history and skin-prick or IgE-radioallergosorbent (RAST) tests. Another type of food reaction, often referred to as "hidden" or "masked" food allergy, has been the subject of controversy for many years. Some practitioners have observed that hidden food allergies are a common cause of (or triggering factor for) a wide range of physical and emotional disorders. According to one estimate, as many as 60 percent of the population suffers from undetected food allergies.1 A wide range of symptoms and disorders are reported to have a significant allergy component. See Table 1. On the other hand, many conventional physiciansdoubt hidden food allergy is a common problem, and some even deny altogether its existence as a clinical entity.

Food allergy or allergic food hypersensitivity is defined as the adverse reaction caused by immunologic mechanisms, which may or may not be mediated by immunoglobulin E (IgE).3 It is important to differentiate from food intolerance or non allergic food hypersensitivity, which is an adverse response caused by the host's physiological characteristics,4 for example, metabolic disorders (lactase deficiency). Toxic reactions can imitate food hypersensitivity and are provoked by factors pertaining to the food such as toxic pollutant (histamine from shellfish poisoning) or pharmacological substances contained in the food (tyramine in staled cheese). These types of reactions can affect any healthy person when these substances are consumed in large amounts.3 Food allergy or allergic food hypersensitivity manifests clinically in diverse ways, depending on the immunologic causing it

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(figure 2). The most common are those measured by IgE, which can affect skin (urticaria, angioedema), followed by the gastrointestinal type (oralallergy syndrome, vomit, diarrhea,etc.).

Pollen is one of the major causes of allergies. Some of the most common allergy-inducing pollens are from birch, olive, oak, maple, plantago, rye grass, and ragweed. Major pollen allergens constitute expansins, profilins and calcium-binding proteins. Food plants such as cooked potatoes, apples, beans, tomatoes, onions, cabbage, soy, peanuts, and the wheat proteins omega-5 gliadin and glutein can also cause allergies.3 Latex is also a strong trigger for allergic disease. 4-6 Allergens can be of animal origin. In most edible fish, parvalbumin has been identified as the major allergen. Fish like cod, salmon, pollack, herring, and wolfish contain the most potent allergens, whereas halibut, flounder, tuna and mackerel are the least allergenic. 7 Eight foods or food groups are thought to account for more than 90% of all IgE-mediated food allergies on a worldwide basis. These top eight food allergens are:

- *Milk*
- *Shellfish (*crab, lobster, shrimp *and mollusks)*
- *Eggs*
- *Wheat*
- *Fish (*bass, flounder, cod*)*
- *Peanuts*
- *Soy*
- *Tree nuts (*almonds, walnuts, pecans, *walnuts)*

Proponents of the food allergy-disease connection argue that hidden food allergies are often overlooked because they are difficult to identify. Unlike the more obvious immediate hypersensitivity reaction that can trigger acute asthma or anaphylaxis, a hidden food reaction frequently can be delayed by many hours or even several days.

SYMPTOMS OF FOOD ALLERGY:

Clinical symptoms of adverse food reactions typically involve the skin, gastrointestinal tract, and respiratory system. These symptoms can occur alone or in combination, with more than one symptom occurring at one time; and in some cases there can be generalized anaphylaxis. IgE-mediated adverse reactions to food or food allergy usually begin within minutes to a few hours after eating the offending food. But in very sensitive people, simply touching or inhaling the food may produce an allergic reaction. Anaphylaxis is a rare but potentially fatal condition in which several different parts of the body experience food allergic reactions at the same time. Symptoms may progress rapidly and may include severe itching, hives, sweating, swelling of the throat, breathing difficulties, lowered blood pressure, unconsciousness and can even lead to death.8-12.

Classic immunoglobulin-E (IgE)-mediated food allergies are classified as type-I immediate Hypersensitivity reaction. These allergic reactions have an acute onset (from seconds to one hour) and may include:

- Hives
- Itching of mouth, lips, tongue, throat, eyes, skin, or other areas
- Swelling (angioedema) of lips, tongue, eyelids, or the whole face
- Difficulty swallowing
- Runny or congested nose
- Hoarse voice
- Wheezing and/or shortness of breath
- Nausea
- Vomiting
- Abdominal pain and/or stomach cramps
- Lightheadedness
- Fainting

Symptoms of allergies vary from person to person. The amount of food needed to trigger a reaction also varies from person to person.

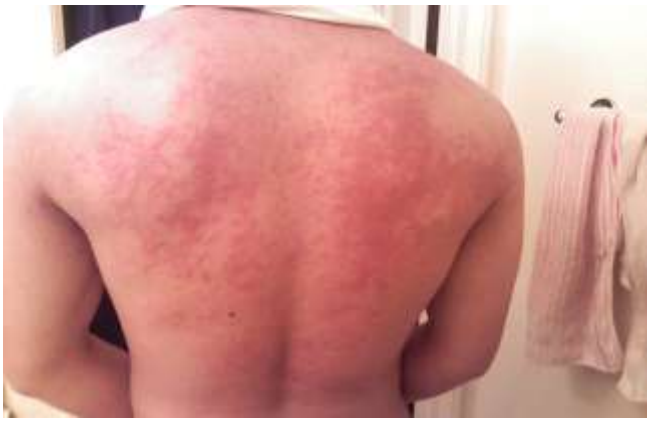

Figure 1: Hives on back

TYPES OF THE ADVERSE FOOD REACTIONS:

Food allergy is thought to develop more easily in patients with the atopic syndrome, a very common combination of diseases: allergic rhinitis and conjunctivitis, eczema and asthma.13The syndrome has a strong inherited component; a family history of allergic diseases can be indicative of the atopic syndrome.

Conditions caused by food allergies are classified into 2 groups according to the mechanism of the allergic response:

1. IgE-mediated (classic):

- Type-I immediate hypersensitivity reaction (symptoms described above)
- Oral allergy syndrome

2. Non-IgE mediated:

- Food protein-induced Enterocolitis syndrome (FPIES)
- Food protein proctocolitis/proctitis
- Food protein-induced enteropathy. An important example is Celiac disease, which is an adverse immune response to the protein gluten.
- Milk-soy protein intolerance (MSPI) is a non-medical term used to describe a non-IgE mediated allergic response to milk and/or soy protein during infancy and early childhood. Symptoms of MSPI are usually attributable to food protein proctocolitis or FPIES.
- Heiner syndrome — lung disease due to formation of milk protein/IgG antibody immune complexes (milk precipitins) in the blood stream after it is absorbed from the GI tract. The lung disease commonly causes bleeding into the lungs and results in pulmonary hemosiderosis.

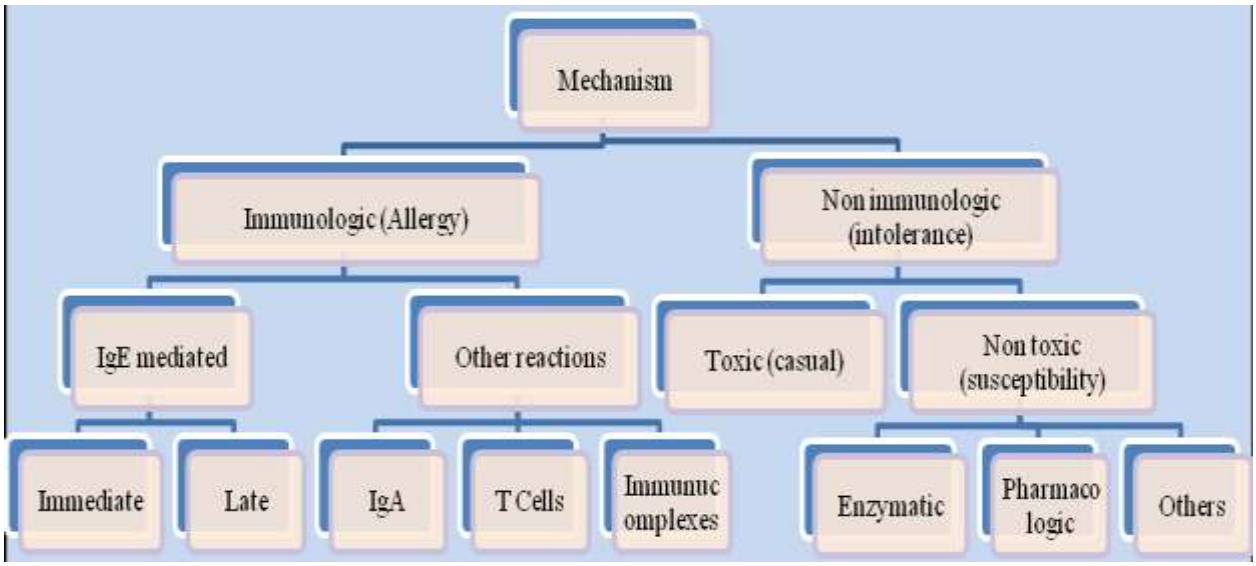

Figure 2: Classification of the adverse food reactions

PREVALENCE OF FOOD HYPERSENSITIVITY:

The prevalence of food hypersensitivities is greatest in the first few years of life, affecting about 6% of infants less than 3 years of age14 and decreasing over the first decade. Virtually all infants who have cow's milk allergy have it in the first year of life, with clinical tolerance developing in about 80% by their fifth birthday.1 About 60% of infants with cow's milk allergy experience IgE-mediated reactions, and about 25% of these infants retain their sensitivity into the second decade of life, with 35% going on to have other food allergies.15 Table I lists the prevalence of various food allergies in the United States on the basis of the most recent studies. Although it was once thought that peanut, nut, and seafood allergies were never outgrown, it has become apparent that clinical tolerance develops in about 20% of young children with peanut allergy.16,17 Recent studies from the United Kingdom and the United States indicate that the prevalence of peanut allergy has doubled in young children during the past decade18,19 Children with atopic disorders tend to have a higher prevalence of food allergy; about 35% of children with moderate-to-severe atopic dermatitis have IgE-mediated food allergy,20 and about 6% to 8% of asthmatic children have food-induced wheezing.21 On the basis of these more recent surveys, 3.5% to 4% of the US population are believed to have IgEmediated food allergy.22

FACTORS ASSOCIATED WITH ELEVATED RISK OF FOOD ALLERGY:

Prenatal and postnatal factors have been studied.

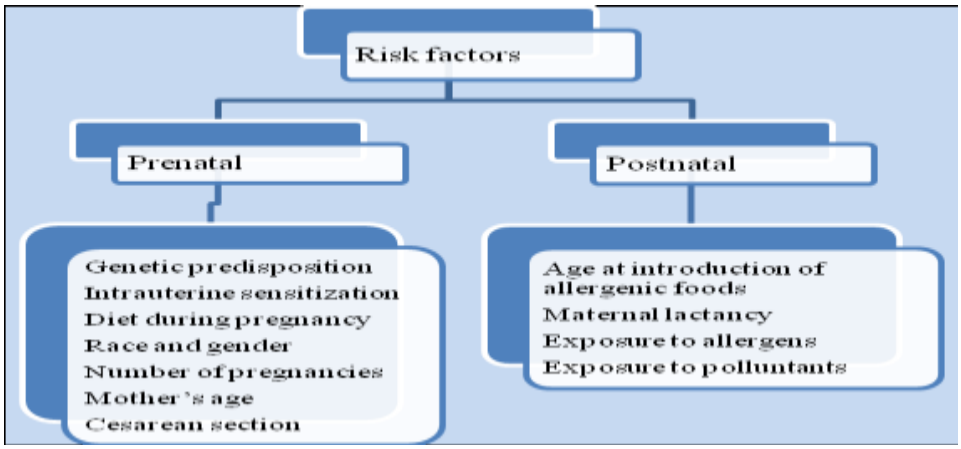

Figure 3: Various risk factors

PRENATAL FACTORS:

GENETIC PREDISPOSITION:

It is believed that in the same way there are genetic factors related to elevated risk of suffering other allergic diseases, there are also genetic factors that predispose to food allergy in individuals.

In the case of peanut allergy, a child has seven times more risk when having a parent or older brother with the same allergy.23 A 64% greater risk is present in the case of monozygotic twins when a sibling or parent suffers this alteration.24The influence of genes HLA class II and an elevated rate of coincidence in monozygotic twins have been shown (64%), in comparison with dizygotic (7%) which indicate a strong genetic contribution in peanut allergy. A study showed association between nut allergy and polymorphism in a signal transducer and a transcript activator.25 Besides, the risk of food allergy being four times greater in children with asthmatic parents has been proved, this in comparison to normal population.26-28 This supports it being an inherit trait with a dominant genetic pattern, weather it be recessive or polygenetic, that is as pattern with variable expression. The risk of food allergy is greater in children born from parents with a strong family background of atopy. In the case of only one parent this corresponds to 50%, in both parents this is 70%. In brothers the risk of being affected is 25 times greater than the general public.26 Japanese population trial showed association between gene IL-10 polymorphism and food allergy.29 Another trial conducted in German population identified IL-13 polymorphism associated to this condition.30-31

INTRAUTERINE SENSITIZATION:

From week 11 in pregnancy small amounts of IgE are produced. In some cases an elevated number of IgE in the umbilical chord at the moment of birth (> 0.8 UI/ mL) and have been associated to a greater risk of allergies duringtheir life. Protein caused intrauterine sensitization is suggested in the amniotic fluid, which pass through the baby's skin and in a lesser degree through aspiration.32, 33 A trial conducted in Vancouver34 with high-risk children, identified before birth by having at least one parent with allergic disease, determined the concentration of IgE in the umbilical chord at moment of birth, with a follow through of 12 months. The authors found that the concentration of IgE is a significant predicting factor for food allergy urticaria.

DIET DURING PREGNANCY:

The option of offering a low allergen diet in pregnant women is still under discussion. There are different postures and recommendations made by the American Pediatric Academy (AAP) and the European Society of Clinical Pediatric Allergy and Immunology (ESPACI).23 The AAP does not recommend a diet during pregnancy with the only exception of excluding peanuts, while the ESPACI and the European Pediatric Gastroenterology Society, in a consensus review of prospective studies in children with high risk (at least one sibling –parent or sibling– with allergy), proved the protective effect different dietary programs have in the prevention of allergies in food allergy incidence, specially in milk protein.35

BIRTH THROUGH CESAREAN SECTION:

This could be a food allergy risk factor, due to the colonization delay in the baby's intestines. In a sample of 2,803 live babies this factor was studied and what was observed was that those born from allergic mothers had seven times greater risk of allergy to egg, fish and nuts,36 according to the observations by parents ($p = 0.005$) and four times greater risk of allergies from the same foods, based on the doctor's observations. In non-allergic mothers no significant differences where found between a Cesarean and a vaginal birth.

Male gender:

Different studies have pointed out male gender being a risk factor in allergic diseases in general, but few assess the specific relation with food allergy. A prospective cohort study37 made in With island

(UK) included patients in prenatal period and followed the babies from birth to the age of four years looking for environmental and genetic influence in the appearance of allergic manifestations, they conducted coetaneous tests positive to food allergies at the age of four with an incidence of 3.7 for boys and 1.9 for girls.

Postnatal factors:

Maternal lactation:

Prospective observational trials report that exclusively maternal lactation, for a period of three to six months, decreases the risk of allergy to milk protein and food allergy by the age of three.38

Saarinen and collaborators39 conducted a prospective trial with followthrough to the age of three without intervention in non-selected children. They found that maternal lactation for a period of at least six months contributes to protection against food allergy. There is no doubt about the nutritional and immunologic importance of maternal lactation; however, the time it should be offered and the exclusiveness in breast-feeding the baby are the factors that influence in the appearance of allergies.

Diverse studies indicate that maternal lactation has a preventative effect compared to cow milk formula feeding.40 Different metanalysis have shown that maternal lactation for a period of at least three months in babies with atopy inheritance is a protective factor against dermatitis atopy (OR 0.58) and recurrent wheezes in the first five years of age (OR 0.52).41

The only random prospective trial compared maternal milk formula to cow milk formula in a sample of premature patients, and found that the cow milk diet increased the risk of atopic dermatitis and allergy to milk protein by the age of 18 months, this specially in the group that had atopic inheritance.42

Other trial in children with atopic risk exclusively breast-fed for more than four months, with a delayed weans, had a significant allergic incidence reduction to cow milk and atopic dermatitis for the firs four years of their life.43This sustains that the introduction of milk formulas before weaning is related to a greater incidence of developing allergy to cow milk protein.44

Meanwhile the European Society of Clinical Pediatric Allergy and Immunology recommends the following:

- Maternal lactation during the firs four to six months of life can reduce the incidence of allergic manifestations and is highly recommended.
- Supplementary food should not be administered before five months of life.
- Children with atopy risk (parents or sibling) and fed with formula should take confirmed low allergenic formula, this reduces food and milk protein allergy incidence.

WEANING:

Beginning weaning between four and six months of life has been related to a greater incidence of cow milk and food allergy, this based on prospective observational trials. These being backed up by the European Society of Clinical Pediatric Allergy an Immunology and the American Pediatric Academy based on a weaning guideline that sustains the introduction of solid meals at a short age is associated with the induction of food allergy.45 Independently, the American Pediatric Association suggests: Maternal feeding during the first year of life; weaning should not be started until the age of six months and introduction of milk until the age of twelve months, eggs and peanuts until two years, nuts and fish until three years. While the European Society of Clinical Pediatric Allergy an Immunology only suggests maternal lactation for four to six months, with weaning after five months of age.

Kajosaari and Saarinen123 observed that introducing meal before six months old is related to the increase of food allergies and atopic dermatitis during the first year of life. Fergusson and collaborators proved in a group of 1,210 children with a follow of ten years that weaning before six months of age is more frequently related to atopic dermatitis.46 Wilson and his group observed in a group of 674 children with a follow up of one year that wheeze incidence are of greater incidence in children weaned before 15 weeks of age.47 Some authors indicate variations as to when begin weaning: some indicate that after four months, others after six, which has demonstrated a similar reduction to cow milk and other food allergy by the first 18 months of life.

UNDERWEIGHT AT BIRTH:

Diverse studies have pointed out that underweight at birth is a high risk factor in developing allergies, but there are no studies that relate this to food allergy in particular.48

Exposure to intra and extra-home allergens

Different tests have been made in order to know the effect of early age exposure to allergens associated to respiratory allergies, intra and extra-home49,50 (asthma, rhinitis); however, no data exist that relate them with food allergies.

EXPOSURE TO ENVIRONMENTAL POLLUTANTS:

Exposure to tobacco fumes (main indoor pollutant) has been studied as a risk factor in allergic diseases. There is significant association between parents smoking (specially mother), asthma and wheezes during infancy, 51, 52 but they are in no relation with food allergies.

EXPOSURE TO INTRA AND EXTRA-HOME ALLERGENS:

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OTHER ALLERGY-RELATED CONDITIONS:

Other conditions which may respond to avoidance of allergenic foods include fatigue, enuresis, frequent urination, epilepsy, bruxism, infantile colic, eczema, psoriasis, urticaria, purpura, thrombocytopenia, obesity, chronic bronchitis, rhinitis, and IgA nephropathy. These conditions have been discussed elsewhere.1, 2, 65

DIAGNOSTIC TESTS FOR ALLERGY:

Food allergies usually can be identified by means of an elimination diet, followed by individual food challenges.5,66 Although double-blind, placebo-controlled challenges are preferable, they may not be feasible in the typical outpatient setting. Fortunately, open challenges are usually reliable. Several blood tests are available which measure antibodies to individual food extracts. Measuring IgE-antibody levels may be helpful for identifying classical allergic reactions

such as those that result in acute asthma or urticaria). IgE levels do not appear to be reliable indicators of hidden food allergy. Tests which measure food-specific IgG4 antibodies are also commercially available. However, while there is evidence that antibodies within the IgG4 fraction act as symptom-provoking antibodies, the IgG4 fraction also appears to contain blocking antibodies, which might prevent allergic reactions.67 Consequently, the theoretical basis for measuring IgG4 antibodies is open to question. At the present time there are no adequate data addressing the incidence of false positives and false negatives with these tests.

Another test, known as ALCAT, measures platelet aggregation and changes in white blood cells after mixing whole blood with various food extracts. ALCAT has been shown to be fairly reliable for identifying reactions to food additives.68 However, in tests for allergyto foods, 18 (24.3%) of 74 positive results were found to be false positives and 21 (30.9%) of 68 negative results were false negatives.69Provocative testing is used by some practitioners to diagnose food allergies.2 This procedure involves intradermal or sublingual administration of various dilutions of food extracts. A similar procedure is used to "neutralize" or desensitize allergies. Although the efficacy of food extract injection therapy has been demonstrated in a double-blind study,70 others have failed to find a beneficial effect,71 and provocative testing and neutralization remain
controversial techniques.

INGRIDENCE FOR REDUCING ALLERGIC REACTIONS:

1. DNA vaccines

Because they are not proteins and can't translate into proteins to become allergens in allergic persons, DNA vaccines can be used to reduce allergic reactions. DNA vaccines can be developed by one of three approaches: (i) using the naked DNA of allergens (ii) using hypoallergenic derivatives of allergen DNAs by modification of nucleotides; or (iii) fragmenting allergen DNA and fusing with ubiquitin, as fragmenting the antigen destroys its native structure61.

2. Anti-IgE antibodies

Binding of IgE antibodies to specific high affinity receptors on basophils and mast cells triggers the release of histamine and other mediators that result in allergy symptoms. Thus developing anti-IgE antibodies against IgE could be a potential therapeutic option for allergy treatment62.

3. Modification of the epitopes

Modification of IgE binding sites, i.e. epitopes of allergens, could be another approach to attenuate hypersensitivity reactions. Epitopes of allergens can be created by modifying allergens and their hypoallergic derivatives. Singh and Bhalla63 have demonstrated that the anaphylactic potential of rye grass pollen can be reduced by introducing a few point mutations in their allergens before using them for immunotherapy. In the shrimp allergen tropomycin, eight IgE epitopes were identified and mutated. These mutations had no effect on their secondary structure (in other words, did not change the basic structure of the IgE) but the allergic response was reduced by 90-98%, so this mutant could be helpful for therapy64.

4. Target mast cells and basophil cells

Another possible option to reduce IgE related hypersensitivity reaction is to directly kill the mast cells and basophils expressing high affinity receptors for IgE. Human originated apoptosis-inducing proteins can be used, as these will be less toxic or less immunogenic than the proteins produced in a different animal or plant65.

5. Immunotherapy

Immunotherapy (biologic therapy) is indicated for people who are extremely allergic to specific allergens.

Immunotherapy is done by gradually exposing the patient to lower doses of allergens to reduce the sensitization. It relies on the progressive production of the blocking antibody IgG and reduction in excessive production of IgE2.

6. Reducing the allergenicity of food crops

Scientists are trying to develop methods to reduce plant allergenicity. Generally it is believed that environmental stress to plants due to pollution, fertilizers, pesticides, heavy metals, etc., reduces their vitality and makes them produce various defense molecules. 66; these defense molecules could be active allergens67.

ALTERATIONS IN ALLERGENICITY

Cooking and processing of foods can affect their allergenicity: Some foods, especially vegetables and fruits, become less allergenic when cooked. The allergenicity of many other foods is unaffected by heat and they cause the same degree of reaction whether eaten raw or cooked. Milk contains 30 potentially allergenic proteins, some of which are sufficiently changed by heating as to no longer cause an allergic reaction, while others are unaffected even by boiling. Whether a person can tolerate boiled milk or not depends on the specific proteins to which they are sensitized: If a person is allergic to milk proteins that are denatured by heat (heat labile proteins) they will tolerate boiled milk, but not milk that has been insufficiently heated. When a person is sensitized to milk proteins that are unaffected regardless of whether it has been boiled or not boiled.

In addition, the ripeness of vegetables and fruits can affect their degree of allergenicity. During the ripening process the plant produces different components, some of which may be less or more allergenic that the unripe form. Thus it is often not possible to predict whether a fruit or vegetable will be less or more allergenic as it ripens. An interesting example of a change in the —reactivity potential of a plant product is the tomato. In this case it appears that it is the histamine content of the fruit that changes, not the protein. The green tomato rarely causes symptoms in a histamine-intolerant person, whereas the ripe fruit does cause a reaction. Tomatoes release histamine during the process of ripening. Although this is not, strictly speaking, an example of a change in allergenicity, it is a very good illustration of how a food in one stage of maturation causes symptoms, but in a later stage does not.

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FOOD ALLERGY PREVALENCE

Food allergy prevalence is greater during the first few years; it affects nearly 6% of patients under three years of age5 and decreases progressively during the person's first decade. Children with allergic illnesses usually have grater prevalence of food allergy, for instance, 35% of children with moderate to severe atopic dermatitis have food allergy mediated by IgE,6 and between 6% to 8% of asthmatic children have wheezes induced by foods. Based on recent studies, 3.5% to 4% of American population have food allergy, the prevalence in the Mexican population is not known.2

CROSS-REACTIONS BETWEEN FOOD AND ENVIRONMENTAL ALLERGENS:

Cross-reactions are frequently observed between pollens and certain foods, especially fruits and vegetables68, 69. This is the oral allergy syndrome, which typically involves mild reactions as previously mentioned. Examples include cross-reactions between birch pollen and apples, ragweed pollen and melons, and mugwort pollen and celery68-70. Cross-reactions have also been noted between latex allergies, a common problem among health-care workers, and certain foods including bananas, kiwis, avocados, and chestnuts.

CONCLUSION:

Food allergy is an important and frequently overlooked cause of (or triggering factor for) a wide range of chronic physical and mental disorders. Routine use of elimination diets in clinical practice can greatly increase the response rate in many difficult-to-treat medical conditions. Food allergies and other food sensitivities are individualistic adverse reactions to foods. The prevalence of cows' milk allergy among infants under the age of two has been studied and found to be approximately 2% in all three countries in well-conducted clinical studies involving groups of unselected infants followed from birth to the age of two years. Eggs and peanuts are also common allergenic foods for infants, along with soybeans, tree nuts, fish, and wheat. Among adults peanuts are probably the most common allergenic food. Eight foods or food groups are thought to account for more than 90% of all IgE-mediated food allergies on a worldwide basis. DNA vaccines can be used to reduce allergic reactions. Modification of IgE binding sites could be another approach to attenuate hypersensitivity reactions.

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