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Review Article

A review on food allergy: pathogenesis, diagnosis methods and treatment approaches

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ABSTRACT

An exaggerated immune reaction to a food that takes place in a vulnerable host is referred to as a food allergy. The two main types of food-induced allergy diseases are those caused by Immunoglobulin E (IgE) antibodies and those caused by non-IgE-mediated mechanisms. These reactions are frequently brought on by food allergens such as egg, seafood, fruits, milk, soy, peanut, etc. In India, roughly 26.5% of the population has been impacted by food-induced allergy diseases. Age, sex, heredity, and geographic location of the patient, as well as vitamin D deficiency and other allergic reactions, are risk factors that might result in life-threatening food allergies. Skin prick test, oral food challenge, component resolved diagnostic testing are the most widely used diagnostic tests for food allergy. Pharmacotherapy of food induced allergic reactions include epinephrine therapy and use of antihistamine drugs. However, the main stay of treatment is avoidance of responsible food and food desensitization. Some home remedies can also be used in order to control allergic reactions caused by food allergens. All these remedies directly or indirectly improve the health of immune system to prevent food induced allergic reactions. The objective of this study was to throw a light on the pathogenesis, diagnostic methods and possible treatment options for food allergy.

Keywords: Food allergy, IgE, Food allergens, Food avoidance, Epinephrine therapy

INTRODUCTION

Clemens von Pirquet first used the word "Allergy" in 1906 to describe how some people have an extraordinary predisposition for exhibiting reactivity symptoms, also known as "Hypersensitivity reactions."¹ Allergy can be defined as the exaggerated reaction which occurs when a person's immune system reacts adversely to the substances in the environment that are harmless to most of the people.²

An allergy is, to put it simply, an abnormal reaction on exposure to specific foreign substances. When a substance is recognised by an allergic person's body as foreign, the allergic immune system produces a reaction. Antigens are foreign substances, which frequently trigger an immunological response by producing antibodies. In

response to certain typically harmless foreign particles like cat dander, pollen, or foods, the allergic person produces a particular form of antibody called IgE. IgE can detect the antigen once it is formed, which can lead to an allergic reaction. Kimishige and Terico Ishizaka discovered and named IgE in 1967.³

Food allergy refers to an abnormal immunological response to a food that occurs in a susceptible host. These reactions are reproducible each time the food is ingested and they are often not dose dependent.^{4,5}

Food allergy is defined as an adverse immunologic response to a dietary protein. A wide range of physical manifestations, including those affecting the skin, gastrointestinal, respiratory, and cardiovascular systems, are linked to food-related reactions. IgE-mediated, Non-

IgE-mediated, and Mixed Reactions are the key components of food allergy pathogenesis. A thorough history and diagnostic procedures, such as serum-specific immunoglobulin E (IgE) testing, skin prick testing, and, if necessary, oral food challenges are used to make the diagnosis. Once a food allergy has been diagnosed, it is usually necessary to completely eliminate the offending food allergen from the diet. The preferred form of treatment for patients with severe systemic symptoms is intramuscular injection of epinephrine into the lateral thigh. The majority of kids outgrow allergies to milk, eggs, soy, and wheat, although peanut, tree nut, fish, and shellfish sensitivities are more common.⁶

METHODS

In contrast to a conventional systemic review, greater care was taken when searching the literature to discover the most significant articles that meet the specific purpose than the range of the available evidences. Several electronic databases, including PubMed, Google Scholar, Science Direct, and many others, were used to conduct a thorough literature search for published peer-reviewed studies. Documented proof was also gathered using organisational reports and other government records. The inclusion criteria only applied to studies that were both published in English and relevant to the topic of the publication.

PATHOGENESIS OF FOOD ALLERGY

Despite the fact that food allergies can develop in response to any food, milk, egg, peanut, tree nuts, shellfish, fish, wheat, sesame seeds, and soy account for more than 85% of all food allergies. Health Canada has designated these allergens as "priority".⁷ These proteins' allergenic portions, or "epitopes," are typically tiny (10–70 kD), water-soluble glycoproteins that are typically resistant to denaturation by heat or acid. As a result, they can continue to function normally even after processing, storage, cooking, and digestion. Examples of these glycoproteins include caseins in milk, vicillins in peanut, and ovomucoid in egg.

Food-induced allergic disorders are broadly categorized into those mediated by immunoglobulin E (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. During initial "sensitization" to the food, consumption of the allergenic food protein stimulates production of IgE antibodies specific to that food. These antibodies subsequently bind to tissue basophils and mast cells. Following consumption of the causative foods, they bind to the IgE antibodies that are unique to them and cause the production of mediators such histamine, prostaglandins, and leukotrienes, leading to "clinical reactivity" and allergic symptoms.

Non-IgE-mediated (cell-mediated) food allergy is less common and results from the generation of T cells that respond directly to the protein, leading to the release of

mediators that direct certain inflammatory responses (e.g., eosinophilic inflammation) and can cause a variety of subacute and chronic disease states.^{8,9}

Mixed IgE/cell mediated reactions include atopic dermatitis, eosinophilic gastroenteritis and eosinophilic esophagitis. In these disorders, the association with food may not be demonstrated in all patients.¹⁰

COMMON FOOD ALLERGENS

Egg

Due to high protein content, egg white allergy is more common. Reactions like anaphylaxis, swelling, flatulence and vomiting may occur.¹¹

Fish

Allergic response due to fish consumption includes respiratory reactions, anaphylaxis, oral allergy syndrome and sometimes vomiting. Fish allergy sufferers have a 50% likelihood of being cross reactive with another fish species, but some individuals are only allergic to one species, such as; salmon, or cod.^{12,13}

Fruits

Mango, strawberries, banana, avocado, and kiwi are common fruits which may cause mild itching, rash, generalized urticaria, oral allergy syndrome, abdominal pain, vomiting, anaphylaxis in susceptible individuals.¹⁴

Garlic

Very few garlic allergens have been reported, and garlic allergy has been rarely studied.¹⁵ Garlic that has been heated/cooked is less allergenic than raw garlic.¹⁶

Milk

Allergy to cow's milk is the most common food allergy in infants and young children showing signs of skin rash, hives, vomiting, diarrhoea, constipation, stomach pain, flatulence, colitis, nasal congestion, dermatitis, blisters, migraine and anaphylaxis.¹⁷

Peanut

It is common and may cause anaphylaxis, swelling and sometimes vomiting.¹⁸

Soya

It is often less common than both cow's milk allergy and peanut allergy. But due to similar protein structures, soya is a common cross-reactive allergen in people with milk and peanut allergies, particularly in infants.¹⁹

RISK FACTORS FOR FOOD ALLERGY

Like all chronic disease, expression of food allergy is influenced by genetics, environment, and genome-environment interactions, including epigenetic effects.²⁰⁻²³ Numerous risk factors have been identified or proposed to contribute to food allergy or sensitization which include: (1) sex- male sex in children, (2) age - with respect to the type of food allergy developed at certain age, (3) other allergic conditions - including asthma, eczema, hay fever, or another food allergy, (4) race/ethnicity- increased among Asian and black children compared with white children, (5) geography - place of living and common food available as regional diet, (6) genetics - familial associations, HLA, and specific genes, (7) atopic disease manifestations - comorbid atopic dermatitis, (8) the influence of the microbiome (microorganisms in a particular environment), (9) vitamin D insufficiency, (10) dietary fat - reduced consumption of omega-3-polyunsaturated fatty acids, (11) reduced consumption of antioxidants, (12) increased use of antacids - reducing digestion of allergens, (13) obesity - being an inflammatory state

Timing and route of exposure to foods -increased risk for delaying oral ingestion of allergens with environmental exposure in the absence of oral exposure leading to sensitization and allergy.

CLINICAL MANIFESTATIONS OF FOOD ALLERGY

The most common clinical manifestations of food allergies are as following:²⁴ (1) Gastrointestinal symptoms- abdominal cramps, flatulence, blood in the stools, nausea, abdominal distension, colic, pain, vomiting, diarrhoea, constipation, mal-absorption, (2) Skin reactions- atopic dermatitis, contact dermatitis, eczema, skin rashes, itching or flushing, tingling, swelling of the lips, palate, tongue or throat, erythema, urticaria, angioedema, (3) mouth, neck, ears- stomatitis, otitis, pharyngitis, itching of mouth, (4) nervous system- irritability, restlessness, fatigue, migraine, (5) blood count- anemia, eosinophilia, thrombocytopenia, (6) other signs- enuresis, nephrotic syndrome, arthritis, (7) hives or eczema, (8) runny/stuffy nose and sneezing, (9) itchy, watery or red eyes, (10) coughing or wheezing, (11) dizziness, light-headedness, (12) funny taste in mouth, (13) chest pain, (14) loss of consciousness.

DIAGNOSTIC TESTS FOR FOOD ALLERGY

In general, diagnostic tests for food allergy should be performed by an allergist.

Skin prick test

The skin prick test (SPT) is a quick, secure, and accurate approach for determining whether a food allergy may be IgE-mediated. When the offending food is pricked into the skin, the result of a positive SPT is a wheal and flare reaction. The sensitivity of a positive SPT is about 90%,

while its specificity is just about 50%. As a result, a positive SPT alone is not enough to diagnose a food allergy; the patient also needs a positive medical history. SPT has a negative predictive value that is more than 95% accurate. Consequently, a negative SPT typically verifies that IgE-mediated responses are not present.^{25,26}

Component resolved diagnostic testing

A relatively recent technique (blood test) called component resolved diagnostic testing (CRD) can be used to assess the likelihood or severity of allergy reactions to particular foods (e.g., peanut, hazelnuts, egg, etc.). Additionally, CRD can detect specific elements that are cross-reactive to other comparable allergens from various pollen species or meals.²⁷

Oral food challenge

Oral food challenge (OFC) involves gradual feeding of the suspected food with medically supervised assessment for any symptoms. If symptoms appear, feeding is stopped and the patient is given the proper care. Only a healthcare professional, typically an allergist with experience in managing food allergies and anaphylaxis should perform OFCs. Additionally, OFCs must be carried out in a professional office or hospital setting with resuscitation tools.²⁸

Other strategies

Other strategies that can help assist in the diagnosis of food allergy are elimination diets and food/symptom diaries. A number of trials are now underway to determine the most effective strategies for preventing food allergies and a number of diagnostic approaches, e.g. allergenic epitope analysis and basophil activation assays are being evaluated for their ability to provide better tools for accurately identifying patients with symptomatic food allergy. The elimination of diet can be used for both the diagnosis and treatment of food allergy Food/symptom diaries require the patient to keep a chronological record of all foods eaten and any associated adverse symptoms. These records may be helpful for identifying the food implicated in an adverse reaction.²⁹

TREATMENT OF FOOD ALLERGY

People should be advised to read food labels carefully, keeping an eye out for any hidden allergen-containing components like "natural flavour" or "spices" as well as "may contain" warnings.³⁰ They ought to speak with a licenced dietician who may help to stop subsequent reactions. All patients with food allergies should wear identification that indicates their condition, such as a MedicAlert® bracelet or necklace. Depending on the signs and intensity of an allergic response, the following techniques can also be applied.

Food avoidance

Once a food allergy has been identified, a strict diet elimination of the offending food allergen is required. An individual will remain symptom-free while preserving nutritional status with a well-managed, balanced elimination diet. When the elimination diet is used as treatment, the relevant food should only be reintroduced once evidence exists that the food allergy has resolved.¹³

Food desensitization

Patients get regular therapy with the food allergen during desensitisation even though they do not react to it. Patients who have developed tolerance, also known as prolonged unresponsiveness, have ceased receiving therapy yet still do not react to the food allergy. The application of food desensitisation has been studied using oral, epicutaneous, and sublingual methods. Patient desensitisation rates have been reported between 35% and 100% (intention to treat), with substantially lower percentages indicated for persistent unresponsiveness.³¹

Pharmacotherapy

Epinephrine therapy

The preferred course of treatment in the event of accidental exposure is epinephrine intramuscular injection into the lateral thigh. The only epinephrine auto-injector (EAI) currently available in Canada is the EpiPen®, which comes in two strengths (0.15 and 0.30 mg) and is prescribed based on weight. For individuals weighing 30 kg or more, the 0.30 mg dosage should be used, and for minors weighing between 15 and 30 kg, the 0.15 mg dosage should be used. Emergency epinephrine recipients must all be taken to a hospital right away (preferably by ambulance) for evaluation and observation. The management of allergic reactions brought on by unintentional exposure to the food should be outlined in a clear, written action plan. Patients and their carers must get education on avoiding certain foods, identifying and treating allergic and anaphylactic reactions, using EAI's properly, and how to get emergency medical help.³²

Anti-histamines

The effects of the histamine that is often released during an allergic reaction are blocked by antihistamines. Some over-the-counter medications including Benadryl, Claritin, and Triaminic are examples of common antihistamines. Sneezing and itching, nasal swelling, and runny noses can all be treated with stronger prescription drugs like Allegra or Zyrtec. The most frequent negative side effects of antihistamines, whether prescribed or purchased over-the-counter, are drowsiness and lack of coordination. However, if the hives appear suddenly, anaphylaxis may be starting. Only an injection of epinephrine can reverse anaphylaxis; over-the-counter antihistamines are ineffective in this situation.³³

Oral immunotherapy

During oral immunotherapy (OIT), food is given gradually under medical supervision and the dose is increased every two weeks until a predetermined maintenance dose is attained. Daily dosage is carried out at home, with the exception of the biweekly dose escalations. Then, to keep the desensitisation going, a maintenance dose is taken every day. An OFC to the questioned food is used to determine effectiveness.³⁴ Most patients only have minor side effects, such as oropharyngeal pruritus and GI issues, which go away on their own or after taking oral antihistamines. However, during OIT, unpleasant reactions that call for epinephrine can happen. Therefore, an EAI and an emergency action plan must be provided to every patient.³⁵

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) involves applying a patch to the skin that contains the meal. In a study of people with peanut allergies aged 4 to 25 years, 250 g peanut patches were found to be safe and to be associated with a mild response after 52 weeks, with younger children showing the strongest responses.³⁶

HOME REMEDIES FOR FOOD ALLERGY

The home remedies for food allergies include increasing stomach acid, activated charcoal, bioflavonoids, vitamin C, pantothenic acid, flaxseed oil, and bananas. Other remedies include fresh fruit juices, castor oil, vitamin E, acupuncture, yoga, and limes. Behavioral and lifestyle changes also help boost the body's defenses against allergens.

Increase stomach acid

Because there isn't enough stomach acid to adequately break down the food, "foreign" proteins are able to enter the body and trigger an immunological reaction. In order to get rid of food allergies, quantity of acid must be increased in the stomach. To increase and maintain a healthy amount of stomach acid, betaine hydrochloride is an easy-to-find supplement that can be found at many health food stores.³⁷

Activated charcoal

By dissolving the proteins and assisting them in passing undetected through the digestive system, activated charcoal is used to counteract the consequences of allergic responses. To regulate the digestive system, it can be used with water or a juice solution that has been sweetened. For it to be effective, a sufficient amount will be required roughly 60 grams.³⁸

Vitamin C

Vitamin C is often linked to improving the health of the immune system which may get affected by an allergic

reaction. However, it is important to make sure that a person is not allergic to any of the fruits and vegetables, as that can be counterproductive to the entire process.³⁹

Castor oil

Castor oil coats the stomach and lessens the harsh symptoms of a food allergy. It works well to consume a modest amount of castor oil each morning on an empty stomach (a cup of water with 5–10 drops of castor oil).⁴⁰

Vitamin E-rich foods

Vitamin E is well known for being extremely anti-allergenic and for strengthening the body's immune system. Tofu, spinach, almonds, sunflower seeds, avocados, shrimp, rainbow trout, olive oil and broccoli are a few examples of foods that are high in vitamin E.⁴¹

Limes

Lime juice can act as a potent detoxifier in the body when mixed with some honey and added to water. This concoction can remove toxins from the body if taken for a few weeks.⁴²

Acupuncture

Acupuncture is a very effective method for re-establishing the body's natural equilibrium, as well as the metabolic processes and immune responses. The wonderful thing about using acupuncture is that it has no negative side effects and can treat a wide range of other potential medical issues. For the greatest outcomes, it is usually advised to choose a qualified acupuncturist, particularly one who is particularly familiar about food allergies.⁴³

Yoga

Numerous yogasanas have been directly connected to lowering allergy reactions in the body, as well as the sensitivity of particularly sensitive stomachs. At least initially, it is preferable to take help of a qualified yoga instructor rather than trying them on your own.⁴⁴

These home remedies can help with food allergy related problems, but food allergies can be extremely severe, and even fatal. One should speak with an allergist to get all of the information about the condition. Depending on the severity of the allergy, avoiding the food altogether is probably the wisest choice. As always, prevention is better than treatment.⁴²

NOVEL TREATMENT APPROACHES

Omalizumab

According to a recent double-blind, placebo-controlled research, using Omalizumab in conjunction with oral immunotherapy (OIT) to milk could considerably

minimise unpleasant effects caused by OIT compared to placebo, improving the risk: benefit ratio of this technique. Omalizumab works by attaching to circulating IgE, decreasing the expression of the IgE receptor, and inhibiting the release of mediators from mast cells and basophils.⁴⁵

Epicutaneous immunotherapy

This therapy has shown promising results in pre-clinical murine models and in a phase I and II clinical trial.³⁶

CpG-coated nanoparticles

These cytosine phosphate guanosine-coated nanoparticles, which are comparable to those used in grass pollen immunotherapy and contain food protein, modified allergenic proteins, and TLR-conjugated proteins, have showed promise in murine models of food allergy.^{46,47}

Alum absorbed peanut vaccine

Additional allergen immunotherapy approaches under phase I study include a modified, alum-absorbed peanut vaccine for subcutaneous immunotherapy administration and a plasmid DNA vaccine platform in which peanut allergen DNA is combined with sequences for lysosome-associated membrane proteins.^{48,49}

Chinese herbal medicines

A unique combination of the herbs Zhi Fu Zi (Radix Lateralis Aconiti Carmichaeli Praeparata) and Xi Xin (Herba Asari) may also aid in the induction of tolerance, according to recent research by Li. These herbs have been effective in treating peanut allergy and anaphylaxis in mouse models. All of the mice given the placebo experienced severe allergic symptoms, elevated plasma histamine levels, and obvious vascular leakage. In contrast, no indication of anaphylactic reactions was seen in the mice receiving active treatment.^{50,51}

CONCLUSION

Severe dietary changes and environmental variables are the most frequent causes of food allergies in today's fast-paced world. Food allergies are prevalent, and they can lead to acute and chronic illnesses that can seriously impair one's quality of life and even be fatal. For diagnosis and therapy, which typically rely on diagnostic tests like SPT, serum-specific IgE testing, and oral food challenges, consultation with an allergist is crucial. Avoiding the offending food and administering epinephrine as soon as an allergic reaction occurs are the cornerstones of treatment. Using novel methods and murine models, it has been possible to better understand the aetiology of both IgE and non-IgE mediated reactions. It is imperative that we rigorously investigate the fundamental immunology of "tolerance" and immunopathogenic processes of food allergy in humans in order to advance the area. Additionally, it's

important to assess the structural characteristics of food allergens, the impacts of food processing and additives, gut and skin microbiota and their effect on immunological tolerance and hypersensitivity. These developments are opening up possibilities for cutting-edge treatments for food allergies. However, the only available remedy at the moment is avoidance. Despite the significant achievements made in the study of food allergies, there are still many unanswered concerns that are likely to keep researchers busy for at least the next 30 years.

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