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A REVIEW

An update on food allergy and potential treatment

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Abstract : Food allergy, an immune response to foods, is a real-world problem for humans affecting about 6–8% of children and 12% of adults, and their prevalence appears to be increasing. Allergies are caused by several food allergens like milk proteins, cereals, nuts, fish, fruits, and vegetables and cross-allergy is also prevalent which may occur through contact surfaces or emerging allergens through new plant-based food products or novel packaging materials. The reactions in the body due to food allergies show the signs and symptoms in the skin, cardiovascular system, gastrointestinal and respiratory tracts.This article provides an overview of advancement in scientific understanding about theprogression of food allergies, their characteristics and underlying mechanisms, various diagnostic tests and possible treatments.

Key Words : Cow milk, Egg, Food allergy, Immunotherapy, Treatment

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INTRODUCTION

In recent years, food allergies are on the riseand are a major public health problem. An immunological response to dietary proteins is classified as a food allergy (Cianferoni and Spergel, 2009). It affects millions of individuals around the world, andmay affects children age between 1.5 to 3 years as high as 10% (Peters *et al.,* 2017 and Burks *et al.,* 2018). It was reported that only around 20% of all food allergies last until adulthood, whereas the rest go away on their own after the age of three years (Svaina, 2008). De Martinis *et al.* (2020) suggest use of prebiotics and probiotics for the possible prevention and treatment of food allergies. In order to prevent food allergy, the latest guidelines overwrite the previous one putting stress on intake of balanced diet by expecting and feeding mothers and also by the weaning infants to include the various food items known to cause allergy (Sampath *et al.,* 2021). Some well-established food allergies are mainly caused by milk (cow), eggs (hen), wheat, soy, peanuts, tree nuts, fish, and shellfish, however, some new emerging food allergens are of increased concern related to food process contact surfaces or new products developed based on plant-proteins (Cavazza, 2022). Among these food allergies, bovine cow's milk allergy is the most typically experienced by newborns and children (Longo *et al*., 2013; de Silva *et al*., 2014; Ho *et al.,* 2014 and Sichererand Sampson, 2014). Fish/seafood and peanuts/

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tree nuts are the food groups which linked to food allergies in adults. IgE mediated, non IgE mediated and mixed IgE mediated-cell mediated are the characterisation of food allergic reactions (Ortolani and Pastorello, 2006 and Davis, 2009). The most widely recognised food allergy is IgE-mediated allergic reactions, which are characterised by a quick onset of symptoms after intake of the allergen as food. The several factorsare responsible for the food allergy development but mainly genetic allergy predisposition, early "foreign" food protein exposure (time, dose and frequency), allergen uptake and handling lead to allergic reactions (Halken, 1997). Nevertheless, the majority of allergic reactions are mild (Iweala *et al*., 2018). But when allergic reactions include respiratory and/or cardiovascular distress, they can be life-threatening. The best approach for preventing accidental allergic reactions is now stringent and meticulous avoidance of the problematic food item (s). In this review, we focus on detailed insight into the current research advances in the prevalence of food allergies, their characteristics, ways of prevention and potential treatments for food allergy.

Food allergies : Prevalence progression and resolution :

On the basis of food recalls, milk, soybean, tree nuts (especially hazelnut and almond), egg, and peanuts are the five main food ingredients causing severe allergy have been selected by the RASFF (Rapid Alert System for Food and Feed) portal (Pilolli *et al.,* 2020). The European Commission (Commission Notice of 13.7.2017) provides information on substances or products causing allergies or intolerances as listed in Annex II of Regulation (EU) No 1169/2011 provides specifications about how the Annex II of Regulation (EU) No 1169/2011.

Cow's milk allergy:

Cow's milk contains more than 20 protein fractions. The significant allergens belong to casein protein (alpha-s1-, alpha-s2-, beta-, and kappa-casein) and whey proteins (alpha-lactalbumin and beta-lactoglobulin) (Wood *et al.,* 2013). The most widespread food allergy among newborns and young children is the cow's milk allergy, affecting about 2.5 per cent of them during the first two years of life. However, out of them resolution of the allergy occurs in 19, 42, 64, and 79 per cent of children at ages 4, 8, 12, and 16 years, respectively (Table 1). The presence of simultaneous allergic rhinitis, asthma, or moderate to severe atopic dermatitis, as well as the development of the allergy in the first month of birth, are clinical factors linked with chronic cow's milk allergy. The higher the milk specific IgE (sIgE) of the cow, the lesser the probability of the child to grow tolerant over time (Skripak *et al.,* 2007).

Egg allergy :

The term "egg allergy" refers to an immune reaction triggered by egg proteins. Egg allergy (hen's egg) is one of the most prevalent childhood food allergies. Like cow's milk allergy, it is usually outgrown by the time a child reaches adulthood. Egg allergy is a predictor of eventual sensitivity to aeroallergens and the development of asthma later in life. Approximately 1% to 2% of young children are allergic to eggs (Sicherer and Sampson, 2014). Based on IgE blood tests, in a national survey, the total prevalence in the United States was estimated to be 0.2 per cent (Liu *et al.,* 2010). At the ages of 4, 8, 12, and 16, children with egg allergies have been shown to resolve in 4, 26, 48, and 68 per cent of cases, respectively (Savage *et al.,* 2007).

Peanut allergy:

Allergic reactions to peanuts include immune reaction on skin, respiratory tract, and gastrointestinal tract. Acute urticaria, acute vomiting, laryngeal oedema, hypotension, and dysrhythmia are all common symptoms of peanut allergy (Bock *et al.,* 2001). 30 to 40 per cent of individuals have both peanut and tree nut allergies, as examined together (Sicherer *et al.,* 2003). Peanut allergy appears to disappear in about 20% of cases, but it's uncertain whether the same is true for tree nut allergy. Children's allergies to peanuts and tree nuts are considered to be somewhat more than 1.0 per cent. Surprisingly, research show that the reported prevalence of peanut allergy has risen with time, from 0.4 per cent in 1997 to 0.8 per cent in 2002 and 1.4 per cent in 2008. Patients who had outgrown their peanut allergy were more likely to outgrow their tree nut allergy.

Treenut allergy :

Tree nuts are responsible for 18–40% of reported food-induced anaphylaxis deaths (Bock *et al.,* 2001). The word "tree nut" refers to all of the nuts that grow on trees. Almond, brazil nut, cashew nut, hazelnut, macadamia, pecan, pistachio, brazil nut, pine nut and walnut are the tree nuts most likely to cause an IgE-

mediated food allergy reaction. After ingesting relatively small amounts of treenut, IgE-mediated food allergy responses can occur (Weinberger and Sicherer, 2018). About 12 per cent of patients suffering one treenut allergy normally associates with another treenut allergy. Additionally, pollen food syndrome can be caused by treenuts in pollen allergic people, most often by almond and hazelnut in birch-allergic people.

Wheat allergy :

Wheat is becoming a more well-known cause for immune-mediated food allergies, both IgE and non-IgE mediated. Wheat allergy is another frequent childhood food allergy that is typically outgrown by the time adolescence arrives. Wheat allergy, which is distinct from celiac disease (gluten-sensitive enteropathy), has been found to afflict 0.4 to 1% of children in the United States and the United Kingdom, where wheat is widely consumed (Keet *et al.,* 2009).

Seafood allergy:

Food allergies to seafood are comparable to those to other foods. Upto 2.5 per cent of the general population is thought to have had a negative reaction to seafood. In contrast to the opposite distribution reported in other food allergies such as egg and milk, seafood allergy is more common in adults than in children (Ben-Shoshan *et al*., 2010 and Kamdar *et al.,* 2015). Early symptoms usually occur after two hours of exposure; however, late phase reactions have been documented up to eight hours after intake (Lopata *et al*., 1997). Seafoods are one of the most prominent triggers of life-threatening anaphylactic reactions, with respiratory reactions and oral allergy syndrome being recorded more frequently than in other food allergies (Matricardi *et al.,* 2016). In the general population, the prevalence of shellfish allergy is generally higher than that of fish allergy. Anaphylaxis is most commonly caused by prawns and crab in both children and adults.

Characteristics of food allergy:

IgE-mediated allergy responses have been described in around 400 proteins from over 170 foods (Boyce *et al.,* 2010). Radauer *et al.* (2008) attempted to characterise food allergies based on their sequence homology and domain architecture. Shellfish tropomyosins (Lopataand Lehrer, 2009), fish -parvalbumins (Ma *et al.,* 2008) and milk caseins are the most prevalent animal food allergies (Broekaert *et al*., 2008 and Jarvinenand Chatchatee, 2009). Proteins having 62 per cent of their sequence identity with human homologs were shown to be allergenic based on bioinformatics analysis of 119 animal proteins catalogued in the Inform All and Food Allergy Research and Resource Programme (FARRP) databases (Jenkins *et al*., 2007). Storage and pathogenesis-related (PR) proteins are found in the majority of plant food allergies (Breiteneder and Radauer 2004). Glutenins and gliadins are the most common allergenic proteins in cereals, while 2S albumins, 7S vicilins, and 11S legumins are found in dicotyledonous seeds. In a wide variety of plant foods, nonspecific lipid transfer proteins, Bet v 1–related proteins, 1,3-glucanases, chitinases, and thaumatin-like proteins (TLPs) are prevalent PR allergens (Jenkins *et al*., 2005). Recently Marzano (2020) advocates the use of mass spectrophotometry-based proteomoics to detect and understand the presence of food allergens.

Known pollen and insect venom glycans capable of causing IgE-mediated cross-reactivity in plant and invertebrate meals, respectively, are 1,3-fucose and 1,2-xylose (Van Ree, 2002). Except for galactose-1,3-galactose, a carbohydrate allergy found in beef, pig and lamb that can cause delayed anaphylaxis, these oligosaccharides rarely cause clinical symptoms. Tick bites were observed to be the most common way for people to become allergic to this allergy (Commins, 2015). In one report, anaphylaxis to D-mannitol, exist naturally in pomegranate and mushroom and is used as food additive by the food industry,has also been documented using SPT (Hegde and Venkatesh, 2004). In the same study, they did not find allergenicity to D-glucitol, D-galactitol, meso-erythritol and L-mannitol.

Immunological mechanism in allergic reactions:

Allergic disorders are very complex unfavourable reactions of the immune system (IS) to a variety of seemingly harmless substances. The IS must distinguish pathogenic stimuli and elicit a strong immune response in the allergic reaction. Sensitization to a specific antigen is required: naive T and B cells identify specific sections of antigens termed epitopes. First, specific major histocompatibility complex (MHC) class II antigens produced on the surface of antigen-presenting cells detect and present allergens to naive T cells (APC). T cell activation causes T helper type 2 (Th2) cells to differentiate and expand (Calzada 2018). It operates on

B cells, causing them to convert their immunoglobulin (Ig) class to Ig type E (IgE). The allergens bind to high-affinity IgE receptors (FcRI) expressed on mast cells and basophils. The cross-linking of FcRI-bound IgE occurs after repeated contact to the allergen, promoting the release of histamine and other mediators that induce the acute symptoms of allergic illness. When allergen-specific cells are reactivated and enlarged locally, the late phase of an allergic reaction occurs 6–12 hours after allergen exposure. Effector cells (mast cells, basophils, and, in particular, eosinophils) release more inflammatory mediators and cytokines, prolonging the proinflammatory response. The symptoms of allergic disorders are caused by this phase, and continued exposure to the allergen leads to disease chronicity (Soyer *et al*., 2013 and Marzano, 2020).

However, to protect the body from increased stimulatory signals triggered by harmless antigens such as self-antigens and environmental chemicals, IS requires careful control. In genetically susceptible patients, an imbalance in the IS regulatory pathways might develop to autoimmune disorders or allergic diseases, depending on the type of the antigen (Soyer *et al.,* 2013 and Akdis and Akdis, 2014). The peripheral T cell tolerance is involved in IS control. The proliferative response and cytokine release are both eliminated as a result of this control, which is characterised by functional inactivation of the cells in contact with the antigen. Several immunosuppressive T cell subtypes have been studied, and are referred as regulatory T cells (Tregs) (Calzada, 2021). They suppress inflammation by regulating immunosuppressive molecules and inhibit the cells' tissue homing. The molecular characterization of B-cell epitopes have been studied by Carrera *et al*. (2019) using shotgun proteomics along with protein-based bioinformatics and IgE-reactive responses.

Diagnostic tests:

The various diagnostic tests for food allergy are skin prick test (SPT), food-specific serum IgE and oral food challenge (OFCs). The SPT suspectsIgE-mediated food allergy and found to be safe, rapid among other diagnostic tests. When food is applied to the skin,it leads to wheal and fare reaction which signifies the positivity of SPT. A positive SPT has a sensitivity that accounts to 90%; while itsspecificity is only around 50%. This concludes that the positive SPT alone is not sufficient for diagnosisof food allergyfor a patient, one should have a supportive history.Negative SPT has a 95% predictive value, indicating that there are no IgE-mediated responses (Sichererand Sampson, 2010). When SPT testcannot be performed or not available then IgE can be measured in serum for diagnosing food allergy but it is costlier and less sensitive than SPT test.

Component resolved diagnostics (CRD) is a relatively new approach (based on blood test) for determining the risk or severity of allergic reactions to specific meals. CRD can also be used to identify cross-reactive specific components to other related allergens from various pollen types or meals. Although the reliable marker for predicting peanut allergy is Ara h 2, Ara h 8 is also positive in people who have an oral allergy syndrome to peanuts. The diagnostic accuracy of a specific level of blood IgE to Ara h 2 varies from study to study (Tuano and Davis, 2015).

Another test OFC, entails gradually feeding the suspected meal while being monitored by a doctor for any symptoms. If the patient develops symptoms, the feeding is stopped and the patient is treated as needed. In addition, properly equipped office or hospital with resuscitation equipment is required for OFC test. Documentation of informed permission should be provided before to the challenge to prove that the risks and benefits of the procedure were explained to the patient or caregiver and that they were understood. Healthcare practitioners who conduct OFCs should have a plan in place for informing patients based on the challenge's outcome.

Elimination diets and food/symptom diaries are two alternative methods for diagnosing allergies. For a specific period of time (usually 1–2 weeks), the elimination diet comprises complete elimination of suspected foods or groupings of foods while monitoring for a reduction in symptoms and can be used for both diagnosis and treatments of food allergy.Because it is dependent on potential patient and physician bias, as well as varying patient adherence to the diet, it should only be done under the medical supervision.

Another method of food/symptom diaries demand the patient to keep a record of foods consumed in a chronological order as well as any undesirable symptoms that may have occurred.These records can assist identify the food that caused an allergic reaction, but they aren't always diagnostic, especially when symptoms are delayed or rare (Sicherer and Sampson 2010).

Treatments for food allergy:

Oral immunotherapy :

Oral immunotherapy (OIT) combines an allergic food into a carrier and then ingesting it in ever higher dosages. It is a potential approach for the treatment of food allergies. OIT protocols vary with the type of food and vehicle used (Wood, 2016).

Sublingual immunotherapy:

For food allergies, sublingual immunotherapy (SLIT) involves placing glycerinated antigen beneath the tongue on regular basis to establish allergen-specific desensitization. The treatment of allergies to hazelnuts, peaches, apples, milk, and with a particular emphasis on the treatment of peanut allergies have been researched by this method. Antigens given by SLIT are picked up by a myeloid dendritic cell population in the oral mucosa, known as oral Langerhans cells (Scadding and Durham 2009 and Jay and Nadeau 2014). The oral Langerhans cells in response to allergen uptake stimulates T-cell production of tolerogenic cytokines such as IL-10 and TGF-. Th2 cytokines such as IL-4 are downregulated, while FOXP3-positive T regulatory cells are activated. However, it's unclear whether the immune response's long-term regulation is handled directly by regulatory T cells with the generation of cytokines like IL-10, or through a skewing of the immune response to Th1 with an interferon-signature. A humoral immune response is triggered in response to changes in T-cell phenotype, which inhibits an allergen-specific IgE response. In the treatment of grass pollen allergy, SLIT stimulates allergen-specific IgG4 and IgG1 synthesis, which competes with antigen-specific IgE binding (Nouri-Aria KT *et al.,* 2004; Bohle *et al*., 2007 and Suarez-Fueyo *et al.,* 2014).

Epicutaneous immunotherapy (EPIT) :

In this immunotherapy, the food containing patch is applied to the skin. EPIT uses an adhesive dermal patch carrying a tiny (microgrammes) quantity of dietary protein to expose tolerance-promoting immune cells in the skin. Patches are being developed to treat peanut, milk and egg allergies. With sustained use of EPIT, a significant drop in specific IgE was seen along with an increase in specific IgG2a (human IgG4). The application site showed the majority of side effects lead to modest to moderate, and severity changes and frequency decreased over time (Waserman *et al.,* 2018).

Pharmacotherapy :

An epinephrine auto-injector (EpiPen) is the only life-saving option in the scenario of accidental exposure and severe reaction (Burks *et al.,* 2018). In the event of an accidental exposure to a food allergen, epinephrine is injected intramuscularly into the lateral thigh as the preferred treatment (Sicherer and Sampson, 2010 and Sicherer and Sampson, 2006). EpiPen®, which comes in two strengths (0.15 and 0.30 mg) and is prescribed based on weight, is the only epinephrine auto-injector (EAI) available in Canada. For children weighing 30 kg or more, the 0.30-mg dosage should be used, and for children weighing 15 to 30 kg, the 0.15-mg dosage should be used. When most children achieve a body weight of >25 kg, switching them from the 0.15-mg dose to the 0.3-mg dose is suggested by the American Academy of Pediatrics (AAP) (Sicherer and Sampson, 2017).

Drug administration :

Palforzia [Peanut (*Arachis hypogaea*) Allergen Powder-dnfp] was permitted by the US Food and Drug Administration to reduce allergic reactions, including

Table 1: Resolution rates of different allergy

Sr. No.	Food allergy	Symptoms of allergy	Rates of resolution (%) during childhood	Age of resolution	References
1.	Cow milk	Wheezing, vomiting, hives and digestive problems	52-79	19% by 4 yr, 42% by 8 yr, 64% by 12 yr, 79% by 16 yr	Skripak *et al*. (2007)
2.	Egg	Difficulty breathing, shortness of breath, coughing or wheezing	49-68	4% by 4 yr, 12% by 6 yr, 37% by 10 yr, 68% by 16 yr	Savage *et al*. (2007)
3.	Peanut	Skin reactions, such as hives, redness or swelling	22 by age 4	22 by 4 yr	Peters *et al*. (2015)
4.	Treenut	Hives, welts or wheals around mouth	9	Insufficient data	Fleischer *et al.* (2005)
5.	Wheat	Swelling, itching or irritation of the mouth or throat	65	29% by 4 yr, 56% by 8 yr, 65% by 12 yr	Keet *et al*. (2009)

anaphylaxis, caused by accidental exposure to peanuts. Palforzia treatment can be started in children aged 4 to 17 years old who have a proven peanut allergy diagnosis, and it can be continued in children aged 4 and up. Palforzia users must continue to avoid peanuts in their diet.

Conclusion:

Food allergy is a growing public health concern that can have a considerable influence on afflicted individuals' socio-economic level, diet, and overall well-being-each with their own set of foods and natural history. Regardless of these distinctions, food allergy management at any age entails careful avoidance of the food allergen and medication treatment for inadvertent exposures. Novel food allergy therapy techniques may reduce the likelihood of allergic reactions, with the ultimate goal of allowing previously avoided foods to be fully reintroduced into the diet. Improved preventative measures have been developed and the first drug has also been approved by FDA for peanut allergy and in near future many more are expected for other food allergies.

Abbreviations: IgE : Immunoglobin E, TLP: Thaumatin-like Proteins SPT: Skin Prick Test, CRD: Component-resolved Diagnostics, OFC: Oral Food Challenge, OIT: Oral Immunotherapy, SLIT: Sublingual Immunotherapy, EOIT: Epicutaneous immunotherapy, FDA : Food and Drug and Administration

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