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REVIEW PAPER

Food Allergy: An Important Health Hazard

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ABSTRACT

An adverse reaction to a food or food component that involves the immune system is called as food allergy. Food allergies are most often immunoglobulin E (IgE) mediated but may also be non-IgE or cell-mediated. On exposure of a sensitive individual to a particular food, the allergen stimulates lymphocytes to produce the IgE-antibody and attached to the surface of the mast cells in different tissues of the body. However, non-IgE mediated food allergy is observed in the first few years of life and it is an easily treatable clinical entity. Food allergy is of several types but Type I, Type II, Type III and Type IV are of key importance. The most common foods having allergens are peanuts, milk, eggs, tree nuts, fish, soybean, wheat etc and these foods account for about 90% of all allergic reactions in humans. People suffering from food allergy can undergo several problems such as digestive disorders, respiratory and circulatory symptoms, skin reactions and sometimes anaphylactic shock. Food processing such as ultrafiltration in milk, steam cooking of kiwi fruits and peeling of peaches may reduce the food allergens up to a certain extent. Therefore, it is utmost important to create awareness in people towards food allergy and save the precious life.

Keywords: Food allergy, Allergen, Food intolerance, Allergy types, IgE-antibody

Food allergy, an adverse reaction to a food or food component that involves the immune system, affecting a higher percentage of population of world affecting as many as 6% of young children and 3–4% of adults all over world (Sicherer and Sampson, 2009). Food allergy is increasing day-by-day but still the difference between the prevalence of clinically proven food allergy and the public's perception of the problem is misinterpreting with food intolerance or other adverse food reactions to food looks like as food allergy (Young *et al.* 1994). A true food allergy is an abnormal response to specific food protein that is triggered by a specific reaction in the immune system and expressed by certain, often characteristic, symptoms (Sicherer and Sampson, 2006). Food allergies are most common among children up to the age of two with weak immune system and then, the incidence decreases with age (Wang and Sampson, 2007). It is much more common and rising in developed countries (Allen and Koplin, 2012). The most common food allergies are from milk, egg, peanut, soybean, wheat, tree nuts, fish and shellfish. The individual food allergy does vary by culture and population (Cianferoni and Spergel, 2009). This suggests that the factors, such as air pollution or environmental allergen exposure outflank the hygiene hypothesis (Wood and Kraynak, 2007). The genetically modified crops get its foreign gene from bacteria. They can

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produce such a protein, which provoke an adverse reaction (Anonymous, 2007). People having food allergies must identify and prevent them because even mild allergy can cause serious illness and in rare instances even death. However, understanding the food intolerance is as much as important that of food allergy. There are various new and quick methods which have been evolved recently (Rady and Guyer, 2015; Ma*et al.* 2017; Pasquini, 2018).

All these and related aspects have been discussed herein.

FOOD ALLERGIC REACTIONS

The allergens are the proteins in food responsible for allergic reaction (Clark *et al.* 2005; Sicherer, 2000). These proteins are usually resistant to the cooking heat, the acid in the stomach and the intestinal digestive enzymes (Brown *et al.* 2001; Ekramirad *et al.* 2017). As a result, the allergens survive and enter the bloodstream and go to the target organs resulting in allergic reactions (Sampson *et al.* 2006; Rady *et al.* 2020). Food allergy is either IgE mediated or non-IgE mediated. The food allergy is a response of poor immune system and heredity. Types of adverse food reactions are described in Fig. 1.

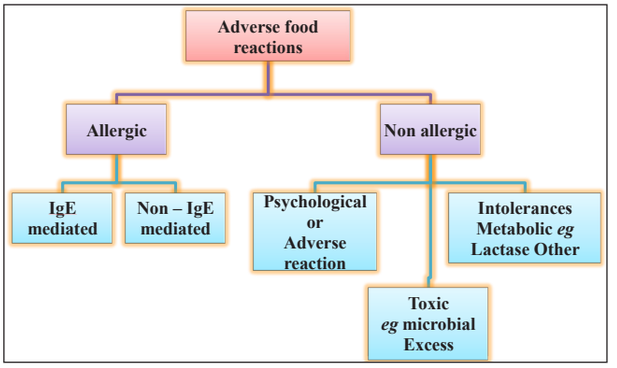

Fig. 1: Types of adverse food reactions

IgE mediated food allergy

Immune system: An allergic reaction to food involves two components of the immune system, immunoglobulin E (IgE) and the mast cells. When IgE antibodies on the surfaces of basophils and mast cells come into contact with food allergens, it result in the release of histamine, prostaglandins and leukotrienes, which cause allergic symptoms (Sicherer and Teuber, 2004; Mari *et al*. 2005).

Heredity: Generally, heredity plays an important role in allergies to people and not necessarily to food but perhaps allergies to pollen, fur, feathers or drugs. Robert *et al*. (2007) predicted that if that no parents is allergic then the chances of food allergy are very less while that if both the parents have the same type of allergy then the chances of food allergy in their offspring are very high.

Mechanism: Food allergy is a hypersensitivity reaction that occurs even before the food is taken. At the initial exposure, the allergen stimulates lymphocytes (specialized white blood cells) to produce the IgE-antibody that is specific for the allergen. This IgE is then, released and get attached to the surface of the mast cells in different tissues of the body. The next time the person eats or even sees that food, it hone in on the specific IgE-antibody on the surface of the mast cells and prompts the cells to release chemicals such as histamine (Taylor and Hefle, 2001, Sicherer and Teuber, 2004) and results in various symptoms of food allergy in human body.

Non-IgE mediated food allergy

Some adverse reactions do not involve the immune system as seen with disorders such as coeliac disease (Troncone *et al.* 2008). These sensitivities may be attributed to the existence of metabolic disorders or the occurrence of reactions with unknown mechanism (Taylor and Hefle, 2001). Both IgE and non-IgE mediated food allergy is frequently seen during this period. Unlike IgE mediated food allergy, non-IgE mediated food allergy is rarely life-threatening; and has critically been reviewed by Jyonouchi (2008).

SYMPTOMS OF FOOD ALLERGY

The food allergy symptoms occur within a few minutes to an hour of eating (Stejskai, 1999; Ebo and Stevens, 2001). Symptoms may be limited or more generalised with involvement of the skin, nose, eyes,

and/or lungs. If allergens reach the skin, induce hives or eczema and when they reach the airways, cause asthma (Sampson, 1999). As allergens travels through the blood vessels, cause light headedness, weakness and anaphylaxis, which result in sudden drop in blood pressure and if not treated quickly, can bring death. The complete clinical symptoms of food allergy are shown in Table 1.

Table 1: Clinical symptoms of food allergy (WHO, 2009)

Site	Symptoms
Skin	Angioedema, urticaria, flushing, warm feeling
Respiratory	Chest tightness, wheezing, cough, tongue, palate, or uvular swelling
Upper airway	Stridor, hoarseness, sneezing
Gastrointestinal	Vomiting, nausea, abdominal pain, diarrhea
Cardiovascular	Tachycardia, hypotension, syncope, arrhythmias
Neurologic	Headache, altered mental status, seizure, dizziness
General	Anxiety, pallor, weakness, feeling of impending doom

In a study of self-reported food allergies, 3–38% answer that they have food allergies, but only 1–11% have their food allergy confirmed clinically (Rona *et al*. 2007). Most of the studies in which food allergy is clinically proven report percentages between 1% and 5% having any food allergy (Zuidmeer *et al*. 2008). Food allergies symptoms related to skin and gastrointestinal generally decreases however, respiratory symptoms increases with age (Saarinen and Kajosaari, 1995).

Table 2. Increase in prevalence over past 20 years (***Source***: Sampson, 2004)

Food	Children	Adults	Outgrown
Milk	2.5%	0.3%	80%
Egg	1.3%	0.2%	60-70%
Peanut	0.8%	0.6%	20%
Tree nut	0.2%	0.5%	No
Fish	0.1%	0.4%	No
Shellfish	0.1%	2.0%	No
Other	6%	3.7%	—

Table 2 shows that the milk, egg and peanut allergy is very common among children and out grown in last 20 years however, tree nut, fish and shellfish is common in adults and there is no increase in these.

TYPES OF FOOD ALLERGIES

Several types of food or metal allergies are there but the major ones include Type I, Type II, Type III and Type IV (Shamberger, 2008).

Type I is common in children, but rare in adults. The IgE-antibodies attach to mucous membranes, which release histamine. Allergic reactions may occur within 1-60 min and affect the skin, airway, and digestive tract, causing classical allergies such as rhinitis, urticaria, angioedema, vomiting, diarrhea and anaphylaxis (Stejskai, 1999). These are more dangerous and can be life-threatening.

Type II food allergy involves lectin allergens, which bind to ABA markers on cells that include red blood cells, mucous membranes, intestinal lining and other cells. It affects IgG-antibodies and killer cells, which will destroy red blood cells, thereby causing anaemia. There are about 70 known food lectins, which could attach specifically to A, B, or O blood types. However, most lectins are destroyed by cooking and digestion and therefore, rarely cause serious problems (Gold and Balding, 1975).

Type III immune reactions are more frequently involved in food allergy than Type I reactions. About 45-60% of the population has been reported as having Type III food allergies. Up to 70-80% of Americans who do not respond well to medical treatment may be suffering from IgG-mediated, delayed-onset food allergies (Power, 1991).

Type IV reactions are involved in many autoimmune and infectious diseases, but may also involve contact dermatitis (e.g. poison ivy). These reactions are mediated by T cells in the skin and soft tissues, monocytes. The best test for Type IV allergy is the ELISA/ACT LRA blood test.

COMMON FOOD ALLERGIES

In children, milk, egg, peanut and tree nut allergies

where as in adults, shellfish, fish, peanut, walnut, and egg are very common food allergies. Most food allergy is acquired in the first 1 to 2 years of life (Robert and Wood, 2003). Cow's milk allergy develops in the 1st year of life, but about 85% become tolerant by the 3rd year, egg allergy develops in the 2nd year of life and half of it become tolerant in 3 years, and up to 66% become tolerant in 5 years. Peanut allergy tends to persist throughout adulthood, although up to 20% of peanut-allergic children lose their allergy (Osterballe *et al*. 2005)

Cow milk allergy

Cow's milk allergy is a common allergy in early childhood, with a prevalence of 2–6% and 90% naturally acquiring tolerance by the age of 5 year (Crittenden and Bennett, 2005). Adulthood incidence remains only 0.1–0.5 per cent. Some patients may be extremely sensitive to milk and even one drop has been reported to cause generalized reactions (Hill *et al*. 1988). It mainly causes hives and asthma but rarely leads to colic, sleeplessness and perhaps blood in the stool or poor growth. Infants are susceptible to allergic syndrome because their immune and digestive systems are immature. It is associated with the development of regulatory $CD4^+CD25^+$ T lymphocytes (Karlsson *et al*. 2004). The main allergens associated with cow milk allergy are Casein, β-lactoglobulin and α-lactalbumin. Lee *et al*. (2010) studied about the specific allergen in cow's milk allergy responses of late eczematous reactions B cell subset in atopic dermatitis. Glucocorticosteroid medicines are prescribed to treat infants with very severe GI reactions to milk formulas (Ascherio and Munger, 2007). Breast feeding to infant is another way to check allergy to milk but some studies indicate that breast feeding has been associated with a reduced incidence of allergy (Gruskay, 1982; Oddy, 1999; Saarinen 2000), whiles other do not support this (Wright, 2001; Sears, 2002).

Wheat allergy

Wheat allergy involves IgE and mast cell response. The allergy is due to proteins of wheat for example serine protease inhibitors, glutelins and prolamins and different responses are often attributed to different proteins (Naoko, 2009). The most severe response is exercise/aspirin induced anaphylaxis attributed to one omega gliadin that is a relative of the protein that causes coeliac disease (Varjonen *et al*. 2000; Akagawa *et al*. 2007). The common symptoms include nausea, urticaria, atopy gastrointestinal manifestations and coeliac disease (Constantin *et al*. 2005; Perr, 2006). In a study, only 1% children were found to have wheat allergy out of 1612 children when they were exposed to cereals after 6 months of age (Poole *et al*. 2006). Patch test is no more reliable diagnosing method for this allergy compared to other methods (Majamaa *et al*. 1999). In most of cases wheat allergy is reduced with age. In a study, 65% children were found to be resistant to wheat allergy by the age of 12 (Keet *et al*. 2009).

Nut allergy

Peanut and tree nut allergies occur in 0.4-1.3% of children and 0.5-1% of adults (Hourihane *et al*. 1998; Hourihane, 2011). Usually, this type of food allergy onset by the age of 5 years and remains for lifelong. But recent studies show that out of this 20-25% may resolve for peanut and around 10% for tree nut (Taylor *et al.* 2010). Allergy to cashew ranks second among the tree nut allergies (Sicherer *et al*. 2003) and has been reported to cause allergic responses in sensitive individuals exceeding those observed for peanut (Venugopal, 2006;Clark *et al*. 2007). The major classes of tree nut allergens include 7S globulins (vicilins), 11S globulins (legumins), and 2S albumins, all of which are classified as food storage proteins (Roux *et al*. 2003; Sathe *et al*. 2005).

Fish allergy

Shellfish allergy persists throughout the life and is often associated with severe reactions, including life-threatening anaphylaxis (Steensma, 2003). Tropomyosin, a heat-stable muscle protein, is the major allergen in shellfish and seafood, with highly homologous proteins being found in the commonly edible crustaceans (WHO, 2001). These homologies

are responsible for the cross-reactive allergies. In addition to being stable to cooking, the allergen leaches from shellfish and seafood into cooking water (Bush and Hefle, 1996).

Green bean allergy

Green bean allergy an IgE mediated allergy, has been reported by various workers (Bernhisel-Broadbent *et al*. 1989; Ibanez *et al*. 2003) but none of these reported the types allergens behind it. Zoccatelli *et al.* (2010) in oral provocation test confirmed green bean allergy is a result of nsLTP and similar structure rLTPs (named LTP1a and LTP1b) and these share 61.3% amino acids. Further, the IgE-binding and histamine release assays provided evidence that rLTPs and nLTPs possess different allergenic potency.

DIAGNOSES OF FOOD ALLERGY

To diagnose food allergy, first step is to see whether presence of hive wheal or any other adverse reaction to a particular food (Lack, 2008). To establish food allergy, a detailed history from the patient, the patient's dietary diary, or an elimination diet *etc*. are required. He or she then, confirms the diagnosis by the more objective skin tests, blood tests, or food challenges (Sampson, 1999). Recently, new methods other than traditional ones are now being used to diagnose food allergy and reviewed by Caubet and Sampson (2012).

History: The history usually is the most important diagnostic tool in diagnosing food allergy. But in many cases infants do not have a family history of food allergy (Sears, 1996; Tariq, 1998). Food allergy is clearly suspected more often than it is found by accurate diagnostic procedures and is confirmed by challenges in less than 20% of the time (Cianferoni and Spergel, 2009). In general, the history can be more helpful in IgE-mediated disorders, because these reactions occur so soon after food ingestion and because multiple target organs are affected. In history certain questions are very common for example; did the reaction come on quickly after eating the food, is the reaction always associated with a certain food and how was the food prepared.

Dietary diary: Relining on a history alone cannot establish a true food allergy. So, keeping a record of the contents of each meal and whether reactions occurred that are consistent with allergy is important. Moreover, the dietary diary provides more details than the oral history to establish a relationship between a food and the allergic reactions (Young *et al*. 1994).

Elimination diet: When multiple food allergens are suspect, an elimination diet is used (Feeney, 1969). It is very important to avoid food allergy for which person is susceptible. If the patient resumes eating the food and the symptoms return, this sequence confirms the diagnosis (Sheldon *et al*. 1967). This technique is however not suitable if the allergic reactions have been infrequent (Young *et al*. 1994).

Skin test: It is also known as scratch-the-skin test. A dilute extract of the suspected food is placed on the skin and then, this portion of the skin is scratched with a needle and observed for swelling or redness. A positive scratch test indicates that the patient has the IgE-antibody. Skin tests are rapid, simple, and relatively safe (Rosen *et al*. 1994). If, food allergens eliciting a wheal at least 3 mm or greater than it indicate positive food allergy while less than 3 mm considered to be negative (Bock *et al*. 1978). In the evaluation of IgE-mediated food allergy, specific tests can help to identify or exclude responsible foods. One method of determining the presence of specific IgE-antibody is prick-puncture skin testing (Sampson and Albergo, 1984; Spergel, 2007). In some highly allergic people, however, especially if they have had anaphylactic reactions, skin tests should not be done because they could provoke another dangerous reaction. Skin tests also cannot be done in patients with extensive eczema.

Blood tests: In those situations where skin tests cannot be done, blood tests such as the RAST, the ELISA and improved ELISA methods are used (Takagi *et al*. 2006). These tests measure the presence of food-specific IgE-antibodies in the blood of patients, but they cost more than skin tests, and the results are not available immediately. As with positive skin

tests, positive blood tests make the diagnosis of a specific food allergy only when the clinical history is compatible (Young *et al*. 1994).

Food challenge: The double-blind food challenge has become the gold standard for objective allergy testing (Bock and Atkins, 1990; Sampson, 2005; Caubet and Sampson, 2012). Various foods, some of which are suspected of allergic reaction, are placed in individual opaque capsules. Both the patient and the doctor are blinded, so that neither of them knows which capsules contain the suspected allergens. The patient swallows a capsule and the doctor then observes whether an allergic reaction occurs. This process is repeated with each capsule. Alternatively, the food to be tested may be disguised in another type of food to which the person is not allergic (Young *et al*. 1994).

TREATMENT

To avoid food allergy now-a-days genetic engineering is gaining popularity for removal of food allergens (Singh and Bhalla, 2008) for example; different workers have gained a success in removal of allergens from tomato. Different therapies available for prevention of food Allergies are summarized in Table 3.

Table 3: Therapies to treat or prevent food allergy (Sicherer and Sampson, 2009)

Standard subcutaneous immunotherapy (native allergens)
• Antigen presentation in non-mucosal site results in Thl skewing
Sublingual/oral immunotherapy
• Antigen presentation to mucosal site provides desensitization and may induce tolerance
Modified protein vaccine
• Avoid activation of IgE by mutation of binding sites but maintain T cell responses
Peptide vaccine (overlapping peptides)
• Avoid activation of IgE by lack of peptides large enough to cross-link IgE but maintain T cell responses
Conjugation of immune stimulatory sequences to allergen
• Enhance Th2 response by activating innate immune receptors, possibly hinder IgE binding
Plasmid DNA encoded vaccines
• Endogenous production of allergen may result in tolerance
Anti-IgE antibodies
• Bind and inactivate IgE while it is not bound to high-affinity IgE receptors
Chinese herbal medicine
• Mechanism unknown, not simply immune suppression, not steroid effect
Cytokine/anti-cytokine
• Interrupt inflammatory signals

Source: *Printer Bring the source here below the every table.*

Dietary avoidance: Avoiding the allergen in the diet is the primary treatment of food allergy. Person sensitive to particular food must be removed from the diet (Pereira *et al*. 2005). But it is not so easy, as peanuts often are used as protein supplements, eggs are found in some salad dressings, and milk is in bakery products. The FDA requires that the ingredients in a food be listed on its label so that they should avoid the food (Altschul *et al*. 2001).

Cross-reactivity: Cross-reactivity is caused by homologous proteins containing IgE-binding epitopes (Ivanciuc, 2009; Bernhisel and Sampson, 1989). If someone has a life-threatening reaction to a certain food, the doctor will counsel that patient to avoid related foods, which also might induce the same reaction. For example, if a person has a history of a severe allergy to shrimp, he or she can also possibly be allergic to crab, lobster, and crayfish another example, allergy to fenugreek evolves mainly from primary peanut allergy (Fæste *et al*. 2010).

Exercise-induced food allergy: Exercise can induce an allergic reaction to food. The usual scenario is that of a person eating a specific food and then, exercising. Body temperature increases with exercise and a results in allergic reactions of hives, asthma, abdominal symptoms, and even anaphylaxis and is most common in females 15–35 years of age (Horan and Sheffer, 1991). So it is better to avoid eating for at least 2 h before exercising.

Use of medicines: Several medicines are available in the market for initial immediate treatment of food allergy antihistamines can relieve gastrointestinal symptoms, hives, sneezing, and a runny nose. Bronchodilators can relieve the symptoms of asthma (Wüthrich, 2000). They are not effective however, in preventing an allergic reaction when taken prior to eating the food (Varjonen *et al*. 1997).

New therapies for the treatment of food allergy: Various new therapies are also available to prevent the food allergy and to treat the food allergy (Sicherer and Sampson, 2009). A complete list of these along with their benefits and limitation are given in Table 3.

Effect of processing on food allergy: Processing can eliminate allergens from food and make food eatable to allergic patients.

Milk: In case of cow's milk low heat treatment ensures the bacteriological safety but not reduces allergenicity. However, a slight decrease in IgE binding seen between unheated and heat-treated milk at 74°C. But a more pronounced decrease was found at 90°C (Sathe *et al*. 2005).

Fruit: Two important types of proteins are responsible for food allergy in fruit are profilins, reduces after cooking whereas, Lipid transfer proteins are more stable to heat. To eliminate kiwi fruit allergy steam cooking at 100°C for 5 min and homogenization is done commercially (Fiocchi *et al.* 2004). Peach allergens are mainly concentrated in the peel therefore, peeling of a peach reduces the allergenic properties of the fruit juice (Brenna *et al*. 2000). Dry heat is also found effective in minimizing the cherryallergen Pru av 1 (Gruber *et al*. 2004). In another study conducted by Hansen *et al*. (2003) reported that patients having hazelnut birch pollenallergy (Cor a 1.04 and Cor a 2), roasting found to decrease the hazelnut allergenicity.

Fish: The purified tropomyosins had a typical alpha-helical secondary structure and the stability of boiled tropomyosinshas lower than that of raw tropomyosins. Extracts from boiled shrimp produce lower IgE binding than extracts from raw shrimp, which suggest that boiling can be used as a tool in attempting to reduce shrimp allergenicity (Liu *et al.* 2009). Cooking processing may destroy existing epitopes on a protein or may generate new ones (neoallergen formation) as a result of change in protein conformation. (Maleki *et al.* 2000; Lehrer *et al.* 2003; Taylor, 2008).

Food grain: Allergens in food grains can also be degraded easily by processing and germination process. Yamada *et al.* (2005) found that germination and heat processing can result in degradation of some of food allergens (14-16-kDa, 26-kDa type) along with soluble proteins in brown rice.

Ultrafiltration: Ultrafiltration followed with proteases treatment removes the traces of intact proteins and suppresses the allergenicity of infant formulas based milk for children (Lehmann *et al.* 2006).

Fermentation: Effects of fermentation on food allergens is rather scant. Soy sauce is an example of a fermented food product containing both wheat and soy. It has recently been demonstrated that soy allergenicity is retained in the finished product (Hefle *et al.* 2005). However, the retained immunoreactivity as assessed by inhibition assays of β-lactoglobulin was significantly impaired in some fermented acidified milk products such as yogurt as compared to that in non-fermented milk (Ehn *et al.* 2004).

7. Probiotics: Probiotic bacteria may promote endogenous barrier mechanisms in patients with atopic dermatitis and food allergy and by alleviating intestinal inflammation, may act as a useful tool in the treatment of food allergy (Majamaa and Isolauri, 1997). *Lactobacillus casei strain* Shirota found to be very effective against IgE and IgG1 mediated food allergy (Shida *et al.* 2002).

SUMMARY

An allergy is a specific reaction to an allergen characterized by a specific IgE response. Common allergies include allergic rhinitis or hay fever, asthma, eczema or atopic dermatitis as discussed above. Allergies affect more than 20 per cent of people and the prevalence of allergic diseases may be increasing. In India, it has become an alarming situation in metro cities more particularly among the

children and infants, because of modern life style that results in weak immune system. So, it is important to create awareness between true food allergy and food intolerance.

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