

Allergy: Effects on Health and Quality of Life

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ABSTRACT: Food allergy has been extensively studied with the advancement of technology and research strategy which gives more insight to the etiology of the condition. The comparative study of various diagnostic and therapeutic methods are crucial to develop a comprehensive management plan for allergic reaction triggered by the accidental food consumption. The diagnosis is based on cumulative results from SPT, IgE titration and oral food challenge. Food-induced allergic reaction and immunotherapy provides an alternative to the use of symptoms-relieving anti-histamine injector. Long term study is needed to evaluate the efficacy of OIT since it is yet to be concluded that the therapy induces permanent tolerance or simply short-term desensitization to the food. Phase II clinical trial should be carried out for the complementary medicine approach. Latest discovery of using interferon-gamma for tolerance induction was enlighten, but its mechanism and other strategy to prolong the tolerance effect remained to be elucidated. Multi-parameter study should be included in future therapeutic study, which may include genetic analysis, histological examination, proteomics and bioinformatics, to assess the pathophysiology and the changes at the molecular, cellular and histological level in order to better equip us towards diagnosis and management of the condition.

KEYWORDS: Allergy, food, health, disorders

I. INTRODUCTION

Food allergy is a clinical condition that results from an exaggerated immunological response of a vulnerable host to the food ingested, with either immediate or delayed manifestation that is reproducible with every exposure, regardless of the dose. The mechanism could be mediated by either immunoglobulin (Ig) E, T cell or a combination of both, and this differentiates food allergy from food intolerance, which is another classification under adverse reaction to food. Rashes, hives and itching can often be tolerated, but when symptoms progress to severe reaction such as breathing difficulty, anaphylaxis and coma, it could be fatal. Health and quality of life can be greatly affected in patient with food allergy, since allergic response can be manifested in the form of skin, respiratory and gastrointestinal (GI) disorders. (Figure 1 & Table 2).

The objective of review is to focus on the current innovation and updates in the epidemiology, contributory factors, pathogenesis, diagnosis and therapy related to food allergy. It is always recommended to identify food allergy at early age which will help to avoid health complications by avoiding that specific food type. Food allergies may cause adverse reaction to health which can be subdivided into two groups, Food intolerance (Non-immunologically mediated reaction) and food allergy (Immunologically mediated reactions). These two groups were further categorized into subgroups as showed in figure 1.

Figure 1: Classification of adverse reaction to food. Food intolerance may be caused because of metabolic, pharmacologic, toxic or other undefined reasons whereas allergy may be caused because of immunoglobulin E mediated, non-immunologically mediated or mixed reasons which will lead to severe conditions.

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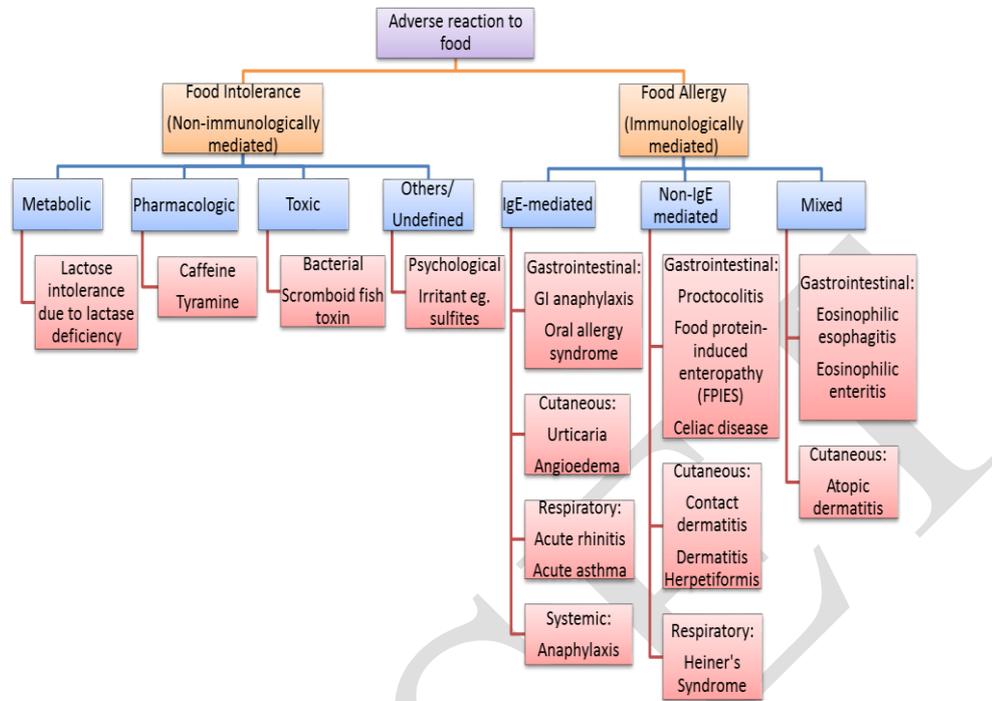


Table 1: Food allergy-related health disorders

Mechanism involved	Food allergy-related health disorders	Description
Systemic	Anaphylaxis	Systemic release of inflammatory mediators. Rapid in onset, potentially fatal.
IgE-mediated	Oral allergy syndrome	Allergy to raw fruits or vegetables, with symptoms localized to the lips, mouth, and throat including itchiness with or without swelling and tingling sensation.
	Acute urticaria	Lesions develop rapidly after ingesting the food as polymorphic, round, or irregular-shaped pruritic wheals, ranging in size from a few millimeters to several centimeters.
	Angioedema	Non-pruritic edematous swelling with well-defined circumference involving subcutaneous tissues such as face, hands, buttocks, genitals, abdominal organs or the upper airway.
Cell-mediated or Non-IgE-mediated	Proctocolitis	Seen in healthy infants but with bloody stool.
	Food protein-induced enterocolitis syndrome (FPIES)	Infants or children with chronic emesis, diarrhea and failure to thrive.
	Contact dermatitis	Reactions to chemical haptens additives to foods or occur naturally in foods. Clinical features include marked pruritus, erythema, papules, vesicles and edema.
Mixed	Eosinophilic esophagitis	Eosinophilic inflammation of esophagus. Children present with feeding disorders, vomiting, reflux symptoms and abdominal pain. Adults experience dysphagia and esophageal food impactions.
	Atopic dermatitis	Also known as atopic eczema, symptoms are urticarial lesions, itching and eczematous flares.

II. EPIDEMIOLOGY

A study has been conducted in 2010 showed the prevalence of food allergy in children of the United States has been raised to 8%, as compared to 4% to 6% reported in previous studies.^{1, 2} Researches found that food allergies are comparatively highest in infants and toddlers, whereas the prevalence decreases with age, as only 4% of adults being food allergic.¹ Increasing trend of the disease could be due to increased public awareness and reporting. Prevalence of allergy according to the food is 2% for peanut, followed by 1.7% for milk and 1.4% for shellfish. Tree nuts, egg, fin fish, strawberries, wheat and soy were also commonly reported.² Prevalence of food allergy are found to be associated with age, race and geographic region, and this relationship is reported in 2008 as illustrated in Figure 2.

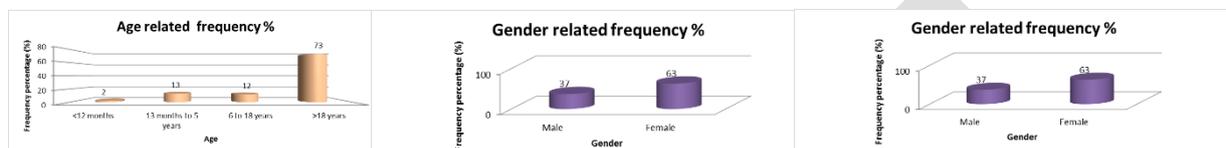


Figure 2: Age (a), gender (b) and race related frequency percentage (c) of emergency departments for food-allergic events in 98 hospitals across US.

Literature showed that there has been an increase in the hospitalization rate in UK, US and Australia due to anaphylaxis.³ Decker *et al.* revealed that food allergy is responsible for about 33.2% or 50,000 cases each year of the potentially life-threatening condition in US.⁴ Statistics from Centre for Disease Control also reported that the mean hospital admittance rate for pediatric food allergy from 2004 to 2006 accounted up to 9,537 a year.⁵

III. CONTRIBUTORY FACTORS TO FOOD ALLERGY

(a) Host factors

Current knowledge about the innate and humoral immune system showed that balance between T helper cell (T_H) 1 and T_H2 is essential for the development of allergic response, and hygiene hypothesis states that the suppression of T_H2-driven allergy reaction is mainly modulated by microbial products found in nature⁶, indicating that early life exposure to environmental microbes helps priming the immune system against infection and allergy. Several studies also demonstrated ‘farm effect’, whereby children exposed to farming environment and consumed raw cow’s milk are protected from asthma and allergies.^{7, 8} Contrary to environmental influences, genetic make-up of individuals is thought to be a less likely cause of food allergy. However, Tsai *et al.* discovered significant association between family history and allergy and sensitization to nine major food allergens.⁹ This reflects that even though genetic factors is not directly contributed to the increasing incidence of food allergy, it is possible that a member in the family will get the condition if close relatives are food allergic. Food proteins when introduced early into diet leads to tolerance induction, as soon as 2 weeks of life for milk and 6 month of age for peanut.¹⁰ Peanut allergy in Jewish children of UK has significant 10-fold higher prevalence than those in Israel, proving that early introduction of peanut in Israeli diet may be protective.¹¹ Such finding is coherent with the hygiene hypothesis model and supports that an immunologically active GI is vital to oral tolerance to food allergens. Healthy gut environment as defined by robust microbiota is also important, where for children delivered through Caesarean section, three out of four studies found an increased IgE-mediated sensitization related to their altered gut environment.¹²

(b) Food Factors

Food protein triggers allergic response when the body recognizes it as foreign particle. The common allergen comes from food protein superfamilies as mentioned in Table 2. Generally, physical characteristics of these proteins are large glycoprotein of hundreds Daltons in size and resistance towards heat, acids and enzymes.⁶ Their strong intramolecular disulfide bonds, repetitive structures, ability to bind ligands, interact with lipid, aggregate and form oligomers also stabilize them in the GI.¹³

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Table 2: Major allergenic food protein families

No.	Food protein superfamily	Example of food source
1	Prolamin -Family members: i. 2S albumins i. Nonspecific lipid transfer proteins i. Cereal amylase and protease inhibitors	Peanut, tree nuts, seeds. Fruits and vegetables. Barley and rice.
2	Cupin -Family members: i. 7S globulin i. 11S globulin	Peanut, tree nuts, legumes, seeds. Peanut, tree nuts, legumes.
3	Profilins	Fruits, vegetables, legumes.
4	Bet v 1	Fruits, vegetables, soy.

Immunoglobulin E is directed towards specific epitopes on allergen, thus the way a food is prepared is significant in determining its allergenicity, since heat application during cooking will destroy the antigenic sites on food protein. Successfully demonstrated in two independent studies, up to 75% of subjects with egg and cow's milk allergy tolerate extensively heated food products.^{14,15} In China, where peanuts are mostly boiled instead of roasted, less prevalence of peanut allergy is found as compared to US¹⁰, where peanut protein is glycosylated during roasting.¹⁶

IV. PATHOGENESIS

The basis behind IgE-mediated food allergic reaction is following the uptake and presentation of allergen by specialized antigen-presenting cell, T lymphocyte is primed and B lymphocyte started to produce allergen-specific IgE. Once IgE binds to high affinity receptor FcεRI expressed on many cells of the immune system, cross-linking of receptors will lead to release of inflammatory mediators, causing allergic symptoms. On the other hand, effector T cell is responsible in triggering non-IgE-mediated food allergy.^{17,18} Major mechanism involved in food allergy is the bypass of oral exposure to food allergen, leading to inappropriate route of antigen presentation. Topical exposure to low dose of peanut allergen contributes to 32% higher rate of peanut sensitization in children who had been using peanut-oil based products such as eczema creams in their first 6 months of life, as compared to the control group.¹⁹ Respiratory route of sensitization initiates pollen-related oral allergy syndrome when the pollen-sensitized individual consumed apple, cherry, hazelnut or peanut, due to homology between proteins found in these foods and the pollen protein Bet v 1, thus resulting in cross-reactivity with the Bet v 1-induced T cell.²⁰

Release of interleukin (IL)-10 and tumor growth factor (TGF)-β upon allergen stimulation helps regulatory T cell (T_{REG}) to suppress immune response.²¹ Food allergy developed when T_{REG} cell fails to suppress T_H2-driven allergic response.²² Latest research focuses on finding new marker to identify subsets of T_{REG} cell for functional study²³, due to the failure of the extensively studied FOXP3 to act as human marker. Liu *et al.* demonstrated that CD127 is another marker that enables efficient isolation of T_{REG}cell²⁴, as well as folate receptor 4.²⁵ Elevated expression of chemotactic factors is also pivotal in pathogenesis of FPIES and eosinophilic esophagitis, where in the latter eosinophils overload is contributed by overexpression of IL-5, eotaxin-3 and thymic stromal lymphopoietin.^{26,27,28}

V. DIAGNOSIS

Skin prick testing (SPT) is the most widely employed diagnostic method for IgE-mediated food allergy. It is advantageous in terms of simplicity, rapidity and cost-effectiveness, with 85% sensitivity and 30 to 60% specificity. Limitation of the method is that it carries high risk of adverse reaction and false-positives²⁹, where in eosinophilic esophagitis patient, coupled immunoblot technique has proved that SPT has low predictive value for food-allergen-specific IgE titre.³⁰ Serum food-specific IgE (sIgE) measurement has higher specificity. Carried out *in vitro*, radioallergosorbent test (RAST) protects patient from suffering severe allergic reactions during testing. However, high IgE titre only indicates sensitization since clinical allergy is not exhibited in some patient while enzyme-linked immunosorbent assay (ELISA) is prone to false negatives.³¹ It is always important to consider clinical history of the patient before interpreting test results from SPT and sIgE testing because recognizing symptoms that arise shortly after food consumption is useful in identifying the cause. Either of the test has superiority over another.³² Latest sIgE testing carried out using microarray technology gives improved result outcome by reducing false-positives with the use of recombinant purified allergens.³³ The component-resolved diagnostic test is advantageous in its utility by allergist in non-hospital set-ups, rapid testing for high-risk patient, less sample amount, accuracy and generation of detailed patient's reactivity profile to multiple allergenic components.³⁴ For non-IgE-mediated food allergy, atopy patch testing (APT) remains the useful diagnostic tool.³⁵ Although it is specific, its low reproducibility renders it less sensitive. Mehl *et.al.* reported that combined test result from APT and SPT or sIgE measurement is recommended to improve sensitivity and specificity.³⁶ Oral food challenge is the gold standard in food allergy diagnosis because it identifies specific food triggers by slowly increasing the dose given to patient. The most rigorous method is double-blinded and placebo controlled, but it is time-consuming, laborious and expensive. Comparatively, single blind and open challenge is more efficient despite giving the same result, especially in diagnosing immediate allergic response, provided patient's bias is low.³⁷ Figure 3 outlines the current scheme in food allergy diagnosis.³⁸

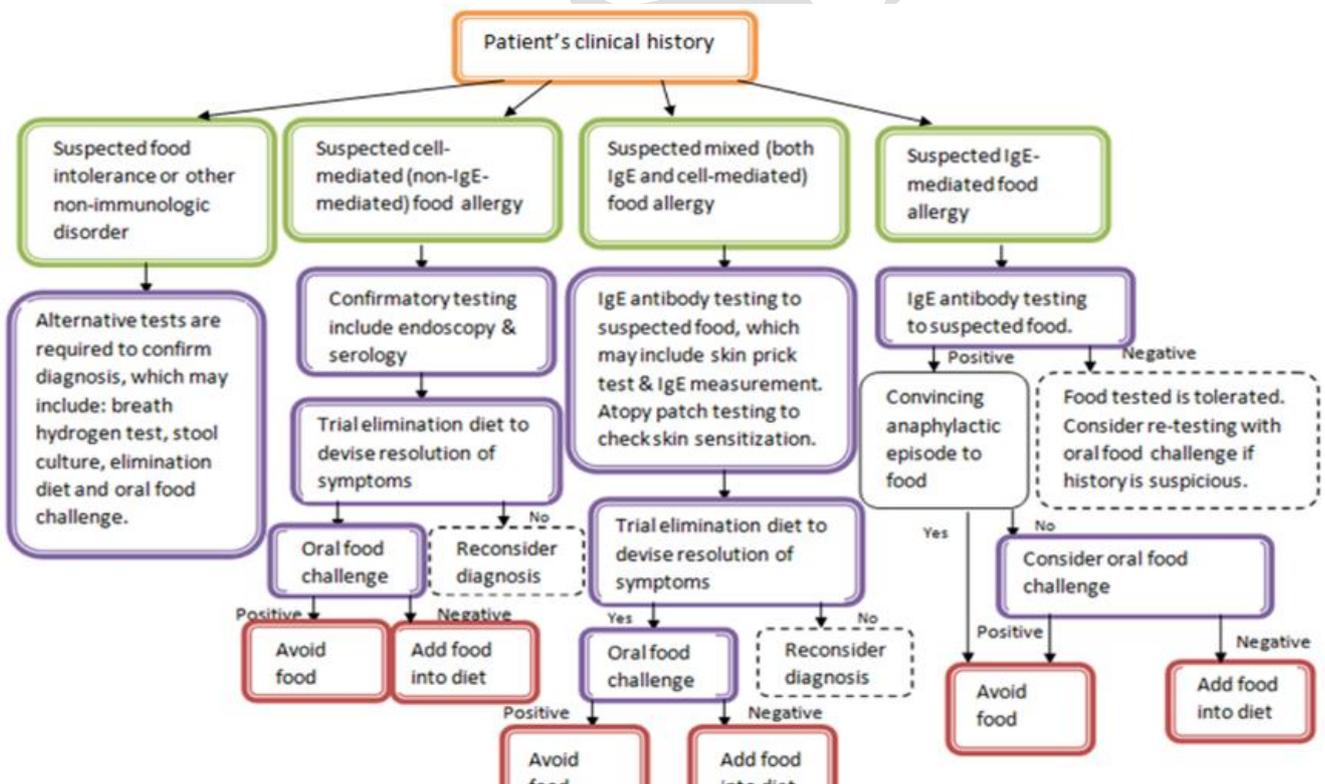


Figure 3: General scheme for diagnosis of food allergy

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VI. THERAPY

Research on discovering novel therapeutic method is highly appreciated since limited patient were benefited from anti-histamine and epinephrine devices.³⁹ Allergen-specific therapy directed against particular causative food using immunotherapy has demonstrated encouraging therapeutic effect with various route of administration. Peanut allergic children given increasing amount of food allergen sublingually subsequently tolerated about 20 times more peanut protein than the placebo group.⁴⁰ Subjects on oral immunotherapy (OIT) ingested 18 times more dose of peanut.⁴¹ Ninety percent of children with milk allergy underwent OIT achieved at least partial tolerance⁴², and Kim *et.al* reported that nearly 50% eventually tolerates unheated milk after baked milk and cheese products are introduced into their diet.⁴³ Epitopes-mutated peanut protein Ara h 1, 2 and 3 can be introduced with heat-killed *Listeria monocytogenes* to lower the risk of possible adverse reaction during immunotherapy by weakening its IgE-binding ability while enhancing T cell-binding.⁴⁴ Non-food-specific treatment utilizes Food Allergy Herbal Formula-2, an aqueous preparation of nine herbs, to significantly reduce IgE receptor expression on mast cell and numbers of inflammatory cells in murine model, which correlates with improved anaphylaxis outcome of the peanut-allergic mice.⁴⁵ The treatment is proven safe in phase I clinical trial. Therapy with probiotics *Lactobacillus rhamnosus* is also feasible as incidence of atopic eczema in children is decreased in half compared to that of placebo group.⁴⁶

VII. CONCLUSION

As a major health concern in modern days, food allergy has been extensively studied and with the advancement of technology and research strategy, we are able to gain more insight to the etiology of the condition. Though food avoidance is the only treatment recommended by physician, which is not full-proof. Thus, the comparative study of various diagnostic and therapeutic methods is crucial to develop a comprehensive management plan for allergic reaction triggered by accidental food consumption. Until recently, the diagnosis is based on cumulative results from SPT, IgE titration and oral food challenge. In the hope of improving food-induced allergic reaction, immunotherapy provides an alternative to the use of symptoms-relieving anti-histamine injector. Long term study is needed to evaluate the efficacy of OIT since it is yet to be concluded that the therapy induces permanent tolerance or simply short-term desensitization to the food. Phase II clinical trial should be carried out for the complementary medicine approach. Latest discovery of using interferon-gamma for tolerance induction are enlightening, but its mechanism and other strategy to prolong the tolerance effect remained to be elucidated. Multi-parameter study should be included in future therapeutic study, which may include genetic analysis, histological examination, proteomics and bioinformatics, to assess the pathophysiology and the changes at the molecular, cellular and histological level in order to better equip us towards diagnosis and management of the condition.

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