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FOOD ALLERGY: mechanisms, diagnosis and management

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Abstract

Food Allergy (FA) is a dynamic field. It is not only evolving but also increasing in prevalence and incidence all over the world. The term 'Food allergy' is often misused, not only by patients, their families but also by health professionals. All Adverse Food reactions are erroneously labeled as 'Food allergy'. This has to be recognized and avoided in order to make a proper evaluation, diagnosis and management.

Keywords: Food allergy, Sensitisation, Skin Prick Test, ImmunoCap, Oral Food Challenge.

INTRODUCTION

Food Allergy (FA) is a dynamic field. It is not only evolving but also increasing in prevalence and incidence all over the world. The term 'Food allergy' is often misused, not only by patients, their families but also by health professionals. All Adverse Food reactions are erroneously labeled as 'Food allergy'. This has to be recognized and avoided in order to make a proper evaluation, diagnosis and management.

Surveys have shown that the prevalence of Food allergy based upon public perception runs as high as 60%, whereas the true prevalence is around is around 2-8%. FA is more common in early childhood days (6-8%) compared to adults (1-2%) [1].

There are several known and unknown reasons for changing picture of Food allergy across the globe. In the developed world, the Peanut sensitivity has doubled in prevalence over the past decade. In the developing world (viz India, China), the prevalence of Peanut sensitivity/allergy is much less, although the consumption of Peanuts is much higher. Lately it has also been observed that early introduction of so called 'allergenic foods' to infants and children early in life seems to actually reduce the incidence of allergies developing later in childhood [2].

Lifestyle factors like activity, animal exposure, microbial exposure, family size, obesity, intake of processed foods, antibiotic usage, environmental tobacco smoke exposure, exposure to sunlight, and psychological factors seem to play a role. Genetic factors along with environment interactions seem to influence the pattern of allergy both for inhalants and foods. In developing countries like India, China, Russia and several other nations, it has been noted that there is an inverse relationship between sensitization and allergy. The exact reasons are still not known and could be nonspecific in nature.

Definitions:

1. Adverse Food reaction: Generic terminology encompassing all untoward reactions to foods

2. Food allergy: Immunologic (IgE) (Milk, Egg, Nuts) or Non Immunologic (Non IgE) mediated reactions (Celiac disease)

3. Food Intolerance: Metabolic (Lactase deficiency)

4. Food aversion: Psychological

5. Food toxicity (Food poisoning): Toxins from bacteria, decaying organisms (Scromboid fish poisoning)

6. Food idiosyncrasy: Unknown mechanisms (Nonspecific Histamine release)

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Due to this confusing usage of terminology, there is significant dichotomy between public perception and true prevalence of Food allergy.

MECHANISMS OF DEVELOPMENT OF FOOD ALLERGY

Majority of children do not develop food allergy. Food allergens are generally weak immunogens. Our gastrointestinal tract by unique mechanisms protects us from developing allergy to multiple food antigens which we ingest daily. Glycocalyx is a sticky lining along the mucosal surface providing the seal between intestinal cells as well as a cementing barrier capable of trapping food particles. This is an efficient barrier system and an essential to maintain the epithelial integrity. Inspite of the efficient barrier system, about 2 percent of ingested food antigens gets absorbed in an immunologically stable form.

Oral tolerance: - Food antigens are generally weak immunogens. The antigen presenting cells in the GI tract are said to be "non professional" and are not capable of eliciting a T cell response. The Treg (T regulatory) cells as well as gut flora also play a role in the propagation of oral tolerance. Exclusive breastfeeding also promotes the development of oral tolerance.

Role of Gut microbiota:-The microbiota inhabiting the normal healthy gut is predominantly gram negative and shed endotoxin, which through a process activates luminal B cell to preferentially produce IgA and IgG antibodies and thus maintain the integrity of mucosal immunity. On the other hand, disturbance of normal healthy microbiota i.e. dysbiosis, will activate luminal B cells to preferentially produce IgE in place of IgA and IgG and increase susceptibility to allergic diseases.

Early use of broad spectrum antibiotics in first year of life and Caesarean section will disturb normal healthy microbiota development in gut resulting in dysbiosis and predilection of allergies.

IgE Mediated Food allergy:

Sensitization to food allergen can occur in two different ways:

The term *allergic sensitization* describes the first induction of an allergic immune response upon allergen encounter. Two routes of allergic sensitization are well established.

Class 1 food allergens (eg, milk, egg, or peanut) are oral allergens that cause sensitization via the gastrointestinal tract.

Class 2 food allergens are aeroallergens (eg, major birch pollen allergen Bet v 1) that cause sensitization via the respiratory tract. Immune responses against these allergens can cross-react with homologous food allergens (eg, major apple allergen Mal d 1) to cause symptoms.

In genetically predisposed individuals, due to the defective epithelial barrier or weak oral tolerance, the food antigens leak through the gut to facilitate sensitization. On reexposure of the food antigens, specific IgE antibodies residing on mast cells and basophils in the gut bind to the ingested food allergen. This leads to the release of several mediators and cytokines responsible for the clinical cascade of an allergic reaction.

Non IgE mediated Food allergy: A number of non IgE mediated food hypersensitivity disorders have also been identified. The exact mechanism involved in such disorders is still a matter of debate in certain situations. Non –IgE mediated food allergy encompasses a wide range of disorders affecting many systems.

A. Gastrointestinal tract:-

Food Protein Induced Enterocolitis Syndrome[FPIES],

Food Protein-Induced Allergic Proctocolitis[FPIAP],

Food Protein-Induced Enteropathy[FPE],

Celiac Disease and

Cow Milk Allergy Induced Anaemia.

B. **Skin**:

Contact Dermatitis to Foods and Dermatitis Herpetiformis

Combined IgE-Mediated and T Cell-Mediated Gastrointestinal Disorders:

Eosinophilic Esophagitis

Diagnostic tests in Food Allergy:

In an immunoglobulin E (IgE) mediated reaction, there are the following components to be considered for diagnosis.

1. Thorough clinical history for possible identification of causative allergens
2. Demonstration of allergen specific IgE by allergen skin prick testing(SPT) or in vitro blood tests (specific IgE immunoassay)
3. To determine whether exposure to the causative allergens will result in symptoms, either by history or challenge, if needed.

1. Investigations in food allergy

Skin tests and *in vitro* specific IgE tests are similar in many ways. They show that the patient harbours IgE antibodies directed against the food allergen, which is the same as saying that he or she is sensitized.

Sensitization must precede the development of an allergic illness but is not sufficient in itself to justify a diagnosis of food allergy. Therefore, specific IgE testing helps to confirm a diagnosis of allergy to a specific food, but is of limited utility if interpreted without or in an inappropriate clinical context.[3]

Skin tests are often preferred to blood testing because skin tests are cheaper (especially when many foods have to be tested), they provide the answer in 20 minutes and they offer a visual cue to the patient. Serum IgE testing is preferred over cutaneous testing when:

a. The patient does not have healthy skin for testing (e.g. severe atopic dermatitis or dermographism);

b. The patient's reaction was anaphylactic and the doctor is not willing to risk even a skin test; and

c. The patient cannot stop using antihistamines.

2. Skin tests in food allergy

Studies on aeroallergens showed that skin tests are generally more sensitive than in vitro specific IgE test[4, 5] though a study on cow's milk and egg allergy in children showed good correlation between the two.[6]

To reduce the likelihood of a false negative result, patients have to stop using antihistamines before skin testing. The length of time of withdrawal depends on the nature of the antihistamine. For example, long-acting antihistamines like loratadine and cetirizine should be avoided for 10 days and short-acting ones like chlorpheniramine and diphenhydramine for 3 days before the test.[7]

Skin test reagents are commercially available for many common food allergens. Another advantage of skin test is its flexibility. The test material is placed on the skin (usually the volar aspect of the forearm or

the back in children) and the skin is pricked through the reagent, just penetrating the dermis, without drawing blood. The skin response is read in 15 to 20 minutes. Positive histamine and negative controls are always included in the test.

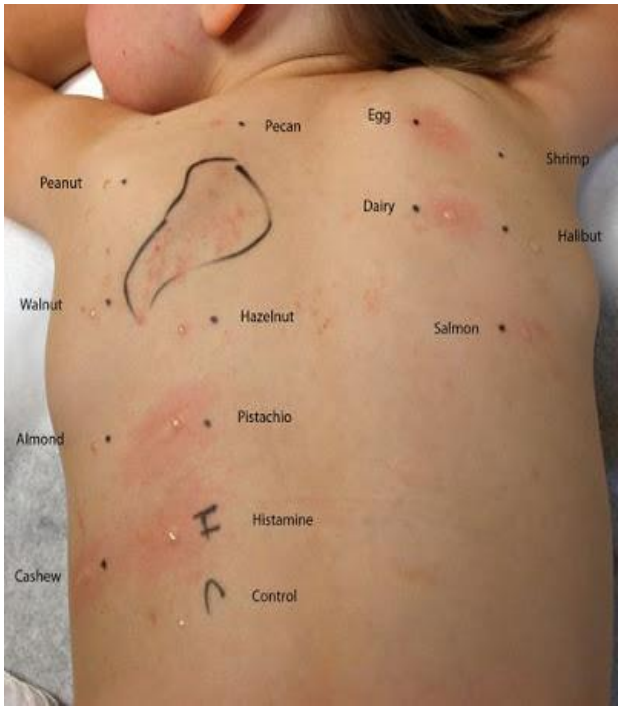

Figure 1: Allergy Prick Skin test for foods with Histamine and Saline controls

3. Measurement of allergen-specific IgE

Quantifying the concentration of allergen-specific IgE in the serum of allergic patients is a standard method of establishing that allergen sensitization has occurred. Radioallergosorbent test (RAST) was the usual way of performing this test, but enzyme methods (for example, fluorescent enzyme immunoassay, FEIA) are more commonly used now. [8]

The classical teaching, albeit not well supported by evidence, is to wait for 4 to 6 weeks to elapse after an IgE-mediated hypersensitivity reaction before assaying the specific IgE concentration because the IgE is consumed during the reaction, and the test may be falsely negative.

4. Interpretation of results

In the skin test, the wheal (swelling) and flare (redness) responses in 15 or 20 minutes are recorded. For the skin test to be interpretable, the positive control must show a strong response and the negative control minimal or no response. A wheal of greater than 3 mm is considered as a positive test. [8]

Skin prick tests for food allergens generally have better negative predictive value than positive predictive value. Overall positive predictive accuracy is < 50 % with negative predictive accuracy > 95 %. In other words, when the skin test is negative, it is reported as 90% chances that the patient is not allergic to that particular food. When the test is positive, the confidence is lower, which is why this result has to be followed by food challenge, in the appropriate clinical context.

The concentration of specific IgE is traditionally reported in terms of classes, even though modern equipment are capable of providing a precise quantitative result. Table 1 shows the seven classes and quantitative IgE levels of one commonly used form of the test.[9]

Table 1: The correlation of the class of the result, the units and the general interpretation

Class	IgE kU/L*	Interpretation
0	<0.35	Negative
1	0.35-0.70	Equivocal
2	0.71-3.5	Positive
3	3.51-17.5	Positive
4	17.6-50.0	Strongly positive
5	50.1-100.0	Strongly positive
6	>100.0	Strongly positive

*Please note that the kU/L is an arbitrary unit of the equipment manufacturer, in this case, Phadia, Uppsala, Sweden.

Though results of class 2 and above are labelled as positive, it is better to know the quantitative IgE concentration as well.

ORAL FOOD CHALLENGES

Oral food challenges are performed by feeding the patient the suspected food under physician observation.

There are several situations in which physician –supervised oral food challenges are required for diagnosis of food allergic disease.

1. In general when several foods are under consideration as a cause of symptoms, tests for specific IgE are positive, the positive predictive value of a positive ST for food is only 50%.Hence it might be necessary to conduct an oral challenge in order to decide regarding reintroduction of food item

2. If tests for specific IgE false positive, challenges may be only way of diagnosis.

3. Oral challenges are also an integral part of following patients likely to lose their clinical reactivity to the food in question. Since skin test may remain positive for years following the achievement of clinical tolerance to a particular food, oral food challenges are often the only means to determine whether the allergy has been 'outgrown'.

Present research in Food Allergy:

As the focus has been shifted to the prevention of infections in keeping the environment more sterile and minimalist interaction between human, animals and microbiota, it has seen the surge of allergic diseases since late 1990s. There has been an increased emergence of food allergies in the last two decades with awareness of common foods causing food allergy. Presently, the research focus is on treatment and any measures which can help in prevention of food allergies.

Even though few studies, initially have shown some promising results of bacterial products in preventing Atopic Dermatitis and augmentation of sustained oral tolerance in food oral immunotherapy [10], not all studies have been promising. Presently, there are no recommendations for use of microbial products in the treatment or prevention of food allergy by the World Allergy organisations.

The earlier recommendations of highly allergenic food avoidance in the West were withdrawn as studies failed to show beneficial effects of the same.

The LEAP study (Learning Early about Peanut Allergy)[11] from United Kingdom, was a very interesting study, which involved high risk babies (with egg allergy, eczema or both) who were randomised to two groups of peanut consumption and peanut avoidance. They reported that in the peanut consumption group, at risk of developing peanut allergy, showed

a marked reduction of odds of 70-80% of peanut allergy. This has led to re-work on guidelines endorsing age appropriate weaning foods and no role of avoidance of highly "allergenic" foods, which are essential for nutrition of a growing child.

A lot of research has been ongoing with promising results, to impart of sustained immune tolerance to allergenic foods by consumption of these foods in desensitisation to foods by Oral Immunotherapy (OIT) or sublingual immunotherapy (SLIT). Tolerance implies that the food can be ingested without the appearance of allergic symptoms despite periods of withdrawal.

There has been promising evidence on adjuvant of Omalizumab with multiple food allergen OIT and has been shown to reduced time (about 67 weeks) taken for developing tolerance to these foods in Phase 1 of these trials, saving them about 67 weeks' worth of time if they had undergone desensitization to individual foods [12].There are some outstanding issues with OIT. Uncontrolled nature of most of the trials, different parameters included in the methods and heterogeneity in protocols is to name a few. But the time may be ripe for the practice of OIT in clinical practice in the coming years.

In conclusion, as we are encountering increased prevalence of food allergy as a part of Allergic March, time has come to build on available knowledge and to set up new studies which can provide us more armor in the near future.

Quick pointers:

1. In the clinical scenario, the emphasis is still on a good clinical history and examination, demonstration of IgE mediated reaction with correlated ingested foods either with skin prick test or in-vitro testing, patient education about avoidance of causative foods and treatment of allergic reactions.

2. The attending medical practitioner must take into account the context in which he or she practices and the patient's condition when choosing between skin testing and in vitro specific IgE testing.

3. Skin prick tests are safe, fast, inexpensive (as compared to serum specific IgE) and easy to perform. It can be safely performed even in the infancy with minimal risk. It is better performed by personnel trained with the technique. It has moderate to good correlation (with sensitivity of 50-60% and specificity of 80-90%) with the serum specific IgE in food allergies. This is reassuring for patients with contraindications/access to either test as the results will likely match. [13]

4. The practitioner should not order a large number of specific IgE tests to screen for allergy when the diagnosis of IgE-mediated food allergy has not been established.

5. The common foods causing food allergies include milk, egg, wheat, fish, peanut among others. Therefore, usually skin prick testing to about 8-10 foods will be able to diagnose majority of food allergies.

6. All the tests will have to be interpreted in the context of clinical history, which should drive the advice on avoidance of particular foods, rather than blanket avoidance of foods. Misconceptions about food allergy exists because of correlation of a positive test result to a particular food (either by skin prick test or serum specific IgE) to having a food allergy. [14]

7. Oral Food challenges (OFC) are the gold standard for the confirmation of a food allergy. In a majority of cases, combination of accurate history and allergy testing (either by skin prick test or serum specific IgE) can accurately diagnose or exclude food allergy. OFC may be needed only when the history or test results or both are inconclusive. [14]

8. Food allergies can cause anaphylaxis, if not recognised and treated, can be life-threatening. Use of intramuscular Epinephrine (0.3mg for adults and children above 30 kg, 0.15 mg for children <30 kg, with repeat dose if needed) should not be delayed in such instances, along with supportive management. Subsequent testing for food allergens must be deferred until 4-6 weeks.

9. Even though there are promising results in the role of probiotics in prevention or augmenting the desensitization or Oral Immunotherapy (OIT) process from few clinical trials, there are yet currently no recommendations for its use in clinical practice by World Allergy associations.

10. In view of results of LEAP study and similar ones, there is more emphasis on introduction of age appropriate weaning foods in the West. It can be attributed to the same fact that food allergy is less prevalent in the Indian scenario as age appropriate weaning foods are traditionally followed in Indian households.

11. There is no role for testing serum total IgE/ absolute eosinophil count in the diagnosis of food allergies as it does not give any useful information regarding the diagnosis, prognosis or management.

12. Children with moderate to severe atopic dermatitis may benefit from investigations to assess for food allergy. The investigations must be interpreted in context and confirmed with food challenges and, if necessary, food avoidance. In most situations, these tests should be carried out by specialists experienced in treating food allergies.

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