

IgE mediated food allergy throughout the life

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ABSTRACT

Food allergy (FA) is an increasing problem throughout the world. In the last two decades, the frequency of FA has increased in both children and adults. The prevalence differs according to the research methodology, age and geographic regions, ranging between 2.0 to 10.0%. The most common form of FA is IgE mediated FA. In this form, patients may present with life-threatening condition as anaphylaxis or milder conditions like urticaria, angioedema, sneezing and nausea alone. The gold standard in the diagnosis of FA is oral provocation tests. Epidermal skin prick tests and specific IgE measurements as well as component resolved diagnostic techniques are helpful in the diagnosis and follow-up of patients. In this review, the epidemiology, diagnosis, follow-up and prognosis of Ig-E mediated FA in children and adults are discussed and some specific forms of FA such as pollen food allergy syndrome, alpha-gal allergy and food dependent exercise induced anaphylaxis are explained.

Keywords: Alpha-gal allergy, anaphylaxis, food allergy, food challenge, IgE, pollen food allergy, skin prick test

Introduction

Food allergy (FA) is defined as “an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” [1]. It should be differentiated from non-immune mediated adverse food reactions including metabolic (eg. lactose intolerance), pharmacologic (eg. caffeine) and toxic (eg. food poisoning) events [2]. Food allergy is classified according to the type of immune response as IgE mediated, non-IgE mediated or mixed. The underlying mechanisms, clinical findings, diagnostic methods, management and prognosis are different for each type [3]. This review focuses on IgE mediated FA.

Pathophysiology of IgE mediated FA is simplified in Figure 1.

Epidemiology in Food Allergy

In children

The prevalence of FA differs between 2%-10% depending on the methods of the studies consist of age, geographical or race differences and the description of allergy whether oral food challenge (OFC) proven or self-report of patients [1]. In the HealthNut study, one –year-old infants were screened for sensitization to common allergens (peanut, raw egg white, sesame) and sensitized infants underwent oral food challenge. More than 10% of one-year-old infants were reported allergic to at least one of the common allergens [4]. The follow-up study evaluated the same participants at the age of 4-years old. This study showed a decrease in the prevalence of challenge proven FA to 3.8% because of high resolution rate of egg allergy [5]. The SchoolNuts study reported the prevalence of clinic-defined and self-reported FA in early adolescence (10- to 14-years old) as 4.5% and 5.5%, respectively. The most common allergen was peanut followed by tree nuts [6]. In the South African Food Allergy study, 12 to 36 months-old toddlers were evaluated for FA

and the prevalence was reported as 2.5%, most prevalent allergens were egg, peanut, cow's milk and fish. Another study from China showed that the prevalence of challenge-proven FA in 0-12 months-old infants was 3.8%; the most common allergen was egg (2.5%) followed by cow's milk (1.3%) [7]. On the other hand, the prevalence of FA was higher when the studies include patients with self-reported FA rather than challenge proven. Gupta et al. reported that 11.4% of the parents considered that their children have FA. As the parent-reported reaction history was not consistent with IgE-mediated FA, they excluded 4% of children. The prevalence of FA in children was estimated as 7.6% in United States and the most common allergens were peanut, milk, shellfish and tree nut [8]. A questionnaire-based study determined that the cumulative prevalence of food allergy was 6.7% in France and cow's milk, egg, kiwi and peanut were the major food allergens [9]. In Turkish children, the foods most commonly cause food allergy were reported as egg (57.8%), cow's milk (55.9%) and hazelnut (21.9%) [10]. Kahveci et al. showed that egg white, cow's milk, tree nuts and sesame were the most prevalent allergenic foods in the East Mediterranean children aged 0-24 months [11]. Kaya et al. showed that OFC proven food allergy prevalence in Turkish adolescents was 0.15% and the most common food allergen was peanut followed by tree nuts [12]. The similar prevalence was reported by Mustafayev et al. but walnut was reported as the most common food for causing allergic reaction [13]. The common allergens vary at the different geographic areas possibly because of culinary differences.

In Adults

As all other types of allergies, the incidence of FA has been increasing both in adults and in children [14]. Allergy to commonly consumed foods in adults may be due to persistence of childhood FA or may be adult onset. The prevalence of IgE mediated FA

in adults depends on the methodology of the studies whether patients have been included depending on self-report or diagnostic workup performed. Most of the FA prevalence studies rely on self-report, ICD coded reactions or demonstration of allergen specific IgE without confirmation of symptoms with specific provocation [15]. Based on those reports, North American population prevalence of FA in adults was reported as 6.6- 10% [15]. However, these prevalence rates would be lower if specific provocation tests were performed. In a meta-analysis, it was shown that there was up to a 15-fold difference between self-reported and challenge proven prevalence of FA, where the discordance was attributed to probable non-IgE mediated mechanisms [16]. In another meta-analysis of the European population, the overall pooled point prevalence of symptoms with positive specific IgE to at least one food was 2.7%, the rate being slightly higher among children than adults [17]. In the population between the ages of 18-60, range of estimates of the frequency of FA in Europe, from studies published between 1 January 2000 and 30 September 2012, by self-report, positive IgE, symptom with positive IgE, and food challenge were 3.5-19.6%, 2-21.9%, 2.2%, 0.1-3.2%, respectively [17]. The lifetime prevalence of FA in this age group was 9.5-35% [17]. Of the 774 patients with seasonal allergic rhinitis in Turkey, the prevalence of food allergy was the most common accompanying allergic disease (14%) [18]. In a large population-based study, among 11810 participants life time prevalence of self-reported FA/ non-allergic food hypersensitivity was reported to be 9.5%, however the rate was 0.1% when double-blind, placebo-controlled food challenge tests were performed [19]. As most studies are based on questionnaire data, and the prevalence of FA may be influenced by many variables like gender, age, nationality, food consumption habits, the true prevalence of FA among adults is currently unknown.

Diagnosis of Food Allergy

The gold standard diagnostic tool for FA is double-blind placebo controlled oral food challenges (DBPCFC). Since, oral food challenge (OFC) has a systemic reaction risk including fatal anaphylaxis, other complementary diagnostic approaches should be performed before the challenge test. Detailed clinical history, skin prick test (SPT), specific IgE (sIgE) level and also component-resolved diagnostic tests (CRD) could help to define the risk of OFC [20]. Intradermal tests, atopy patch tests, allergen specific IgG₄ measurement, kinesiology, hair analysis, electrodermal testing are not recommended for the diagnosis of FA [21-23].

Medical History

Clinical history and physical examination are the first and most important procedures for the diagnosis of FA. Although there are no specific symptoms, atopic dermatitis or clinical findings at the acute phase of the reaction might be a clue for diagnosis [1, 3]. The clinical history should include suspected allergens, form of the food (baked, extensively heated or raw), amount of the consumed food, time interval between ingestion and the reaction, outcomes of the previous exposure to the same allergen before the reaction, recurrence of the IgE-mediated reaction after ingestion of the same culprit food, cofactors during the reaction (eg. exercise, alcohol, infection, non-steroidal anti-inflammatory drugs), treatment and the duration of the symptoms, time of the last reaction [1, 21, 24]. Cutaneous (urticaria, angioedema), respiratory (rhinorrhea, sneezing, stridor, cough, wheezing, dyspnea), gastrointestinal (nausea, vomiting, abdominal pain, diarrhea) or cardiovascular (hypotension, shock) system symptoms within 2 hours after ingestion of the culprit food, recurrent symptoms after further exposure to the culprit food are significant clues for the diagnosis of FA [25]. Accompanying atopic diseases including

atopic dermatitis, allergic rhinitis, asthma and eosinophilic gastrointestinal disease should also be recorded [24]. Clinical history alone is inadequate to establish diagnosis of FA [26]. Diagnostic work up should include SPTs, sIgE and CRD results.

Skin Prick Testing

SPT is a widely used diagnostic tool for IgE mediated allergies because the procedure is easy to perform, reproducible, inexpensive, time effective and highly sensitive. SPT detects allergen sIgE antibodies in vivo [27]. Allergen extracts, negative (usually 0.9% NaCl) and positive controls (histamine, 10mg/ml) are dropped to the volar surface of the forearm or upper back of the patient separately and they are imported into the skin layer via 1 mm lancet or similar device. The wheal size is measured after 10-15 minutes. If the wheal size is 3 mm or more greater than the negative control, the test result for that allergen is considered positive, in other words the patient is sensitized to that allergen [24]. In contrast to low positive predictive value, SPT has a high negative predictive value. Therefore, when the SPT result is negative, the diagnosis of FA is unlikely [26]. H1 antihistamines, long term or high dose systemic corticosteroids, omalizumab should be stopped 4-5 days, 1-3 weeks and 6 weeks, respectively before performing the SPT to avoid false-negative results. In addition to that, topical steroids and calcineurin inhibitors could suppress the immediate skin test response when applied to the SPT area [27]. Although it is not standardized, prick-to-prick test with fresh food can be performed when the allergen extract for the suspected food is unavailable or SPT result with extract is inconsistent with the clinical history [24]. For cow's milk, hen's egg and peanut, 95% positive predictive SPT values of clinical reactivity have been described (Table 1) [28, 29]. In addition, larger wheal size is more likely to be associated with clinical reactivity to the culprit food. However, the wheal size does not indicate the severity of the reaction

[30, 31]. There is no international consensus at 95% positive predictive SPT values for other foods including wheat, tree nuts and fish [32].

Allergen-specific IgE levels

Like SPT, positive sIgE measurement results indicate sensitivity to culprit allergen, and results should be carefully interpreted [24]. Different test methods have been used to measure sIgE level. Each of them has advantages and disadvantages. The common feature of these systems is *in vitro* determination of the allergen sIgE antibody and results are reported in kilounits per liter (kU/L). Follow up of sIgE levels should be made using the same method, as the measurement differences might alter the results' accuracy [27]. Similar to SPT, 95% positive predictive values of sIgE for cow's milk, hen's egg and peanut were reported and a high level of sIgE is a significant predictor of the clinical reactivity. The predictive value of sIgE level is affected the patient's age (Table 1) [28-30].

Role of Component -Resolved Diagnosis

In CRD, allergen specific food antigens and epitopes are detected by qualitative, semi-quantitative or quantitative assays. Therefore, high levels of sIgE due to cross-reactive components of another food antigens could be distinguished from allergenic ones [27]. Cow's milk, hen's egg, peanut and tree nuts have well-defined components that if positive, indicate increased likelihood of reactivity. Patients who have high levels of casein (Bos d8) and ovomucoid (Gal d1) can not tolerate extensively heated (baked) cow's milk and hen's egg, respectively. In addition, increased levels of casein and ovomucoid sIgE indicate the persistence of the FA [33, 34]. Ara h 2 for peanut, Gly m 8 for soybean, Ana o 3 for cashew, Jug r 1 for walnut, Cor a 9 and 14 for hazelnut, Ses I 1 for sesame and Fag e 3 for buckwheat are associated with clinical FA [35-42]. Unlike the

SPT and sIgE results, CRD can predict the severity of the reaction. Ara h 2 and 6 for peanut, Cor a 9 and 14 for hazelnut were reported as a risk factor for severe allergic reactions [43, 44]. Cross-reactive components of foods allergens are described in Table 2. Although CRD is used widely, the diagnostic accuracy, cut-off values and cost-effectiveness for FA are the problems that should be addressed.

Oral Food Challenges

OFC is the only procedure that could establish the diagnosis of FA. Since, DBPCFC which is the gold standard method for the diagnosis is a time-consuming procedure and requires a standard method of food processing, patients frequently undergo open or single-blind food challenges. DBPCFC should be performed to patients who define subjective and psychological symptoms in order to avoid false positive results and unnecessary food restriction [25]. In addition, OFCs for research settings should be performed with double-blinded procedure [45]. OFC with suspicion of IgE mediated allergy must be performed in an office or hospital setting where personnel and equipment are adequate to treat a severe allergic reaction [20]. Similar to SPT, certain medications (H1- and H2- antihistamines, atypical antidepressants/sedatives, benzodiazepines, tricyclic antidepressants) which have suppressant effect on the test results should be stopped before the procedure. The interval between the last dose of the drug and challenge test depends on the half-life of the medication. In addition, the patient should discontinue the medications, including ACE inhibitors, beta-blockers, cromolyn, non-steroidal anti-inflammatory drugs, proton pump inhibitors, short, medium and long-acting bronchodilators, oral bronchodilators, 5 half-lives before the OFC to avoid severe reactions [45]. In Japanese FA guideline, low, medium and full dose food challenge procedures are described. It is proposed that the decision of challenge dose should be

made according to the patient's risk analysis including clinical history, SPT, sIgE and CRD results. Though, high dose challenge should be performed for FA delabelling [46]. In PRACTALL consensus report, at least 2 gr of food protein is suggested as the top dose to prevent false negative results. General challenge schedule consists of half-logarithmic dose increments from 3 mg to 3 g of food protein in order to avoid severe reactions. Dose intervals should be at least 20 minutes. Challenge test should be stopped when the patient has any objective symptoms and proper treatment should be done [20]. If the patient describes subjective symptoms, the challenge may continue until objective symptoms occur or dose interval can be extended or the dose in the previous step can be repeated or the test can be repeated as DBPCFC [47].

Prognosis of Food Allergy in Children

Children who have cow's milk, hen's egg, soy and wheat allergies could tolerate the allergen in the range of rate resolution 52-79%, 49-68%, 69% and 65%, respectively. In contrast to these allergens, peanut, tree nut and fish allergies remain throughout life span in most cases [1]. Sicherer et al. reported that 49.3% of children who have egg allergy could tolerate egg at a median age of 72 months [48]. Savage et al. predicted 68% resolution rate of egg allergy at the age of 16 years [49]. Similar to hen's egg, cow's milk allergy may resolve in 52.6% of the patients at a median age of 63 months, and 79% of patients could be tolerant by the age of 16 years [50, 51]. Keet et al. showed that median age of tolerance to wheat allergy is approximately 78 months-old and the rate of resolution is 65% by 12 years [52]. HealthNuts study demonstrated that peanut allergy resolves in 22% of the patients at the age of 4 years [53]. The rate of resolution of tree nut allergy was reported as 10% in 3-21 years-old patients [54].

Treatment of Food Allergy

241 Up to now, no curative treatment option has been reported for FA [1]. Acute treatment
242 includes the management of allergic reactions and anaphylaxis [55]. Elimination diets,
243 education on allergen labeling, cross-contamination, scheduled clinical follow-up are the
244 main tools of management [56]. Strict avoidance of the culprit food might cause
245 nutritional deficits. Therefore, dietary consultation should be performed especially if the
246 patient has multiple FAs and nutritional support should be considered in order to avoid
247 nutritional deficiency [25].

248 Three decades ago, allergen specific immunotherapy for FA was described. Several
249 studies about the efficacy of the oral, epicutaneous and sublingual immunotherapies for
250 peanut, egg, cow's milk and hazelnut were reported [57-60]. The main aim of
251 immunotherapy is to provide desensitization or sustained unresponsiveness to offending
252 allergen. Desensitization could be accomplished after months of therapy and it provides
253 tolerance to allergen during the treatment phase. After cessation of immunotherapy, most
254 of the desensitized patients could not tolerate the allergen. However, in sustained
255 unresponsiveness, patients could ingest the allergenic food with no clinical reaction for
256 several months after the end of the therapy. This could be achieved only in some patients
257 who receive immunotherapy for years [56].

258 In oral immunotherapy (OIT), an allergen powder is ingested daily with increasing doses
259 (initial dose escalation and dose build up, from micrograms to 300- 4000 mg protein/per
260 day) until the maintenance phase. Initial and built up dose escalation phases should be
261 performed under a physician's supervision. Maintenance doses could be self-ingested at
262 home. This phase may take months or years [61]. OIT has higher desensitization and
263 sustained unresponsiveness ratio than those of other immunotherapy modalities.
264 However, OIT has the risk of serious adverse events including systemic reactions and

development of eosinophilic esophagitis. Gastrointestinal side-effects are reported as the most common dose-limiting adverse reactions [62, 63]. Omalizumab, a monoclonal anti-IgE antibody, can be administered during the escalation phase in order to decrease the severity of IgE-mediated adverse events [64]. More recently, FDA has approved the first drug for peanut oral immunotherapy [65].

In sublingual and epicutaneous immunotherapy, allergen extract drops and patches are applied respectively with lower doses than OIT. Compared to oral immunotherapy, those methods are safer, however the rates of desensitization and sustained unresponsiveness are lower than those of OIT [56].

A practical approach to diagnosis and follow-up of IgE mediated food allergy is presented in Figure 2.

Prevention of Food Allergy in High Risk Children

The Learning Early About Peanut (LEAP) study is the most informative research to understand the prevention approach for FA. High risk infants (4-11 months old) for FA who have severe eczema, egg allergy or both were included in the study. Patients were randomized into two groups as the avoidance group and the consumption group. The infants in the avoidance group avoided peanut until 5 years old, whereas infants in the consumption group started consuming peanut around 6 months of age. At the age of 60 months, the prevalence of peanut allergy was reported to be 13.7% and 1.9% in the avoidance and consumption groups ($p=0.004$), respectively. According to the LEAP study, early introduction of peanut to high risk infants was suggested to prevent peanut allergy [66]. In contrast to LEAP study, the studies which investigate the effects of early egg exposure in infants reported inconsistent results for the prevention of egg allergy [21]. Oniwaza et al. reported that delayed introduction of cow's milk could be associated with

IgE-mediated cow's milk allergy [67]. Urashima et al. demonstrated that avoiding cow's milk formula for at least first 3 days of life could prevent from sensitization to cow's milk [68]. In addition, restriction of allergenic foods during pregnancy or breast-feeding is not recommended to prevent FA [69].

Adult onset Allergy to Common Foods

Cow's milk allergy persists in one's adulthood is uncommon, and most egg allergic children also develop tolerance as they grow older [70]. On the other hand, the majority of peanut allergic adults acquire it in the childhood [70]. Adult onset milk, egg and peanut allergy may be rarely observed.

The underlying mechanism of FA in adults is primary sensitization to a non-food allergen that has antigenic similarity to food, and is a cross-reactive type which results in loss of tolerance to previously consumed foods (class 2 FA) [71]. Although less common, sensitization may occur directly to the food allergen (class 1 FA). IgE mediated FA in adults may present with anaphylaxis, pollen food allergy syndrome (PFAS, oral allergy syndrome), alpha-gal allergy, or food dependent exercise induced anaphylaxis [71].

Seafood allergy is one of the most common types of adult FA. Sensitization occur upon consumption, skin contact or inhalation of aerosolized allergens during cooking or food processing [72]. Tropomyosin and arginine kinase are the allergens responsible for cross-reactivity of shellfish with parasites, mites, and insects. However, component resolved diagnosis will allow the identification of shellfish specific allergens in the near future [72]. Parvalbumin is the major fish allergen that varies among species. Herring, codfish, salmon, and pollock were reported to be the most allergenic and cross-reacting whereas, mackerel, tuna and halibut reported as the less allergenic species [73]. Anisakis is a parasite that may contaminate fish and cause allergic sensitization and misdiagnosis of

fish allergy. Scombroid poisoning is another type of reaction that mimics an allergic reaction and results from ingestion of improperly processed or stored fish which contains high level of histamine. Although the reaction is clinically typical for IgE-mediated type, it is non-IgE mediated and is not reproducible.

Evaluation and Management of Food Allergy in Adults

After consumption of the offending food, the typical symptoms of IgE mediated FA usually develops in 1 to 2 hours. The symptoms range from mild urticaria/angioedema, gastrointestinal symptoms to severe anaphylaxis and even death. The diagnosis of FA in adults should involve a stepwise approach. A detailed history of the reaction, list of all possible allergens ingested at least 6 to 8 hours prior to reaction should be documented. A food that cross-reacts with an inhalant allergen (latex, pollen, house dust mite) may be responsible for the current sensitization. Reaction history upon ingestion of cross-reacting foods with those inhalant allergens should be questioned.

Diagnosis and treatment is similar to childhood cases, however most of the food allergies in adult population persist throughout life.

Pollen Food Allergy Syndrome (PFAS)

Instead of the commonly used term “oral allergy syndrome” (OAS), the term PFAS has better characterized the pathogenesis since its introduction in 1995 [74]. PFAS is defined as the development of allergic symptoms after ingestion of fruits or vegetables in patients with pollen allergy associated rhinoconjunctivitis. Because of wide geographic variability, the true prevalence of the syndrome is difficult to determine. However, as 47-70% of pollen allergic patients have PFAS, the prevalence should range between 9.4-35% in the general population [74].

Plant food allergens belong to 3 protein superfamily classes, namely the prolamin, cupin and pathogenesis related (PR) proteins. Lipid transfer proteins (LTPs) belong to prolamin superfamily that are both heat and digestion resistant (e.g. Mal d 3, Pru p 3) and are found in many vegetables and fruits as pan-allergens [74]. The 2S albumins are also members of prolamin superfamily, however their role in PFAS is limited. There is no described 2S albumin aeroallergen, so any identified 2S albumin allergen (e.g., Ana o 3, Ara h 2) is a food allergen that sensitization occurred through the gastrointestinal tract (class 1 FA) not a cross-reactivity. Similar to 2S albumin, no cross-reacting aeroallergens have been found in cupin superfamily (class 1 FA) and seed storage proteins (7S and 11S) are mostly related to allergy in cupin superfamily of proteins [74]. PR-10 proteins are the most studied of PR family. These proteins often denature with processing or cooking. Profilin family proteins are easily degraded in the stomach therefore systemic symptoms beyond oral symptoms are rare. However, due to the extensive homology amongst themselves, profilin sensitization occurs with multiple pollen associated FA [74]. Table 1 shows the protein components of foods and pollens.

The most common cross-reacting foods to profilins are melon, watermelon, tomato, banana, and citrus. The reactions are usually mild nevertheless more severe reactions have been reported because of co-sensitization to LTPs and profilins [75]. PR-10 protein and Bet v 1 are responsible for symptoms of Birch pollen allergic people upon ingestion of apple, hazelnut, carrot and celery. LTPs are abundant especially in the peels of Rosaceae fruits (pears and apples) and apricots, peaches, cherries and plums. In the case of LTP sensitization, there is an increased risk of more severe reactions, and LTPs may cause food allergy in the absence of pollen allergy [75]. The severity of the reaction depends on the sensitization pattern, whether it is to a stable (LTP) or labile (PR-10, profilin) protein.

Most patients with PFAS initially exhibit oral symptoms like lip and mouth itching and/or angioedema with allergen exposure that will progress to systemic symptoms and even anaphylaxis with further exposure to the offending food. Misclassification of those patients as having simple oral allergy may lead to underdiagnosis and under treatment [76]. Symptoms restricted to the oral cavity and lips are usually self-limited and do not progress with time, however in a small number of patients this reaction may progress to a more serious systemic type [76].

PFAS management includes avoidance of the offending foods and provision of well-cooked or canned foods to patients. If there is uncertainty about the tolerance to known cross-reacting foods, challenge tests should be performed. Decision on the prescription of an adrenaline autoinjector should be carefully made considering the risk of systemic reaction and LTP sensitization. Patients with any form of systemic reaction should be prescribed adrenaline autoinjector for precaution [75].

Alpha-gal Allergy

There are three distinct forms of red meat allergy which are primary, pork-cat syndrome, and alpha-gal syndrome [77]. Primary beef allergy typically presents in childhood, pork-cat syndrome is most common in adolescents, whereas alpha-gal syndrome may present at any age [77].

Galactose- alpha-1,3-galactose (alpha-gal) is a newly identified food allergen. Reactions to this allergen occur in 2 forms; delayed reactions after ingestion of beef, pork or lamb products, and immediate reactions after cetuximab exposure [78].

In 2009, it was shown in a group of patients that after eating mammalian meat, they experienced delayed anaphylaxis or urticaria/angioedema with lack of immediate oral symptoms, and demonstrate IgE antibodies to alpha-gal [79]. There are alpha-gal epitopes

within the saliva of tick and it is certain that sensitization to alpha-gal is related to bites of hard ticks [77].

On the contrary to other types of FA, even with high titers of sIgE to alpha-gal, earliest symptom onset is 150 min (120 to 750 min) on average [77]. This raises the suspicion on the non-IgE mechanism, however all evidence supports that alpha-gal syndrome is an IgE-mediated disease.

A study including 261 meat allergic patients (35 children, 226 adults) admitted to University of Virginia Allergy Clinic reported that serum sIgE to alpha-gal was >0.35 IU/mL in 94%, compared to adults there was male preponderance among children (74% vs 42% males), meat allergy was due to alpha-gal syndrome in 95% of these cases. It was observed that presence of blood group B was protective against development of the syndrome, and the syndrome was not associated with other atopic diseases [80].

Alpha-gal hypersensitivity is not only associated with food-related symptoms but also other exposures including gelatin or porcine/bovine containing bioprosthetic heart valves, medications (e.g., heparin) and vaccines can elucidate symptoms [81]. However, the amount of alpha-gal that is present in certain medications and safety of them in alpha-gal allergic patients is currently unknown [82].

Management of alpha-gal syndrome includes dietary counseling for avoidance and prescription of an adrenalin autoinjector. The titers of sIgE to alpha-gal may decrease over time, and reintroduction of red meat into diet may be possible when proof of tolerance is established over several years [77].

Food Dependent Exercise Induced Anaphylaxis (FDEIA)

Exercise-induced anaphylaxis can occur in 2 forms: anaphylaxis caused exclusively by exercise and that occurs after eating and exercising (FDEIA). If anaphylaxis occurs after

408 ingestion of a certain food that the patient is sensitized, it is named as specific FDEIA and
409 if anaphylaxis occurs with any type of food then it is called non-specific FDEIA [83].
410 The true prevalence is unknown because in most cases the sensitized food cannot be
411 identified and patients are categorized as idiopathic anaphylaxis, or a lack of awareness
412 among physicians.

413 Underlying mechanism of FDEIA is IgE mediated FA that is aggravated by cofactors like
414 exercise, nonsteroid anti-inflammatory drugs, or alcohol. The symptoms, which may
415 begin at any stage of exercise or just after exercise, may be aggravated with another
416 cofactor, and may be unpredictable [83]. The responsible food is usually ingested within
417 4 hours preceding exercise or after exercise [84]. Reaction starts as a sudden feeling of
418 fatigue, flushing, pruritus w/wo urticaria. Maintaining exercise may lead to severe
419 anaphylaxis with hypotension and collapse. On the other hand, if patients stop exercising
420 the symptoms usually resolve [83].

421 Depending on the region and dietary habits, culprit foods may change and almost any
422 food or combination of food allergens can cause FDEIA. Diagnosis is not easy and
423 requires detailed clinical history and high level of suspicion. The suggested criteria for
424 diagnosis are: [84]

- 425 • Diagnosis of anaphylaxis during (within 1 hour) exercise that occurs only if
426 preceded by food ingestion.
- 427 • No other situation that can explain the clinical presentation.

428 In case of presence of a specific food trigger:

- 429 • Demonstration of sIgE to that food either by skin or serum testing
- 430 • Patients usually consume the specific food safely without exercise, or safely
431 exercise without consuming the specific food (in the absence of cofactors).

Skin testing, and/or in vitro sIgE testing and if inconclusive, skin testing with fresh food is performed to show sensitization. A positive food + exercise testing confirms FDEIA diagnosis however a negative test does not always exclude diagnosis [84]. Identification and avoidance of contributing factors and food(s) is vital. Patients should carry adrenaline autoinjectors, stop exercise immediately if any symptoms occur, avoid culprit food 4-6 hours (at least 2 hours) before exercise, do not exercise alone and preferably exercise with an informed individual [84].

Future perspectives

The true prevalence of food allergy especially among adult population is currently unknown, self-reported and proven FA rates significantly differ. Specific IgE measurement has low specificity and may increase overdiagnosis rates, and in most cases food challenge is not performed. Highly cross-reactive carbohydrate epitopes and cross-contamination with other allergens contribute to lower specificity of allergen extracts both for skin prick test and sIgE measurement.

Many proteins can be probed simultaneously and epitope pattern analysis can be done with microarray-based assays using very small amount of patient serum. However, more studies on clinical application of the method should be performed.

Basophil activation test (BAT) with a specific antigen shows the biologic response and specificity of the test is probably higher than sIgE measurement. However, the method is not widely available, fresh serum is needed, and more clinical research investigating role of BAT in FA should be conducted.

Greater microbial diversity in the gut may favor tolerance induction to foods. Mouse studies have shown that therapy with protective clostridial species suppressed FA, and gut microbiota dysbiosis would be a potential future target for therapy [85]. However,

well designed prospective studies on humans is needed to understand if microbial changes or dysbiosis in gut predispose to development of FA, and if so what strategies could be used to induce tolerance. For FA prevention and treatment diet manipulations, pro-pre-synbiotic supplementation, fecal microbiota transfer may be potential future research topics.

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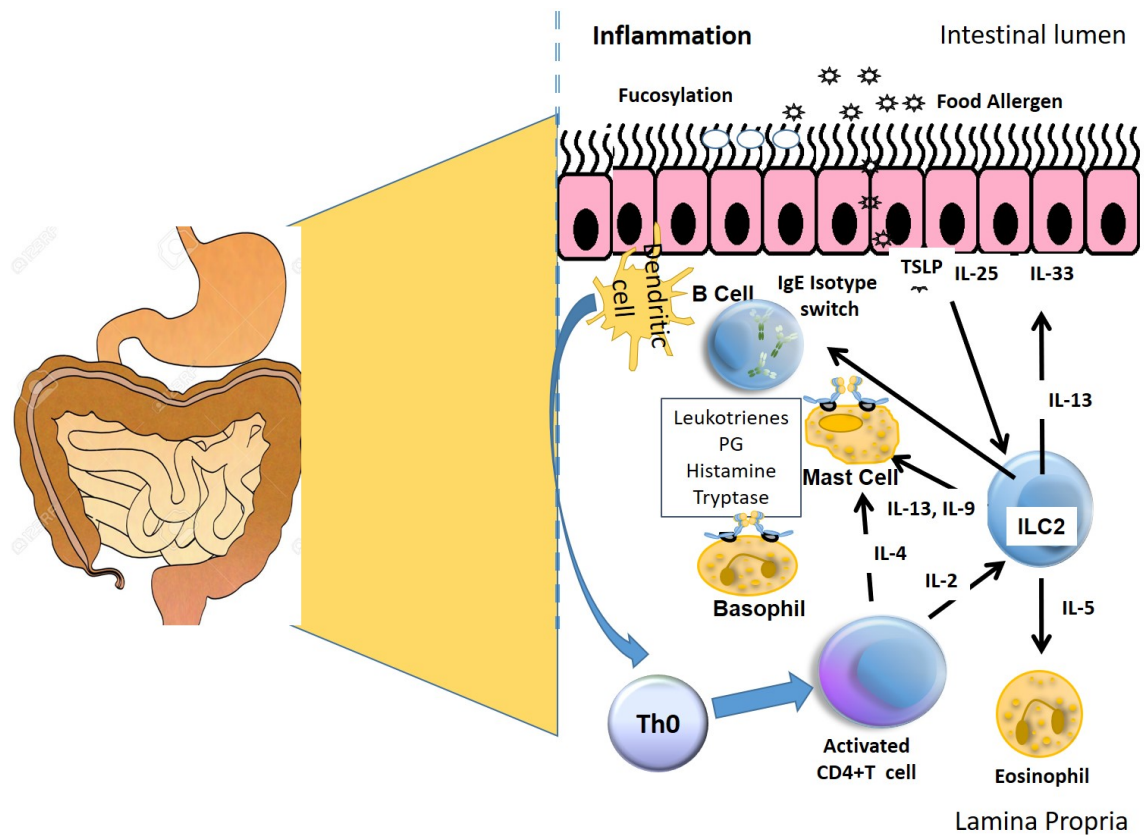
Table 1. For different foods 95% positive predictive SPT and sIgE values of clinical reactivity have been described for children. [22, 23, 24]

Allergen	Age Group	95% PPV	
		sIgE kU/L	Skin Prick Test (mm)
Cow's Milk	All ages	≥ 15	≥ 8
	≤ 1 years	≥ 5	
	≤ 2 years	≥ 11.1	≥ 6
	≤ 4 years	≥ 11.7	
	≤ 6 years	≥ 13.7	
Hen's Egg	All ages	≥ 7	≥ 7
	≤ 2 years	≥ 2	≥ 5
Peanut		≥ 15	≥ 8

Table 2. Major allergen components involved in cross-reactivity between pollen and food allergens

Allergen families	Allergen components involved in cross-reactivity
LTP(heat and digestion stable)	Ar v 3 (mugwort), Pla a 3 (London plane tree), Amb a 6 (short ragweed) Pru p 3(peach), Mal d 3 (apple), Api g 2 (celery), Sin a 3 (yellow mustard)
2S albumins	No aeroallergens Ana o 3 (cashew), Ara h 2 (peanut), Pis v 1 (pistachio), Gly m 8 (soybean)
Cupin	No aeroallergens Pr udu 6 (almond), Cor a 9 (hazelnut), Pis v 2 (pistachio), Ara h 1 (peanut)
PR-10 (denature with cooking/processing)	Bet v1 (birch), Que a 1 (White oak), Aln g 1 (alder), Fag s 1 (beech) Mal d 1 (apple), Pru ar 1 (apricot), Api g 1 (celery), Ara h 8 (peanut)
Profilin (denature with digestion)	Bet v 2 (birch), Art v 4 (mugwort), Amb a 8 (ragweed), Phl p 12 (timothygrass) Mal d 4 (apple), Api g 4 (celery), Pru p 4 (peach), Ara h 5 (peanut)

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793 Figure 1. Simplified pathophysiology of IgE mediated food allergy

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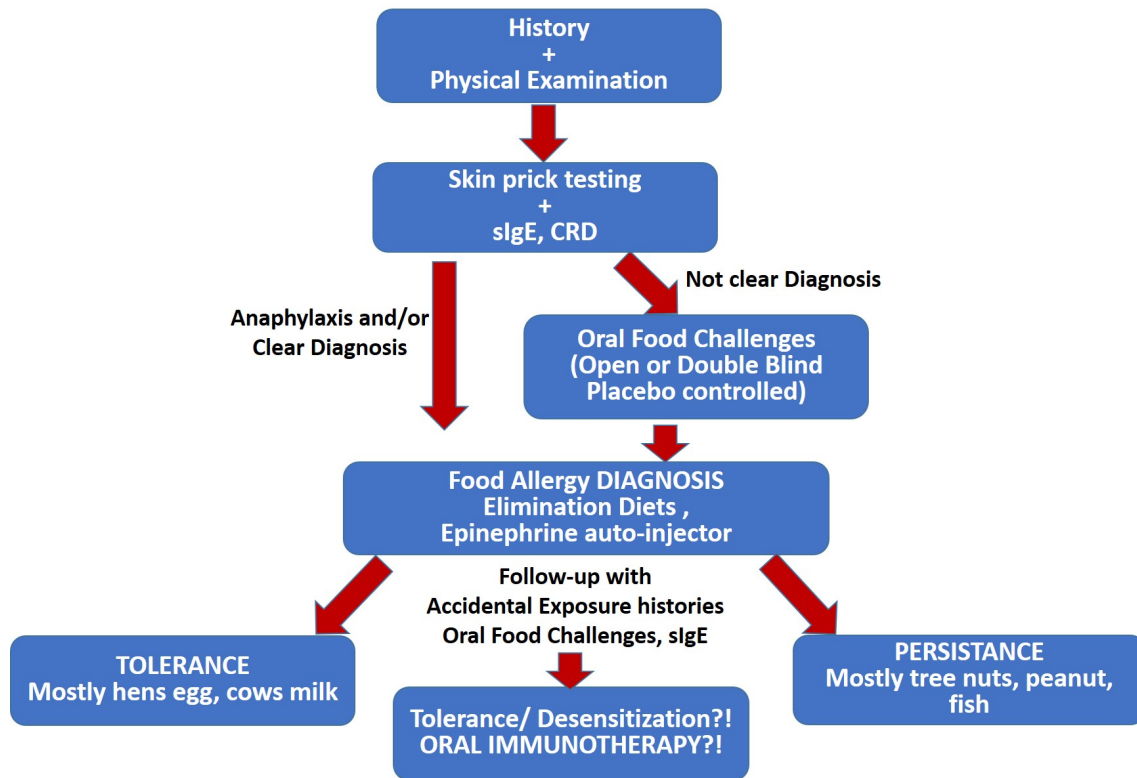


Figure 2. A practical approach to the diagnosis and follow-up of food allergy