OVERVIEW OF FOOD ALLERGY DIAGNOSIS

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Abstract

Food allergy is a condition with significant social and economic impact and a topic of intense concern for scientists and clinicians alike. Worldwide, over 220 million people suffer from some form of food allergy, but the number reported is just the tip of the iceberg. Recent years have brought new perspectives in diagnosing food allergy. Elucidating incriminated immunological mechanisms, along with drawing the clinical phenotype of food hypersensitivity reactions ensures an accurate diagnosis of food allergy. Moreover, molecular based allergy diagnosis, which is increasingly used in routine care, is a stepping-stone to improved management of food allergy patients.

The aim of this review is to summarize the topic of IgE-mediated food allergy from the perspective of current diagnostic methods.

Keywords: food allergy, IgE-mediated hypersensitivity, diagnostic tests

Background

Food allergy is a condition with significant social and economic impact and a topic of intense concern for scientists and clinicians alike. Worldwide, over 220 million people suffer from some form of food allergy, but the number reported is just the tip of the iceberg. In the United States of America, 4 to 6 percent of children and 4 percent of adults suffer from food allergy, accounting for approximately 15 million people, according to the Center for Disease Control and Prevention [1]. According to estimates by the European Academy of Allergology and Clinical Immunology (EAACI), the prevalence of food allergy has doubled in the last ten years, and in Europe the number of people suffering from food allergies currently exceeds 17 million. Furthermore, an increasing number of severe life-threatening reactions in children have been linked to food allergies [2].

The umbrella term of food hypersensitivity reactions encompasses “any adverse reaction to food” [3]. Food allergy refers to the subgroup of reactions triggered by food allergens in which immunologic mechanisms are involved, IgE mediated, non IgE-mediated or mixed IgE and non IgE-mediated [4]. Non-allergic food hypersensitivity reactions, known in the past as “food intolerance”, have different etiologies, clinical presentation and approach from immune mediated reactions to trophallergens and are not the focus of this paper.

Recent years brought new perspectives in diagnosing food allergy. Elucidating incriminated immunological mechanisms, along with drawing the clinical phenotype of food hypersensitivity reactions ensures an accurate diagnosis of food allergy. Moreover, molecular based allergy diagnosis, which is increasingly used in routine care, is a stepping-stone to improved management of food allergy patients.

The aim of this review is to summarize the topic of IgE mediated food allergy from the perspective of current diagnostic methods.

Food allergy diagnosis

Clinical history and examination are the first-line approach in diagnosing food allergy. The evaluation of a patient with suspected food allergy begins with obtaining a thorough clinical history that considers the symptoms indicative of allergic reactions to food. The clinical presentation of food allergy reactions varies within wide ranges and provides information about the incriminated mechanism (Table I).
Potential triggers, the existence of co-factors, reaction type, the evaluation of the temporal relationship between food ingestion and onset of symptoms, as well as clinical reproducibility are key-points when obtaining the medical history.

IgE-mediated food allergy most often presents with immediate symptoms, with onset within two hours after ingesting the culprit food. There are no pathognomonic symptoms for food allergy; however, immediate onset of oropharyngeal or skin signs and symptoms make the diagnosis of food allergy more likely. Age is another factor indicative of an IgE-mediated hypersensitivity to food. Therefore, a systemic reaction occurring in a child upon exposure to a food allergen is highly suggestive of an IgE-mediated disease [5,6].

In order to improve the accuracy of diagnosing an allergic reaction to food, the clinician should consider food that consistently elicits allergic reactions. Eight types of food cause approximately 90% of food allergies: milk, eggs, fish, crustacean shellfish, nuts, peanuts, wheat and soy [7]. Nevertheless, any food can trigger an allergic reaction.

The quantity ingested, preparation of the suspected food, frequency of symptoms associated with ingestion are relevant historical aspects, which must be taken into consideration by the clinician. Food that has been tolerated in numerous previous occasions is less likely to be incriminated. However, exposure to small amounts of certain preparations (extensive baking, for instance) might result in ingestion without reaction [8,9]. Review of food labels might be useful when considering hidden or unidentified allergens in processed food. Review of the history might also reveal the existence of co-factors, such as exercise, alcohol consumption, or drugs. Absence of such co-factors is equivalent to tolerance of the otherwise incriminated food. Although rarely serving as diagnostic on their own, food diaries may be helpful in identifying food containing hidden ingredients, food that was overlooked by the patient, or patterns of reactions (existence of co-factors). Food diaries are written records of everything that is ingested by a patient, including condiments, alcohol, and candies.

Physical examination may reveal signs of an immediate acute reaction or chronic findings compatible with atopic diatheses (asthma, allergic rhinitis, atopic dermatitis). However, physical examination is not per se relevant in diagnosing food allergy.

The clinical history and examination lack sufficient specificity and sensitivity to establish the diagnosis of food allergy. In vivo (skin testing) and in vitro (food-specific serum IgEs) investigations of sensitization are essential adjunct tools in assessing patients with a suggestive clinical history of food allergy and represent the second line of approach of these patients.

**In vivo testing**

Skin prick tests (SPTs) are a fast and effective method of assessing sensitization to food allergens. Commercially prepared food extracts or fresh food can be used. In evaluating sensitisation to fruit and vegetables, or to food for which extracts are not available, the prick-to-prick method may be used with fresh food or slurry made from food and sterile saline solution. SPTs are highly reproducible and less expensive than in vitro testing. Skin testing can be safely performed in patients of any age; it causes minimal patient discomfort, and yields results within 15 minutes.
SPTs for food allergens are highly sensitive (greater than 90%), but moderately specific (approximately 50%) [12]. However, there are a few exceptions to this rule, as it was shown that a positive skin test indicates a greater than 95% likelihood of clinical reactivity in patients with a relevant clinical history to certain food and in whom sensitization to the respective food is documented (see Table II). In addition, the accuracy of negative predictive values provided by skin testing is uniformly high; a negative skin test to food excludes an IgE-mediated reaction by 90 to 95% [13]. Thus, skin testing is highly useful to confirm the absence of an IgE-mediated food allergy [14,15]. Apart from low specificity, STPs were reported to lead to variable wheal sizes depending on the population and the food being studied [16]. Therefore, skin reactivity should not be interpreted as clinical reactivity. When considering the diagnosis of food allergy, the clinician should perform STPs only for the suspected food allergens, and interpretation of results should be considered in the light of the clinical history. Determining the clinical relevance of sensitization is crucial to reducing over-diagnosis and unnecessary dietary eliminations.

Intradermal testing to food is not recommended in the diagnosis algorithm of food allergy, because of the high rate of false-positive results, and the high risk of systemic life-threatening reactions [17,18].

Atopy patch tests (ATPs) involve the topical application of a food-containing solution to the skin for 48 hours. Currently, there are no standardized reagents, application methods, or guidelines for interpretation of ATPs. Although ATP is not routinely recommended for investigating patients with suspected food allergy, it can be useful in assessing the relevance of food triggers in pediatric patients suffering from eosinophilic esophagitis [19].

**In vitro testing**

In vitro evaluation, or the determination of food-specific serum IgE (sIgE), prevails when in vivo testing is contraindicated or ineffective (extended dermatitis, dermographism, severe atopic dermatitis, medication that inhibits cutaneous reactivity). Radioallergosorbent tests (RASTs) and fluorescence enzyme immunoassay (FEIA) tests are in vitro assays used to identify food-specific IgE antibodies in the serum [20].

Serum IgE testing is an important adjunct tool in accurate identification of causal food allergens [21]. Testing to large panels of food allergens disregarding the clinical history is not recommended, as false positive results can lead to unnecessary dietary elimination of safe food, and subsequently to unjustified nutritional deficiencies [22]. Thus, selecting in vitro testing for sensitization to food should be based on medical history.

The negative and positive predictive accuracy of *in vitro* testing varies within wide ranges, with a few exceptions. Clinical studies have provided predictive thresholds for certain food (egg, milk, peanuts, nuts, and fish) [23,24,25,26,27]. These cut-offs correlate with clinical reactivity with a positive predictive value greater than 95% (Table II), which proves their utility in determining whether an open food challenge is warranted, and also to accurately advise patients.

Overall, higher sIgE levels are more likely to indicate clinical reactivity. However, the predictive value of sIgE levels varies within wide ranges and with different factors (population, age, time since last ingestion of suspected food, other associated disorders) [27,28,29,30]. A negative result does not exclude the diagnosis. Arguing in favor of reintroduction of food based solely on negative sIgE results is not recommended because of the risk of systemic life-threatening allergic reactions.

Both in vivo and in vitro testing only detect sensitization, not clinical allergy; they cannot predict prognosis or severity of subsequent reactions. It is of utmost importance that results be interpreted within the framework of the patient’s clinical history.

**Table II. Relevance of SPT and sIgE in the diagnosis of food allergy.**

| Illergen | Age | Wheal | Probability of Reaction |
|----------|-----|-------|------------------------|
| Milk     | 3 years | 8 mm | ≈ 1                     |
| Egg      | 3 years | 8 mm | ≈ 100%                  |
| Peanuts  | 3 years | 8 mm | ≈ 100%                  |

| Food specific IgEs<sup>1</sup> |  |
|-----------------------------|---|
| Sensitivity of sIgE = 60-95% |  |
| Specificity of sIgE = 30-95% |  |

| sIgE levels associated with 9% PP |  |
|-----------------------------------|---|
| Egg                              | ≥7 IU/mL |
| Egg (infants ≤2years)            | ≥2 IU/mL |
| Milk                             | ≥15IU/mL |
| Milk (infants ≤2years)           | ≥5 IU/ml |
| Peanuts                          | ≥15 IU/ml |
| Peanuts (infants ≤2years)        | ≥15 IU/ml |
| Nuts                             |  |
| Fish                             | ≥20 I/ml  |

<sup>1</sup>a level of 0.35 kU/l indicates sensitization
Factors that dictate the impact of sensitization on the severity of the food allergy reaction (such as ingested amount, concomitance of other atopic diseases, asthma, general health) are currently the subject of study and interpretation. A recent study published in the Journal of Allergy and Clinical Immunology revealed that 1.6-10.1 mg of hazelnut, peanut or celery protein, and 27.3 mg of fish and 2.5 g of shrimp protein are needed to trigger allergic reaction in highly sensitized patients. This discovery is a new step in understanding food allergies and could also contribute to improving food labeling [31].

In certain situations, as is the case of allergy to cow’s milk, in dynamic results of in vivo and in vitro tests to sensitization along with the clinical context are factors with prognostic role in the natural history of the disease and provide important information on when to reintroduce the food into the diet [32,33].

Other tests detecting sensitization include the basophil activation test (BAT), which evaluates the in vitro basophilic activation by specific allergens. According to a recently published study, BAT effectively discriminates between allergy and tolerance in peanut-sensitized children, showing 97% accuracy, 95% positive predictive value, and 98% negative predictive value [34]. Therefore, BAT promises to bring real improvement in diagnosing food allergy.

Component-resolved diagnosis

The last decade brought about a “refining” of food allergy diagnosis by identifying clinically relevant allergenic fractions. Molecular-based allergy diagnostics also referred to as component-resolved diagnostics (CRD), uses purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules [35].

This method of investigation is not routinely recommended in diagnosing food allergy. However, it proved to increase the accuracy of food allergy diagnosis and establish sensitization patterns with particular prognostic outcomes in a relatively small number of foods.

Recent studies propose Arah2 (storage proteins found in peanuts), as well as Cor a 9 and Cor a 14 (hazelnuts) as the most common allergens to be associated with clinical reactivity, whereas Arah 8 (Bet v1 related) is more likely to cause mild, local reactions or to be tolerated [36,37,38,39,40]. These findings suggest that component-resolved diagnosis has the potential to enhance diagnostic accuracy by discriminating between clinically significant and irrelevant sIgE results, as well as to enhance therapeutic approach by excluding the need for unnecessary open food challenges. Although the search for other clinically relevant molecules is needed and on going, studies are limited and inconsistencies exist. Thus, in certain geographic areas, such as the Mediterranean area, Arah 9 proved to be the major allergen, while a number of studies brought inconsistent CRD results across different parts of the world [41,42,43]. Further studies are needed to define the clinical utility of component resolved diagnosis.

Elimination diets are used in the management of patients suffering from food allergies, as well as a part of evaluation for food allergy, and refer to the avoidance of incriminated food. Therefore, elimination diets target different aspects in clinical practice:

- removing one or several suspect food from a patient’s diet is sometimes useful in determining if they are causing or exacerbating a condition;
- prescribing an “oligo-antigenic” diet in which food that is commonly-involved in allergic disorders is removed temporarily from the diet may be useful in the evaluation of patients with chronic conditions, such as atopic dermatitis or chronic urticaria, in which food allergy is suspected, but no specific food can be incriminated;
- elemental diets, such as extensively-hydrolyzed or amino acid-based formulas, are used by some allergy specialists in the evaluation of disorders associated with multiple food sensitivities, such as eosinophilic esophagitis. Such diets should only be prescribed with great caution, particularly in infants and children, to avoid nutritional deficiencies;
- complete removal of the suspected trophallergen is recommended prior to food challenges, to ensure that the specific food is not interfering with the ability to appreciate a reaction [44,45].

Although elimination diets can be used as an adjunctive mean of diagnosing food allergy, they cannot confirm the diagnosis on their own.

Supervised food challenges are structured protocols in which the patient ingests the suspected food under a clinician’s supervision. They are sometimes required for the definitive diagnosis of food allergy, with double-blind placebo-controlled food challenge (DBPCFC) being the most accurate form of challenge. Food is selected for testing based upon the history and the results of skin and/or in vitro testing. DBPCFC is currently the “golden standard” in the diagnosis of food allergy [46]. It helps identify the causative agent, the amount of food needed for a reaction / tolerated dose, and establish the significance of existence of co-factors (e.g. exercise in patients with food dependent anaphylaxis, induced by exercise). Challenge tests are often the only way to confirm the clinical relevance of sensitization. At the same time, they are time-consuming, resource-intensive and produce the risk of inducing systemic, severe allergic reaction.

Conclusions

Food allergy is a common health problem, which demonstrates a significant socioeconomic impact, especially in pediatric population. A reliable diagnosis of food allergy is crucial to avoid the unnecessary exclusion diets and to formulate personalized dietary recommendations. Recent years have brought considerable progress in clarifying the diagnostic algorithm in food allergy. Clinical reactivity
can be effectively predicted in patients with a relevant history and in whom a certain level of in vivo and/or in vitro sensitization is documented. However, in some cases, oral provocation tests may still be required to establish or exclude the diagnosis of food allergy. The characterization of the biology and cross-reactivity patterns of food allergens has allowed a shift of the in vitro diagnosis of IgE-mediated hypersensitivity to food from an extract-based approach to an allergen-specific or “component-resolved” diagnosis. The latter has brought new insights in the approach of food allergic patient; it helped increase the accuracy of food allergy diagnosis and to establish sensitization patterns with particular prognostic outcomes in peanut, hazelnut, milk and egg allergy. Molecular based diagnosis is a topic of major interest in the search for an improved diagnostic of food allergy, and the research of other clinically relevant molecules is needed and ongoing. Molecular based diagnosis is a topic of major interest in the clinical search for an enhanced diagnosis of food allergy, and further research to discover other relevant molecules is needed.

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