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Research Article

Food Allergy: Diagnostic Approach beyond the Clinic

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Abstract

Adverse reactions to food include immune mediated food allergies and non immune mediated food intolerances. Food allergies and intolerances are often confused by health professionals, patients and the public. Food allergy has emerged as an increasing medical problem with main burden occurring in childhood. Careful diagnosis is important because over diagnosis by parents and even medical professionals results in a restrictive and inadequate diet which can impair both growth and limit participation in social activities. Diagnosis of food allergies in children starts with a careful dietary history to define the potential food triggers. Skin prick test (SPT) results and measurement of serum-specific IgE antibodies (sIgE) can be helpful in identifying offending foods. The oral food challenge (OFC) test is the definitive mean to ascertain clinical reactions to food.

ABBREVIATIONS

OFC: Oral Food Challenge; ATP: Atopic Patch Test; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; SPT: Skin Prick Test; IgEs: Specific IgE

INTRODUCTION

Allergic diseases in the recent years have increased by more than 50% of the population, becoming an important public health problem. Food allergy represents one of the allergic conditions in childhood, without leaving aside that it can occur in adulthood. At the moment there are more than 170 food allergens capable of causing a reaction which can range from mild to severe systemic reactions [1-3].

The prevalence of these food reactions varies between 4.9% - 33% [4], with the highest prevalence in childhood, and even some studies report that it can vary depending on the diagnostic method [5]. A meta-analysis reported a prevalence of food allergy of 12% for pediatric patients and 13%; for all foods, clinical symptoms were compared with double blind placebo-controlled challenge, where it was found that the prevalence of food allergy significantly decreases. The highest prevalence was found for milk in 3% with symptoms only, 0.6% with symptoms and skin tests, and 0.9% with oral food challenge [6]. In general, the series report prevalence between 2-8%, most often associated with cow's milk, egg, peanut, wheat and soy [2,7,8]. In practice, only 8 foods are responsible of more than 90% of food allergies, also known as major foods, and they are milk, egg, soy, wheat, peanuts, tree nuts, fish, and shellfish [9,10].

There have been reported in Latin America self-reports of reactions to foods, as well as data of suspected food allergy from sensitization to some foods, however the prevalence of food allergy is not well known, and depends on the diagnostic method. In Colombia a study in adults and children shows a prevalence of self-reports of 14.9%, in Argentina 5.1% [11]. In Mexico the main foods related with food allergy are fish, cow's milk, shellfish and soy. In 1996 at the Hospital Infantil de Mexico a prevalence of 1.04% was reported. In 2002 a 5 year review was conducted of sensitization by skin test to foods and was associated with comorbidities such as asthma (31.9%), allergic rhinitis (16%), and urticaria (3.3%) [12]. In 2009 at the Hospital Universitario de Monterrey a similar study reported that 51% of food sensitized patients were children, and the foods were dairy, egg, fish, shrimp, beans, soy, chili, mango, chocolate, and strawberry; the more frequently reported symptoms were cutaneous 58% and most common associated morbidity was urticaria 38% [13]. In 2015 a study from the Hospital Infantil de Mexico Federico Gomez was published with patients with suspected food allergy who had elimination diets. The foods that were found most frequently were milk, soy, egg, wheat, and corn. A nutritional disorder was found in those with elimination to more than 3 foods, the z score of weight for age, height for age, and weight for age were lower, and the most affected was the fat reserve. In these patients only in 5% of the children food allergy was confirmed [14].

The diagnosis of food allergy varies according to the clinical practice from one place to another. Over-diagnosis can be done since the patient tends to confuse the allergic reaction, or even the doctor can confuse some aspects of food allergy with food

intolerances. That is why the different health institutions have created diagnostic guidelines for this pathological entity, with different proposals that have been refined over the years, and so far are only aid and support for the diagnosis of this disease [9,15].

Food allergy diagnosis has been proposed to be performed according to different situations. The first is to demonstrate an actual reaction to a certain food; this would be the clinical diagnosis. Later, confirm by elimination diet or provocation with the same food; however all the tests are mainly guided to immediate type reactions, to which we have easier access, especially skin tests and specific IgE. Thus it has been considered that a suspected diagnosis is based on medical history, skin tests, specific IgE, and atopic patch test that can guide us about an immediate, delayed or mixed type reaction. On the other hand, it is well known that the definite diagnosis is done through double blind, placebo-controlled oral food challenge; however, it has been chosen to do other kind of tests such as open challenges, and elimination diets with reintroduction [16-18].

Any diagnostic approach to food allergy should start with a detailed medical history, including the patient's background, the history of signs and symptoms, especially if there are related or not with food intake, time of symptoms onset from food intake, type of reaction, time or duration of that signs and symptoms, classification according to severity, the amount of food, if it is a new food or had previously submitted a reaction to that food, plus a detailed physical exam and nutritional assesment; all of this will help us integrate a suspected diagnosis and guide our tests according the suspected mechanism involved [17-19].

IN VIVO TESTS

Skin tests

Useful to detect IgE-mediated reactions, is a fast, inexpensive technique, but not without risks. This test has a sensitivity of over 90% and specificity around 50%. The negative predictive value of the skin prick test in a patient with an immediate reaction is 90-95% [9,15,20-23].

By themselves are not used to consider food allergy, its use is justified because they are safe and useful for identifying foods potentially guilty of the IgE symptoms, but have low predictive value for the clinical diagnosis of food allergy. The disadvantage is that certain reagents are not standardized, so they can present positive without having a clinical association to talk about sensitization [2,15,21,22,24].

There have been established cutoff values of the average Wheel diameter and positive predictive values to determine clinical reactivity vs. tolerance in oral food challenge (Table 1).

Prick to prick

It is recommended that this test is not used for diagnosis of food allergy, there is insufficient information to support its use for diagnosis, it only helps to guide diagnosis, and they are more likely to develop adverse reactions than skin tests. This test is helpful in IgE-mediated food allergy. Results are less standardized than with the available allergenic extracts [2,25,26].

Table 1: Proposed cutoffs that predict 50% and 95% likelihood of a reaction to an OFC based on Skin prick test for egg, cow's milk.

	>95% positive	**≈50% negative**
Food	Skin prick test (mm)	Skin prick test (mm)
Egg white	≥7	≤3
Milk	≥8	-
Peanut	≥8	≤3
Fish	-	-

The negative predictive value of skin prick test in patients with immediate reaction was 90-95% and if fresh milk (pasteurized whole cow's milk) is used by prick to prick test it can reach up to 97% [27,28].

Patch test

Patch tests should not be used routinely for food allergy diagnosis. There is not enough evidence to support their routine use, and several studies have reported that they may be useful in patients with atopic dermatitis, or processes that are suspected to be a late reactions.. The disadvantage is the type of reagent or food to be used, the preparation method and interpretation. When compared to the oral food challenge the sensitivity and specificity are variable [22,29] (Table 2).

IN VITRO TESTS

Total IgE determination

Determination of IgE total: It is not used for the diagnosis of food allergy, there is no justification for its use, even though this immunoglobulin is high in sera of allergic patients, the sensitivity and specificity is poor compared to other test; the ratio total IgE/ specific IgE has been used as a predictive value compared with double blind, placebo-controlled oral food challenge [30].

Specific IgE determination: Its use is recommended when there is suspicion of an IgE-mediated mechanism, but do not make diagnosis of food allergy. They are useful for identifying foods potentially causing symptoms, have a predictive value of 95%, and have better value than skin tests. They are useful for finding antibodies that indicate sensitization. It is responsible for linking a positive test with clinical symptoms, but it would be necessary to perform the oral food challenge. Quantitative techniques are useful in monitoring patients. They allow confirming the suspected diagnosis by medical history and are particularly important when skin tests are contraindicated as in the case of urticaria, atopic dermatitis or history of severe anaphylaxis. Several studies that evaluated the relationship between the oral food challenge and the results of specific IgE reported that lower specific IgE levels correlate with oral tolerance, therefore they have been taken as a predictive value for tolerance [31] (Table 3,4).

IGG1, IGG4, IGA

IgG1, IgG4, IgA

Recent research suggests that the development and maintenance of clinical tolerance involves IgG4 antibodies. High levels of IgG4 vs. beta lacto globulin and ovalbumin and

Table 2: Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of atopy patch test (APT) at different concentrations of egg, cow's milk, and casein compared with OFC.

	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
APT +	24 (12-43)	80 (66-90)	43 (2167)*	0.63 (50-75)*
APT++	19 (0.9-36)	71 (63-78)	14 (0.6-27)*	0.79 (71-85)
APT (cow´s milk plus casein) +	15 (0.4-42)	80 (58-92)	33(10-70)	0.59 (41-75)
APT (cow´s milk plus casein) ++	17 (0.3-56)	74 (60-84)	0.07 (0.1-0.31)	0.88 (75-95)
APT (egg) +	33 (14-81)	81 (60-92)	0.50 (22-78)	0.68 (48-83)
APT (egg)++	20 (0.7-39)	70 (59-78)	0.17 (0.7-34)	0.74 (63-83)

Concentration of egg was 5% + or 10% ++, of casein was 5%+ or 10% ++, of cow´s milk was 10% + or 20% ++
Abbreviations: APT: Atopic Patch Test; CI: Confidence Interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value
Caglayan Sozmen S, Povesi Dascola C, Gioia E, Mastrorilli C, Rizzuti L, Caffarelli C. Diagnostic accuracy of patch test in children with food allergy.Pediatr Allergy Immunol 2015: 00.

Table 3: Positive predictive value (PPV) of skin prick test, specific IgE and atopy patch test (APT) for reactivity to egg, milk to positive oral challenge.

	Milk		Egg	
Test	**Positive test**	**VPP >95% (Positive predictive value)**	**Positive test**	**VPP >95% (Positive predictive value)**
Skin Prick test	>3mm	<2 años, 6mm >2 años, 8 mm	>3mm	<2 años, 5mm >2 años, 7 mm
Specific IgE	>0.35 kUIa/ml	<2 años, 5kUIa/ml >2años,15 kUIa/ml	>0.35kUIa/ml	<2 años, 2 kUIa/ml >2 años, 7 kUIa/ml
Patch test	+-+++		+-+++	

APT: Atopic patch test, PPV: positive predictive value
Jorge Sánchez, María Nelly Restrepo, José Mopan, Alergia a la leche y al huevo: diagnóstico, manejo e implicaciones en América Latina. Biomédica 2014; 34: 143-56.

Table 4: Schema for considering diagnosis of food allergy in children and teenagers using specific IgE testing.

		Likelihood of allergy from specific IgE (kU/L)		
		LOW (eg. Nut<0.35)	**INTERMEDIATE (eg. Nut 0.35 a <15)**	**HIGH (eg. Nut>15)**
Likelihood of allergy from history	HIGH Egurticaria and wheeze on 2 exposures	Possible allergy	Possible allergy	Allergy
	INTERMEDIATE Eg urticaria on single exposure	Possible allergy	Possible allergy	Possible allergy
	LOW Eg non-IgE symptoms	No allergy	Possible allergy	Possible allergy

JL Turnbull*, HN Adams† & DA Gorard. Review article: the diagnosis and management of food allergy and food intolerances. Aliment Pharmacol Ther 2015; 41: 3–25

the specific ratio of IgG4/IgE talk about clinical tolerance to cow's milk or egg. Additionally to IgG, specific serum IgA levels successfully increased during immunotherapy for grasses [32].

The IgG4 antibodies are tested through Inmmuno CAP. The levels of these immunoglobulin's are not supportive for diagnosis, but they do indicate tolerance [33,34].

MOLECULAR DIAGNOSIS OF FOOD ALLERGY

The application of molecular biology has identified different allergens responsible for clinical syndromes where a shared epitope is causing the reaction, this type of proteins were difficult to explain few years ago. The term pan allergens is currently used for all those ubiquitous proteins in the animal and plant kingdom that have a primary role and are responsible for cross-reactivity between species, without having a direct relationship between them [35,36].

With the application of DNA, molecules have been sequenced and allergens have been cloned, creating databases with increasingly complex data which allows us to compare one allergen to another and show the percentage of homology between each other, which helps to understand many syndromes which were previously difficult to explain. Since 1980 component resolved diagnosis or molecular diagnosis has been positioning significantly as part of allergy diagnosis. Unlike other diagnostic methods such test does not use protein extracts, it uses natural allergens or recombinant purified allergens, allowing these

allergens to be adequately standardized [35,37,38].

From the formation and molecular identification of these allergens, it has been possible to develop diagnostic tools by means of components which can be used in conventional methods for IgE specific detection such as Immuno CAP® or microarrays that allow simultaneous detection of specific IgE against more than one allergenic component with a small serum sample. This multiplex technology based on microarrays of the ISAC (Immuno Solid-phase Allergen Chip System®, Thermo-Fisher Scientific) system is a new *in-vitro* method that uses purified allergens coupled to a microchip, which would be recognized by a patient's serum IgE and whose interaction would be revealed using a secondary anti-IgE antibody coupled to a fluorescent marker [37,39-42].

This breakthrough of component diagnosis helps us have a greater diagnositic accuracy, allowing to identify previously unexplained allergens and being able to demonstrate some food allergy syndromes related to airborne allergens, and helping us to predict some answers depending on the involved protein [35-39].

FOOD CHALLENGES

Clinicians should consider the food challenges for diagnosis of IgE mediated food allergy. There are different types of challenges and they should be chosen depending on the previously presented clinical symptoms especially if they are severe. The more currently used challenges are open challenge, following single-blind placebo-controlled, double-blind placebo-controlled, the latter the gold standard. However, performing a double-blind placebo-controlled challenge requires a great effort, skilled staff, time and cost. Open and single-blind challenges are the most frequently used challenges in clinical practice [2,43-46].

The diagnosis by oral food challenges is based on the administration of graded doses of the food to reach the recommended dose. This graduated dosage reduces the risk should of a serious adverse reaction, and identifies the dose at which symptoms occur. Some studies have proposed the process of making oral challenges, the preparation form, dose and the interpretation of results. Blinding of a food challenge reduces any bias either by the patient, family or medical staff to apply it [43-46].

The risks and benefits of performing oral food challenges include making an accurate diagnosis of the patient, reintroducing foods that were avoided, so, a negative oral challenge has potential benefits for the patient reducing anxiety to intake, or fear to have a reaction, and more importantly improves the quality of life of the patient, as an additional benefit elimination diets that may affect nutritional status can be avoided, preventing malnutrition or growth impairment of the patient [43-46].

Moreover you can use a symptoms diary and elimination diets as diagnosis, although it is clear for physicians to suspect a food allergy, it is difficult to diagnose because of the large amount of subjective symptoms presented by the patient and that frequently do not correlate immediately after the intake [43-46].

This method can be used in those patients without a clear medical history of a clinical reaction of after ingestion o a food or when a not mediated IgE or mixed mechanism is suspected. In many cases clinical symptoms can't be related to a food, so identifying the food is more difficult. The elimination diet and reintroduction with one or more foods is valid in the daily practice and especially if after 4-6 weeks removal there is no clinical improvement, we can make the diagnosis of food allergy; this elimination diet should be to one or a few foods and with the supervision of a clinical dietician expert on the subject, also, the physician should consider associated atopic comborbidities, such as atopic dermatitis or asthma, as these may be related to some foods. In the case of atopic dermatitis it is estimated that one third of patients have exacerbations secondary to a food, in this case we can combine diagnostic methods including skin tests, if allowed by the patient, specific IgE, elimination diets and oral food challenges, as in the pathophysiology of this entity the mechanism involved is mixed (IgE mediated and non-IgE mediated) [43-47].

DISCUSSION & CONCLUSION

Allergists and immunologists are particularly well qualified to conduct oral challenge to assist patients with correct identification of foods causing adverse reactions. In appropriately selected patients, the potential risks, inconvenience, and expense are warranted by facilitating avoidance of unnecessary dietary restrictions and improving quality of life. But it is very important before making an oral challenge, make the clinical diagnosis of the patient through an interrogation directed and after that support with other diagnostic tests such as tests *in vivo / in vitro,* depending on the positivity that could guide us to predict a positive oral challenge or tolerance in a patient with diet and restriction.

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