Sensitivity and specificity of food specific IgE and IgG determinations for the diagnosis of food allergy

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Abstract

Among the methods currently used to demonstrate a sensitization to foods the measurement of food specific IgE antibodies (sIgE) is the most practical but not the most accurate. The "sensitivity" of food sIgE determinations is, for example, suboptimal with unstable allergens in fruits and vegetables that are involved in the (birch) pollen-related immediate oral allergy syndromes. In this particular syndrome the history is often conclusive and can be substantiated by skin prick tests with fresh foods. The "sensitivity" of sIgE tests is much better when sIgE are directed to stable plant or animal food allergens which often cause non-immediate generalized reactions. Foods, usually, contain many different (glyco)proteinic allergens of which some are stable and others not. The "sensitivity" of the sIgE test with a particular food, therefore, varies according to the type of allergen that is recognized by the patient. The "specificity" of sIgE tests with foods is affected by the existence of homologous food allergens which induce cross-reactive IgE that may or may not be clinically relevant. While variable, clinical cross-reactivity is more common among botanically-related fruits, among different nuts, among mammalian foods and among seafood than among cereals, grains and legumes. The "specificity" of food sIgE tests is much better when sIgE are directed to unique non-cross-reactive food allergens. Unfortunately, neither the presence of food sIgE nor its level are predictive of clinical reactivity. The identification of individual allergens in foods and the characterization of the relevant IgE binding sites in these allergens might lead to the development of tests that only measure sIgE to clinical relevant food allergens. (Acta gastroenterol. belg., **2006**, 69, **43-48**).

Introduction

Adverse reactions to foods can be differentiated into food allergies (FA), which involve an immune mechanism, or food intolerances which are not caused by a sensitization. Food allergic reactions can be either IgE-mediated or non-IgE-mediated. *IgE-mediated FA* are caused by specific IgE antibodies (sIgE) to food allergens which are (glyco)proteins. Food sIgE can be detected in vivo by skin prick tests (SPT) and in vitro by sIgE tests. Although the presence of food sIgE indicates a sensitization it is not necessarily associated with an allergic reaction upon ingestion of the tested food. A sensitization to foods, therefore, does not equal FA. Most foods contain many different (glyco)proteins which can induce sIgE and thus behave as allergens. Some allergens in a particular food show homology with allergens in other foods. Consequently, IgE directed to one allergen show cross-reactive binding to these homologous allergens. When such cross-sensitization is clinically relevant the term cross-allergy is used (1).

IgE-mediated FA can be classified in "primary" and "secondary". A "primary" FA is caused by a stable food allergen that resists gastrointestinal (GI) degradation (2). It has been shown that administration of antacids may favour the development of food-induced allergic reactions in mice by protecting allergenic proteins from degradation (3). "Primary" food allergens are able as well to sensitize as to cause allergic and cross-allergic reactions to foods. In the "secondary" FA the sensitizer is not a food but an inhalant allergen that cross-react with allergens in foods. Such cross-reactive food allergens are mostly too unstable to act as primary sensitizers but yet are able to bridge mast cell bound sIgE and thus cause clinical reactions. Inhalant allergens such as pollen (4), latex (5) or house dust mite (6) all may induce "secondary" FA. The increasing prevalence of pollen allergies has caused a substantial increase in the pollen-related FA. This holds in particular for the birch pollen-related allergy to fresh fruits and nuts that results from the recognition of Bet v 1, the major birch pollen allergen (7). *Non-IgE-mediated FA*, like the gluten-sensitive enteropathies and the food protein-induced enterocolitis syndromes (8), are rather caused by cellular sensitization mechanisms than by antibodies. In some of these food protein-induced GI diseases food patch tests may, therefore, be helpful. Except perhaps for the Heiner syndrome, there are currently no other food allergic syndromes known that are definitely caused by IgG antibodies. This review will focus in particular on the diagnosis of IgE-mediated FA which are in children as well as in adults the most frequent among all the immunological food hypersensitivities.

IgE-mediated food allergy

Clinical picture (9)

Although the GI tract is the first to come in contact with food and is probably the most commonly affected by FA, overt GI symptoms are not common, even when histologic and immunologic changes in the GI mucosa

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Table 1. — **IgE-mediated food allergy : clinical manifestations**

Immediate reactions (within seconds)
- oral allergy syndrome
- pharyngo-laryngeal syndrome
- esophageal spasms or dysphagy
  (→ allergic eosinophilic esophagitis possible)

Non-immediate reactions (a few minutes to 4 hours postprandial)
- generalized urticaria and/or anaphylaxis
- nausea, stomach pain, vomiting
- abdominal pain, cramps, bloating, diarrhea
  (→ allergic eosinophilic gastroenteritis possible)

Table 2. — **False diagnostic meaning of food sIgE tests**

False negative sIgE tests
- Low total IgE
- Presence of sIgE to unstable allergens in foods
  e.g. Bet v 1-related sensitization to fresh fruits, vegetables, nuts

False positive sIgE tests
- High total IgE and/or non-specific IgE binding
- Presence of sIgE to
  - cross-reacting allergens in taxonomically related foods
    e.g. IgE to wheat → IgE to other cereals
  - "panallergens" with little or no biological activity
    e.g. carbohydrates : cross-reacting carbohydrate determinants (CCD) present on many plant food, pollen and insect venom glycoproteins
    e.g. peptides : e.g. profilins in plant foods and pollen

are observed. The classical clinical manifestations of IgE-mediated FA are summarized in table 1. The most frequent *immediate* reaction is the oral allergy syndrome which is caused by type I mucosal contact allergic reactions. It is the dominant symptom of the pollen-related FA and can be associated with pharyngolaryngeal oedema. Occasionally esophagal symptoms may occur and allergic eosinophilic esophagitis may develop. *Non-immediate* IgE-mediated reactions to foods often involve the skin. Urticaria is the most frequent initial manifestation but is in the more severe cases complicated by anaphylaxis with GI, respiratory and/or cardiovascular symptoms. Isolated GI symptoms may nevertheless occur in FA and are even common in food allergic patients with eosinophilic gastroenteritis.

Diagnostic methods (9)

Although a double-blind placebo-controlled food challenge is considered the gold diagnostic standard, the diagnosis of IgE-mediated FA is currently based on history and on the demonstration of a sensitization to the suspected foods by means of SPT or measurement of sIgE. The interpretation of SPT and sIgE tests is, however, influenced by the prior probability that the food is causal. The diagnostic accuracy of both tests is much less when systematically used for the purpose of screening. Consequently, much depends on the history taking and on information given by the patient. Patients with immediate reactions know well which are the offending foods, whereas those with delayed reactions often do not. Chronic GI symptoms might for example be caused by a sensitization to foods such as egg white, milk casein, wheat and peanut, which are often present as hidden food ingredients and are as such daily consumed. SPT with fresh foods, are in general more sensitive than food sIgE tests. SPT, indeed, investigate the presence of *mast cell bound* food sIgE as well as the ability of the food allergen to cause cross-linking of these sIgE which is a prerequisite to cause mast cell degranulation and thus clinical reactivity. Unfortunately, the diagnostic accuracy of SPT is not optimal because SPT may be false positive, especially in patients with cross-reactive IgE to vegetable foods. In contrast with the low positive predictive value, the negative predictive accuracy of SPT with fresh foods is very good (10). For practical reasons SPT are often substituted by determination of food sIgE that can be measured by methods that currently use enzyme-linked anti-IgE. Such sIgE tests only measure *circulating* food sIgE but are not indicative for the biological activity of these sIgE. The reliability of sIgE tests may greatly vary from one laboratory to another and from one method to another. The Pharmacia CAP assay appears to be the most sensitive of the currently available systems (11). In recent years it has become clear that, as compared to the history of the patient, there are different situations in which sIgE tests to foods have a low sensitivity (false negative) or a low specificity (false positive) (Table 2).

Determination of food sIgE

Sensitivity

As shown in table 3, the sensitivity of sIgE tests with foods depends in particular on the stability of the allergens and is in this respect comparable with the sensitivity of SPT with "commercial" food extracts. "Primary" food allergens which frequently cause non-immediate postprandial reactions are often stable. An allergy to animal foods or to high protein plant foods is, therefore, mostly associated with true positive sIgE tests. The "secondary" pollen-related vegetable food allergens which cause immediate contact allergic symptoms are usually unstable. Unstable allergens may be lost during the extraction procedure. Consequently, pollen-related FA may be associated with false negative sIgE tests (10). In such cases SPT with "fresh" foods, in which unstable allergens are still intact, are positive. Most foods are mixtures of stable and unstable (glyco)proteins. The sensitivity of the sIgE tests with foods depends on the type of food, and for a given food on the type of allergen that is recognized. The IgE recognition pattern is determined by individual characteristics and by geographical determinants. The sensitivity of the sIgE test with cherry and probably with many other fruits and vegetables is for example high in Mediterranean countries but low in Western Europe because different allergens are recognized by the 2 population groups. In general the

Table 3. — **Sensitivity of food sIgE tests**

Food	Allergen	Sensitivity of sIgE test
Immediate (within seconds)		
fresh fruits**,** nuts and some vegetables*	unstable	low
Non-immediate (minutes to 4 hrs)		
fruits, vegetables****	relatively stable	moderate
peanut, soy, cereals, seeds****	stable	good
fish, shellfish, meat, poultry, milk, egg*****	very stable	very good

***** fresh pomes, stone fruits, nuts, carrots, potatoes, celery
****** high degree of cross-reactivity between different plant foods which is not often clinically relevant
*** high degree of cross-reactivity between "related" animal foods which is often clinically relevant.

Table 4. — **Primary food allergy : cross-sensitization and cross-allergy**

Sensitization to	Cross-sensitization with	Risk of cross-allergy
Cow's milk	Mammalian milks (excl. mare, camel) Beef	90% 10%
Hen's egg white	Avian egg-whites Chicken meat, egg-yolk	high 5%
A fish	Other fish Amphibians	≥ 50% ?
Shrimp	Crab, lobster, scampi Oyster, mussel Clams	75% ? ?
Meat Beef Chicken	 Lamb, pork, game, (horse ?) Turkey, pheasant, quail	 high high
Peanut	Pea, soy, beans Tree nuts	5-10% 2.5%
Soy	Peanut	?
Tree nut	Other tree nuts Seeds Peanut	≥≥ 40% ? ?
Wheat	Cereals	20%
Peach ("Lipid transfer protein")	Fruits (rose family)	55%

sensitivity of the sIgE tests with birch pollen-related food allergens is low and lays between 50 and 75% for kiwi, apple, carrot, celery and other unstable Bet v 1-related food allergens (12,13). The sensitivity of the sIgE test with latex-related food allergens such as banana, chestnut, kiwi and avocado and with house dust mite-related food allergens such as snails and shellfish is much better, whereas the sensitivity of the sIgE tests with primary food allergens, most of which are very stable such as those in cereals, nuts, peanut and legumes, milk, egg, fish, shellfish, meat and poultry is high.

Specificity

The specificity of sIgE tests with foods is particularly hampered by the occurrence of IgE to cross-reactive allergens which may or may not be clinically relevant. The specificity of sIgE tests therefore greatly depends on which allergen, -food specific or not-, in the food is recognized (14). A "primary" sensitization to stable cross-reactive allergens in animal or in plant foods (1, 10, 15-20) is often associated with clinical cross-allergy to phylogenetic-related foods and consequently with true positive sIgE tests for all these foods. Examples are the cross-allergic reactions to mammalian milks or to birds' eggs or to many fish species or to different meats (Table 4). Other examples are the cross-allergic reactions to botanically non-related plant foods caused by IgE that are directed to "lipid transfer proteins" that are very stable cross-reactive allergens in many plant foods (14,21). The situation is different for the "secondary" FA where cross-sensitization is far more frequent than cross-allergy (1) (Table 5). In recent years there has been a substantial increase in the pollen-related sensitization to multiple plant foods which is caused by the recognition of panallergens such as profilin or other allergenic proteins, that are present in a wide range

Table 5. — **Secondary food allergy : cross-sensitization and cross-allergy**

Sensitization to	Cross-sensitization with	Risk of cross-allergy
Birch pollen	"Fresh" fruits (rose family), kiwi, tree nuts, potato, carrot, celery, soy	50-80%
Mugwort pollen	Celery, carrot Spices	5% low
Grass pollen	Peanut, tomato, kiwi, cereals, orange	low
All pollen	Many fruits and vegetables	low
Latex	Banana, chestnut, avocado, kiwi, tomato, potato, bell pepper	35%
Ficus	Fig	low
Molds	Mycoproteins in cheese, quorn	low
House dust mite	Shellfish, molluscs	low
Bird feather	Egg-yolk, avian meat	high
Cat	Pork	low

of plants and of vegetable foods (14,22). These patients often demonstrate positive SPT and sIgE tests with different fruits and vegetables that apparently do not cause clinical reactions after ingestion (23). The specificity of the sIgE tests with plant glycoproteins is, in addition, greatly affected by the occurrence of anti-glycan IgE (24). Anti-glycan IgE are directed to the so called "cross-reactive carbohydrate determinants" (CCD) which are present on glycoproteins in pollen, many vegetable foods and even insect venoms. Such anti-CCD IgE have little biological activity, are not associated with positive SPT but yet are measured by sIgE tests (25). Anti-CCD IgE are highly cross-reactive which makes the situation even more complex. The presence of anti-CCD IgE, indeed, results in multiple false positive sIgE tests with fruits, vegetables, nuts and seeds and often leads to misdiagnosis of FA particularly in patients with a polyvalent pollen allergy, who often produce anti-CCD IgE (23). Anti-CCD IgE can be detected in vitro by determining sIgE to the CCD containing glycopeptide bromelain.

Predictive value

Although the presence of food sIgE does not equal FA the risk of a clinical reaction rises with increasing concentration of sIgE. There is, however, little correlation between the absolute sIgE level to a particular food and the severity of the reaction after ingestion of that food. There are different reasons for this discrepancy. First of all, the level of circulating food sIgE does not exactly reflect the concentration of mast cell bound food sIgE which is from a clinical point of view more important than serum sIgE. Secondly, the ratio total IgE/sIgE may be more indicative than the absolute sIgE levels. Very low total IgE levels are often associated with borderline positive sIgE tests and nevertheless severe clinical reactions. In contrast, very high total IgE levels are usually associated with clear positive sIgE levels which, however, may be caused by non-specific IgE binding. It, therefore, is important to measure, in addition to the sIgE level, also the total IgE level. Finally, many circumstantial factors, food-related or not, can influence the appearance of, or aggravate a clinical reaction. The most important facilitating factors are mentioned in table 6.

Table 6. — **IgE-mediated food allergy : facilitating factors**

The occurrence of a clinical reaction and the reaction severity are influenced by :

- amount / combination of food allergens
- concomitant ingestion of alcohol or NSAID
- treatment with ß-lytic agents or ACE-inhibitors
- postprandial exercise ("food dependent exercise-induced" anaphylaxis)
- increase in core temperature

Different investigators have tried to assess threshold levels of sIgE to individual foods that would predict the clinical relevance with a high degree of accuracy. Diagnostic decision points for sIgE concentrations and SPT have been described for peanut, egg, milk and fish. They, however, vary widely between individuals and between different study populations and are therefore of a low sensitivity (26,27). Furthermore, for wheat, soy and other foods no threshold levels could be established. This illustrates that it will be very difficult to determine sIgE levels beyond which no reaction will occur or food threshold doses that can safely be ingested in association with a given sIgE level (28).

Practical guidelines

Where *immediate* oropharyngeal reactions to fresh fruits, vegetables, or even other foods are concerned the history alone, if necessary completed with SPT with fresh foods, is mostly conclusive. Food sIgE tests will be negative or positive, depending on the type of food.

The reliability of food sIgE tests is better when *non-immediate* reactions to specific foods are concerned. In case of postprandial reactions suspected of FA without suspicion of a particular food, the diagnosis may be very difficult. It may be helpful to determine whether the patient is sensitized to pollen, latex or house dust mite because this might direct the further investigation towards an inhalant-related FA. If no inhalant allergy, it is mandatory to start with sIgE tests with the different food allergen mixtures. If one or more of these are positive, sIgE determinations to the different food components are performed at a later stage. With plant food allergen mixtures, sIgE tests may be positive with all the components due to cross-reactive IgE. In these cases SPT with fresh foods should be performed. If both SPT and sIgE are positive with many different foods, double-blind placebo-controlled oral food challenges, will be needed to find out which of the cross-reactive foods are clinically relevant.

IgG mediated food allergy

IgG tests measure either total sIgG or sIgG4 towards a food. The production of sIgG and sIgG4 to common dietary antigens is a physiological response and can be detected in health and disease. Strongly positive results are common in atopics with high total IgE regardless whether FA exists or not. There is only one very rare disease, the Heiner syndrome (pulmonary hemosiderosis), that has been related to very high levels of sIgG to food antigens, visualized in a precipitin assay. This has been reported rarely in *children* with cow's milk hypersensitivity and in case reports with egg and pork. According to Teuber (29) similar cases in which food sIgG has been demonstrated by an enzyme-linked immunosorbent assay have not been published. There are no data which prove in a scientific way that food sIgG and sIgG4 antibodies are pathogenic or can cause FA in *adults*. A recent study (30) in patients with irritable bowel syndrome reported a beneficial effect of dietary elimination of foods to which IgG antibodies had been found. However there were no determinations of sIgE to these foods and double-blind, placebo-controlled food challenges were not performed. The presence of IgG and IgG4 to particular foods is only indicative for exposure to these foods and there is at present no evidence to support the diagnostic efficacy of food sIgG in any particular disorder (31, 32). Therefore the determination of food sIgG or sIgG4 or even sIgA should not be part of the diagnostic work-up of FA.

Conclusion

It is clear that there is a need for more accurate tests for the diagnosis of FA. One of the difficult but important issues will be the identification of clinically relevant allergens and cross-allergens. Once this is achieved, SPT and sIgE tests with purified or recombinant allergens, instead of whole food allergen extracts that contain different allergenic proteins, will considerably improve the diagnosis of FA (33).

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