

Introducing chemists to food allergy

Adverse reactions to food may be toxic or non toxic, depending on the susceptibility to a certain food; non toxic reactions that involve immune mechanisms are termed *allergy* if they are IgE-mediated. If no immunological mechanism is responsible, it is termed *intolerance*. The following disorders are considered a consequence of food allergy: gastrointestinal reactions (oral allergy syndrome, vomiting, diarrhea, protein-induced enterocolitic syndrome, eosinophilic gastroenteritis); respiratory reactions (rhinitis, asthma, laryngeal edema); cutaneous reactions (urticaria-angioedema, atopic dermatitis); anaphylaxis. There is much recent evidence to consider celiac disease an immunological disorder. Food allergy diagnosis is based on history, SPT, specific IgE, food challenges. DBPCFC is fundamental for diagnosing true food allergy; patients who have had anaphylaxis to food must not undergo DBPCFC. Rapidly progressive respiratory reactions and anaphylactic shock are life-threatening reactions that can be caused by food allergy. The doses of food inducing anaphylaxis can be very low, therefore commercial cross-contamination with an unsuspected food during food processing can be risky for the food allergic patient. The prevention of severe anaphylactic food reactions may lie in interdisciplinary collaboration among allergologists, chemists, food technologists, and experts in food industry research.

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Foods can provoke adverse reactions that produce different clinical pictures, at times very severe. Many reactions to food are toxic and have an effect on all individuals. Other food reactions depend on an individual's susceptibility to a certain food; such foods are harmless to unsusceptible individuals. This particular reaction to food is termed *allergy* and has an immunological mechanism. If no immunological mechanism is responsible, the reaction is termed *intolerance*.

Allergic reactions are almost always related to immunoglobulin E (i.e. they are IgE-mediated). In 1995, the EAACI published a position paper on adverse reactions to food which proposed the classification of food reactions according to the pathogenic mechanism involved (Fig. 1) (1).

The prevalence of food allergy in the general population has been estimated to be about 2%. In children the prevalence is about 8%; allergy to cow's milk constitutes the most important form, with a prevalence of between 2.2% and 5.2%. Patients with a respiratory allergy to pollen can also present a food allergy to fruits and vegetable. In this case, the allergic reaction takes place in the oral mucosa and has been termed oral allergy syndrome (OAS). The prevalence of OAS varies from 6% to 47% and depends on the type of pollen that the individual is sensitized to.

The normal individual usually develops a tolerance to ingested food proteins. Hence, the food proteins that are ingested and digested are harmless (2). However, during early childhood, when the gastrointestinal

immune system is still immature and intestinal physiology is incomplete, IgE sensitization toward food protein can take place, especially in atopic infants. Consequently, food tolerance is broken down. Another mechanism that can lead to a breakdown in food tolerance may occur later in life in patients with pollen respiratory allergy. Patients that are allergic to pollens can produce IgE antibodies to food proteins that cross-react with respiratory allergens (which have a highly homologous molecular structure). In this case, pollen sensitization occurs first and sensitization to the cross-reactive food allergen later (3, 4).

There is sufficient scientific evidence to regard the following disorders as being the consequence of food allergy. This evidence is based primarily on diagnostic workup using the double-blind placebo-controlled food challenge (DBPCFC).

Gastrointestinal reactions

Oral allergy syndrome

Acute vomiting and diarrhea

Food protein induced enterocolitic syndrome

Eosinophilic gastroenteritis

Gluten-sensitivity enteropathy

Respiratory reactions

Rhinitis

Asthma

Laryngeal edema

Cutaneous reactions

Urticaria angioedema

Atopic dermatitis

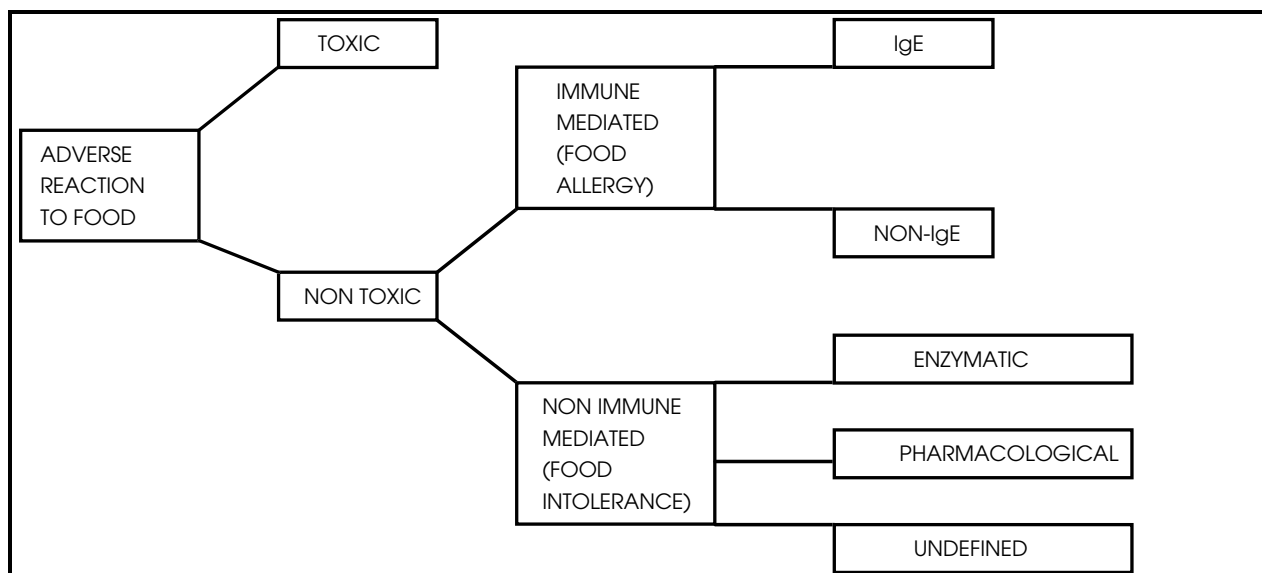


Figure 1. Classification of food reactions.

Herpetiform dermatitis

Generalized reaction

Anaphylaxis

The relationship between food allergy and other conditions such as headache, irritable bowel syndrome and otitis media with effusion has been described only in occasional reports. And there is no scientific evidence supporting the food allergic nature of chronic fatigue syndrome, neuropathy, psychological distress, hyperkinetic syndrome, collagen vascular disease or joint symptoms (5).

Given that the present diagnostic tests for food allergy lack sensitivity and specificity, the cornerstone for the diagnosis of true food allergy is a sound diagnostic workup. This workup should be based on history, skin-prick tests, determination of specific IgE (sIgE), elimination diets and challenge testing with the suspected food (1). In many cases, sIgE to food have shown good sensitivity but limited specificity. The problem in evaluating the diagnostic performances of an *in vitro* test for the measurements of food sIgE lies essentially in comparing the results of such a test with those obtained with a reliable test, such as the DBPCFC test. A recent study evaluated the sensitivity and specificity of CAP-RAST[®] for eight main allergenic foods in 197 children diagnosed as food allergic by DBPCFC (6). The results were discouraging. Sampson & Ho concluded that a good Positive Predictive Value (PPV, the parameter giving the diagnostic direct value of a test) could be reached only when sIgE were >32 kU (A)/l for milk, >6 kU (A)/l for eggs, >15 kU/l for peanuts and >21 kU/l for fish.

However, the same study showed that an sIgE value of 5 kU /l for wheat had an excellent negative predictive

value, i.e. a wheat specific IgE titer of 5 kU/l allows one to exclude the presence of food allergy to wheat and attribute the positivity to the cross-reactivity with grass pollen.

These results once again underscore the fact that a positive CAP/RAST or positive skin-prick tests provide insufficient diagnostic certainty in clinically relevant food allergy. The “gold standard” for food allergy diagnosis remains the DBPCFC (7). The following list illustrates some of the inherent problems of DBPCFC:

- 1) the suspected food often cannot be placed in capsules and needs to be masked by an inert test meal;
- 2) the test meals (verum and placebo) have to be prepared by experienced dieticians
- 3) the double-blind procedure is time consuming and costly in terms of trained personnel-hours, especially if more than one food has to be tested;
- 4) the masking procedure can cause loss of allergens and it can also reduce the delivery of the suspected food; these two factors may lead to false negative results. This problem is more relevant in OAS to fresh fruits and vegetables. In these cases, one can expect to evoke symptoms only if sufficient quantities of the fresh food come in contact with the oral mucosa. It is clear that “dilution” of the suspected food with the masking ingredients could lead to false negative results;
- 5) thorough blinding can become difficult with fruits and vegetables because the consistency of the food may be difficult to mask;
- 6) the DBPCFC is not risk free inasmuch as patients can manifest allergic reactions that can deteriorate and require emergency treatment, especially if capsules are employed. The use of capsules could lead to the administration of higher doses of the suspected food before symptoms are evoked. The capsule allows the food

to by-pass the oral cavity. This precludes the early symptoms of allergy that usually take place when even small amounts of allergen come in contact with the oral mucosa.

Nevertheless, the DBPCFC remains the fundamental test for a diagnosis of true food allergy and should always be carried out in all those patients suspected of having food allergy; patients with a history of anaphylactic shock clearly provoked by a food must not undergo DBPCFC.

The skin-prick test and specific IgE determination are sufficient for testing as long as there is a clear link between the anaphylactic reaction and the ingestion of a specific food (8).

Rapidly progressive respiratory reactions (e.g. laryngeal edema, asthma) and anaphylactic shock are life-threatening reactions that can be caused by IgE-mediated food allergy. The doses of food necessary to cause an allergic manifestation can at times be very low, in the order of 100 ppm, and perhaps even lower. Therefore commercial cross-contamination with an unsuspected food during food processing can be risky for the food allergic patient. Incomplete labeling represents another risk factor for these patients. With current labeling standards unlisted ingredients may be present in sufficient amounts to provoke severe reactions in exquisitely sensitized patients. This issue has come to be known as the hidden food allergen issue.

Two journal reports described 12 and 13 fatal reactions due to food allergy, respectively (9, 10). Almost all of these patients had the allergic reaction after the ingestion of a meal prepared outside the home and were unaware that the meal contained the food they were allergic to.

Both the prevalence and the incidence of severe food allergy reactions have been analyzed in several studies. A prospective study was carried in 1992 in 73 emergency departments in the state of Colorado: 25 severe reactions were reported (11). In the last few years many prospective and retrospective studies have been performed on emergency ward statistics; these reports conclude that food is the most frequent cause of all anaphylactic reactions seen in the emergency room (12–15).

We recently evaluated the incidence and the causes of anaphylactic reactions in the emergency room (ER) of a general hospital in Milan during a 2-year period, 1998–1999 (16). We found that 140 of the 38 685 patients that were admitted to ER had an anaphylactic reaction. In the majority of the patients (38.5% – 54/140), the anaphylaxis was caused by food; drug reactions were responsible for 35.7% (50/140) of the cases. The most relevant finding was the high prevalence of severe reactions to fresh fruits and vegetables, which were the culprit foods in 15 out of the 54 food reaction patients. This data is in contrast to previous literature data that

reported nuts and legumes as the most frequently incriminated food. Pumphrey has recently reported a case of fatal anaphylaxis to nectarine, thus confirming the potential danger of fresh fruit allergy in Northern Europe (17). A cooperative study in eight countries of the European Community (EC) was able to ascertain 20 fatal reactions and more than 500 severe food allergy reactions in 1993–1996 (18). A register for severe anaphylactic reactions has been set up in the UK (17). Twenty-seven life-threatening reactions have been registered: 25/27 were due to severe respiratory obstruction (laryngeal edema, asthma); 2/27 were respiratory reactions combined with anaphylaxis; no cases of pure anaphylactic shock were reported.

What strategy can be adopted for the prevention of severe anaphylactic food reactions?

The solution to the problem may lie in interdisciplinary collaboration among allergologists, chemists, food technologists, and experts in food industry research. Collaboration also needs to take place between representatives of concerned government bodies, supra-governing organizations such as FAO and EC, scientific societies and, lastly, consumer committees.

The role of the allergologist is as follows:

1) *Identification of allergenic foods.* This can be accomplished by either a) formulating consensus documents that classify allergenic foods on the basis of existing journal reports or b) carrying out clinical research aimed at demonstrating that a food is responsible for an allergic reaction (i.e. via the DBPCFC). An example of a consensus document is the ILSI report that confirmed that the foods considered by FAO are really allergenic (19). Clinical research, on the other hand, can contribute new data that may be incorporated in reports such as the ILSI position paper, e.g. studies that showed that celery and hazelnut are allergenic foods (20, 21).

2) *Classify allergenic foods according to risk of provoking a reaction.* For example, Sweden has done a fine job of studying all the severe food allergic reactions. This undertaking has allowed Sweden to identify soy as the food causing a high prevalence of severe allergic reactions (22).

3) *Identify allergens.* This task should be approached in collaboration with chemists and food technology specialists. Studies should focus on molecular structure as well as allergen stability with respect to digestion procedures and industrial manipulation of food sources. It will be the allergologist's task to verify the allergenicity *in vivo* and *in vitro*.

4) *Develop reagents and diagnostic tests* that improve the diagnosis of food allergy.

5) *Develop hypoallergenic foods* with the combined efforts of the allergologist, the food technology specialists and the food industry.

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