

Cross-Reacting Allergens in Clinical Syndromes

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Allergic reactions to foods are a challenging aspect in the field of allergic diseases, as some major problems remain. One of these is our incomplete knowledge of all the mechanisms favoring IgE sensitization to foods at the various ages of life. In fact, the completely different clinical patterns of IgE-mediated food allergy in children and adults are enough to suggest different immunological processes.

The overall prevalence of food allergy is higher among children [1] than adults [2] and while in youth it mainly regards the most commonly eaten foods, such as milk, egg and wheat, and shows a significant tendency to be outgrown with time [3], in adults the foods involved are often not the most common ones, for instance milk and egg are rarely involved, and there is no tendency for the symptoms to resolve spontaneously. An impaired development of oral tolerance may adequately explain sensitization to foods in infancy and the full maturation of gastrointestinal immunity would justify the disappearance of symptoms within the first 3 years of life, but these factors cannot account for the persistence or even the appearance of a new food allergy in adults, who are unlikely to have abnormalities of gastrointestinal immunity.

Thus, the mechanisms of sensitization in adulthood presumably proceed through a different route, which may be represented by inhalation or contact. Very often in fact, adults develop allergic reactions to foods as a consequence of sensitization to other allergenic sources, giving rise to association of respiratory and cutaneous and/or anaphylactic manifestations.

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The best defined examples of this kind of sensitization are: (1) pollinosis and oral allergy syndrome (OAS) from fruits and vegetables [4]; (2) latex anaphylaxis and allergy to fruits [5], and (3) the bird-egg syndrome [6]. In addition, there are increasing reports of an association between mite asthma and allergic reaction to shrimp. These associations can really be termed allergic clinical syndromes as they are manifestations in which respiratory and/or anaphylactic reactions, due to a certain inhalant or contact allergen, are associated with cutaneous, gastrointestinal, and even cardiovascular reactions due to the ingestion of one or more particular foods. The two allergenic sources appear unrelated, but in vitro they can be seen to cross-react as they share homologous allergens.

Essential requirements to consider the association of allergic reactions to different allergenic sources as a clinical syndrome are their appearance in statistically significant clusters of hypersensitivity in a large number of patients, the clinical demonstration of food-allergic symptoms by food challenge, and the in vitro evidence of cross-reactivity with the identification of the homologous allergens.

Pollinosis and OAS from Fruits and Vegetables

From recent studies hypersensitivity to fresh fruits and vegetables appears as the most common kind of food allergy in adults. Two studies evaluated the prevalence of hypersensitivity to fruits and vegetables in patients allergic to pollen: a prospective study from Switzerland reported a prevalence of 47% [7], very similar to the 46% we retrospectively observed in patients with hay fever in Italy [8].

In a prospective evaluation we are currently doing on pollinotic patients, we have preliminary found that 79 of 359 patients (23%) presented with OAS. Considering that hay fever affects about 10–15% of young adults in Europe [9], prevalences of hypersensitivity to vegetable foods ranging from 2 to 4% in this population can be presumed. Thus OAS seems to be the most frequent and relevant kind of food allergy in adults.

The preliminary results of our study showed that the mean starting age of OAS was about 26 years and that there was a significant correlation between the number of years from onset of hay fever and the development of allergy to fruits and vegetables. These data indicate that allergic reactions to vegetable foods are closely related to sensitization to pollens and suggest the need for a careful analysis of their clinical expression. For example, even though the pollens most commonly causing hay fever in Italy are grasses and *parietaria*, we observed that only sensitization to birch and mugwort were significantly more frequent among patients with OAS than among those without, with a significance respec-

tively of $p < 0.001$ and $p < 0.004$. Skin tests for birch and mugwort, interpreted as an index of specific IgE levels, gave significantly larger wheals in pollinotic patients with OAS, thus confirming data reported for birch demonstrating a significant correlation between high levels of birch-specific IgE and frequency of sensitization to foods [10]. Thus, hypersensitivity to these pollens seems to imply sensitization to allergens which also condition allergic reactions to foods.

Bet v I and *Bet v II* are the cross-reacting allergens demonstrated so far as being mainly responsible for the best defined clinical syndromes of pollen and food allergy. Allergy to birch pollen and apple is due to an allergen highly homologous to *Bet v I* [11], allergy to hazel pollen and hazelnut is due to allergens homologous to *Bet v I* and *Bet v II* [12], and allergy to birch pollen and celery is due to an allergen homologous to *Bet v II* [13]. *Bet v I* and *Bet v II* are two proteins particularly widespread in nature as their structure is related to some functional properties shared by the majority of plants. They can therefore be considered panallergens.

It is important to assess the role of the single allergens in clinically well-defined allergic reactions, meaning in a large number of patients in whom symptoms have been soundly demonstrated. In our current study the most common cluster of hypersensitivity was towards the *Prunoideae* family; as we have already noted, this is not related to any particular pollen even though it arises in pollinotic patients. We found by analyzing sera of patients with positive oral challenges with peach, apricot, plum, and cherry, that the major allergen is a 13-kD protein. This allergen was found to be responsible for the in vitro cross-reactivity between the four *Prunoideae*, but it did not cross-react with grass or birch pollen [14].

Another noteworthy cluster of hypersensitivity is marked by allergic reactions to the so-called 'nuts' group, peanut, hazelnut, and walnut, in patients with pollinosis from birch. Forty-one percent of our birch-allergic patients reported symptoms to two or three components of the 'nuts' group, which were highly significantly associated.

We therefore designed a study to verify the presence of cross-reactivity between the three nuts and birch and, if it was true, to identify the responsible allergen. To this aim we selected a group of 10 patients with documented anaphylactic shock from peanut and severe systemic reactions after the ingestion of hazelnut and walnut. The in vitro study was done by SDS-PAGE/immunoblotting and blotting inhibition.

The results of blotting inhibition using a pool of sera from all patients showed that peanut extract and walnut extract completely inhibited the IgE binding to the 14-kD allergen of hazelnut, whereas the birch extract completely inhibited both the allergens of 14 and 18 kD, which are likely to be homologous to *Bet v I* and *Bet v II*. The same complete inhibition was observed using hazelnut,

walnut and birch extracts with peanut blotting. These findings show that the in vivo association of allergic reactions to the components of the 'nuts' group and birch pollen is due to the presence of cross-reacting allergens, the main one being a 14-kD allergen. The molecular weight and the pattern of inhibition by birch seem to suggest that this allergen belongs to profilins, which are ubiquitous proteins regulating actin polymerization probably involved in plant fertilization [15].

Latex Anaphylaxis and Allergy to Fruits

Several reports noted an association between allergy to latex, which is the natural rubber extracted from the tree *Hevea brasiliensis*, and to a variety of fruits [16]. A recent study conducted on 25 patients with latex allergy, 36% of whom with systemic anaphylaxis, found that 13 subjects (52%) had had allergic reactions to fruits. The fruits most frequently involved were avocado, chestnut, banana, kiwi and papaya. Lavaud et al. [17] detected by immunoblotting the allergen cross-reacting between latex, avocado, and banana as a 30-kD protein. As we identified the major allergen of kiwi as a 30-kD component [18] we inhibited blotting of kiwi with banana extract using pooled sera from patients with allergic reactions to kiwi and specific IgE antibodies to banana and latex. The good inhibition led us to think that this 30-kD allergen may be very important in multiple sensitizations, though their clinical relevance has yet to be verified as only few of these patients were symptomatic for banana and latex.

The Bird-Egg Syndrome

The association between allergic reactions to egg and respiratory symptoms from exposure to birds, after a number of case reports, was defined in studies including small groups of patients [6, 19]. A recent study investigated 31 patients with egg allergy, bird allergy, or both, and found that the bird-egg syndrome mainly affects adults and that the two allergenic sources have cross-reacting allergens, as demonstrated by complete blocking of IgE binding to allergens of egg yolk and bird feather extract by respectively budgerigar and egg yolk [20]. In particular, the most relevant cross-reacting allergen seems to be a 70-kD protein in egg yolk corresponding to α -livetin (chicken serum albumin).

In some cases the detection of in vitro cross-reactivity has not yet been followed by the demonstration of an in vivo clinical expression. This is true for the sensitivity to shrimp and mites. The group of Aalberse recently identified the cross-reactive allergen between shrimp, mites, and other arthropods, as a 36-kD

component with physicochemical properties described for tropomyosin [21]. This is a protein involved in actin activation during muscle contraction which has been identified as the major allergen of shrimp *Penaeus aztecus* [22].

We studied a group of patients with suspected reactions to shrimp by performing double-blind, placebo-controlled food challenges with shrimp, skin tests and CAP/RAST with *Dermatophagoides pteronyssinus* extract, SDS-PAGE/immunoblotting and blotting inhibition. Clinical results showed that about half of patients had a positive challenge to shrimp and that these patients had a convincing history of mite asthma. All sera from challenge-positive patients reacted to the 37-kD allergen, which is likely to be tropomyosin, and the complete inhibition of shrimp blotting by mite extract gave evidence of the cross-reactivity of this allergen thus providing a basis to the clinical expression of association of mite and shrimp allergy.

Conclusions

We can state that the sensitization to allergens which are functionally essential organic components seems to be the basis of allergic reactions to various different allergenic sources giving rise to true clinical syndromes. Only a rigorous clinical observation will enable us to establish the significance of these allergens in the context of well-characterized in vitro cross-reactivity.

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