

The Relevance of Crossreactivity in Pediatric Allergy

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Introduction

Allergic diseases are caused by a great number of allergens that originate from many diverse sources. The study of the relationship between allergens is of growing interest for both clinical and basic researchers. Crossreactions between allergens have been reported increasingly in recent years, but this is not a new subject in the history of allergy. In the first decades of this century, clinicians reported good clinical descriptions of adverse reactions associated with the ingestion of food, and they developed the use of skin testing in the diagnosis of food allergy. However, they were not able to explain the so-called "false-positive" skin test reactions that occurred in patients who had no clinical manifestation of the apparent sensitivity. In spite of the limitations of their skin test methods at a time when alternate test methods did not yet exist, what they were actually observing was the phenomenon of cross-sensitization, that is, the induction by an allergen of specific IgE antibody that can react with an apparently altogether different allergen (1).

The concept of crossreacting IgE antibodies is still sometimes confusing. It is well-known that detection of a specific IgE antibody to a particular allergen does not always imply previous contact with the same allergen; cross-sensitization may have occurred. For example, an individual with IgE antibody that reacts with a food allergen may have been sensitized in the first place by a pollen, the "priming allergen" as it were (2). The significance of immunological crossreactivity in clinical

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allergy varies considerably. Sometimes crossreacting allergens elicit clinical symptoms; at other times, they are just "innocent bystanders." Despite the large number of publications on crossreactivity, the complete cellular and molecular basis of these phenomena is still unknown (3,4). The introduction of molecular biology techniques for the study of allergens has allowed a more complete analysis of their primary structure, biological function, and homologies, and, consequently, there is now the possibility of greater understanding of crossreactivity between allergens (3,5). Nevertheless, it is clear that the study of allergens at the immunological level must be accompanied by a detailed study of associated clinical and epidemiological findings. This latter kind of information should guide the search for shared antigenic determinants and lead to a better understanding of the pathogenic mechanisms implicated in IgE-mediated hypersensitivity reactions in general (6-8).

Natural History of Allergic Sensitization in Children

Until recently, it has been taken for granted that respiratory sensitization precedes food allergy symptoms in the general population (9). In contrast, allergy in children often begins with allergy to food(s), most often cow's milk, hen's eggs, legumes, or fruits. Only later in life do children become sensitized to aeroallergens. In our own experience as pediatric allergists, 99% of children with allergy to cow's milk, 97% of those allergic to eggs, and 74% of those with fish allergies became allergic before the age of two, in the period when these foods are first introduced into their diet. It is possible that the first few contacts with the proteins of these foods are essential for the development of clinical sensitization. Clinical symptoms begin after the second year in 70% of fruit allergy cases and 90% of legume allergy cases. However, they begin in 56% of other vegetable allergy cases, but we have not been able to establish a relationship between the age of first intake and the age when sensitization occurs. Moreover, food allergy constitutes a dynamic pathology, with the onset being a function of the child's age (10). For example, the onset of allergy to shellfish has a bimodal distribution, with 38% of these allergies beginning at 2-3 yr of age and another 31% beginning at 10-11 yr of age (6).

Legumes have been shown to have the greatest degree of immunological crossreactivity. Broadbent et al. found that only 2 out of 41 patients suffered challenge test-confirmed allergic reactions to more than one legume. However, when these authors studied the degree of immunological crossreactivity among different legumes, they found that 49 of 62 patients (79%) had evidence of immunological crossreactivity to two or more legumes (10,11). In our own patient population, 43 of 67 (64%) food-allergic children had allergic crossreactions to

more than one legume. These results suggest that an important factor in crossreactivity to vegetable foods may be the possible functional analogy of their storage proteins, which translates to a structural similarity among these foods (6). Only a small proportion of patients with food allergy (between 13 and 20%) have allergy to three or more foods, and allergies to fruits and legumes prevail in this particular group of patients (6,10,12). This fact strongly suggests the existence of an elevated degree of crossreactivity among these two types of foods (10,13,14,15).

Atopic individuals are genetically prone to produce IgE antibodies to specific allergens and to have allergic diseases. Until now, no distinguishing features have been found to suggest that allergens are unique antigens (4,16,17). While the overall prevalence of atopic diseases in childhood seems to be increasing (18,19), there is still no reliable information with respect to the prevalence of food allergies. Bock, who followed the growth and development of 480 infants to their third birthday, found that, while 133 reported to have experienced at least one adverse reaction to food, only 38 (8%) had their symptoms confirmed by an oral food challenge test and only 1–2% were found to have an immunological basis for their reactions (7). In a similar study of 1759 Danish infants, the prevalence of cow's milk allergy alone was 2.2% (8). All carefully controlled prevalence studies have revealed that the vast majority of food allergic reactions appear in the first few years of life. In our experience, 69% of them begin before two years of age (6).

The prevalence of reactions to specific foods obviously depends on the eating habits of a given population. In the United States, 60% of food allergies are caused by peanuts and eggs (19); whereas, in the Scandinavian countries, allergy to fish (20) and to hazelnuts (21) apparently predominates. In a study done on the Finnish population (22), the foods most frequently implicated in allergic reactions were citrus fruits, tomatoes, and eggs. Not surprisingly, food allergy in Japan is often due to soybean proteins (23). In Spain, three foods—eggs, fish, and cow's milk—account for approx 50% of all food allergies. If legumes (specifically, lentils, and chick peas), peaches, nuts (peanuts, hazelnuts, and walnuts), and crustaceans are added, this list accounts for approx 80% of all IgE-mediated hypersensitivity reactions to food in our pediatric population. Unlike the findings from the United States, peanuts were involved in only 4% of the food allergies in Spanish children, whereas fish were involved in 18% (6). However, comparisons of the results from different countries are difficult because of the use of different diagnostic criteria, since the diagnosis of food allergy continues to be one of the most controversial topics in the clinical practice of allergy. One problem is that specific IgE to a variety of apparently unrelated food allergens is often found in patients in whom a single sensitizing allergen is

implicated, even though the patients deny previous contact with the other foods (24,25).

Crossreactivity of Protein Allergens of Animal Origin

Related foods share allergenic determinants, and specific IgE molecules against these shared determinants can be shown to recognize similar epitopes in unrelated foods. The transformation of such serological crossreactivity into a clinically significant reaction depends, partially, on the nature of the food. For example, cow's milk-specific IgE crossreacts with goat, sheep, and mare's milk (26), and these milks should not be given to children allergic to cow's milk. Children who are sensitized to bovine serum albumin and/or bovine γ -globulin (proteins present in both cow's milk and beef), can have allergic reactions if children allergic to cow's milk. The marked heat lability of both of these allergens, however, means that only a few cow's milk-allergic children do not tolerate well-cooked beef and veal (27).

It has been demonstrated that patients who react to dog serum albumin (35% of dog-allergic patients) show IgE reactivity to purified cat, mouse, chicken, and rat albumins. When the amino acid sequence of dog serum albumin was compared with published sequences, a significant degree of homology was found with the following albumins: human (82%), pig (81%), cow (77%), sheep (78%), mouse (75%), and rat (76%) (28). Albumin, which is present in dander, is therefore an important crossreactive animal allergen and can be regarded as a panallergen of mammalian animal origin. For example, it has been confirmed to be the common allergen in the so-called "pork-cat syndrome" (29).

Egg allergy in children usually begins in the first 2 yr of life, clearly related with the introduction of food in the diet. Ovomucoid (Gal d 1) has been shown to be more allergenic than ovalbumin in egg-allergic children. In most cases, the apparent skin reactivity to ovalbumin is due to its contamination with ovomucoid (30,31). However, the majority of children allergic to hen's egg do not react to chicken meat or feathers. Of our patients sensitized to egg, only 8% were also sensitized to chicken feathers and/or meat, and no other food sensitization was associated with these allergens. In all of our cases, sensitization to eggs preceded sensitization to feathers (32). This could be due to the presence of common allergenic determinants in yolk livetines and the hen serum albumin present in feathers. A case of allergy to chicken egg yolk induced by inhalation of parrot detritus was described in 1985 in an adult patient (33). This type of sensitization has been designated as the "bird-egg syndrome." The livetin fraction of egg yolk induces IgE antibody that crossreacts with serum albumin and is the protein responsible for this syndrome (34,35). This route of sensitization to eggs is uncommon in infants, but it has been described in an older child (36).

As long ago as 1937, De Besque (37) published the first report describing fish as an alimentary allergen, an inhalant allergen able to trigger asthma and also an allergen that caused immediate skin symptoms on contact. He also described patients with selective sensitization to a single fish species who were able to tolerate other fish. Since then, a high degree of immunological crossreactivity among fish species has been established (20). The major allergen of cod, Gad c 1, (38) is considered to be the major allergen of fish in general. Fish allergy has been studied mostly in children (39–42). IgE binding patterns of serum from fish-allergic patients are more alike as the species become more closely taxonomically related. We have studied a group of 79 children with fish allergy, of whom 29 tolerated the ingestion of white tuna (*Thunnus alalunga*), and we investigated their specific IgE to six fish species, including white tuna, which is commonly eaten by children in our area. Skin prick tests were positive for all six species in all the patients. This means that the specificity of the skin-prick test for the individual species is low because of this crossreactivity. Among all the fish studied, white tuna appears to be the least allergenic, while hake (*Merluccius merluccius*) is the fish that provokes the strongest IgE response (39,43). Bernhisel-Broadbent and Sachs (41,44) also found that the sera of their patients showed specific IgE antibodies to a number of fish species that were clinically well-tolerated. Therefore, it is strongly recommended that fish-allergic patients have complete controlled oral food challenge tests before being advised that they can consume any fish to which they have had a positive skin test.

Two other important sorts of animal-derived food allergens are the mollusks (snails, mussels, oysters, scallops, clams, squid, octopus, and so on) and the crustaceans (lobster, crabs, prawns, shrimp, and so on). In a pediatric population, the prevalence of IgE-mediated reactions to this group of allergens has been reported to be up to 5% of all IgE-mediated reactions (6). Among this group, shrimp allergens have been extensively studied (45,46). Although considerable crossreactivity among various crustaceans has been demonstrated (47,48), thorough oral challenge studies have not been performed to determine the exact extent of clinically significant crossreactivity to these allergens. Recently, several groups have described the occurrence of crossreactivity of mollusks and crustaceans (which are a class of arthropods) with aeroallergens from other arthropods (49–51). For example, food allergy caused by snails (mollusks) seems to prevail in patients sensitized to mites (arthropods) (49). Crossreactivity exists between the larvae of midges (nonbiting chironomid arthropods) and shrimp (50), and also between shrimp and cockroaches (51). In a recent study, we used a serum pool from children sensitized to German cockroach and to boiled Atlantic shrimp, and the results strongly suggested that several IgE-bind-

ing components, mostly tropomyosins, are shared by these allergens. Witterman et al. identified tropomyosin as a crossreactive allergen among members of the classes Crustacea (*Crangon crangon*), Arachnida (*Dermatophagoides pteronyssinus*), and Insecta (midges, mosquitoes, and cockroaches) (52). Tropomyosin may be an important panallergen, connecting food allergens and aeroallergens of animal origin. Recently, immunotherapy with mite extract has been shown to induce food-specific IgE—for example, that to shrimp or snail allergens, as well as IgE reactive to tropomyosin (53).

Larvae of the *Anisakis* nematode genera, with four known *anisakis* species (*Anisakis simplex*, *Anisakis physeris*, *Anisakis typica*, and *Anisakis schupakovi*), parasitize fish, and cephalopods worldwide. The ingestion of seafood contaminated with third-stage *Anisakis* spp. larvae can induce a specific IgE response in humans with clinical symptoms, usually urticaria. This occurs even if the parasitized fish, have been frozen, and the fish is consumed cooked, since the larvae are killed, and their invasive power is destroyed by heating or after 48 h at -20°C (54,55). The prevalence of *Anisakis* species-specific IgE in the general population in Spain is about 15%, whereas in atopic children with crustacean sensitization and urticaria the prevalence is 81% (56,57). Crossreactivity also exists between certain arthropods (German cockroach and *Chironomus species*) and *anisakis* larvae, possibly by a common tropomyosin allergen (58). Considering that nematodes can survive for years in the infected host and create elaborate immune evasion strategies, including the induction of tolerance to parasite antigens, the natural history of this *anisakis*-induced IgE reaction and its connections with the tropomyosin panallergen requires further investigation (59).

Crossreactivity of Allergens of Plant Origin

Patients having clinically significant allergy and specific IgE to pollen to only one species of plant are relatively rare. It is not unusual to see patients with positive skin test reactions and serum IgE antibodies to various apparently unrelated plants, some of which have never been encountered by the patient. Therefore, the presence of a particular pollen-specific IgE does not necessarily indicate the source of that antibody (60), which is true for allergens in general, as we have previously indicated.

With the advent of molecular biology as a tool for the study of allergens, a new group of panallergens and interrelations among allergens has been revealed. Proteins such as the profilins, exemplified by birch allergen Bet v 2, exist in many plant and animal sources. It has been suggested that they are one of the causes of the multiplant sensitizations existing in some allergic patients (14). There are other plant proteins, such as the pathogenesis-related proteins (PRP), and a number of

enzymes, one being the major birch allergen, Bet v 1, that have been identified as allergens (61,62).

The first case of the oral allergy syndrome (OAS), in which a birch pollen-sensitive patient had itching in the mouth when he ate apples, was reported more than 50 yr ago (63). Thirty-five percent of patients with IgE antibodies to pollen also have specific IgE to plant-derived food allergens (15). Well-known examples are mugwort pollen and vegetables such as carrot and celery (64), also members of the *Rosaceae* family (15). It has been reported that up to 53% of food-allergic pediatric patients suffer from pollinosis (32). The frequency of pollen sensitization in the general pediatric population is not well-established, but it is believed that as many as 75% of atopic children are sensitized to one or more types of pollen (65). Our own data indicate a somewhat lower rate—only 52% of our food-sensitive children being sensitive to pollen. The difference is probably due to differences in the age distribution of the groups studied. Since the peak period of pollen sensitization is about 15 yr of age, our patients (average age, 5.4 yr) were considerably younger. In fact, it is unusual to find clinical sensitization to pollens before the age of 5 yr. All of our young patients were first sensitized to plant foods, either legumes and/or fruit, at an age average of 3 and 2 yr, respectively, and they then developed clinical pollinosis after a mean time of two years. The food allergies most frequently associated with pollen sensitization in our patients are walnuts, chestnuts, sunflower seeds, melon, almonds, and hazelnuts (32).

The OAS, in which patients with ragweed or birch pollinosis react to fresh melons and bananas or to apples and hazelnuts, respectively, is now well-known. Another such association is birch pollen and kiwi (66). In patients with OAS, symptoms appear a few minutes after ingestion of the plant food. Direct contact with the oral mucosa is necessary to produce the clinical symptoms. In most cases, the involved allergens are destroyed on cooking. Homologous proteins widely distributed in unrelated plants and foods (i.e., profilins and PRP) are thought to be responsible for the claimed crossreactivity in OAS (10,13,67). Recently, a young adult with allergic rhinitis and OAS to any fresh fruit was treated successfully by pollen immunotherapy, with resolution of both the allergic rhinitis and the food problem (68). In contrast, in a previous study in children with birch allergic rhinitis and OAS who were treated parenterally with birch or mixed tree extract or orally with birch extract, there was no significant improvement in the OAS after the immunotherapy (69).

Individuals with frequent exposure to products manufactured from natural rubber latex (derived from the rubber tree *Hevea brasiliensis*) are at risk for allergic sensitization. Latex protein allergens (such as those coming from medical- or household-use gloves) can be trans-

ferred to individuals by direct contact with the product or indirectly via airborne allergen-bearing corn starch powder (used as glove lubricant). Children with spina bifida or other congenital malformations that need multiple surgical procedures, frequent bladder catheterization, and other manipulations requiring latex contact are at risk for the development of latex allergy (70,71). Some authors support the hypothesis that children with spina bifida may be genetically prone to the development of latex allergy (72). On the other hand, it may simply be that excessive exposure to latex products at an early age may be a critical factor in this population. Most of the sera from latex-sensitive children with spina bifida have been shown to react with a 14-kDa protein identified as rubber elongation factor (73) and also to a 20-kDa protein (74,75). However, it must be noted that there are no clear associations between the patterns observed on immunoblots of latex protein with sera from latex-allergic patients and the symptoms reported by these mainly adult patients (74). Most interestingly, latex allergy in adults is frequently associated with allergy to a growing number of foods, including, among others, chestnut, avocado, banana, kiwi, potatoes, and tomatoes (76–79). Up to 70% of adult latex-allergic patients have a positive skin-prick test to at least one food, but the majority of these positive skin reactions to foods are not associated with symptomatic food allergy (79). The reason for many of the crossreactions between natural rubber latex and certain fruits is not completely known, but some of the latex allergens have structural homologies with fruit and other plant allergens. A 27-kDa polypeptide allergen with lysozyme activity has been detected in extracts of latex gloves and in liquid ammoniated latex. It is structurally similar to fruit lysozymes and representative of plant-associated defense-related proteins (PRP) (61). Hevein preprotein is a 20-kDa polypeptide that is cleaved into the 4.7-kDa hevein and a 14-kDa C-domain protein. Hevein has structural homology with ragweed allergen, and the 14-kDa fragment has homology with potato stress proteins. In addition, a 46-kDa allergenic latex protein has been found to have structural homology with patatin from potatoes (79). Patatins are storage proteins of plants in the *Solanaceae* family, which includes potatoes and tomatoes, and they could potentially crossreactive with latex allergens. In sera from patients with clinical allergy to latex, banana, and avocado, prominent IgE-binding to a common protein of 30 kDa has been observed (80). In cases of latex allergy associated with pollinosis, profilins in latex may be crossreactive allergens.

Crossreactive Carbohydrate Determinants

Finally, the sugar side chains of a number of glycoproteins that are present in plant and invertebrate organisms should be regarded as

potential allergenic determinants. Such structures have been identified in fungi and in insect venoms (81,82). Lately, it has been suggested that polysaccharides may be responsible for allergenic crossreactivity between *Pityrosporum ovale* and *Candida albicans* in atopic children (83). However, clear evidence of polysaccharide allergenicity is difficult to obtain, more so for pollen than for fungi. Nevertheless, glycosidic determinants have been identified in pollen of the *Oleaceae* family (84,85), and some glycosidic pollen allergens have been found to have homologies with polysaccharides from plant foods.

Concluding Remarks

During the first period of life, between 1 and 5 yr of age, some atopic children become polysensitized to diverse foods at an early age; later, they become allergic to aeroallergens. This is a result of the existence of common allergens that are widely distributed in the plant world. The presence of IgE antibodies to a range of different allergens is not always accompanied by symptoms related to the related allergens. Rather, this may simply be an expression of the crossreactivity produced by panallergens. On the other hand, when allergic symptoms are well-established with a clear relation to multiple allergens, such children should be considered to be high-risk polysensitized atopics, with a lifelong increased risk of becoming sensitized to any allergen that they may have contact with in the future. More work needs to be done, as there are still only a small number of studies in which the influence of crossreactivity between allergens both at the immunological and clinical or epidemiological level has been evaluated in large groups of patients (9,12,86,87).

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