

Sensitivity to tomato and peanut allergens in children monosensitized to grass pollen

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Possible associations between allergy to grass pollen and positive skin tests to food allergens were studied in 102 children monosensitized (as to inhalant allergens) to grass pollen, and in 117 children monosensitized (as to inhalant allergens) to *Dermatophagoides*. Thirty-two foods were tested by an epicutaneous method. Positive skin tests to food allergens were more frequent in children with allergy to grass pollen (59.8%) than in children with allergy to *Dermatophagoides* (9.4%). A considerably high frequency of positive reactions to tomato (39.2%), peanut (22.5%), green pea (13.7%), and wheat (11.7%) was observed in children with allergy to grass pollen. Positive skin tests to peanut closely correlated with positive RAST results and nasal provocation tests, whereas in children with skin test positivity to tomato a close correlation with nasal provocation tests but a 45% correlation with a positive RAST result were observed. RAST inhibition experiments were carried out, and the results may suggest the presence of cross-reacting IgE to grass pollen, tomato, and peanut antigens. Clinical implications of these findings are discussed in the light of histories of food hypersensitivity, urticaria-angioedema, and atopic dermatitis in children with allergy to grass pollen.

Key words: cross-reacting IgE; food allergy; grass pollen allergy; RAST inhibition test.

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A correlation exists between some pollinosis and food allergies. In Nordic countries allergy to birch pollen is closely linked to allergy to apple (7, 12, 15, 18). A correlation has been also described between allergies to mugwort pollen and to celery (15). In the United States, hypersensitivity to melon and banana coincides with ragweed pollinosis (4).

It is not well known whether further associations exist in areas where these pollens are of limited clinical importance. In northern Italy grasses are by far the major cause of pollinosis (20). In this study, possible associations between grass pollinosis and food allergies have been investigated in children with grass pollen monosensitization.

MATERIAL AND METHODS

Patients

Two hundred and nineteen children were selected for this study. The patients had been referred for asthma and/or rhinitis and had undergone routine skin tests for inhalant allergens. Allergens tested included *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, skin derivatives of cat and dog, moulds (*Alternaria tenuis*, *Cladosporium herbarium*, *Penicillium notatum*, and *Aspergillus fumigatus*), pollen of grasses, weeds (*Parietaria officinalis*, *Artemisia vulgaris*, and *Taraxacum officinalis*) and trees (*Olea europea*, *Cupressus sempervirens*, and *Betula pendula*). The glycerin-

preserved crude extracts were obtained from a commercial supplier (Hollister-Stier, Spokane, WA). All extracts were used in the standard w:v strength of 1:20, except for the danders, which were 1:10 w:v.

This study comprised 102 children (69 males and 33 females aged 3–13, mean age 7.9 years) who were (as to inhalant allergens) monosensitized to grass pollen. One hundred and seventeen children (82 males and 35 females aged 3–13, mean age 7.4 years) constituted the control group. They were selected because monosensitized (as to inhalant allergens) to *Dermatophagoides*. The parents gave their informed consent to their children taking part in this study.

Skin testing for food allergens

Skin testing was carried out by an epicutaneous (prick) method, on the palmar surface of the forearm, using 1 mm prick lancets (Hollister-Stier, Spokane, WA). Though rarely, in the case of bleeding, a second test was performed. Both a positive (histamine dihydrochloride 1 mg/ml)

and a negative (allergen diluting fluid) control were included. The concentration of histamine positive control was as in Aas & Belin (2), and has been used in previous studies of associations between allergies to foods and inhalants (10, 15). Thirty-two food allergen crude extracts, obtained from a commercial supplier (Hollister-Stier, Spokane, WA), were employed (Table 1). The extracts were diluted 1:20 (w:v) in glycerol solution (50% glycerol, 0.5% NaCl, 0.6% NaHCO₃, 0.4% phenol, in distilled water). Allergy to cow milk, chicken egg white, peach, apple, pear, and tomato was also assayed by a prick + prick method (10), pricking or soaking the lancet into the fresh food and immediately thereafter into the skin.

Results were recorded after 10 min for positive and negative control solutions, and after 15 min for allergen extracts. Two perpendicular diameters of the wheals were recorded and their mean calculated. The reactions were graded according to the suggestions of Aas & Belin (2). A wheal of the same size as the positive histamine reference was recorded as three plus (+++), and a reaction of half the size was recorded as two plus (++) . Children with skin test reactions of strength $\geq ++$ were defined as positive to the allergen tested. This skin test evaluation method has been previously used in studies of associations between allergy to inhalants and to foods (12, 13, 15, 19). When (on two occasions) reactions occurred to the negative control, they were subtracted from the size of the allergen reactions for subsequent analysis. Any medication was withdrawn at least 10 days before skin testing.

In 94 children with allergy to grass pollen, and in 105 children with allergy to *Dermatophagoides* we skin tested for food allergens 1 year after the first evaluation. In 67 children allergic to grass pollen, and in 79 children allergic to *Dermatophagoides* a second skin test was performed after another year.

Total and allergen-specific IgE levels

Total IgE levels, and levels of specific IgE to grass pollen, tomato, and peanut were determined in 20 children with positive skin tests to grass pollen

Table 1
Food allergens tested

Animal	Vegetable	
Milk cow goat	<i>Bromeliaceae</i>	<i>Leguminosae</i>
	pineapple	bean
		green pea
Egg chicken egg white	<i>Drupaceae</i>	peanut
	apricot	soybean
	cherry	
Fish cod	peach	<i>Pomaceae</i>
	plum	apple
		pear
Meat beef chicken	<i>Fagaceae</i>	
	chestnut	<i>Rutaceae</i>
		orange
lamb pork rabbit	<i>Juglandaceae</i>	
	walnuts	<i>Solanaceae</i>
		potato
	<i>Gramineae</i>	tomato
	barley	
	corn	<i>Umbelliferae</i>
	oats	carrot
	rice	celery
	wheat	

and tomato. Twelve of these patients were also positive to peanut. Because of the ethical problem involved in taking blood from children for research purposes, these patients were selected because a blood drawing was programmed for minor clinical conditions unrelated to allergy. The above mentioned reasons prevented us from carrying out a follow up-study of total and allergen-specific IgE levels.

A radioimmunoassay technique (PRIST and RAST, respectively, Pharmacia Diagnostics AB, Uppsala) was employed, according to the test procedure instructions. Total IgE levels were calculated as International Units/ml, whereas allergen-specific IgE were expressed as a percentage of total counts added. According to the reference standards, positive sera bound more than 2.3 % added radioactivity for all allergen discs employed.

Nasal provocation tests

Nasal provocation tests with tomato and peanut antigens were carried out on children who also underwent tomato and peanut RAST. In addition, 8 children with allergy to grass pollen and 10 children with allergy to *Dermatophagoides* were evaluated as controls, as they had negative skin tests to tomato and peanut. Lyophilized crude tomato and peanut preparations (kindly provided by Lofarma, Milan) were reconstituted in saline immediately before use. Fifty μ l were nebulized into each nostril starting with a saline control and increasing (in steps of 2 mg/ml every 15 min) from 1 mg/ml to a maximum of 10 mg/ml of antigen. Positive results were determined as described (3).

RAST-inhibition experiments

Twenty μ l of serum and 30 μ l of saline or of the inhibiting allergen solution in saline were incubated for 3 h at room temperature (15). Subsequently a RAST disc was added and the assay was continued using the standard RAST technique. Commercially available allergen preparations were used: mixed grass pollen (5×10^5 biological units/ml) from Pharmacia Diagnostics AB, Uppsala, tomato and peanut (1

mg/ml) both from Lofarma, Milan. Their optimum dilution was ascertained in preliminary experiments. Sera RAST-positive to both the inhibiting allergen and the RAST disc coupled allergen were studied. In four experiments tomato - or peanut - RAST was carried out after incubation of sera with a mixture of grass pollen and peanut - or tomato - allergen preparations. In control experiments the specificity of results was tested by incubating sera with cat epithelium allergens (Pharmacia Diagnostics AB, Uppsala) or with the same allergens as that coupled to the RAST disc.

History of hypersensitivity symptoms, atopic dermatitis or urticaria-angioedema

Parents were carefully questioned as to whether their children when eating any of the test foods had manifested itching and oedema of the lips and/or of the tongue, perioral dermatitis, colic, rhinitis, and conjunctival irritation. A history of atopic dermatitis or urticaria-angioedema was investigated.

Statistical methods

The chi-square test was used for differences between proportions. Differences in allergen-specific IgE levels were analysed by Student's *t* test, after angle transformation of data. Correlations between variables were determined by calculation of linear regression (*r*).

RESULTS

Positive skin tests

The number of subjects with positive skin tests to one or more food allergens was significantly ($P = 0.00001$) higher in children with allergy to grass pollen (61/102; 59.8 %) than in children with allergy to *Dermatophagoides* (11/117; 9.4 %). By contrast, these two groups did not differ as to frequency of positive family history of atopic diseases (33/102 = 32.3 % and 44/117 = 37.6 %, respectively) and age at onset of symptoms (mean age 4.9 and 4.1 years, respec-

tively), and an equal percentage of children (12/102 = 11.7% and 14/117 = 11.9%, respectively) had previously undergone specific immunotherapy. A significantly ($P = 0.00007$) higher frequency of rhinitis as an isolated manifestation was instead reported in children with allergy to grass pollen (35/102 = 34.3%), compared with children with allergy to *Dermatophagoides* (14/117) = 11.9%).

Most children with allergy to grass pollen and positive skin tests to foods reacted to one (25/61 = 40.9%) or 2 (14/61 = 22.9%) food allergens. In the remaining 22 children (30.06%) 3 or more positive reactions (mean 5.6) were observed. These children did not differ from those who were negative to foods as to age, sex distribution, age at onset of symptoms, frequency of a positive family history of atopic diseases and of patients who had undergone specific immunotherapy or had rhinitis as an isolated clinical manifestation.

A strong association was found between allergy to grass pollen and positivity to tomato, peanut, green pea, and wheat (Table 2). Of the 61 children with allergy to grass pollen and positive skin tests to foods, 40 (65.5%) were positive to tomato and 23 (37.7%) were positive to peanut. Positivity to both tomato and peanut were present in 18 children (29.5%). A positive correlation was also found with rice, bean, orange, and chestnut (Table 2). The distribution of positive reactions to the remaining foods

showed no significant differences between children with allergy to grass pollen and children with allergy to *Dermatophagoides*.

Reproducibility of skin tests to foods

In a group of children skin tests to foods were carried out 1 and 2 years after first evaluation. In these patients no modification was observed in positive reactions to food allergens recorded at first evaluation. In a small portion of children (5 with allergy to grass pollen and 1 with allergy to *Dermatophagoides*) new positivities were observed, but they did not significantly influence the distribution of positive reactions to food allergens in children with allergy to grass pollen or *Dermatophagoides*.

Concordance between allergen extracts and fresh material

Tests performed using fresh material generally elicited larger wheals than allergen extracts. Positive reactions to fresh material but negative to allergen extracts were observed using apple (5 cases), peach (4 cases), and tomato (4 cases). These reactions were recorded as positive.

Total and allergen-specific IgE

Grass pollen RAST and peanut RAST closely correlated with skin test results (20/20 and

Table 2
Food allergen positives associated with allergy to grass pollen

	Children with allergy to		
Food allergen	grass pollen (n = 102) positive subjects	<i>Dermatophagoides</i> (n = 117) positive subjects	<i>P</i>
Obvious association			
tomato	40 (39.2 %)	2 (1.7 %)	0.00001
peanut	23 (22.5 %)	5 (4.2 %)	0.00005
green pea	14 (13.7 %)	2 (1.7 %)	0.00006
wheat	12 (11.7 %)	1 (0.8 %)	0.00065
Possible association			
rice	9 (8.8 %)	2 (1.7 %)	0.00161
bean	8 (7.8 %)	2 (1.7 %)	0.03010
orange	8 (7.8 %)	2 (1.7 %)	0.03010
chestnut	8 (7.8 %)	2 (1.7 %)	0.03010

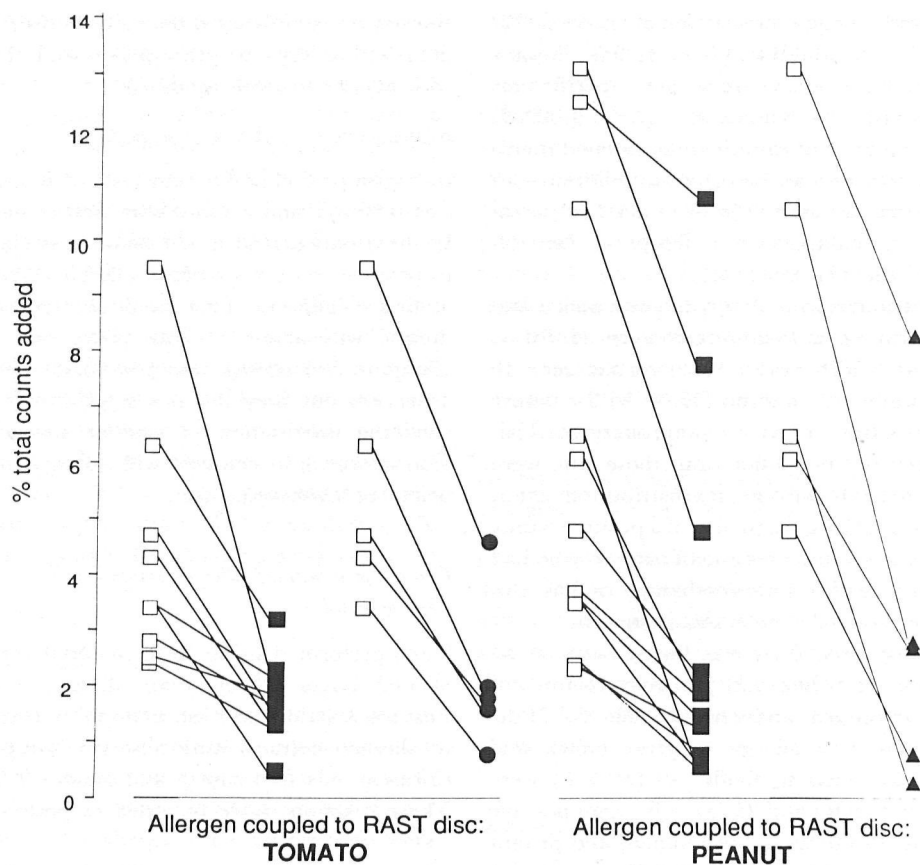


Fig. 1. RAST inhibition experiments. The experiments were carried out on sera RAST-positive both to the inhibitor allergen and the allergen coupled to RAST disc. Inhibitor allergen: none (□); grass pollen (■); peanut (●); tomato (▲).

12/12 positive results, respectively). Positivity for tomato RAST was observed in 9 of 20 (45%) children with positive skin tests to tomato. Incubation of positive sera at 56°C for 4 h led to a loss of reactivity to tomato of more than 91% and to peanut of more than 93%.

Grass pollen-specific IgE levels were uniformly high, and they did not correlate with total IgE levels. On the contrary, both tomato- ($r = 0.8539$; $P < 0.01$) and peanut- ($r = 0.6935$; $P < 0.02$) specific IgE correlated with total IgE levels. Tomato- and peanut-specific IgE levels correlated each other ($r = 0.9437$; $P < 0.01$).

Nasal provocation tests

A close correlation was observed between skin tests to tomato and peanut and nasal provocation tests. A positive response was observed in all children with positive skin tests. Negative results were observed in all grass pollen or *Dermatophagoides*-positive children who had negative skin tests to tomato and peanut.

RAST inhibition experiments

Tomato and peanut allergens did not significantly affect grass pollen RAST (mean inhibition 3.7 and 1.8%, respectively). On the contrary, grass pollen allergens significantly inhibited tomato (mean inhibition 54.9%; $P =$

0.00350) and peanut (mean inhibition 41.9 %, $P = 0.01579$) RAST (Fig. 1). In addition, tomato RAST was significantly inhibited by peanut allergens (mean inhibition 60.2 %; $P = 0.01193$) and peanut RAST was significantly inhibited by tomato allergens (mean inhibition 62.9 %; $P = 0.01894$) (Fig. 1). A double inhibition with grass pollen and tomato allergens or with grass pollen and peanut allergens did not inhibit peanut and tomato RAST (respectively) significantly more than single allergens did.

Control experiments showed that cat epithelium allergens did not affect grass pollen, tomato, or peanut RAST (inhibition constantly less than 6.4 %), whereas grass pollen, tomato, and peanut allergens each inhibited respective RAST by at least 82 %.

History of hypersensitivity symptoms, atopic dermatitis, or urticaria-angioedema

A convincing history of immediate reactions when eating was recorded in 9 (8.8 %) children with allergy to grass pollen. Symptoms consisted of itching of the lips and throat (5 cases) or slight dermatitis in the perioral area (4 cases). Eight children had complaints with tomato, and one with peach. These children had positive skin tests to the food in question. By contrast, hypersensitivity symptoms were not recorded in children with allergy to *Dermatophagoides*.

A history of atopic dermatitis was present in 8 of 102 (7.8 %) children with allergy to grass pollen and in 7 of 117 (5.9 %) children with allergy to *Dermatophagoides*, with no significant difference between these two populations. By contrast, a history of urticaria-angioedema was significantly ($P = 0.00214$) more frequent in children with allergy to grass pollen (12/102; 11.7 %) than in children with allergy to *Dermatophagoides* (2/117; 1.7 %). A history of urticaria-angioedema and of hypersensitivity symptoms coincided in one patient.

Among children with allergy to grass pollen, an increased frequency of positive histories of urticaria-angioedema was reported in patients with positive skin tests to tomato (4/22; 18.1 %), peanut (1/5; 20.0 %), tomato and pea-

nut (4/18; 22.2 %), as compared to patients with some other (1/16; 6.2 %) or no (1/41; 2.4 %) positivity to food allergens, but these differences were not significant.

DISCUSSION

Patients with pollen allergy are also frequently sensitive to allergens in vegetable foods. The birch pollen-apple cluster has been extensively studied (7, 12, 15, 18) and ragweed pollen-melon-banana (4) and mugwort pollen-celery (15) clusters have been described. On the other hand, the relationship between allergy to grass pollen and food allergy is a controversial point. No correlation has been found in studies carried out by means of questionnaires (11, 12, 13), but common structures in grass pollen antigens and in antigens of some vegetables have been observed with RAST (1, 5, 6, 15) and crossed line immunoelectrophoresis (16).

The present study clearly demonstrates that children with allergy to grass pollen manifest positive skin tests to foods far more frequently than children with allergy to *Dermatophagoides*. This increased frequency is due to a high percentage of positivity to some vegetable foods, essentially tomato and peanut. Since only a portion (< 20 %) of all the children studied was positive to tomato and/or peanut, and the large majority (> 95 %) of positive reactions were observed among children with allergy to grass pollen, it is clear that possible non-specific irritants in tomato and peanut allergen extracts and in tomato fresh material were unimportant in eliciting positive skin test reactions. On the other hand, it is possible that positivity to some other vegetable food has been underestimated, as in the present study only four vegetables were tested using fresh material, which is more sensitive than allergen extracts (10, 17). This difference in potency may explain the difference in wheal reaction we observed when fresh material or allergen extract was used.

RAST confirmed skin test results in a group of children positive to peanut, but in children with positive skin tests to tomato a 45 % correlation was found. This latter finding does not significantly invalidate the findings in the present study, since it is known that RAST has an

overall accuracy of about 75%, but is less accurate when a single major allergen is not present, as in some vegetable foods (14), and in particular tomato (21). In addition, a close correlation was observed between skin tests with tomato and nasal provocation tests, which together are an accurate indicator of a Type I reaction to foods (3). Finally, even identically transposing the RAST results to the whole population of children with a positive skin test to tomato, a 10-fold frequency of tomato positivity was present among children with allergy to grass pollen, compared to children with allergy to *Dermatophagoides*.

It has been suggested that the presence of lectins (19), a common carbohydrate side chain in glycoproteins (1), or cross-reacting IgE to common antigens (7, 8, 15, 16, 18) may explain why pollen allergy is associated with sensitivity to botanically unrelated vegetable foods. Analogous to the birch pollen-apple cluster (8, 15, 18), RAST inhibition experiments suggest that grass pollen-tomato-peanut cluster depends on the presence of cross-reacting IgE to common structures. We observed that grass pollen allergens could significantly inhibit IgE specific to tomato and peanut, but when tomato or peanut allergens were used as inhibitors the binding of IgE antibodies to grass pollen RAST disc was not modified. Also in birch pollen-apple association pollen allergens were good inhibitors of IgE to food allergens, but not *vice versa* (8, 15). It is possible that the allergen in pollen sharing a common structure with the allergen in vegetable foods is a minor allergen in pollens but a major allergen in vegetable foods. In the apple-birch pollen model immunoelectrophoretic methods have been employed, which have elucidated this point (16). We are convinced that these techniques will be helpful also in the tomato-peanut-grass pollen model.

In children with allergy to grass pollen, the increased frequency of sensitivities to foods may have some clinical implications. In these children histories of urticaria-angioedema were more common than in children with allergy to *Dermatophagoides*. Allergy to foods may have a pathogenetic role in this con-

dition, at least in some of the affected subjects. In addition, the sensibilizing food (mostly tomato) had clearly caused hypersensitivity symptoms considered to be associated with food allergy (11, 12). By contrast, histories of atopic dermatitis were equally present in children with allergy to grass pollen and in children with allergy to *Dermatophagoides*, and this observation may lead to speculations on the pathogenetic role of allergy to foods (22) and to *Dermatophagoides* (9) in this condition. Considering all of these findings, we are conscious that retrospective inquiries may not be very precise. The criteria we used may have led to under- rather than overestimated results, but it is not likely that error differs between children allergic to grass pollen and those allergic to *Dermatophagoides*.

In this study a new clustering of allergy to pollen and sensitivity to vegetable foods has been reported. It is possible that cross-reacting IgE explain this association, which may be of clinical relevance in countries where grasses are a prevalent species and tomato is a deeply rooted dietary habit.

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