

Allergic sensitization and clinical reactions to latex, food and pollen in adult patients

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Summary

Background Many latex-allergic patients are sensitized to one or more foods. Patients allergic to tree and/or grass pollens are also often sensitized to plant-derived foods. Atopy, defined in most studies as sensitivity to an aeroallergen, is a risk factor for latex allergy. The relative importance of pollen sensitivity, a sign of atopy, as a risk factor for food allergy in latex-allergic patients has not, however, been examined.

Objective To investigate the relationship between pollen sensitivity and sensitivity to food in latex-allergic patients.

Methods Forty-four latex-allergic patients (Groups 1 and 2), 24 of whom were also allergic to tree and/or grass pollen (Group 1) and 25 pollinosis patients who were not allergic to latex (Group 3) were studied. We obtained a history of reactions to food and skin tested them with 12 fresh-frozen fruits.

Results All 12 foods induced a skin test reaction in at least one patient in each of the three Groups. There were, however, twice as many positive skin test reactions to food in patients with pollinosis, whether or not they were allergic to latex, as there were in patients allergic to latex but not to pollen. Latex-allergic patients were most likely to have a positive skin test and a history of a reaction to avocado or banana whereas patients with pollinosis only were most likely to have a positive skin test and a history of a reaction to apple, peach or celery.

Conclusions These results suggest that concomitant allergy to pollen is an important risk factor in determining which plant-derived foods sensitize latex-allergic patients.

Keywords: atopy, food allergy, latex allergy, pollen allergy

Clinical and Experimental Allergy, Vol. 30, pp. 270–275. Submitted 7 April 1999; revised 10 June 1999; accepted 13 July 1999.

Introduction

For more than 10 years now, latex allergy has been an important clinical problem, affecting mainly people who have frequent contact with products made from natural rubber latex (NRL) [1]. It is clear that atopy, defined in most reports as the presence of a positive skin prick test to at least one common aeroallergen, is an important risk factor for allergy to NRL. In addition, many patients allergic to NRL are also allergic to plant-derived foods. Thus, up to three-quarters of individuals who are clinically allergic to NRL have been found to be sensitized to one or more plant-derived foods, most notably banana, avocado, kiwi

and chestnut [2–6]. This has sometimes been referred to as the 'latex–fruit syndrome' [2,5,7]. Conversely, a large majority of fruit-allergic patients have been found to be sensitized to NRL [8]. At the same time, many patients suffering from pollen allergy, but especially those allergic to birch or mugwort pollen, are also allergic to particular foods, among which are apple, pear, carrot, celery and/or potato [9–11]. In areas where birch trees are rare, cosensitization to grass pollen and fruit is frequently observed [9].

These associations have been attributed to the presence of various cross-reacting immunoglobulin (Ig) E antibodies. For example IgE antibodies in a majority of sera from NRL-allergic individuals cross-react with one or more food allergens [12–19]. NRL allergens have been reported to bind to the IgE antibodies in sera from one-third of ragweed-sensitive patients [20,21]. Grass pollen extract has been

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shown to inhibit the binding of NRL to antilatelx antibodies in blood donor sera, and the same authors also found that sheep antisera raised to grass pollen and rabbit antisera raised to latex proteins cross-react with latex and pollen, respectively [22]. Given that proteins with common functions (conserved proteins) exist widely in the plant kingdom, and that a number of these proteins have been shown to be allergenic, this is not surprising. Indeed, structural homologies have been demonstrated between a growing number of plant-derived allergens and NRL allergens, and between grass and weed pollens and NRL [13,16,18,23].

However, the significance of a positive skin test and/or specific IgE in the absence of clinical reactivity remains imprecise. We hypothesized that in many NRL-allergic patients sensitization to foods, except for a few well-known examples, i.e. banana, avocado and kiwi, was related much more to pre-existing pollen sensitivity than to their NRL allergy. Thus, patients allergic to NRL and pollen, as well as patients allergic to pollen but not to NRL, might be sensitized to a different list of foods than patients sensitized to NRL but not to pollen. Therefore, we recruited patients who had a clear-cut history of latex or pollen allergy and we questioned them extensively about possible pollen and food allergies. Then, after confirming their allergy to NRL and/or to grass and/or tree pollens with skin tests, we skin tested them to determine their sensitivity to 12 common plant-derived foods. The present report describes the clinical histories and skin test responses of these patients.

Materials and methods

Patients

Sixty-nine outpatients (56 females and 13 males, age range 18–57 years, mean 33 years) with a history of immediate-type hypersensitivity either to NRL or to tree or grass pollen were recruited consecutively at the Allergy Centre of the Hôpital Rothschild between March and July, 1995. All subjects gave informed consent in accordance with the local ethical committee guidelines. They responded to a standardized questionnaire designed to provide, in addition to a general allergy history, details about the clinical aspects of their allergy to latex, pollens and foods. Allergic reactions to latex included a recent history of localized urticaria, angioedema, rhinoconjunctivitis, asthma and/or an anaphylactic reaction occurring after contact (either direct or indirect) with goods containing NRL (most often latex gloves). Patients diagnosed as being allergic to grass and tree pollen had to have typical symptoms of rhinoconjunctivitis and/or asthma during the corresponding season(s). Patients were excluded if their history was not confirmed subsequently by a positive skin prick test with the relevant allergen(s). In some latex-sensitive patients, the diagnosis

was also confirmed by the presence of serum antilatelx IgE antibody.

The diagnosis of an allergic reaction to food was based on a solid history of localized urticaria, tingling, itching and swelling of the lips and/or buccal mucosa, palate and pharynx (the oral allergy syndrome) and/or rhinoconjunctivitis and/or an exacerbation of pre-existing atopic dermatitis and/or generalized urticaria and/or angioedema (Quincke's oedema), respiratory obstruction (with deep repetitive cough, stridor, dyspnea and/or laryngeal oedema) and/or gastrointestinal symptoms (including nausea, vomiting, cramp-like abdominal pain and/or diarrhoea) and/or an anaphylactic reaction (with acute hypotension) within 1 h after contact with or ingestion of one of the 12 foods listed below.

Additionally, 18 healthy subjects (12 female) with neither clinical symptoms of latex, pollen or food allergy nor positive skin prick tests (SPTs) to latex and pollen allergen extracts were included as a control group.

Allergens

Commercially available latex, a mixed grass pollen glycerinated extract, containing dactylis, poa, ryegrass, timothy and vernal grass pollens and five mixed tree pollen glycerinated extracts, consisting of Betulaceae (alder, birch, hornbeam and hazel), Fagaceae (beech, oak and chestnut), park trees (plane, maple, chestnut, lime and robinia), southern trees (cypress, mulberry, olive and privet) and damp area trees (ash, poplar, willow and elder) were purchased from Laboratories Stallergènes (Antony, France). This NRL extract had previously been shown to have excellent sensitivity and specificity [24]. The same is true for the pollen extracts. Twelve fresh foods (bananas, avocados, papaya, chestnuts, kiwi, mango, celery, apples, peaches, pineapple, cantaloupe/melon and tomatoes) were purchased locally, brought to our laboratory and immediately cut into 1 × 1 × 1 cm cubes. The cubes were placed individually in wells of a microtitre plate and then frozen and stored at –20 °C until used.

Skin prick tests

SPTs were done in singlicate on the volar side of a forearm using Stallerpoint, needles (Laboratories Stallergènes). H₁ antihistamines were stopped for at least 1 week before skin testing. SPTs with latex and pollen extracts were done by placing a drop of extract on the skin and pricking through the drop. Tests with the foods were done as follows: a sample of each of the 12 foods was removed from the freezer, thawed at room temperature (10–15 min) and then placed on the patient's forearm. The skin was pricked through the piece of food using a Stallerpoint needle and the food was then removed from the skin site. A negative

control (glycerinated extract diluent) and a positive control (9% codeine phosphate, Laboratories Stallergènes) were included in each series of tests. The tests were read 12–15 min after application and the mean diameter of the resulting weals and erythema was calculated. A positive test consisted of a weal of at least 5 mm in mean diameter with surrounding erythema greater than the weal, a negative response to the glycerinated diluent and a positive response to the codeine phosphate solution. In this study, only those patients who had a positive SPT to at least one of the pollen extracts were considered to be atopic.

Statistical analysis

The Chi-square test was used for statistical comparisons between different groups. The correlations between SPT diameters were tested by the Spearman non-parametric rank correlation test. A *P*-value of 0.05 was taken as the upper limit of significance. The percentages were expressed with 95% confidence intervals (95% CI).

Results

Latex and pollen allergies

Based on their clinical history of latex and/or pollen allergy, and with confirmation by skin testing, the 69 patients were divided into the following three groups:

- Group 1 (latex-and pollen-allergic) included 24 patients (22 female, two male, median age 33 years) whose presenting complaint was allergy to latex and who were also allergic to pollen. Fourteen (58%) in this group were allergic to both trees and grasses, seven (29%) only to trees and three (13%) only to grass.
- Group 2 (allergic to latex but not to pollen) included 20 NRL-allergic patients (19 female, one male, median age 33 years) who claimed to have no symptoms of tree or grass pollen allergy and whose pollen SPTs were negative.
- Group 3 (allergic to pollen but not to latex) included 25 pollen-allergic patients (15 female, 10 male, median age 32 years) without a history of NRL hypersensitivity.

Thirteen (52%) of these patients were tree- and grass-pollen allergic, nine (36%) were allergic only to trees, and three (12%) only to grass. NRL SPTs were negative in all the patients in this group.

A majority (63%) of those in Groups 1 and 3 (all patients with pollinosis) were also allergic to house dust mites and/or cats (data not shown). Ninety-five percent of the 43 NRL-allergic patients (Groups 1 and 2) were young women; 90% of them were health care professionals. Allergic reactions to NRL were related to contact with powdered NRL gloves in 86% of these patients; 19 of 24 in Group 1 and all 19 in

Group 2. Three of the Group 3 patients were also health care professionals.

Food allergies

Nearly half of the 69 patients reported having had at least one allergic reaction to one or more of the 12 foods included on the list below and some reported having more than one such episode. The frequency of any clinical reaction reported to each of the 12 foods is shown in Table 1. Group 3 patients reported more food allergies than Group 1 patients and Group 2 patients reported even fewer food allergies. Avocados and bananas were the most frequent cause of allergic reactions in patients in Groups 1 and 2. Group 3 patients suffered most often from allergic reactions to apples, peaches, celery and kiwi. None of the Group 1 and 2 patients reported intolerance to celery. Forty percent of the food-induced reactions were systemic in nature. These reactions were caused by the following foods: in Group 1, five were caused by avocado, three by banana, two by mango, two by tomato and one by chestnut. In Group 2, four systemic reactions were caused by avocado, four by banana and one by cantaloupe. In Group 3, celery caused four systemic reactions and kiwi caused one. Overall, there were very few reports of allergic reactions to chestnut, mango, pineapple, cantaloupe and tomato, and none at all to papaya, in spite of relatively frequent evidence of sensitization to these fruits.

According to their histories, the onset of pollinosis most often preceded that of latex allergy and/or food allergy in most Group 1 and 3 patients. In contrast, the onset of food allergy in Group 2 patients was recognized as having begun before or after their latex allergy with about equal frequency.

Food skin prick tests

SPTs with all 12 foods were negative in all the nonallergic control subjects. Eighty-four percent (95% CI 64–104%) of the 69 patients had a positive SPT to at least one of these 12 foods (83, 80 and 88% in Groups 1, 2 and 3, respectively). However, as shown in Table 1, the percentage of positive SPTs in Group 1 (46%; 95% CI 41–51%) and the percentage in Group 3 (45%; 95% CI 40–50%) were significantly higher compared to the percentage in Group 2 (24%; 95% CI 21–27%) (*P* < 0.001). All 31 patients who had a history of allergic reactions to foods (11 in Group 1, seven in Group 2 and 13 in Group 3) had a positive SPT for the corresponding food(s), except two who had had only an itchy throat after eating kiwi. Except for these two patients, none of the 11 patients with negative food SPTs had had a clinical reaction to any of the 12 foods tested.

Table 1. Food SPT and clinical allergic reactions to foods in latex- and/or pollen-allergic patients

Food	Group 1; L+/P+; (n = 24)		Group 2; L+/P-; (n = 20)		Group 3; L-/P+; (n = 25)	
	No. of clinical reactions to:	No. (%) of patients with a positive food SPT to:	No. of clinical reactions to:	No. (%) of patients with a positive food SPT to:	No. of clinical reactions to:	No. (%) of patients with a positive food SPT to:
Banana	3	16 (67%)	4	8 (40%)	1	11 (44%)
Avocado	7	14 (58%)	4	8 (40%)	2	10 (40%)
Papaya	0	14 (58%)	0	10 (50%)	0	11 (44%)
Chestnut	2	12 (50%)	0	7 (35%)	0	9 (36%)
Kiwi	1	12 (50%)	2*	6 (30%)	5*	11 (44%)
Mango	2	12 (50%)	0	4 (20%)	0	11 (44%)
Celery	0	8 (33%)	0	1 (5%)	5	18 (72%)
Apple	1	7 (29%)	0	3 (16%)	12	14 (56%)
Peach	2	11 (46%)	1	4 (21%)	8	17 (68%)
Pineapple	1	7 (29%)	0	3 (15%)	0	3 (12%)
Melon	0	9 (38%)	1	1 (5%)	1	8 (32%)
Tomato	2	11 (46%)	0	3 (15%)	0	12 (48%)
Total	21	133+/288 tests (46%)	12	58+/240 tests (24%)	34	135+/300 tests (45%)

*One patient in each of these two groups had a possible allergic reaction (itchy throat) to kiwi but the SPT was negative. Significance of the difference between the percent of positive SPTs in pairs of Groups: between Groups 1 and 3, $\chi^2 = 0.07$ (NS); between Groups 1 and 2, $\chi^2 = 27.5$ ($P < 0.0001$); between Groups 2 and 3, $\chi^2 = 25.2$ ($P < 0.0001$).

Among the 58 patients with at least one positive food SPT, the likelihood of having had an allergic reaction to food was higher in those who had positive SPTs to at least four foods (27 out of 41 patients) compared with those with positive SPTs to between one and three foods (four out of 17) ($\chi^2 = 20.3$, $P < 0.0001$; Odds Ratio 6.27; 95% CI 4.8–7.8%).

In the 20 patients in Group 2, positive SPTs were most often observed with banana (40%), avocado (40%), papaya (50%) and chestnut (35%) (Table 1). Overall, 33 out of 80 (41.3%; 95% CI 29.8–46.2%) of the SPTs with these four foods were positive in Group 2. This percentage is significantly lower than the 58% (95% CI 46.7–69.3%) observed in Group 1 ($\chi^2 = 7.6$; $P < 0.05$) but not different from the 41% (95% CI 32.9–49.1%) in Group 3 ($\chi^2 = 0.2$; NS). The percentage of positive SPTs with these four foods is also significantly higher in Group 1 compared with Group 3 ($\chi^2 = 5.9$; $P < 0.02$). On the other hand, for the 20 Group 2 patients the percentage of positive SPTs with the other eight foods (15.6%; 95% CI 13.2–17.9%) was clearly less than observed in the 24 Group 1 patients (40.1%; 95% CI 34.5–45.7%) ($\chi^2 = 25.4$; $P < 0.001$) and also less than observed in the 25 Group 3 patients (47%; 95% CI 40.6–53.4%) ($\chi^2 = 39.6$; $P < 0.001$). Finally, there was no significant difference between Groups 1 and 3 ($\chi^2 = 1.9$; NS).

There were no significant correlations between the diameter of the weals induced by any of the 12 food allergens and those induced by the NRL extract, nor between the diameter of the latex reaction and those induced by grass or

tree pollen extracts. In contrast, there were significant correlations between the weals induced by the banana and avocado extracts, the banana and kiwi extracts, the banana and papaya extracts, and the banana and peach extracts, and also between the avocado and peach extracts and the avocado and papaya extracts (Table 2).

Discussion

As has been noted in a large number of published reports, sensitization to NRL and/or foods, with or without clinical allergy, occurs preferentially in atopic individuals, which in the present study we defined as a positive SPT to either a mixed tree and/or a mixed pollen extract. It has been

Table 2. Correlations (r) between the weal diameter of simultaneously positive SPT reactions to food allergens (n)

	n	r	P
Banana/kiwi	29	0.6	<0.0001
Banana/papaya	35	0.5	<0.002
Banana/peach	32	0.4	<0.007
Avocado/papaya	35	0.6	<0.0001
Avocado/peach	32	0.4	<0.003

(r = Spearman rank correlation coefficient).

proposed that sensitization to certain foods in pollen-allergic patients is due to pre-existing sensitization to pollen [25]. We hypothesized that sensitization to many foods in NRL-allergic patients is related much more to their coexisting atopy than to their NRL allergy, except perhaps for allergies to a limited number of foods, such as banana, avocado and kiwi. Consequently, patients allergic to both NRL and pollen, as well as patients allergic to pollen but not to NRL, might be sensitized to a different set of foods than patients sensitized to NRL but not to pollen.

To test this hypothesis, we did food SPTs in three groups of patients. The first two groups were allergic to NRL and the patients in one of the two groups were also allergic to pollen while the patients in the other group were not allergic to pollen. The patients in the third group were not allergic to NRL but they were allergic to pollen. We also included a group of healthy subjects who were neither atopic nor sensitized to NRL. Since the poor quality of commercially available food extracts is well known, we used fresh foods in order to increase the sensitivity of the food SPTs [26]. The high specificity of these food SPTs was demonstrated by the negative responses observed in all 18 nonatopic, non-NRL allergic control subjects.

The choice of the 12 foods was based on published reports of the prevalence of sensitization to certain foods of plant origin in patients allergic to NRL on the one hand and in pollen-sensitive patients on the other. We were surprised to find that the frequency of positive food SPTs was identical in patients allergic to pollen whether they were (Group 1) or were not (Group 3) allergic to NRL. In contrast, as predicted, the prevalence of positive food SPTs was significantly less in patients allergic to NRL who were not sensitized to pollen (Group 2).

In any individual, the results of SPTs are often positive for allergens which have no apparent antigenic similarity, for example, grass pollen and house dust mites. In such cases, the size of the responses will vary according to the level of sensitivity of the subject for each of the allergens, which is a function of the amount of specific IgE on the individual's cutaneous mast cells. Accordingly, there is usually no significant correlation between the size of simultaneously positive tests for unrelated allergens. One would therefore not be surprised by the lack of correlation between the size of the responses to latex and banana or between latex and avocado, for example. This suggests that if these substances have allergens or epitopes in common then these allergens must contribute very little to the degree of positivity of the responses. In contrast, for two similar allergens, for example *Dermatophagoides pteronyssinus* and *D. farinae*, the size of simultaneously positive tests are significantly correlated, implying that the tests are detecting one or several common major allergens or epitopes in the two extracts. The fact that in the present study

there was a very strong correlation between the size of the SPT responses to certain fruits (avocado and banana, avocado and papaya, etc.) suggests that these substances contain one or more closely identical allergens or epitopes that react with cross-reacting antibodies and that these allergens or epitopes have a major influence on the results of the SPT.

The SPT results led us to analyse the importance of the association of sensitivity to NRL and/or sensitivity to pollen (i.e. atopy) with sensitivity to certain foods. We noted that the frequency of positive SPTs to four particular foods, namely banana, avocado, papaya and chestnut, was as high in patients allergic to NRL but not to pollen (Group 2) as it was in patients allergic to pollen but not to NRL (Group 3). On the other hand, the percentage of patients who reacted to the eight other foods used in the present study was significantly less in Group 2 patients than in the two groups of pollen-sensitive patients, whereas there was no difference between these latter two groups with respect to these same eight foods. Thus, our data support the hypothesis that sensitization to many foods other than banana, avocado, papaya, kiwi and chestnut, and perhaps a few others such as tomato and potato, is a reflection of sensitization to pollen and not to NRL.

Concerned about advice which should be given to latex-fruit-allergic patients but not to those allergic only to NRL, Breiteneder and Scheiner [18] proposed that panels of certain specific NRL allergens could be used to differentiate patients allergic only to NRL from those who are allergic to both NRL and fruit. Our results suggest that the picture is more complex than that. To have sufficient information on which to base reasonable advice, we recommend that two standard panels of food extracts should be used when skin testing NRL-allergic patients. One set would include foods which are frequent causes of allergic reactions in NRL-allergic patients and the other set would include those which are frequent causes of such reactions in pollen-allergic patients. With the results of these tests the allergist would be better equipped to tell NRL-allergic patients which foods they should avoid.

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