

Latex allergy: clinical features and cross-reactivity with fruits

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Background: Latex IgE-mediated allergy is an important medical problem, but its clinical characteristics and association with food allergies are not well defined.

Objective: Our objectives were to determine the clinical features of latex-allergic patients, and latex-associated food hypersensitivities.

Methods: A prospective study was performed in our outpatient clinic. It consisted of a clinical questionnaire, skin prick tests with aeroallergens and foods, skin test with a latex extract, determination of total and specific IgE by CAP/RAST methods, and RAST inhibition. Latex and food allergies were diagnosed on the basis of a suggestive clinical history and a positive skin test with the corresponding allergen.

Results: Twenty-five patients were diagnosed as having latex allergy. Their mean age was 33 ± 9.0 years, with female predominance (23:2). There were nine greenhouse and six hospital workers. Latex-induced reactions included systemic anaphylaxis in nine patients (36%). Average total IgE was 161 kU/L, and it was within normal limits in 16 cases. Latex skin prick tests had excellent diagnostic precision with no adverse reactions, and CAP for latex diagnostic sensitivity was 80%. Forty-two food allergies were diagnosed in 13 of our patients (52%), and 23 of these consisted of systemic anaphylaxis. The most frequent food hypersensitivities were to avocado (9), chestnut (9), banana (7), kiwi (5) and papaya (3). Through RAST-inhibition, cross-reactivity among latex, avocado, chestnut, and banana was demonstrated.

Conclusions: In our experience, latex allergy affects middle-aged women in certain professions at increased risk. Our data suggest the existence of a "latex-fruit syndrome," because 52% of our latex allergic patients had allergies to certain fruits.

INTRODUCTION

Latex or natural rubber is extracted from a tree, *Hevea brasiliensis*, originally from Brazil. For many decades, latex has been used widely in medical supplies (eg, gloves, catheters, and odontology dikes), balloons, condoms, shoe soles, etc. In 1979, Nutter described the first case

of contact urticaria due to the latex used in the manufacture of gloves¹; later, various similar cases were published.²⁻⁸ In 1986, Carrillo et al reported a case of professional contact urticaria, rhinitis, and angioedema caused by sensitization to latex gloves,⁹ showing that the antigens involved are present in natural latex and that they are of a protein nature. Since then, numerous cases of latex IgE-mediated allergy have been described with clinical manifestations that vary from urticaria to bronchial asthma¹⁰ or anaphylactic shock.¹¹⁻¹³ In general, this peculiar hypersensitivity affects persons with professions that "entail risk"¹⁴⁻¹⁶ (ie, that involve prolonged and repeated

exposure to latex, as hospital workers) or patients who have had many operations, such as those with spina bifida,^{17,18} although it could also affect some individuals with no recognizable prior risk factors.

Various authors have investigated the characteristics of the antigens responsible for latex hypersensitivity. With the use of immunoblotting techniques, it has been demonstrated that latex antigens are various proteins with molecular weights between 10 and 100 kD.^{14,19-22}

The association of latex hypersensitivity with banana and chestnut allergy has been described recently, and the existence of cross-reactivity among them has been shown through RAST inhibition.²³⁻²⁷ Subsequently other cases of clinical association between latex and banana and avocado allergy have been described, suggesting that they may share antigenic determinants.²⁸⁻³⁰

There has been no exhaustive study to determine the importance, type, and frequency of food hypersensitivity in latex-allergic patients. We have studied a group of 25 subjects with latex allergy whose clinical features and association with food immediate hypersensitivity we describe in this paper.

MATERIALS AND METHODS

Patients

To determine the clinical features of latex allergy and its association with food hypersensitivity, a prospective study was designed in the outpatient service of our Allergy Section. The study was approved by our hospital Institutional Review Board and was described in detail to all participants before obtaining informed consent

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and admission into the study. It consisted of a detailed clinical questionnaire, in vivo skin tests and obtaining serum for in vitro tests. Twenty-five patients (seen in our Section from March 1992 to March 1993) were included in our protocol; they described immediate reactions in relation to latex exposure, suggestive of being IgE-mediated, and had positive skin prick tests with a latex extract. Fifteen healthy volunteers and 15 patients allergic to *Dermatophagoides*, of similar age and sex to our latex-allergic patients, were used as a control group after obtaining informed consent from them. The same in vivo and in vitro tests were carried out on the control group.

Food immediate hypersensitivity was diagnosed on the basis of a suggestive clinical history and a positive skin prick test with the corresponding food. Before performing skin tests, the clinical histories were evaluated by two different investigators who considered only recent reactions (within the last 5 years) and those foods implicated in at least two episodes for each patient.

In Vivo Tests

Commercial PRICK. Skin prick tests were carried out in the volar side of the forearm by puncture with a Morrow-Brown needle (Bayer S.A., Madrid, Spain), a 30-mm long stainless steel device with a 1-mm point. One sterile device was used for each test and was then discarded. Skin tests with a battery of commercial aeroallergens (mites, fungi, pollens, and animal dander) [Abelló Laboratories, Madrid, Spain], and of the most commonly allergenic foods (milk, egg, fish, nuts, leguminous vegetables, peach, and cereals) [Bencard, Worthing, UK] were performed. Histamine phosphate (10 mg/mL) was used as positive control and physiologic saline as negative control. The results were the mm measurements of the larger wheal diameters 15 minutes after puncture. A wheal $\geq$ histamine

phosphate control was considered positive.

PRICK with latex. Skin prick testing was done with the extract obtained by washing the inside of a latex glove (Baxter Healthcare Co, Valencia, CA) for ten minutes with phosphate-buffered saline (PBS), prepared just before performing the test.

PRICK with fresh foods. Skin prick tests with fresh foods³¹ were carried out with avocado, chestnut, banana, kiwi, walnut, pineapple, melon, and papaya.

Patch skin tests. Patch skin tests were carried out with a standard battery of 25 contact allergens from the International Contact Dermatitis Research Group, including the rubber additives thiuram mix, mercapto mix, and carba mix (TRUE-test, Pharmacia Diagnostics, Sweden).³² They were read at 48 and 72 hours after application.

In Vitro Tests

Total IgE. This was determined by the DELFIA method (Pharmacia Diagnostics, Sweden), following the manufacturer's instructions.

Specific IgE was determined against latex, avocado, banana, kiwi, and melon with the Pharmacia IMMUNOCAP System (CAP), and against pineapple and walnut with the Phadezym RAST technique, following the manufacturer's recommendations (Pharmacia Diagnostics, Sweden). A result of ≥ 0.7 kU/L for CAP and ≥ 0.7 PRU/mL for RAST was considered as positive.

Antigenic extracts. A natural latex (kindly supplied by Perrins S.A. Barcelona, Spain) extract was prepared by diluting it at 10% wt/vol ratio in PBS at pH 7.2 and centrifuging it at 1000 g for 30 minutes. The supernatant was then filtered through a 45- μ m Millipore filter (Millipore Co, Bedford, MA). The protein concentration, estimated with Lowry method was 1 mg/mL.

Avocado extract was prepared by degreasing the avocado pulp with acetone, then diluting it at 10% wt/vol in PBS at pH 7.2 at room tem-

perature and centrifuging it at 1000 g for 30 minutes. The supernatant was then gathered and passed through a 45- μ m Millipore filter. The protein concentration, estimated with Lowry method, was 1.75 mg/mL.

An extract of crushed dried chestnuts was also prepared, degreased with acetone and then the proteins were extracted in PBS, following the same procedure as described with the avocado. The protein concentration with Lowry method was 1.5 mg/mL.

RAST inhibition. Latex extract was fixed to nitrocellulose discs for RAST testing according to the usual procedure.³³ The standard curve of Pharmacia was used as a reference for its interpretation and RAST ≥ 0.7 PRU/mL was considered positive. RAST inhibition was carried out in a pool of sera from our food-allergic patients against latex-marked discs, incubating sera with four increasing concentrations (1/1.000, 1/100, 1/10, 1/1) of avocado, chestnut, and latex extracts, and of a banana commercial extract (Bencard, Worthing, UK, at a 10 mg/mL concentration), processing all samples in duplicate. Last, corresponding inhibitions of avocado and chestnut RASTs with latex extract were also performed.

RESULTS

Table 1 summarizes the general characteristics of our patients. The age (mean $\pm$ SEM) was 33.0 ± 9.0 years (a range of 18–54), with a clear predominance of females (23:2). There were nine agrarian workers (flower and vegetable greenhouses), six hospital workers (four nurses, one surgeon, and one cleaner), four housewives, and six miscellaneous. A total of 17 persons (68%) needed to use gloves in their working environment. Eight of our patients (32%) were atopic (positive skin prick tests to major aeroallergens), while four had had contact dermatitis (Table 1). Average total IgE was

Table 1. General Characteristics of Latex Allergic Patients

Patient Number	Age, yr/Sex	Profession	Atopy	Total IgE, kU/L	Latex Symptoms	Latex SPT,* mm	Latex IgE, kU/L
1	43/F	Agriculture	Nickel CD	78	U/AE	8 x 7	16.9
2	30/F	Agriculture	Pollen RC	65	LU	7 x 6	6.0
3	44/F	Nurse	—	224	A	18 x 13	5.6
4	39/F	Housewife	—	31	A	12 x 12	3.2
5	25/F	Administrative	—	29	U/AE/RC	9 x 9	3.5
6	23/F	Agriculture	Mite RC	289	LU	5 x 5	0.4
7	25/F	Agriculture	—	18	U/AE/RC	7 x 6	3.6
8	28/F	Agriculture	—	87	U/AE/R	8 x 7	>100
9	54/F	Agriculture	—	27	A	14 x 10	22.4
10	29/F	Nurse	—	26	A	14 x 12	5.2
11	29/F	Nurse	—	49	RC	14 x 14	6.8
12	18/M	?	Mite RC	386	RC	14 x 12	>100
13	39/F	Cleaner	—	268	A	11 x 10	48
14	28/F	Housewife	Mite RC/BA	333	AE	7 x 5	0.5
15	30/F	Administrative	Nickel CD	38	A	6 x 5	0.8
16	46/F	Cleaner	Thiuram Mix CD	20	U/AE	8 x 7	4.1
17	33/F	Nurse	Nickel CD	293	A	8 x 5	2.8
18	30/F	Agriculture	—	54	A	14 x 8	5.4
19	47/F	Housewife	Mite BA	86	A	9 x 5	0.0
20	22/F	Esthetician	Mite RC/BA	1028	LU	12 x 10	5.9
21	25/F	Administrative	Mite RC/BA	259	U/AE/R	16 x 15	1.6
22	33/F	Surgeon	—	21	U/AE/R	9 x 9	2.0
23	39/M	Agriculture	Mite RC	69	U/AE/RC	17 x 14	0.4
24	42/F	Housewife	—	28	U/AE	18 x 10	0.0
25	25/F	Agriculture	—	224	U/RC	10 x 9	2.0

* SPT, skin prick test; F, female; M, male; CD, contact dermatitis; RC, rhinoconjunctivitis; R, rhinitis; BA, bronchial asthma; U, urticaria; AE, angioedema; LU, local urticaria; and A, systemic anaphylaxis.

161 kU/L, (a range of 18–1,028), and it was within normal limits (<100 kU/L) in 16 patients.

The most frequent clinical manifestations of latex exposure were generalized urticaria with facial angioedema $\pm$ rhinoconjunctivitis in ten patients, and urticaria/angioedema with bronchial asthma $\pm$ hypotension in nine. In at least 11 of our patients latex reactions had become progressively more serious over time (usually starting with only local urticaria). Average evolution time, from the onset of latex clinical manifestations until diagnosis, was 4.5 years. No adverse reactions were observed during the latex skin tests. The skin prick tests with our latex extract were negative in the controls tested. The CAP to latex was positive in 20 of our patients (mean 10.4 kU/L), therefore showing a diagnostic sensitivity in relation to the clinical

history and the skin prick test of 80%, being negative in the controls. There was no relation between total IgE and latex-specific IgE.

Thirteen of our patients (52%) had food immediate hypersensitivity (Table 2). A total of 42 food allergies were diagnosed in these 13 patients. Twenty-three of these reactions were classified as systemic anaphylaxis. The most frequent food hypersensitivities were to avocado in nine patients (seven with systemic anaphylaxis), chestnut in nine (four with anaphylaxis), banana in seven (five with anaphylaxis), kiwi in five (two with anaphylaxis), papaya in three (two with anaphylaxis), and fig in two patients (both with anaphylaxis). Seven of our patients had three or more food allergies and it was usual for the spectrum to widen with time. In five cases, latex allergy preceded clinically

significant food hypersensitivity; in another five patients, there was a simultaneous onset; and in three cases food allergies were present before latex hypersensitivity. Kiwi allergy onset could be simultaneous ($n = 2$) or follow ($n = 3$) latex sensitivity onset. Papaya allergy occurred after and fig allergy occurred together with the latex sensitivity. We found no differences in general characteristics between patients with and without food associated allergy. No food allergies were diagnosed in the control group. (The general prevalence of food hypersensitivity in our allergy clinic is of 1.1%).

The skin prick tests with fresh fruits showed an 80% concordance with the clinical diagnosis, being negative in all the controls. Specific IgE to fruits with commercial CAP was positive to avocado in ten cases, chestnut in two, banana in three, papaya in two, and melon in one; RAST was positive to walnut in two cases. The CAP diagnostic sensitivity in our group of food-allergic patients was 37%, being better for avocado (70%) than for the other fruits evaluated. The CAP diagnostic specificity was 77% for avocado and from 90% to 100% for the other fruits. In the control group, CAP to fruits gave no positive results.

RAST with the pool of sera from our patients against discs marked with latex extract was positive (3.5 PRU/mL). On incubating the pool of sera with avocado extract at increasing concentrations, a progressive RAST inhibition that reached 56% at the maximum concentration was obtained (Fig 1). On incubating with chestnut extract, the maximum inhibition was 65%, and with banana extract, it reached 42%. Avocado RAST in the pool of sera was 1.2 PRU/mL, and a progressive RAST inhibition which reached 79% was obtained on incubating with latex extract. Finally, chestnut RAST was 5.2 PRU/mL, and on incubating with latex extract, the maximum inhibition was 76%.

Table 2. Associated Food Immediate Hypersensitivities in Latex Allergic Patients

No.*	Avocado			Chestnut			Banana			Other Food Allergies			
	CM	SPT†	IgE‡	CM	SPT†	IgE‡	CM	SPT†	IgE‡	Food	CM	SPT†	IgE‡
1	A	4 x 4	13.1	A	6 x 5	0.0							
2	A	18 x 17	3.8	AE	4 x 4	0.0	U/AE	11 x 9	0.4	Papaya	U	6 x 4	nd
										Peanut	AE	9 x 9	0.0
										Mustard	AE	10 x 9	nd
										Pepper	AE	15 x 12	nd
3	AE	4 x 4	0.0	AE	4 x 4	0.0	U	3 x 3	0.0				
4	A	5 x 3	2.4				A	3 x 3	0.4	Walnut	U/AE	7 x 6	0.0
										Kiwi	RC	3 x 3	0.0
										Kiwi	RC	3 x 3	0.0
5	A	6 x 5	2.7	AE	7 x 5	0.0							
6				RC	3 x 3	0.0							
7				A	9 x 9	0.0							
8	A	12 x 12	15.2	A	11 x 7	20.6	A	10 x 10	5.1	Papaya	A	15 x 8	0.6
										Pineapple	A	5 x 4	0.0
9	A	9 x 8	0.4	A	3 x 3	0.0	A	5 x 5	0.0	Kiwi	AE	4 x 4	0.6
										Fig	A	5 x 5	nd
10	AE	5 x 5	0.4										
11										Kiwi	A	4 x 4	0.0
12				U/AE	12 x 11	0.5	A	4 x 4	0.0				
13	A	7 x 7	3.9				A	3 x 3	2.0	Kiwi	A	8 x 8	0.0
										Papaya	A	4 x 4	1.9
										Peach	AE	4 x 4	0.0
										Fig	A	5 x 4	nd
										Potato	AE	6 x 5	2.5

* No., patient number; CM, clinical manifestations; nd, not done; RC, rhinoconjunctivitis; U, urticaria; AE, angioedema; A, systemic anaphylaxis.

† Skin prick test in mm.

‡ IgE in kU/L.

DISCUSSION

In the last few years, immediate hypersensitivity to latex has acquired great importance because of its increasing frequency, its presentation as an occupational disease in hospital personnel, and the potential seriousness of the reactions it induces. The increase in frequency could be related to increased use of latex gloves and to better recognition of this pathology.

We contribute 25 new cases of latex IgE-mediated sensitivity. Both the average age (33 years) and the clear predominance of females (92%) in our patients agree with previous series.^{14,34} Female predominance could be explained because women usually predominate in professions that require use of latex gloves. Naturally, children with spina bifida and multiple operations with latex hypersensitivity^{17,18} are a different population and should therefore be studied separately.

More than half of the cases of latex allergy previously described have involved hospital personnel.¹⁴⁻¹⁶ The fact that in our series 36% (9/25) were agricultural workers (employed in vegetable or flower cultivations and usually in greenhouses), who use latex gloves while working, is a new observation. In our daily practice, agricultural workers are only 4% of our patients. Epidemiologic studies are necessary to determine the prevalence of latex sensitivity among greenhouse workers to determine whether they constitute another risk group for latex allergy. Perhaps any profession that requires the use of latex gloves should be considered a risk factor. In contrast with other series,^{15,16,34} only 32% of our patients were atopic, and 16% had contact dermatitis; so our data do not support the hypothesis that atopy and contact dermatitis favor latex hypersensitivity. The fact that seven of our

patients were allergic to dust mites may be due to the high prevalence of mite allergy in our geographic area.

It is noteworthy that 36% of reactions were systemic anaphylactic reactions; this was somewhat higher than other series (24% in that of Jaeger et al¹⁴). This can be explained because patients with latex hypersensitivity are not usually referred to our Section.

To confirm *in vivo* the diagnosis of latex allergy in a patient with suggestive clinical history, a skin prick test with a latex extract showed excellent sensitivity and specificity.³⁵ In our experience, skin prick test with the extract obtained by washing the inside of a latex glove with PBS is a simple method with no risk, and with a diagnostic precision close to 100%. Nevertheless, as anaphylactic reactions during skin testing with latex extracts have been reported,³⁶ caution must

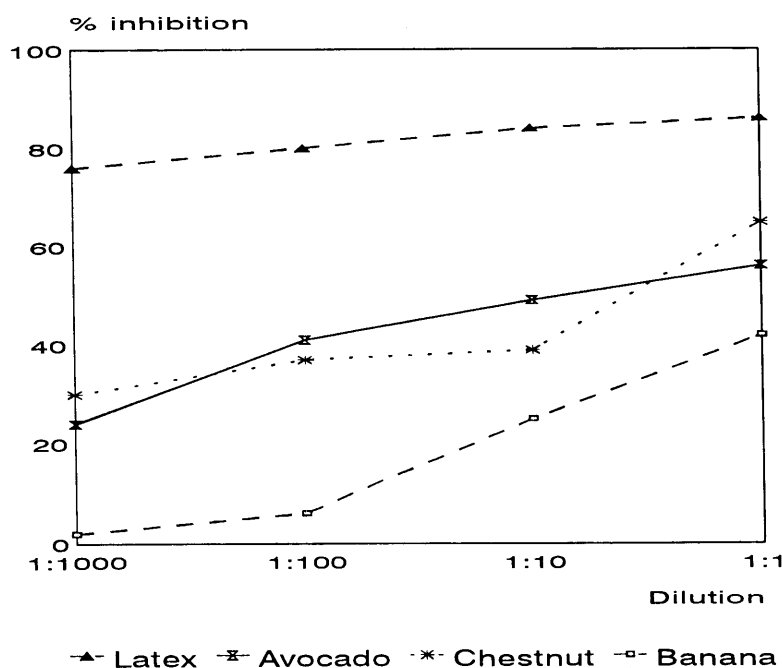


Figure 1. Latex RAST-Inhibition.

taken until a standardized extract is available. In our opinion, these reactions reported might be related to the use of multi-test prick devices or to different antigenic extraction procedures. To date, commercial in vitro tests available offer low diagnostic sensitivity.^{11,14,15,34,35} In our series, commercial CAP to latex showed 80% sensitivity. We did not find any relationship between severity of symptoms and latex IgE levels.

Only isolated cases of clinical association of latex allergy with food allergy have been described,²³⁻³⁰ with cross-reactivity among latex, banana, and chestnut through demonstrated RAST inhibition.²³⁻²⁷ It was surprising that 52% of our patients had immediate hypersensitivity to foods. The seriousness of the food reactions, with systemic anaphylaxis in more than half, also is of concern. Our study showed that certain fruit allergies (previously considered exceptional) were surprisingly frequent in latex-allergic patients. The most common hypersensitivities were to avocado (36%), chestnut (36%), banana (28%), kiwi

(20%), and papaya (12%); multiple sensitivities were frequent. Thus, it is very important to advise latex-allergic patients about possible cross-reactions with certain foods, and for them to avoid them strictly if not regularly consumed.

We have shown the existence of cross-reactivity between latex, avocado, chestnut, and banana through RAST-inhibition; this suggests that these four foods share common antigenic determinants. Other fruits that show lower association rates with latex (kiwi, papaya, and fig) could also share some epitopes. In any case, latex is an important allergen that shares antigenic determinants with various fruits not botanically related, a fact that has clear clinical consequences. If latex shares epitopes with other additional fruits, the associated food hypersensitivities in a certain geographic area could depend on the type and proportion of the fruits consumed.

In our opinion, food allergy should be carefully considered in any patient with latex hypersensitivity, and in every patient allergic to

any of the mentioned fruits, associated allergy to latex and to the other fruits should be sought. It is very important to consider that by carrying out a simple skin prick test to latex in patients with a history of allergy to certain fruits (or with professions that entail risk), one might prevent serious intraoperative IgE-mediated reactions to latex and anaphylactic reactions to foods. Additional studies are necessary to determine which fruits are included in the "latex-fruit syndrome," which antigens the fruits share in common and with latex, and their relative importance in clinical manifestations.

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