

THE CLINICAL MEANING OF POSITIVE LATEX sIgE IN PATIENTS WITH FOOD/ POLLEN ADVERSE REACTIONS

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Natural rubber latex allergy (NRL-A) is an international problem of public health. About 50-60% of NRL-A patients may present adverse reactions after ingestion of cross-reacting vegetable foods. This condition, called "Latex-fruit Syndrome", is a matter of research. The aim of our study is to distinguish between clinical/subclinical latex-fruit syndrome and cross-sensitization to latex and food/pollen allergens on the basis of latex recombinant allergens. We studied 51 patients with food hypersensitivity and serological evidence of NRL sensitization. The subjects underwent an accurate allergological evaluation (skin prick test with latex, food and pollen extracts, specific IgE to latex and recombinant allergens, challenge provocation tests). The patients were divided in two groups: group A) 34 patients with clinical and serological latex and fruit/vegetable allergies; group B) 17 patients allergic to fruits/vegetables and/or pollens, with serological, but not clinical NRL-A. All the latex challenge tests resulted positive in group A patients and only two patients of group B presented positive cutaneous challenge tests. Moreover, specific IgE-antibodies were detected to rHev b 5, to rHev b 6.01, to rHev b 6.02 and to rHev b 8 (and other profilins) of group A patients, while in group B we observed a monosensitization to Hev b8, probably linked to a cross-sensitization to pollens and foods. At the present state of knowledge, we need a multi-parametric approach based on a combination of clinical history, diagnostic tests (CRD) and latex challenge tests to make diagnosis of latex-fruit syndrome.

Natural rubber latex (NRL) allergy has become an important health problem that is increasing both in prevalence (0.3% and 0.7%, in paediatric and adult population, respectively) (1) and in severity of manifestations, especially in some groups at risk (health care workers, children submitted to many surgical procedures, etc.). The relationship between latex and plant-food allergies is an emerging clinical problem, involving about 30-50% of NRL allergic

patients (2, 3). This cross-allergenicity probably depends on the occurrence of structurally-related B-epitopes on ubiquitous allergens in both NRL and food products (4). In 1994, Blanco et al. defined this kind of hypersensitivity as "Latex-fruit syndrome". The main allergens responsible for this cross-reactivity are latex-hevein (Hev b 6.02) and class I chitinase (Hev b 11) (5, 6). Other involved allergens are β -1,3- glucanase (Hev b 2), acidic protein (Hev b

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5) and patatin (Hev b 7) (7). An additional candidate associated with these cross-reactions is profilin (Hev b 8), but its clinical relevance is not yet clear (8). Profilin is considered to be an allergen involved in a wide range of cross-reactivity among pollens (e.g. birch, mugwort, timothy grass), a variety of vegetable foods (e.g. peanut, celery, carrot) and NRL (2).

The diagnosis of latex-fruit syndrome in patients with vegetable food adverse reactions is difficult and physicians generally identify this clinical disorder by skin tests and quantification of latex specific IgE (sIgE) (9). Sometimes, this clinical approach can generate false positives, especially in patients without history of latex hypersensitivity.

The aim of our study is to clarify the significance of the link between NRL allergy and plant food allergy. In particular, we evaluated whether a component-resolved diagnosis (CRD) may have clinical usefulness and prognostic relevance to distinguish between genuine clinical latex-fruit syndrome and food/pollen allergy with cross-sensitization to NRL.

MATERIALS AND METHODS

Patients

The study was carried out on 51 subjects (11 males and 40 females, mean age of 28.3 years) referred to the Allergy Department of the Policlinico "A. Gemelli" in Rome between December 2008 and June 2010.

We enrolled patients with evidence of:

1. plant-derived food hypersensitivity, suggested by a clinical history of oral allergy syndrome (oral itching; perioral erythema; oedema of the lips, tongue and pharynx), generalized urticaria-angioedema, respirator (dyspnoea, cough, rhinitis) and/or gastrointestinal symptoms (abdominal pain, diarrhoea, meteorism) due to the consumption of vegetables and confirmed by positive skin prick tests with commercial food-allergens or fresh food;
2. positive specific IgE (≥ 0.35 kU/L) to latex.

All subjects were questioned about symptoms after latex exposure (ranging from contact urticaria to anaphylaxis), possible risk factors (atopy; occupation as healthcare workers, dentists, rubber manufacturer workers, etc.; multiple surgical operations; myelomeningocele). The diagnosis of latex allergy was confirmed by challenge tests (cutaneous, conjunctival and sublingual tests). Finally, we investigated whether they suffered from pollinosis or respiratory symptoms induced by indoor aeroallergens.

Exclusion criteria were: pregnancy, lactation, known

autoimmunity disorders, therapy with β -blocking drugs, severe renal and cardiovascular disease. All participants provided written informed consent.

Skin test

All the patients underwent skin prick test (SPT) with:

- NRL extract (Alk-Abellò, Milan, Italy);
- commercial extracts of inhalant allergens present in our geographical area (timothy grass pollen, parietaria, mugwort, ragweed, olive tree, cypress, birch, hazel tree) (Alk-Abellò);
- fresh fruits/vegetables (prick by prick method) or commercial extracts of some plant-derived foods according to the clinical history.

All SPT were performed and read after 15 minutes according to the EAACI guidelines (10): a wheal diameter greater than or equal to 3 mm was considered as a positive result. SPT with histamine (10mg/ml) and saline solution were carried out as positive and negative controls, respectively.

Serological tests

Measurement of specific IgE to latex and its recombinant allergens (rHev b 1, rHev b 3, rHev b 5, rHev b 6.01, rHev b 6.02, rHev b 9, rHev b 11), bromelain and profilins (Pru p 4, Bet v 2 and Hev b 8) was performed according to the manufacturer's instructions (UniCAP, Phadia, Uppsala, Sweden). Samples with specific IgE concentrations of ≥ 0.35 KU/l were considered as positive.

Challenge tests

Latex provocation tests were performed in day hospital regimen under physician observation and vital parameters were monitored during each test.

The cutaneous provocation test consisted of wearing a latex glove (Triflex Allegiance Health Care Co., McGaw Park, IL, USA) on one hand for 60 minutes. The conjunctival challenge was performed instilling alternatively into the inferior fornix of each eye the commercial extract (Alk-Abellò), starting with the concentration of 500×10^{-8} μ g/ml up to 50 μ g/ml. In the sublingual challenge the patient had to maintain one drop of latex solution (Alk-Abellò) from the concentration of 500×10^{-8} μ g/ml up to 500 μ g/ml under the tongue for 3 minutes and then spit.

The tests were considered positive if symptoms such as itching, erythema, urticaria, oedema with or without systemic manifestations occurred. In this case the challenges were immediately stopped (11).

Definition of groups

Finally, the total sample was divided into 2 groups (group A and B):

- Group A included patients with clinical and serological latex and fruit/vegetable allergy;
- Group B patients allergic to pollens and fruits/vegetables with serological, but without clinical sensitization to NRL.

Statistical analysis

Descriptive statistics was performed using frequency tables for qualitative variables and mean $\pm$ standard deviation (SD) for quantitative variables.

In order to evaluate the association between the positivity to latex allergological evaluation and possible risk factors *chi-square* or Fisher's exact probability test for qualitative variables and Student's *t* test or nonparametric Wilcoxon test for quantitative variables were used.

Statistical significance level was set at $p \leq 0.05$. Statistical analyses were performed using the statistical software Stata release 9.0.

For latex sIgE a receiver operating characteristic curve (ROC-curve) analysis was used in order to find the cut-off value that best predicted the positivity to the challenges. Sensitivity and specificity as well as positive predictive value (PPV) and negative predictive value (NPV) were calculated for each cut-off value.

RESULTS

Characteristics of patients

The clinical features of the study population,

group A and B are shown in Table I. We found a significant difference between females and males in the two groups ($p = 0.028$), showing a predominance of females.

We did not find an association between atopy ($p = 0.39$) and myelomeningocele ($p = 1.00$) in the same groups. There is a significant sensitization to grass pollen, mugwort and olive tree pollens, in group B ($p < 0.05$) (Table II).

Only the fagaceae family (i.e. chestnuts) was significantly related to the patients with positive latex anamnesis. In contrast, these data were not confirmed by allergological evaluation. On SPTs (Table III), the patients with negative latex history showed a higher prevalence of allergy to *Apiaceae* (celery, carrot, etc), *Solanaceae* (tomato, potato, etc.) and citrus family (orange, lemon, etc).

No significant differences between these groups were observed regarding clinical symptoms, although in the second one the oral allergy syndrome prevails.

Latex skin prick tests

In the total population of latex skin prick test mean diameter was 5.86 mm (SD = 5.99). The mean diameter of latex skin prick test was 8.44 mm (SD = 5.60) and 0.71 mm (SD = 2.26) in group A and group

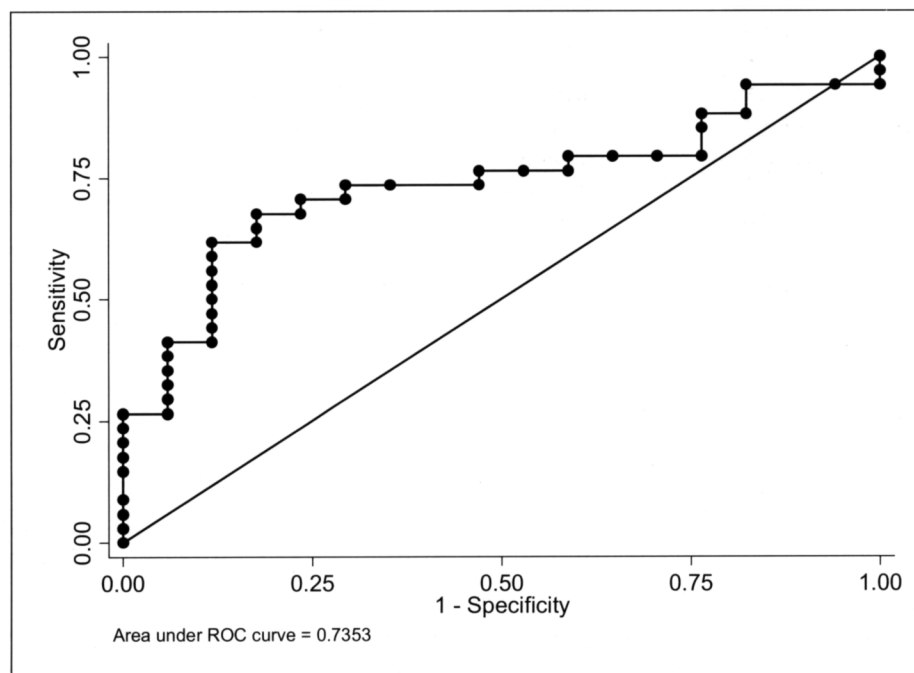
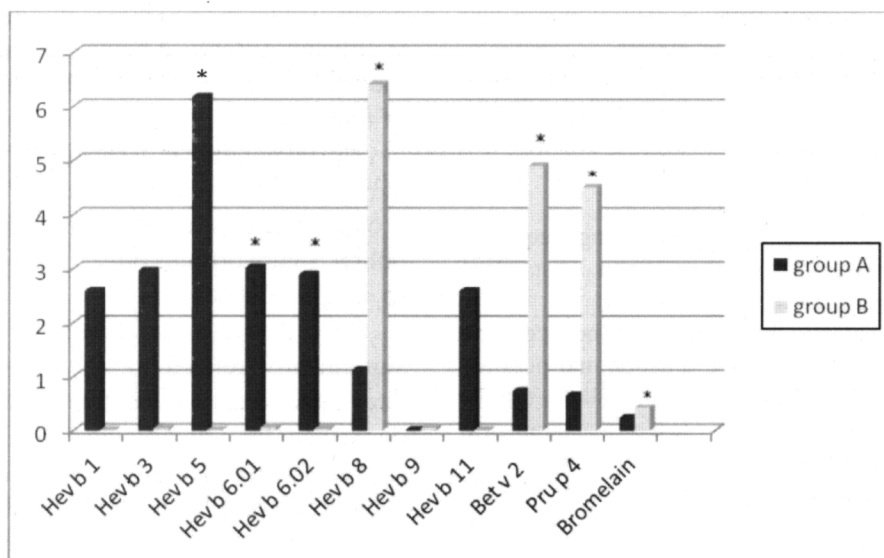


Fig. 1. ROC curve analysis.



* significant value ($p \leq 0,05$).

Fig. 2. Latex recombinant proteins in group A and B.

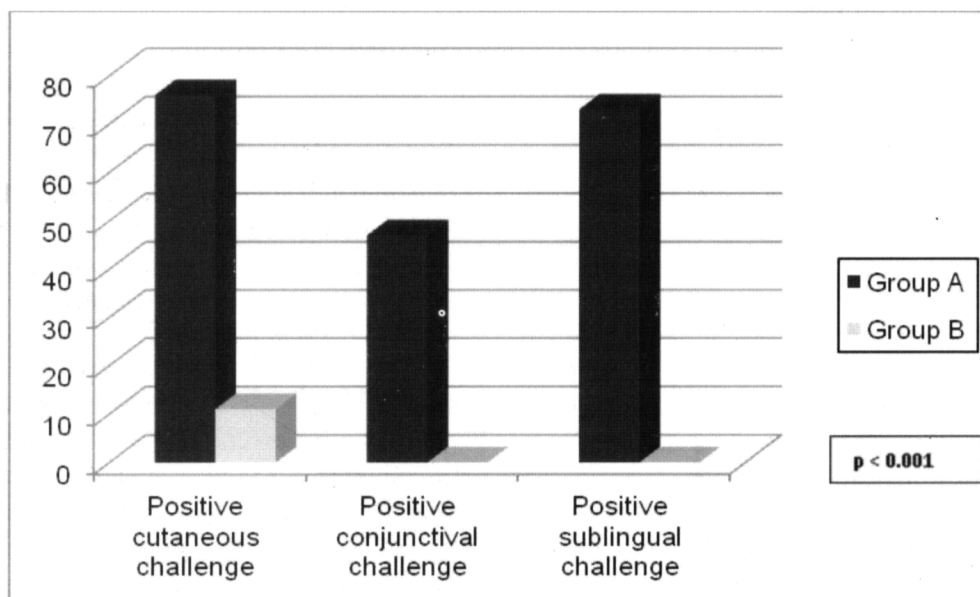


Fig. 3. Challenge tests results in group A and B.

B, respectively. This difference was statistically significant ($p < 0.001$).

Latex specific IgE assays

In all subjects the mean value of latex specific IgE was 7.44 kU/l (SD = 16.3), while this value was 10.3 kU/l (SD = 19) in group A and 1.62 kU/l (SD =

2.54) in group B ($p = 0.007$).

The ROC curve analysis showed an area under the curve (AUC: 0.74) acceptable for latex specific IgE (Fig. 1). ROC curve analysis yielded a cut-off value of 1.19 kU/l for specific IgE (sensitivity 70.59%; specificity 76.47%). Positive and negative predictive values (PPV and NPV) respectively, for

Table I. The clinical features of the study population.

Clinical features	Total population N=51	Group A N=34	Group B N=17	p
Mean age (years)	28.29 (12.11)	29.82 (11.87)	25.24 (12.38)	0.21
Mean (SD)				
M/F (N)	11/40	4/30	7/10	0.028*
Reporting pollens allergy (%)	60.78	44.12	94.12	0.001*
Latex skin prick test (mm) Mean (SD)	5.86 (5.99)	8.44 (5.60)	0.71 (2.26)	< 0.001*
Latex specific IgE kU/l Mean (SD)	7.44 (16.3)	10.3 (19)	1.62 (2.54)	0.007*
Total IgE	256 (6.10)	239 (2.6)	263.6 (2.5)	NS

SD: standard deviation

* significant value ($p \leq 0.05$)

each cut-off value are shown in Table IV.

DISCUSSION

Latex recombinant allergens IgE assays and bromelain (Fig. 2)

Specific IgE-antibodies were detected to rHev b 5 in 47 %, to rHev b 6.01 in 70%, to rHev b 6.02 in 74% and to rHev b 8 and other profilins in about 30% of group A patients. These sera recognized rHev b 5 (median 6.187 kU/l) and rHev b 6.01 and rHev b 6.02 (median 3.021 Ku/l and 2.893 KU/l, respectively) as major latex allergens.

The opposite was shown in the population with asymptomatic sensitization to NRL. Their sera strongly reacted only with the profilin family (Hev b 8, Bet v 2, Pru p 4).

Regarding bromelain, the mean of this recombinant allergen resulted significantly lower in group A ($p = 0.0311$).

Challenge tests

All the latex challenge tests resulted positive in patients with clinical allergy to latex ($p < 0.001$). In only two patients with negative latex history the cutaneous challenge test was positive (Fig. 3).

The relationship between latex, pollen and plant food allergies is an emerging clinical problem. The aim of this study is to improve the diagnostic tools to distinguish real or false latex allergy using the CRD and challenge tests.

Because of the fear of allergic reactions to latex, the most common therapeutic approach to patients who show cutaneous and/or serological sensitization to NRL is to forbid the use of NRL, falsely labelling these patients as being allergic to NRL (even if they did not show a history of NRL hypersensitivity). This raises a doubt about the meaning of NRL sensitization in patients with pollen and vegetable food hypersensitivity.

In our population we distinguished two phenotypes on the basis of positive or negative clinical history for latex allergy, who showed different characteristics. The group with positive anamnesis to latex likely had a latex-fruit syndrome. In these patients, the only referred offending food significantly involved seems to be chestnut which belongs to the *Fagaceae* family. In fact, the chestnut

Table II. Pollen sensitization in groups A and B.

Positive respiratory allergens	Group A (%)	Group B (%)	p
<i>Grass pollen</i>	32.3	88.2	
<i>Parietaria</i>	17.7	35.3	
<i>Compositae</i>	5.9	29.4	
<i>Olive tree</i>	11.8	64.7	
<i>Birch</i>	5.9	11.8	
<i>Hazelnut tree</i>	5.9	11.8	
<i>Cypress</i>	8.8	23.5	

* significant value ($p \leq 0.05$)

is frequently responsible for latex-fruit syndrome ,together with banana, avocado and kiwi (12-14).

Class I chitinases with a hevein-like domain (HLDs) as well as latex hevein (Hev b 6.02), latex β 1,3-glucanases (Hev b 2) and patatin (Hev b 7) have been identified as the major allergens responsible for these cross-reactions (15-19).

In our patients (group A) we observed positive NRL challenges and sensitization to rHev b 5, rHev b 6.01, rHev b 6.02 and profilin family. Moreover, hevein and profilin seem to be the main responsible allergens. On the other hand, our results are partially in contrast with those of other authors (3) that suggest a lack of correlation between sensitization to hevein (Hev b 6.01 and Hev b 6.02) or to HLDs and latex-associated plant food allergy. In fact, Radauer et al. explain the latex-fruit syndrome on the basis of other families of cross-reactive allergens such as profilins, β 1,3-glucanases and non-specific lipid transfer proteins (Hev b 12). Unfortunately, Hev b 2, Hev b 12 and Hev b 13 are currently not readily available for *in vitro* diagnosis.

The subjects with negative latex history instead

seem to show a different pattern of recombinant latex allergen sensitization: mono-sensitization to Hev b8 (and other profilins), as a consequence of primary sensitization taking place via pollens and foods.

Patients allergic to pollens and vegetables might display serological evidence of latex sensitization, which is probably due to structurally-related epitopes. Moreover, patients of this group often had oral allergy syndrome and showed a higher frequency of pollen sensitization. In fact, in this group, allergological tests confirm the so-called "pollen-food allergy syndrome" (20, 21), due to cross-reactivity between pollens (mainly timothy grass pollen, mugwort, olive tree) and plant-derived food (*Solanaceae*, *Cucurbitaceae*, *Citrus*, *Apiaceae*).

Our findings support those of previous authors (22-24), reporting that the presence of latex-specific IgE antibodies detected in the serum of people with no other evidence of latex sensitization or allergy had pollen sensitization.

Recently, two studies compared ImmunoCAP and microarray methods in an attempt to realize CRD (25, 26). In particular, Ebo observed that both the

Table III. Allergological evaluation for food in groups A and B.

Foods family	Group A (%)	Group B (%)	p
<i>Cucurbitaceae</i>	32.4	76.5	0.003*
<i>Rosaceae</i>	67.6	76.5	0.514
<i>Fagaceae</i>	50.0	47.06	0.843
<i>Leguminose</i>	32.4	47.1	0.306
<i>Ombrellifere</i>	41.2	70.6	0.048*
<i>Solanaceae</i>	52.9	88.2	0.013*
<i>Graminaceae</i>	17.7	41.2	0.093
<i>Citrus</i>	17.7	52.9	0.009*
<i>Other fruits</i>	73.5	88.2	0.297
<i>Other vegetables</i>	38.2	35.3	0.838

*significant value

Table IV. Performance characteristics of latex sIgE at different cut-off levels.

Parameter	Cut-off value (kU/l)	sensitivity	specificity	PPV	NPV
<i>IgE</i>	0.53	94.12%	17.65%	69.57%	60%
	0.71	79.41%	41.18%	72.97%	50%
	1.19	70.59%	76.47%	85.71%	56.52%
	2.08	61.76%	82.35%	87.50%	51.85%
	5.26	38.24%	94.12%	92.86%	43.24%
	11.8	26.47	100.00%	100.00%	40.48%

methods fail to discriminate between true latex allergy and asymptomatic sensitization by the detection of profilin sIgE. However, only the ImmunoCAP is able to identify bromelain sIgE as marker of cross-reactive carbohydrate determinants (CCDs). This finding, although statistically significant, was detected only in small number of patients in our group B (only 4).

On the basis of these data, a panel including all the recombinant latex allergens could allow to distinguish the authentic latex-fruit syndrome from

an asymptomatic sensitization, mimicker of latex allergy.

In our study we tried also to establish IgE cut-off values for latex in order to make the diagnosis of latex allergy in patients with hypersensitivity to plant foods cross-reacting with latex or with suspected latex-fruit syndrome. This is to assess whether there is a value of latex specific IgE that can avoid the challenge tests and their risks. The ROC curve analysis demonstrates the variation of sensitivity and specificity of a test as a

function of threshold values and helps to determine a positive threshold value. So analysing the ROC curves, we found that the optimal cut-off value for latex sIgE was 1.19 kU/L (CAP class 2), with a 85.7% positive predictive value and a low negative predictive value (56.5%). So patients with latex specific IgE values ≥ 1.19 kU/l have a probability approximately 85% to suffering from latex-fruit syndrome, regardless of history for latex adverse reactions. Conversely, specific IgE value lower than cut-off does not exclude a diagnosis of latex-fruit syndrome, even in the absence of positive clinical history for adverse reactions to latex products. Therefore, in these patients the diagnosis of latex-fruit syndrome cannot ignore the provocation test, which remains the gold standard and could be useful to follow the natural history of latex allergy and to assess the efficacy of specific desensitization (27).

Therefore, unlike other authors (28, 29) who used only the cutaneous challenge tests to identify a real clinical latex allergy, we performed also the conjunctival and sublingual tests. In fact these procedures present a good positive predictive value and specificity and faithfully reproduce natural exposure (11).

In conclusion, our data suggest that profilin seems to be a marker of cross-sensitization to latex, pollens and plant derived foods and determines false positivity to NRL. Consequently, the observed *in vitro* reactivity to NRL is not clinically relevant in all patients with adverse food reactions and it does not determine necessarily a latex-fruit syndrome. For this reason, the use of cut-off values, able to differentiate the latex-fruit syndrome compared to asymptomatic sensitization alone, should be considered with caution, particularly in those patients who do not report adverse reactions to latex. We therefore need a multi-parametric approach based on a combination of clinical history, diagnostic tests (CRD) and latex challenge tests to make diagnosis of latex-fruit syndrome.

At the present state of knowledge, before making diagnosis of latex-fruit syndrome, it is essential to assess all latex recombinant allergens and in particular Hev b 5, Hev b 6.01, Hev b 6.02 and Hev b 8. In fact, only in latex-fruit syndrome those allergens seem to be increased, whereas in patients with pollinosis, adverse reactions to foods and negative symptoms

with latex, profilin appears to prevail.

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