

Original Article

Prevalence of IgE antibodies to an extract from rubber tree (*Hevea brasiliensis*) latex and recombinant pollen allergens (Phl P 1, Phl P 2, Phl P 5, Bet v 1 and Bet v 2) in the sera of Italian atopic patients

Renato E Rossi,¹ Georgio Monasterolo² and Serena Monastero²

¹Unita di Immunoallergologia Ospedale SS Annunziata, Savigliano and ²Laboratorio Analisi, Ospedale SS Trinita, Fossano, Italy

ABSTRACT

Background: Previous studies have reported cross-reactivity between latex and grass allergens. Inhibition studies have indicated cross-reactivity of IgE with latex and grass pollen proteins. A panel consisting of a few recombinant allergens, namely rPhl p 1, rPhl p 2, rPhl p 5 and profilin, was sufficient to diagnose grass pollen allergy in patients allergic to grass pollen.

Methods: Serum samples from 528 consecutive outpatients with IgE antibodies towards at least one allergen (IgE level > 0.35 kAU/L) were selected for this retrospective study. Total and specific serum IgE to rPhl p 1, rPhl p 2, rPhl p 5, rBet v 1, rBet v 2, latex, birch, hazel, mugwort, wall pellitory, *Dermatophagoides pteronissinus*, *Alternaria tenuis*, cat and apple were measured by the immunoenzymatic capsulated hydrophilic carrier polymer (CAP) FEIA system (Pharmacia & Upjohn).

Results: Of 123 polysensitized patients with antilatel IgE, 12 (9.76%) had symptoms after latex exposure. Ten of 12 subjects monosensitized to latex had symptoms after latex exposure. Symptomatic patients had higher IgE levels to latex than symptomless patients ($P = 0.046$). A higher prevalence of antilatel IgE was seen in sera containing specific IgE to rPhl p 1, rPhl p 5 and rBet v 2. A good correlation (Spearman's

$r = 0.52$; $P = 0.001$) between high levels of antilatel IgE and total serum IgE was found.

Conclusions: The findings of the present study may support the concept that a high proportion of sera containing IgE to rBet v 2, rPhl p 1 and rPhl p 5 simultaneously contain antilatel IgE. Therefore, patients with specific IgE to these recombinant allergens with no history of current latex exposure may need additional evaluation.

Key words: Bet v 1, Bet v 2, latex, Phl p 1, Phl p 2, Phl p 5, recombinant allergen.

INTRODUCTION

Previous studies have reported cross-reactivity between latex, ragweed and blue grass allergens.^{1,2} Merret *et al.* have shown that the off-season prevalence of antigress IgE in unselected British blood donors was approximately 20%, while among the donors who were latex positive, 84% showed antigress IgE.³ Moreover, IgE antibodies to recombinant pollen allergens Phl p 1, Phl p 2, Phl p 5 and Bet v 2 account for a high percentage of grass pollen-specific IgE.^{4,5}

The relevance of profilin in fruit and vegetable allergy, as well as its possible relevance in latex allergic patients, was demonstrated by Vallier *et al.*⁶

Several commercial latex antibody assays are available for use in diagnosis. Unfortunately, *in vitro* latex-specific IgE determinations are problematic with regards to sensitivity and specificity of the tests. Commercial latex extracts are total protein extracts with varying compositions of allergenic and non-allergenic proteins and over

Correspondence: Dr Renato Enzo Rossi, Unita di Immunoallergologia Ospedale SS Annunziata, via Ospedali 14, 12038 Savigliano (CN), Italia. Email: us117@isiline.it

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250 polypeptides have been reported from the crude preparation.⁷⁻¹⁰

The purpose of the present study was to determine the prevalence of detectable *Hevea brasiliensis* latex-specific IgE in atopic patients. It was thought useful to perform a simultaneous series of IgE tests specific to allergens to which the sensitivity of the general allergic population is well documented. Moreover, patients were divided into 17 groups depending on their sensitization pattern to recombinant allergens (patient's individual IgE: reactivity profile) and we evaluated the allergens against which IgE most frequently reacted in these groups.

METHODS

Serum samples from 528 consecutive outpatients (287 males, mean age 27.27 years, range 4–77 years; 241 females, mean age 30.21 years, range 5–80 years) referred to the allergy unit during the period from January

1996 to March 2000 with a positive capsulated hydrophilic carrier polymer (CAP) result of at least class I to at least one allergen (IgE level > 0.35 kAU/L) were selected for this retrospective study. Of 528 atopic patients, 423 (80.1%) had symptoms of asthma and/or rhinitis, 24 (4.55%) suffered from rhinitis and dermatitis, 36 (6.82%) had chronic urticaria and rhinitis and 45 (8.52%) had chronic pruritus associated with allergic rhinitis. All patients had a history of rhinitis and/or asthma after allergen exposure and positive skin tests (wheal diameter > 5 mm).

Total and specific serum IgE to rPhl p 1, rPhl p 2, rPhl p 5, rBet v 1 and rBet v 2, the major allergens of grass and birch, latex (k82), birch (t3), hazelnut tree (t4), mugwort (w6), wall pellitory (w21) *Dermatophagoides pteronissinus* (d1), *Alternaria tenuis* (m6), cat (e1) and apple (f49) were measured by the immunoenzymatic CAP FEIA system (Pharmacia & Upjohn Diagnostics). The ImmunoCAP latex is a non-ammoniated product derived

Table 1 Median value of serum latex-specific IgE in two groups of sera obtained from patients with and without symptoms after latex exposure

	n	Mean age (years)	IgE (kUA/L)	P
Symptomatic patients	12	38.88	3.94 (1.47–> 100)	0.046
Symptomless patients	111	28.37	1.18 (0.42–8.88)	0.028

Data for IgE show median values with the 25th–75th percentile range given in parentheses.

P values were determined by the Mann–Whitney U-test.

Table 2 Patient's individual IgE reactivity profiles

Sensitization pattern	n (%)	Phl p 1	Phl p 2	Phl p 5	Bet v 1	Bet v 2	Total IgE (kAU/L)
1	108 (20.45)	N	N	N	N	N	171 (57–465)
2	80 (15.15)	P	P	P	N	N	207 (74–541)
3	69 (13.07)	P	P	P	N	P	339 (140–799)
4	42 (7.95)	P	P	P	P	P	428 (290–723)
5	37 (7.01)	P	N	N	N	N	296 (109–612)
6	34 (6.44)	N	N	N	P	N	80 (40–109)
7	29 (5.49)	P	N	P	N	N	141 (64–433)
8	23 (4.36)	N	N	P	N	N	163 (50–345)
9	21 (3.98)	P	P	P	P	N	209 (52–379)
10	16 (3.03)	P	P	N	N	N	121 (56–411)
11	15 (2.84)	P	N	N	P	N	254 (158–400)
12	15 (2.84)	P	N	P	P	N	121 (93–123)
13	15 (2.84)	P	N	P	N	P	135 (15–321)
14	12 (2.27)	P	N	P	P	P	586 (260–808)
15	4 (0.76)	N	N	P	P	N	85 (40–210)
16	4 (0.76)	P	N	N	N	P	177 (81–165)
17	4 (0.76)	P	P	N	P	N	124 (66–171)

Data for total IgE are presented as the geometric mean with 25th–75th percentile ranges given in parentheses.

N, negative; P, positive; n, number of patients.

Table 3 Geometric mean (25th–75th percentile) of specific IgE in sera of patients with different sensitization patterns (for individual IgE reactivity profiles, see Table 2)

Sensitization pattern	Phl p 1 (kAU/L)	Phl p 2 (kAU/L)	Phl p 5 (kAU/L)	Bet v 1 <kAU/L	Bet v 2 (kAU/L)	K82 n (%)	g6 n (%)
1	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	10 (9.2)	20 (18.5)
2	11.5 (0.35–44.7)	6.5 (2.2–17.6)	11.5 (3.3–43.7)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	8 (10)	90 (100)
3	20.9 (7.4–59.5)	8.4 (2.8–24.2)	25.1 (11.1–65.2)	< 0.35 (< 0.35–< 0.35)	3.4 (1.3–8.8)	46 (66.7)	69 (100)
4	22.4 (11.0–65.8)	11.6 (4.5–27.9)	26.6 (20.8–54.0)	14.6 (4.9–52.9)	4.7 (2.0–9.1)	32 (76.2)	42 (100)
5	3.2 (1.1–7.4)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	1 (2.7)	37 (100)
6	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	3.0 (2.0–31.6)	< 0.35 (< 0.35–< 0.35)	1 (2.9)	7 (20.5)
7	3.9 (1.2–11.4)	< 0.35 (< 0.35–< 0.35)	4.4 (1.25–15.1)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	0 (0.00)	29 (100)
8	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	0.6 (0.39–0.9)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	2 (8.7)	23 (100)
9	12.6 (4.7–26.3)	5.2 (1.8–12.6)	15.0 (8.86–33.3)	11.3 (4.1–26.2)	< 0.35 (< 0.35–< 0.35)	2 (9.5)	21 (100)
10	4.9 (2.5–12.1)	1.7 (0.7–3.7)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	1 (6.2)	16 (100)
11	2.1 (1.3–2.8)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	21.1 (3.51–> 100)	< 0.35 (< 0.35–< 0.35)	3 (20)	15 (100)
12	3.6 (2.2–6.2)	< 0.35 (< 0.35–< 0.35)	4.6 (1.6–13.9)	7.6 (3.06–23.5)	< 0.35 (< 0.35–< 0.35)	0 (0.0)	15 (100)
13	9.9 (3.7–22.5)	< 0.35 (< 0.35–< 0.35)	9.9 (3.4–41.6)	< 0.35 (< 0.35–< 0.35)	2.9 (1.1–5.8)	11 (77.3)	15 (100)
14	17.4 (4.2–17.4)	< 0.35 (< 0.35–< 0.35)	17.3 (12.3–41.2)	4.9 (2.23–7.9)	4.5 (3.5–8.1)	11 (91.7)	15 (100)
15	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	0.4 (0.4–0.4)	4.8 (2.25–17.4)	< 0.35 (< 0.35–< 0.35)	0 (0.0)	4 (100)
16	4.3 (2.7–11.8)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	< 0.35 (< 0.35–< 0.35)	0.9 (0.6–1.5)	2 (50)	4 (100)
17	4.3 (1.9–13.2)	1.1 (0.8–3.4)	< 0.35 (< 0.35–< 0.35)	2.3 (2.0–18.2)	< 0.35 (< 0.35–< 0.35)	3 (20)	4 (100)

Sensitization pattern	t3 n (%)	t9 n (%)	w6 n (%)	w21 n (%)	d1 (kAU/L) n (%)	149 n (%)	e1 n (%)
1	7 (6.5)	13 (12.0)	13 (12.0)	11 (10.2)	1.5 (0.6–1.7)	6 (5.5)	21 (19.4)
2	16 (20)	0.9 (0.4–1.5)	49 (61.2)	2.0 (1.0–3.7)	2.3 (1.0–6.4)	36 (45)	12 (15)
3	58 (84)	4.2 (1.4–9.3)	55 (79.7)	7.2 (3.0–19.4)	3.7 (1.5–7.03)	26 (37.7)	7 (10.1)
4	37 (88.0)	28.8 (15.9–57.7)	23 (54.8)	15.1 (6.2–37.5)	27 (64.3)	3.8 (1.3–9.92)	20 (47.6)
5	2 (5.4)	3.2 (1.8–5.6)	14 (37.9)	1.9 (0.8–2.7)	6 (16.2)	1.2 (0.3–2.7)	2 (5.4)
6	31 (91.2)	9.9 (2.5–26.2)	4 (11.8)	1.6 (0.7–5.2)	1 (2.9)	3.3	16 (47.0)
7	4 (13.8)	1.6 (0.8–3.5)	13 (44.8)	1.9 (0.9–3.0)	5 (17.2)	1.1 (0.5–1.4)	3 (10.3)
8	3 (13.4)	3.9 (0.7–13.1)	2 (8.7)	0.9 (0.6–1.5)	3 (13.0)	5.4 (2.3–21.3)	5 (21.7)
9	18 (85.7)	12.2 (3.1–23.1)	13 (61.9)	3.0 (1.3–4.7)	5 (23.8)	0.7 (0.4–0.8)	12 (57.1)
10	1 (6.2)	6.7 (–)	7 (43.7)	0.9 (0.5–1.5)	0 (0.0)	–	2 (12.5)
11	15 (100)	21.7 (6.4–76.6)	5 (33.4)	5.7 (1.0–8.0)	7 (46.7)	4.3 (0.6–21.6)	10 (66.7)
12	14 (93.3)	7.9 (2.7–15.9)	11 (73.3)	1.5 (0.8–3.7)	3 (20)	1.7 (1.4–2.03)	2 (13.5)
13	15 (100)	2.4 (1.05–3.9)	7 (46.7)	3.0 (1.3–8.2)	12 (80)	1.7 (0.6–3.3)	5 (33.3)
14	12 (100)	16.7 (26.2–16.6)	9 (75)	15.0 (23.5–15.0)	9 (75)	5.8 (8.6–5.8)	3 (25)
15	3 (75)	4.6 (0.53–24.9)	0 (0.0)	–	0 (0.0)	–	0 (0.0)
16	4 (100)	1.4 (0.6–4.4)	3 (75)	2.5 (0.8–8.9)	2 (50)	5.0 (0.9–27.3)	0 (0.0)
17	2 (50)	2.2 (0.9–5.5)	4 (100)	2.7 (0.6–11.9)	3 (75)	3.0 (0.9–13.4)	3 (75)

k82, latex; g6, Phleum pratense; t3, birch; k9, olive tree; w6, mugwort; w21, pellitory of the wall; d1, Dermatophagoides pteronissinus; 149, apple; e1, cat.

Table 4 Correlation between recombinant allergens and 11 allergen extracts; the correlation analysis is based on test positivity (value above 0.35 kAU/L)

	k82	g6	f49	i3	i4	i9	w6	w21	d1	e1	m6
g205	0.34 (< 0.001)	0.90 (< 0.001)	0.24 (0.01)	0.17 (0.007)	0.18 (0.003)	0.60 (< 0.001)	0.34 (< 0.001)	0.24 (0.005)	-0.06 (0.31)	0.16 (0.12)	0.18 (0.28)
g206	0.19 (0.02)	0.73 (< 0.001)	0.12 (0.08)	0.11 (0.08)	0.11 (< 0.08)	0.42 (< 0.001)	0.2 (0.001)	0.14 (0.11)	-0.12 (0.06)	0.06 (0.52)	0.18 (0.29)
g207	0.19 (0.02)	0.87 (< 0.001)	0.06 (0.49)	0.14 (0.02)	0.17 (0.008)	0.58 (< 0.001)	0.32 (< 0.001)	0.12 (0.17)	-0.17 (0.008)	0.01 (0.008)	0.30 (0.07)
f215	0.10 (0.23)	0.11 (0.017)	0.44 (< 0.001)	0.73 (< 0.001)	0.73 (< 0.001)	0.23 (0.002)	0.13 (0.08)	0.09 (0.2)	-0.02 (0.23)	-0.004 (0.9)	-0.10 (0.54)
f216	0.57 (< 0.001)	0.55 (< 0.001)	0.2 (0.02)	0.22 (< 0.001)	0.24 (< 0.001)	0.63 (< 0.001)	0.45 (< 0.001)	0.19 (0.03)	-0.12 (0.06)	0.16 (0.11)	0.11 (0.50)

g205, rPhl p 1; g206, rPhl p 2; g207, rPhl p 5; f215, rBet v 1; f216, rBet v 2; K 82, latex; g6, Phleum pratense; f49, apple; i3, birch; i4, hazel; i9, olive tree; w6, mugwort; w21, pellitory of the wall; d1, Dermatophagoides pteronissinus; e1, cat; m6, Alternaria tenuis.

from latex collected in Thailand from *H. brasiliensis*. The molecular weights of the proteins cover the range from < 10 to > 100 kDa.⁸

One hundred and eight atopic patients lacking specific IgE to rPhl p 1, rPhl p 2, rPhl p 5, rBet v 1 and rBet v 2 were also evaluated. These patients are part of the total 528 patients. Six patients had specific IgE to g6 but not to Phl p 1, rPhl p 2, rPhl p 5, Bet v 1 and Bet v 2 (1.42% of subjects allergic to grass pollen).

Statistical analysis

The different data did not approach a normal distribution. Results are expressed as median, geometric mean and 25th–75th percentile. The non-parametric Mann–Whitney *U*-test was used to compare specific IgE to recombinant allergens and natural extracts. Correlation between variables was assessed by Spearman's correlation coefficient (ρ). Statistical analysis was performed with SPSS for Windows. $P < 0.05$ was considered significant.

RESULTS

Of 123 polysensitized patients with antilatex IgE, 12 (9.76%) had symptoms after exposure to latex. Eight patients (6.50%) had asthma and rhinitis, and four (3.25%) had dermatitis and rhinococonjunctivitis. Ten patients were monosensitized to latex and all had symptoms after latex exposure.

Symptomatic patients had higher IgE levels to latex than symptomless patients (Table 1).

Table 2 shows different patient's individual IgE reactivity profiles and total IgE found in the sera from 528 atopic patients.

Although the overall prevalence in the entire group containing antilatex IgE was 25.8% ($n = 133$), the prevalence in the different IgE reactivity profile groups differed considerably from this value, with the prevalence in sera from patients with sensitization pattern numbers 3, 4, 13 and 14 (Table 3) being the greatest at 67–92%.

A higher prevalence of antilatex IgE was seen in sera containing specific IgE to rPhl p 1, rPhl p 5 and rBet v 2. As shown in Table 3, a good correlation ($r = 0.52$, $P = 0.001$) between high levels of antilatex IgE and total serum IgE was found in patients with sensitization pattern numbers 3 and 4. Patients with reactivity profiles numbers 2 and 14 (Tables 2,3) did not show a clear correlation between antilatex IgE and total serum IgE.

A higher prevalence of anti-apple IgE was seen in sera containing specific IgE to rBet v 1 and rPhl p 1, a higher prevalence of specific anti-olive tree IgE was found in sera containing IgE to rPhl p 1, rPhl p 5 and rBet v 2, and a higher prevalence of antimugwort IgE was observed in sera containing IgE to rPhl p 1, rPhl p 5 and rBet v 2.

Other results are summarized in Table 3.

A good correlation ($P = 0.001$) was found between rPhl p 1 and latex, olive and mugwort, rPhl p 2 and olive, rPhl p 5 and olive and mugwort, rBet v 1 and apple, and rBet v 2 and latex, timothy grass, birch, hazel and mugwort. Other results are summarized in Table 4.

DISCUSSION

In the present study, we found that latex sensitization is overrepresented among patients with IgE to rBet v 2, rPhl p 1 and rPhl p 5. Subjects selected for IgE to rBet v 2, rPhl p 1 and rPhl p 5 may, as a group, have an enhanced overall propensity to form IgE to different environmental allergens. If true, this would make them more likely than unselected subjects to exhibit total and specific IgE to any allergen source, including latex. Thus, in the present study, the higher frequency of latex sensitization among subjects with IgE to rBet v 2 is not necessarily a function of molecular cross-reactivity, as demonstrated in previous studies.⁶ In contrast, an excellent correlation between IgE to Bet v 2 and latex (g6 and t9) was found.

Moreover, in sera from patients with sensitization pattern numbers 3, 4 and 14, in whom IgE levels to Bet v 2 were higher, the prevalence of sensitization to latex was increased as well as total IgE. In contrast, subjects with the number 13 sensitization pattern showed a high prevalence of antilatax IgE and low levels of total IgE. Of course, it is not obvious that the formation of several groups of patients showing different IgE antibody reactivity combinations or the statistical analysis performed serves the purpose of identifying serological associations in the best way possible; nevertheless, if confirmed in other studies, this approach may be useful for the practical allergologist. A number of proteins and peptides from *H. brasiliensis* latex have been identified as reacting with IgE-relevant antibodies from latex-sensitive patients.¹³⁻²⁴ Crude antigens contain relevant and non-relevant protein and their use may produce variable results and interpretations. Several latex allergens have been cloned and sequenced; others have been partially characterized.^{7,11-14,16-18,22,23}

Some authors suggest that Hev h 1 and Hev b 3 are major allergens for children with multiple congenital anomalies.^{24,25} However, Hev b 2 and Hev b 4 are more important for health-care workers with latex allergy.¹⁸ Hev b 5 is recognized by specific IgE in a majority of both health-care workers and latex-allergic children.¹⁹ However, it is important to recognize that recombinant proteins derived from sequences cloned from *Hevea* plant material may not represent naturally expressed proteins or proteins that are present in finished products. Moreover, recent studies indicate that additional antigens may be needed to reach the diagnostic accuracy obtained with crude latex.²⁶

Fuchs *et al.*¹² reported that sera from certain individuals with latex allergy showed IgE reactivity with protein bands of different molecular weights in western-blotted latex milk and glove extracts, both containing common IgE epitopes. Although preincubation with rBet v 1 and rBet v 2 did not significantly inhibit IgE binding to latex proteins, weed and, in particular, timothy grass extract strongly inhibited IgE binding to latex allergen.⁹

To support our statement that the correlation between rBet v 2 and latex is based on a possible profilin cross-reactivity, IgE inhibition experiments should have been performed; however, the present study is retrospective.

Earlier studies²⁷ have shown latex-specific IgE in atopic individuals, especially patients aged < 18 years, with no history or recurrent latex exposure and no history of adverse reactions to latex. The higher prevalence of positive sera among subjects aged < 18 years suggests that children are more frequently exposed to allergens that cross-react with latex. Indeed, we have found previously that patients in the age group 0-20 years had higher IgE levels to rBet v 2, rPhl p 1, rPhl p 2 and rPhl p 5 than subjects in an older age group.²⁸

Moreover, a grass allergen extract may induce immune reactions against components not recognized before treatment.²⁹⁻³¹ This has to be taken into consideration when grass extracts are used for immunotherapy. This supports the concept of using defined allergens (molecules) for a component-resolved immunotherapy.

Finally, we found that patients with symptoms after latex exposure had higher levels of IgE to latex than symptomless subjects. This supports the findings of previous reports.³³

In conclusion, patients with specific IgE to rBet v 2, rPhl p 1 and rPhl p 5 and total high IgE levels, with no history of recurrent latex exposure, may need additional evaluation.

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