

Short communication

Cross-reactivity between *Ficus benjamina* (weeping fig) and natural rubber latex

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The importance of hypersensitivity to *Ficus* allergens is reported. Cross-sensitization between fig (*Ficus carica*), weeping fig (*F. benjamina* [Fb]), and natural rubber latex (NRL) was confirmed by RAST inhibition. We performed skin prick tests with fresh Fb tree sap and NRL extracts in 346 consecutive patients and in 151 patients with immediate-type hypersensitivity to NRL. Total serum IgE and IgE antibodies to NRL and *Ficus* spp. were analyzed in sera. By the RAST-inhibition method, we studied cross-reactivity among latex, fig, and weeping fig. Sensitization to Fb was diagnosed in 23 of the 346 consecutive patients, and the simultaneous presence of latex-specific IgE was highly significant. Of 151 NRL-allergic patients, 35 were also sensitized to Fb. Cross-reacting IgE antibodies recognizing latex and *Ficus* allergens were demonstrated by RAST inhibition. The present study reinforces the importance of Fb as an indoor allergen. Cross-reacting IgE antibodies to NRL and *Ficus* spp. allergens are frequently found in the sera of atopic patients. Development of commercially available standardized extracts for skin tests is urgently necessary.

Key words: cross-reactivity; *Ficus benjamina*; immediate-type hypersensitivity; indoor allergens; natural rubber latex.

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Since IgE-mediated hypersensitivity to *Ficus benjamina* (Fb) (weeping fig) as an occupational disease in plant keepers and gardeners was reported by Axelsson et al. (1), several reports have demonstrated the importance of Fb proteins as indoor allergens (2–4). Fb allergens derived from the dust of leaf surfaces have been found in house-dust samples (5).

A frequent association between sensitization to *Ficus* spp. (weeping fig or fig) and natural rubber latex (NRL) has been reported (5, 6) and attributed to cross-reactive IgE antibodies (7–9).

The present study aimed to investigate the frequency of IgE antibodies against NRL and *Ficus* spp. in a representative group of German patients. Immunologic cross-sensitivity between NRL and Fb allergens was proved by RAST inhibition.

suffering from atopic diseases. Total serum IgE and specific IgE antibodies to *Ficus* spp. and NRL were analyzed. Skin prick tests were performed with NRL extract in all 346 patients, freshly obtained Fb leaf sap in 296 patients, highly ammoniated latex in 127 patients, and extracts of different latex gloves in some patients. Secondly, the material included 151 patients with clinically relevant immediate-type allergy to NRL (116 female and 35 male, age range 8.7–63.1 years, median 29.9 years). Diagnosis was confirmed by skin prick tests with NRL and glove extracts and IgE antibodies to NRL. Freshly obtained Fb leaf sap was used for skin prick tests in all patients, and 123 were tested with fig extract additionally. Sera were analyzed for specific IgE antibodies to *Ficus* spp.

Material and methods

Patients

The material included, firstly, 346 consecutive, non-NRL-allergic patients (218 female and 128 male, age range 7–76 years, median 34.4 years) mostly

Total and specific IgE determination

Total serum IgE and allergen-specific IgE antibodies (k81, k82) were analyzed with the CAP-FEIA system, according to the manufacturer's instructions. Values of allergen-specific IgE above 0.35 kU/l were considered to be positive.

Skin prick tests

Prick tests were carried out on the volar forearm. Wheal diameters were measured 20 min after puncture. A wheal diameter larger than 3 mm was considered to be positive. Skin tests with 0.1% histamine hydrochloride solution served as the positive control, and 0.9% NaCl and 0.4% phenol as the negative control.

Test extracts

Latex extracts. Latex extracts comprised the following:

- 1) Self-prepared extract from freshly collected NRL of Malaysian *Hevea brasiliensis* (9).
- 2) Highly ammoniated latex (gift from Regent Hospital Produkte, Mönchengladbach, Germany).
- 3) Glove extracts produced by shaking glove pieces (Peha Taft glove, Hartmann, Germany; Biogel glove, Regent Hospital Produkte, Mönchengladbach) in 0.9% NaCl solution overnight. After centrifugation, the liquid phase was filtered through a 0.22- μ m membrane, and phenol was added in a final concentration of 0.4% (w/v).

Fb leaf sap. Fresh sap was obtained from cut leaves of weeping fig.

Pulp of fresh figs (*F. carica*). The pulp was mixed with 0.9% NaCl solution (2/1 v/v) and shaken overnight at 4°C. After centrifugation and filtration through a 0.22- μ m membrane, extracts were stored at -20°C. The protein concentration of NRL and fig extracts was analyzed by a commercial protein assay (Pierce BCA Assay), bovine serum albumin being used as standard. The protein concentration of the NRL extract was 1.6 mg/ml; of the fig extract, 17.9 mg/ml.

RAST-inhibition test

For RAST-inhibition tests, we separated the aqueous phase of the NRL extract by centrifugation. A volume of 50 μ l of patient serum was preincubated with 0.01, 0.1, 1, and 10 μ l NRL extract, respectively, with NaCl (0.9%) as negative control, overnight, followed by analysis of allergen-specific IgE antibodies with the CAP-FEIA system. By comparison of the values, the extent of inhibition of IgE binding could be evaluated.

The allergenicity of the NRL and fig extracts was analyzed by RAST autoinhibition. Pooled sera of three patients with IgE antibodies to NRL and fruits were preincubated with fig extract, followed by analysis of IgE antibodies to *Ficus* spp.; five sera

of NRL-allergic patients were preincubated with the NRL extract, followed by analysis of NRL-specific IgE.

Statistical analysis

Statistics were analyzed with SPSS software. Total serum IgE levels were analyzed by the Kruskal-Wallis test; patients' age by the Mann-Whitney test. Correlation of specific IgE to *Ficus* spp. and NRL was analyzed by chi-square test statistics.

Results

Patients

The total serum IgE of the 346 consecutive patients was in the range 2->2000 kU/l (median 80 kU/l, SD 229). In 44.5% of the serum samples, the total IgE was >100 kU/l; in 5.6%, >1000 kU/l. Exactly 60.7% of the patients had a history of atopic diseases.

The total serum IgE of the 151 NRL-allergic patients was in the range 5.1->2000 kU/l (median 202.5 kU/l, SD 478.8). In 65.6% of the samples, total IgE was >100 kU/l; in 10.6%, >1000 kU/l. Exactly 62% of the patients gave a history of atopic diseases.

Allergen-specific IgE

In the 346 non-NRL-allergic patients, we found allergen-specific IgE antibodies to NRL in 44 and to *Ficus* spp. in 23 patients. A history of atopic diseases was significantly more frequent in patients with IgE antibodies to NRL and *Ficus* spp. ($P=0.0034$), who had significantly elevated total serum IgE ($P<0.00001$) (Table 1). Patients with allergen-specific IgE antibodies only to NRL were significantly younger ($P=0.0004$) and had higher total serum IgE levels than nonsensitized patients ($P<0.00001$). Females were overrepresented, and sensitization only to *Ficus* spp. was exclusively found in females, whereas sensitization to *Ficus* spp. as well as to NRL was significantly more frequent in males ($P=0.001$).

IgE antibodies to *Ficus* spp. were detected in 35 out of 151 serum samples of the NRL-allergic patients (Table 2). Total serum IgE was significantly higher ($P>0.00001$) than in the non-NRL-allergic patients. No significant differences in age, sex, and history of atopic diseases were observed.

In the whole group of 497 patients, we found a significant coincidence of IgE antibodies to NRL and *Ficus* spp. ($P<0.000001$) (Table 3).

Table 1. Characteristics of 346 patients in relation to allergen-specific IgE to *Ficus* spp. and NRL

Specific IgE	n	Age (years) median	Male %	History of atopic diseases	Total IgE (kU/l) median/SD
Negative to NRL and <i>Ficus</i>	292	35.3	35.6	56%	63/303
Positive only to NRL	31	26.6	48.4	89.3%	180/460
Positive only to <i>Ficus</i>	10	33.7	0	75%	187/628
Positive to <i>Ficus</i> and NRL	13	32.7	69.2	92%	1054/698

Table 2. Characteristics of 151 NRL-allergic patients in relation to allergen-specific IgE to *Ficus* spp.

Specific IgE to	n	Age (years) median	Male %	History of atopic diseases (%)	IgE (kU/l) median/SD
NRL	116	30.3	20.7	60.3	129.5/389.9
NRL and <i>Ficus</i>	35	26.9	31.4	67.6	410/613

Skin prick tests with *Fb* leaf sap

Skin prick tests with fresh sap from *Fb* leaves were performed in a total of 447 patients. Results were negative in 303 patients, positive (wheal weaker than histamine control) in 75 patients, and strongly positive (wheal diameter as large as histamine control) in 69 patients (Table 4). Strongly positive prick tests with *Fb* leaf sap correlated highly significantly with IgE antibodies to *Ficus* ($P < 0.00001$) and to NRL ($P < 0.00001$) (Table 5).

RAST-inhibition test

Equal allergens in fig extract and *Ficus* spp. were confirmed by complete inhibition of IgE to *Ficus* spp. after preincubation of pool serum with fig extract. After preincubation of five serum samples from NRL-allergic patients, complete inhibition of IgE to NRL demonstrated the relevant allergens in our NRL extract.

Preincubation of five serum samples containing IgE antibodies to *Ficus* spp. and NRL with NRL extract resulted in complete inhibition of IgE antibodies to *Ficus* spp. in each case. Preincubation with fig extract of six serum samples containing IgE antibodies to *Ficus* spp. and NRL resulted in an inhibition of specific IgE antibodies to NRL of 21–100% (median 57.4%).

Controls

Nonspecific inhibition by lectins or similar molecules contained in fig or NRL extracts was excluded by preincubation with fig or NRL extracts of well-defined serum samples from patients with allergies to pollen and house-dust mites. No significant inhibition of specific IgE to birch pollen (t3), grass pollen (gx1), and house-dust mite (d1) was observed.

Table 3. Allergen-specific IgE to NRL and *Ficus* spp. in 497 serum samples

CAP class	<i>Ficus</i> spp.		
	0	1	2–6
NRL			
0	293	1	9
1	28	1	1
2–6	118	16	30

Table 4. Prick tests with NRL and *Fb* extracts in 447 patients

Prick test	<i>F. benjamina</i>			
	0	1	2	3
NRL				
0	253	40	11	5
1	8	5	5	1
2	12	7	12	2
3	30	23	25	8

After preincubation of five serum samples from patients sensitized to *Ficus* spp., but not to NRL, with NRL extract, no inhibition of *Ficus* spp.-specific IgE antibodies was observed.

Discussion

In recent years, attention has been drawn to immediate-type hypersensitivity to *Fb* and related house plants (1–5, 10). The allergens, originally located in the tree sap of *Fb*, have been found in dust collected from leaf surfaces, and in house dust, where they persist over a period of some months after removal of the plant (5).

By investigation of 346 consecutive patients, we found 6.65% of them to be sensitized to *Fb* allergens. This agrees with studies from other countries; IgE-mediated allergy to *Fb* was reported in 6% of exposed

Table 5. Skin prick tests with fresh *Fb* leaf sap in correlation with detection of IgE antibodies to *Ficus* spp. and NRL in 447 patients

Prick test	IgE to <i>Ficus</i> spp. CAP class			IgE to NRL CAP class			Sum
	0	1	2-6	0	1	2-6	
<i>Ficus</i>							
Negative	287	6	10	224	19	60	303
+	59	8	8	22	8	45	75
++	41	2	10	5	1	47	53
+++	5	1	10	5	0	11	16
Sum	392	17	38	256	28	163	447

atopic patients in Sweden (2) and in 7.6% of 156 Swiss patients (3, 11). In 50% of these patients, sensitization was considered to be clinically relevant and caused rhinoconjunctivitis, asthma, eyelid edema, and contact urticaria (2, 3, 11).

Commercial *Fb* extracts suitable for skin tests are not available yet. Using fresh leaf sap, we found that the slightly positive reactions of 16.8% of the patients may be irritative, as confirmed by absence of IgE antibodies to *Ficus* spp. In contrast, most patients with strongly positive skin prick test reactions also had *Ficus*-specific IgE. In six of them, *Fb* sensitization clearly was clinically relevant; five patients suffered from rhinoconjunctivitis only, three from asthma, and two from contact urticaria. We did no provocation testing. Anamnestic data concerning the relevance of *Fb* sensitization have been discussed very carefully, considering the simultaneous sensitization of most patients to other ubiquitous allergens which can cause identical symptoms. Association between sensitization to NRL and *Ficus* spp. has been reported (5, 6), and cross-reacting IgE antibodies binding NRL and *Ficus* allergens have been demonstrated by RAST inhibition (5, 7, 9). An association of sensitization to NRL and *Ficus* spp. was found in 24.3% of NRL-allergic patients (9). The significance of *Fb* sensitization for development of NRL allergy, a known problem, especially among medical personnel (12, 13), patients with congenital malformation (14), children with more than three surgical interventions (15), and other frequent wearers of latex gloves (16), is not proved yet. In the present study, we found the coincidence of IgE antibodies to both NRL and *Ficus* spp., in 48/497 investigated serum samples (9.7%), to be highly significant.

NRL-specific antibodies were found in 44 of the 346 patients without clinical symptoms of NRL allergy by CAP-FEIA, combined with negative NRL prick tests. Mäkinen-Kiljunen & Turjanmaa reported false-positive CAP-FEIA in 12/40 serum samples of atopic patients, a finding which means that latex-specific IgE antibodies were detected, although these patients showed no symptoms of latex allergy, and skin prick tests with a panel of latex extracts

were negative (17). Finding banana-specific IgE antibodies in 10/12 serum samples, the authors interpreted this as due to cross-reacting antibodies. The present study indicates that IgE to *Ficus* spp. may also be responsible for false-positive CAP-FEIA to NRL. The high prevalence (7.9%) of IgE antibodies detecting NRL in a collection of 1436 blood donors (18) may have been the result of cross-reactive antibodies against allergens of different sources.

As a consequence of this study, *Fb* must be added to the important indoor allergens. Strong skin prick test results due to native *Fb* leaf sap, in combination with allergen-specific IgE antibodies, indicate sensitization to *Fb*. We think it also advisable to screen NRL-allergic patients for *Fb* allergy in case they are frequently exposed to both allergens.

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