Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2012;158:281–287
DOI: 10.1159/000332929

Received: March 31, 2011
Accepted after revision: September 2, 2011
Published online: March 6, 2012

Diagnostic Value of Specific IgE Analysis in Latex Allergy

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Key Words

Allergen-specific nasal challenge · IgE antibodies, specific · ImmunoCAP · In vitro tests · Latex allergy · Profilin · Skin prick test

Abstract

Background: The precision of the methods used to diagnose latex allergy is of great importance due to false-positive results. Neither the skin prick test (SPT) nor the latex-specific IgE assay has 100% diagnostic accuracy. We analysed the diagnostic value of latex-specific IgE by the first-ever concomitant use of the SPT and nasal provocation test (NPT). ***Methods:*** Twenty-seven latex-sensitive patients (group 1), 46 aeroallergen-sensitive patients (group 2a) and 33 healthy subjects (group 2b) participated in the study. All groups underwent an SPT with latex and aeroallergens and an NPT with latex. Latex-specific IgE and total IgE levels were measured by the ImmunoCAP assay. ***Results:*** Latex-specific IgE was positive in 92.6, 30.4 and 9.1% of groups 1, 2a and 2b, respectively. The 11 aeroallergen-sensitive patients in group 1 and all of the patients in group 2a were predominantly sensitised to pollens (grass, weed and tree) and reacted to a lesser degree to house dust mite, moulds and animal dander. Combined pollinosis was remarkably more prevalent in patients with positive latex-specific IgE in group 2a than in those with negative latex-specific IgE ($p = 0.001$). The NPT was positive in 84.6% of group 1 and negative in all control subjects. The sensitivity, specificity, negative predictive value and positive predictive value of the latex-specific IgE assay were 90.9, 72.2, 96.3 and 50%, respectively. ***Conclusion:*** The high rate of false-positive results for latex-specific IgE by ImmunoCAP should be taken into account when making a diagnosis of latex allergy in patients with pollinosis, especially in those sensitised to more than one pollen species.

Introduction

Latex allergy is a serious disease that presents with a spectrum of clinical signs and symptoms, including urticaria, allergic rhinitis, asthma and anaphylaxis. Latex allergy is the second most important cause (16%) of perioperative anaphylaxis after the use of neuromuscular blocking agents [1]. The precision of the diagnostic methods used for latex allergy is of great importance because false-positive IgE results may negatively influence the patients' quality of life due to the stringent measures required to ensure latex-free environments. The skin prick test (SPT) and in vitro tests detecting latex-specific IgE, such as the Pharmacia CAP system (ImmunoCAP), the DPC Ala-

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STAT and the Hycor HyTEC, are used in the diagnosis of latex allergy. The diagnostic performance parameters [sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV)] of the in vitro tests have been evaluated using patient history and/or SPTs as references [2, 3]. Although the SPT is the more sensitive diagnostic method when compared to specific IgE analysis, it may be positive in some patients without a history of latex allergy [4, 5]. Therefore, in such patients, provocation tests are needed for a definite diagnosis of latex allergy. Several different provocation tests have been employed in the diagnosis of latex allergy. Of these tests, the nasal provocation test (NPT) is the most reliable [5]. Until now, the provocation tests have never been used to evaluate the diagnostic performance of in vitro tests. In this study, we assess the diagnostic value of latex-specific IgE analysis by concomitant use of the NPT and SPT.

Subjects and Methods

Subjects

A total of 5,456 patients referred to the clinic of the Ege University Medical Faculty, Department of Internal Medicine, Division of Allergy, between July 2003 and January 2008 were evaluated. Of these patients, 2,073 demonstrated positive SPT reactivity to common aeroallergens (pollens, mites, moulds, animal dander). Thirty-eight of them were found to have a positive SPT to latex.

These 38 patients with a positive SPT to latex were asked to take part in the study and were designated the latex-sensitive group (group 1). Fifty subjects randomly selected from the 2,073 aeroallergen-sensitive patients and 50 subjects randomly selected from a healthy population were asked to participate in the study as an aeroallergen-sensitive group (group 2a) and a healthy control group (group 2b), respectively.

Study Design

The patient and control groups were evaluated at three different visits. At the first visit, a detailed history with respect to latex allergy (rhinitis, contact urticaria, asthma and anaphylaxis) and other allergies was taken after obtaining informed consent from the patients who agreed to take part in the study. At the second visit, another SPT with latex and common aeroallergens was performed, and a blood sample was taken in order to measure the latex-specific IgE and total IgE. The patients with total IgE values lower than 2,000 kU/l were selected to continue to the third phase. At the third visit, patients underwent an NPT. For pollen-allergic patients, the NPT was performed outside of the pollen season.

This study was approved by the Ege University Ethics Commission (approval number 05-11.2-3).

Skin Prick Test

SPTs were performed with a standardised prick test needle (Stallerpoint). SPTs were performed with latex and commercially available common aeroallergens (grass, weed, tree pollen, house dust mites, moulds, animal dander; ALK-Abello, Madrid, Spain). Latex SPT material contained 500 μg/ml latex protein. Physiological saline was used as a negative control, and histamine (10 mg/ml) was used as a positive control. SPT results were assessed after 20 min. The presence of an induration with a diameter at least 3 mm greater than that of the negative control with associated erythema was considered positive.

Serological Analysis

We used the ImmunoCAP, currently marketed as the Phadia ImmunoCAP (Pharmacia, Uppsala, Sweden), because it is the most widely employed and reliable method [6]. For the latex-specific IgE analysis, values higher than 0.35 kU/l were considered positive. The results were graded on a 6-point scale as recommended by the manufacturer.

Nasal Provocation Test

The 4th vial (ALK-Abello) produced for latex-specific sublingual immunotherapy was used as the allergen source. One millilitre of this vial contains 500 μg/ml latex protein, 0.5 ml of glycerol, 3 mg of phenol and 9 mg of sodium chloride. The diluent portion of this vial containing no latex protein was used as a placebo. The diluent was produced at Ege University Pharmacology Laboratories. The allergen was diluted 10, 100, 1,000 and 10,000 times, corresponding to 50, 5, 0.5 and 0.05 μg/ml latex protein, respectively, and the placebo was diluted 10 times with physiological saline prior to the NPT. The placebo and incremental doses of allergen were applied to all groups using nasal applicators spraying 0.1 ml per application. Symptoms observed during the NPT were scored as follows: sneezing, 0–2 times = 0 points, 3–4 times = 1 point, ≥5 times = 3 points; itching, 1 point each for itching of the nose, ear or palate, for a total of 3 possible points; rhinorrhoea, none = 0 points, mild = 1 point, moderate = 2 points, severe = 3 points; nasal block, none = 0 points, mild = 1 point, moderate = 2 points, severe = 3 points; eye symptoms (watering of the eyes, itching, redness), 1 point each, but with only 1 point possible. The test was discontinued if the symptom score reached 5 or reached 4 with a decrease in the nasal flow rate of 40% of the basal value [5].

Statistics

Kruskal-Wallis and Mann-Whitney U tests were used for comparison of the groups. Categorical variables were compared by the χ^2 test. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 15.0 for Windows. Data were expressed as means ± standard deviations. A p value less than 0.05 was accepted as statistically significant. Sensitivity, specificity, PPV and NPV were calculated.

In evaluation of the diagnostic performance, three different gold standards (SPT positivity alone, concomitant positivity of SPT and latex allergy history or concomitant positivity of SPT and NPT) were taken into account.

Results

Subjects

Twenty-seven, 46 and 33 patients in groups 1, 2a and 2b, respectively, participated in the study. Group 1 comprised

Table 1. a Clinical and laboratory results of the patients in the three groups

Group	Total subjects	Positive history	Latex SPT positive	Latex-specific IgE positive	Latex NPT[1] positive
1	27	24 (88.9)	27 (100)	25 (92.6)	22 (84.6)
2a	46	0	0	14 (30.4)	0
2b	33	0	0	3 (9.1)	0

Values represent numbers of subjects, with percentages in parentheses.

[1] NPT was not performed in 1, 8 and 3 subjects in groups 1, 2a and 2b, respectively.

Table 1. b Distribution of immunoCAP results in latex-specific IgE-positive subjects

Group	Total subjects	ImmunoCAP class					
		I	II	III	IV	V	VI
1	25	3 (12)	5 (20)	10 (40)	4 (16)	2 (8)	1 (4)
2a	14	3 (21.4)	9 (64.3)	2 (14.3)	0	0	0
2b	3	1 (33.3)	2 (66.7)	0	0	0	0

Values represent numbers of subjects, with percentages in parentheses.

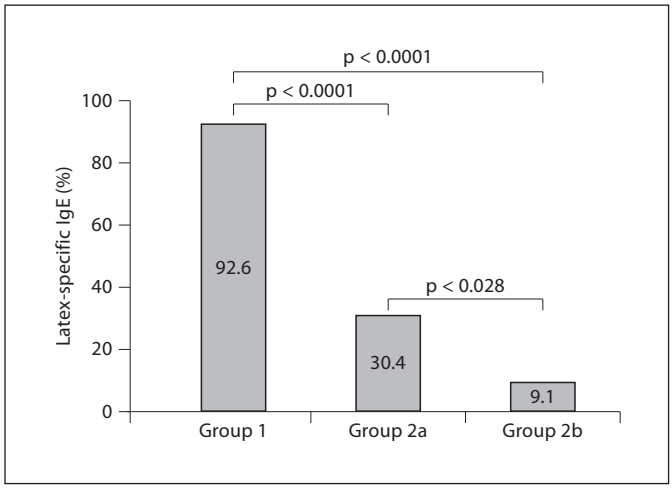

Fig. 1. The rates of positive latex-specific IgE in the three groups.

4 male patients (14.8%) and 23 female patients (85.2%). Their ages ranged from 19 to 45 years (mean 30 ± 6.52). In group 2a, 19 patients (41.3%) were males and 27 (58.7%) were females, with ages ranging from 17 to 48 years (mean 30.41 ± 9.82). In group 2b, 8 out of 33 patients were males (24.2%) and 25 (75.8%) were females, with ages ranging from 18 to 49 years (mean 31.36 ± 8.32). There was no statistically significant difference among the groups in terms of age or gender.

Twenty-three (85%), 3 (6.5%) and 0 patients (0%) in groups 1, 2a and 2b, respectively, were health care personnel.

None of the patients in either control group had a history of latex allergy. Twenty-four of the 27 patients in group 1 had a history of latex allergy (table 1a). Eleven of the patients in group 1 and all of the patients in group 2a had a history of allergic rhinitis and/or asthma.

Latex-Specific IgE and Total IgE Analyses

Latex-specific IgE was found to be positive in 25 of 27 patients (92.6%) in group 1. Latex-specific IgE test results ranged from class I to class VI. Latex-specific IgE was positive in 14 of 46 patients (30.4%) in group 2a, and positivity ranged from class I to class III. Latex-specific IgE was positive in 3 of 33 patients (9.1%) in group 2b, and the results ranged from class I to class II (table 1a, b).

The rate of positive latex-specific IgE was found to be significantly higher in group 1 when compared with either control group ($p < 0.0001$, Fisher's exact test). When the control groups were compared to each other, the rate of positive latex-specific IgE was found to be significantly higher ($p = 0.028$, Fisher's exact test) in group 2a (fig. 1).

All patients participating in the study had total IgE levels lower than 2,000 kU/l. Total IgE levels ranged from 8 to 532 kU/l (median 72), 5 to 1,190 kU/l (median 75) and 5 to 104 kU/l (median 46) in groups 1, 2a and 2b, respectively. The total IgE levels in patients with positive latex-specific IgE and negative latex-specific IgE in group 2a ranged from 7 to 1,195 kU/l (median 71.5) and 5 to 464 kU/l (median 75.5), respectively. The total IgE levels in patients with positive latex-specific IgE in group 2b ranged from 20 to 58 kU/l (median 45).

Skin Prick Test

The SPT with latex was positive in all of the patients in group 1. Sixteen of these patients (59.3%) had a positive SPT only to latex. Eight of the remaining 11 patients (72.7%) were sensitised to grass pollens, 5 (45.5%) to tree pollens, 3 (27.3%) to weed pollens, 1 (9.1%) to house dust mites and 1 (9.1%) to other allergens (moulds and/or animal dander). Six of the 11 patients (54.5%) were sensitised to more than one aeroallergen. Two of the 11 patients

Table 2. Diagnostic performance of the latex-specific IgE assay (ImmunoCAP)

Parameter	Based on SPT[1]	Based on SPT and H[2]	Based on SPT and NPT[3]
Sensitivity, %	92.6 (82.7–100)	92 (81.4–100)	90.9 (78.9–100)
Specificity, %	78.5 (69.4–87.5)	76.5 (67.3–85.8)	72.2 (61.9–82.6)
NPV, %	96.9 (92.6–100)	96.9 (92.6–100)	96.3 (91.2–100)
PPV, %	59.5 (44.7–74.4)	54.8 (39.7–69.8)	50 (34.5–65.5)
PV, %	82.1 (74.8–89.4)	80.2 (72.6–87.8)	76.6 (68–85.2)

Values in parentheses show 95% confidence limits. H = History of latex allergy; PV = predictive value.
[1] SPT positivity alone. [2] Concomitant positivity of SPT and latex allergy history. [3] Concomitant positivity of SPT and NPT.

(18.2%) presented combined grass, weed and tree pollinosis.

All of the patients in group 2a had a negative SPT to latex. In this group, 39 patients (84.8%) were sensitised to grass pollens, 33 (71.7%) to tree pollens, 29 (63%) to weed pollens, 12 (26.1%) to house dust mites and 3 (7.6%) to other allergens. Thirty-five of 46 patients (76%) in group 2a were sensitised to more than one allergen. Eighteen of 46 (39.1%) had combined pollinosis.

All of the 14 patients with positive latex-specific IgE in group 2a were sensitised to grasses, 13 (92.9%) to weed, 11 (78.6%) to tree, 2 (14.3%) to house dust mite, 1 (7.1%) to other allergens and 11 (78.6) to combined pollens.

Twenty-five of the 32 patients (78.1%) presenting negative latex-specific IgE in group 2a were sensitised to grasses, 17 (53.1%) to weed, 11 (34.4%) to tree, 10 (31.3%) to house dust mite, 4 (12.5%) to other allergens and 7 (21.9%) to combined pollens.

A statistically significant difference was observed between latex-specific IgE-positive and -negative patients in group 2a in terms of combined pollinosis ($p = 0.001$, Fisher's exact test).

SPTs were found to be negative in all the patients in group 2b.

We did not record any adverse reactions to the latex SPT.

Nasal Provocation Test

One patient in group 1 could not undergo an NPT due to a history of anaphylaxis. In group 1, the NPT was positive in 22 of the 26 patients (84.6%; table 1a). All of these patients had a positive history of latex allergy. Latex allergy history was absent in 3 of the 4 patients (15.4%) with a negative NPT, and their nasal symptom scores during the NPT were all zero. One patient with a negative NPT had a latex allergy history. This patient developed nasal symptoms (4 points) during the NPT; however, the test was accepted as negative by virtue of an unmet criterion for positivity.

The NPT was not attempted in 8 patients in group 2a due to nasal deviation in 2 of them and reluctance regarding the NPT in the remaining 6. Three patients in group 2b were not subjected to an NPT because they declined the procedure. The NPT was found to be negative in the remaining 38 and 30 patients in groups 2a and 2b, respectively.

Diagnostic Performance

All performance parameters are shown in table 2.

Discussion

Few studies have been conducted to evaluate the diagnostic performance of latex-specific IgE analysis based on SPT and patient history together. Hamilton et al. [2] compared three different latex-specific IgE analyses (ImmunoCAP, DPC AlaSTAT and Hycor HyTEC). Although the assays gave similar results, the best performance (sensitivity 76.3%, specificity 96.7%, PPV 94.3% and NPV 85%) was obtained with ImmunoCAP when a positive SPT was accepted as the gold standard (table 3). Ownby et al. [3] demonstrated that the diagnostic performances of both ImmunoCAP and DPC AlaSTAT showed similar and acceptable results for latex-specific IgE analysis. When concomitant positivity of history and SPT was accepted as the gold standard, ImmunoCAP had a sensitivity of 79.5%, specificity of 90.2%, PPV of 91.7% and NPV of 76.4% (table 3). In both of the aforementioned studies, the control groups consisted of individuals who had a nega-

Table 3. Results of three different studies evaluating the diagnostic performance of the latex-specific IgE assay (ImmunoCAP)

Parameter	Hamilton et al. [2] (based on SPT[1])	Ownby et al. [3] (based on SPT and H[2])	Present study (based on SPT and NPT[3])
Sensitivity, %	76.3 (69–84)	79.5	90.9 (78.9–100)
Specificity, %	96.7 (94–99)	90.2	72.2 (61.9–82.6)
NPV, %	85 (80–90)	76.4	96.3 (91.2–100)
PPV, %	94.3 (90–99)	91.7	50 (34.5–65.5)

Values in parentheses show 95% confidence limits. H = History of latex allergy.
[1] SPT positivity alone. [2] Concomitant positivity of SPT and latex allergy history. [3] Concomitant positivity of SPT and NPT.

tive SPT to latex and no history of latex allergy. However, those groups were not designed as healthy and allergic control groups, in contrast to the control design in our study.

In our study, latex-specific IgE analyses were performed in three different groups (latex-sensitive patients, aeroallergen-sensitive patients and healthy subjects), and different results were obtained. Latex-specific IgE was found to be positive in a high percentage of patients (30.4%) in the aeroallergen-sensitive group, and the NPT was negative in all of these patients. Therefore, the false-positive rate for latex-specific IgE was remarkably high in the aeroallergen-sensitive group. When concomitant positivity of the SPT and NPT was accepted as the gold standard in the diagnosis of latex allergy, the sensitivity, specificity, NPV and PPV of latex-specific IgE were determined to be 90.9, 72.2, 96.3 and 50%, respectively. While sensitivity and NPV were found to be higher, specificity and PPV were lower as compared with the two previous studies (table 3). These discrepancies may be caused by the differences in the gold standards and control group profiles. The lower specificity and PPV and higher NPV observed in our study as compared to the previously published studies may be related to a high false-positive IgE rate in the aeroallergen-sensitive group. When diagnostic performance was recalculated after exclusion of the aeroallergen-sensitive group, sensitivity did not change, but a decrease in NPV (96.3 vs. 93.1%) and an increase in specificity and PPV (72.2 vs. 79.4% and 50 vs. 74.1%, respectively) were observed. The sensitisation profiles of the 11 aeroallergen-sensitised patients in the latex-sensitive group and all of the patients in the aeroallergen-sensitive group were similar. These 11 patients in the latex-sensitive group may have contributed to the high rate of positive latex-specific IgE (92.6%) in this group. This may explain the higher sensitivity observed in our study compared with the other two studies.

The NPT identified those patients representing false positives with latex-specific IgE and the SPT. The inclusion of the NPT in the diagnostic criteria led to a decrease in all of the diagnostic performance parameters of the latex-specific IgE analysis (table 2), whereby more accurate results were obtained.

The most salient feature of the aeroallergen-sensitive group was the high sensitivity rate to pollens, with grass pollens being the most prevalent (84.8%), followed by tree pollens (71.7%), weed pollens (63%), house dust mites (26.1%) and other allergens (7.6%). To date, 13 latex allergens have been identified (designated Hev b 1 to Hev b 13). Hev b 8 and Hev b 12, known as pan-allergens, correspond to profilin and lipid transfer protein (LTP), respectively [7, 8]. Cross-reactivity has been shown to occur between grass, weed and tree pollens (ragweed, mugwort, birch, timothy grass and rye grass) and latex. Hev b 8 has been determined to be responsible for this cross-reactivity [9–12]. Although Hev b 8 has been accepted as a minor allergen, the clinical role of this allergen in the development of latex allergy is still debated. Ganglberger et al. [12] showed that 12 out of 50 health care personnel and 2 out of 34 patients with spina bifida and latex allergy had specific IgE to Hev b 8. All patients who had specific IgE to Hev b 8 presented with pollen or plant food allergies. The authors suggested that pollen or food profilins account for this sensitisation to Hev b 8 and that patients who have a pollen allergy and profilin-specific IgE have an increased risk of development of latex allergy [12]. In the Rihs et al. [13] study, specific IgE to recombinant (r) Hev b 8 was found to be positive in 2 of 17 spina bifida

patients and in 5 of 25 health care workers with latex allergy, and Hev b 8 was accepted as a minor allergen in the development of latex allergy.

Antonicelli et al. [4] reported 7 patients who had a positive SPT to latex (ALK-Abello, Denmark) and/or latex-specific IgE (ImmunoCAP) in the absence of a history of latex allergy in a study of the clinical relevance of Hev b 8-specific IgE. In this study, 2 patients had a positive latex SPT (3+ and 1+, respectively) and the remaining 5 patients presented a negative SPT. All patients had a positive SPT to grass pollens. Although all of the patients had latex- and Hev b 8-specific IgE, the provocation test using latex gloves was negative. Antonicelli et al. [4] did not define the role of Hev b 8 in latex allergy because they could not show the presence of Hev b 8 in two different surgical latex gloves. Taking into consideration the absence or undetectable amounts of Hev b 8 in latex gloves (known to be prominent sensitisers), Hev b 8 does not seem to be responsible for latex allergy development [4, 11].

The 2 patients with a positive latex SPT in the study by Antonicelli et al. [4] and 3 patients in the latex-sensitive group in our study had common features. Although latex-specific IgE as determined by ImmunoCAP was found to be positive in these patients, they did not have histories of latex allergy and their provocation tests with latex material were negative. The other salient point shared between the two studies was the demonstration of a positive SPT to grass pollens in all patients. The test material used in ImmunoCAP (k82) contains sufficient Hev b 8; however, its IgE-binding capacity is low [14]. Therefore, in some patients who have pollen allergy, but not latex allergy, as shown in the 14 patients in the aeroallergen-sensitive group and the 3 patients in the latex-sensitive group, this serological assay may give positive results arising from cross-reactivity between Hev b 8 and pollen profilins. The natural latex protein contains scarce latex profilin [13]. Thus, the profilin level, although not known exactly, can be expected to be low in the prick test material we used. This may lead to a positive latex SPT in the absence of a true latex allergy in a very small proportion of patients with pollen allergies. If the SPT material had contained a sufficient amount of Hev b 8, the latex SPT would have been found to be positive in more patients suffering pollen allergies, as was shown in latex-specific IgE analysis.

There is little information regarding Hev b 12 in the literature. LTP cloned from *Hevea brasiliensis* RNA was produced as a recombinant protein (rHev b 12) by Beezhold et al. [15]. Specific IgE for rHev b 12 was detected in sera from 9 of 37 patients with latex allergy. Two of them had clinical reactivity to fruits of the Rosaceae family. In conclusion, rHev b 12 was not considered a probable major allergen but rather a potentially important cross-reactive allergen [15]. Like profilins, LTP is one of the important allergens of some of the grass, weed and tree pollens (mugwort, ragweed, olive, plane tree, pellitory) [16], but cross-reactivity between pollen LTPs and Hev b 12 has not yet been reported. Additionally, it is unknown whether k82 contains Hev b 12. Thus, the role of LTP in aeroallergen-sensitive patients with clinically irrelevant IgE for latex remains to be clarified through further studies.

Like profilins, cross-reactive carbohydrate determinants (CCDs) have been linked to false-positive IgE for latex in pollen-allergic patients. The prevalence of anti-CCD IgE has been found to be 41.7% in patients sensitised to at least one pollen and 62.4% in patients sensitised to more than one pollen. [17]. Ebo et al. [18] investigated the prevalence of sensitisation to CCDs and profilin by ImmunoCAP in patients with pollinosis and latex allergy. They demonstrated bromelain-type CCD sensitisation in 4 of 17 patients with isolated grass pollinosis and in 5 of 25 patients with combined pollinosis (birch, timothy, mugwort). While 17 of 21 patients with false-positive specific IgE for latex had anti-bromelain-type CCD IgE, none of the 17 patients with latex anaphylaxis had it. False-positive IgE for latex stemming from pollinosis was inhibited by bromelain in 3 of 5 sera. None of the 17 patients with isolated latex anaphylaxis showed sensitisation to rHev b 8. However, rHev b 8 was detected in 4 of the 7 patients with combined pollinosis. Recombinant birch profilin was shown to inhibit false-positive IgE for latex related to pollinosis in 4 of 5 test sera [18]. In summary, in this study, CCDs and profilins were determined to be responsible for clinically irrelevant specific IgE for latex.

Likewise, in our study combined pollinosis was found to be higher in patients with false-positive specific IgE than in those who had negative latex-specific IgE in the aeroallergen-sensitive group (78.6 vs. 21.9%; $p = 0.001$). As in the study of Ebo et al. [18], profilins and CCDs may have been responsible for the high percentage of clinically irrelevant latex-specific IgE in the aeroallergen-sensitive group.

When total serum IgE is extremely elevated, it can be responsible for non-specific IgE binding. It is reported in regard to the Phadia ImmunoCAP that the likelihood of a false-positive latex-specific IgE stemming from high total IgE levels (e.g. 5,000–10,000 kU/l) is quite low. Total IgE levels in all the groups in our study were markedly lower than these IgE levels.

In summary, in this study, for the first time, the diagnostic value of ImmunoCAP was evaluated by concomitant use of the NPT and SPT. We determined that the high rate of false-positive latex-specific IgE with ImmunoCAP should be taken into account when making a diagnosis of latex allergy in patients with pollinosis, especially in those sensitised to more than one pollen species. Profilins and CCDs may be responsible for clinically irrelevant specific IgE to latex. It is anticipated that more robust results could be obtained by using test materials devoid of profilins and CCDs.

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