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Original article

The importance of nasal provocation test in the diagnosis of natural rubber latex allergy

Background: Most studies regarding natural rubber latex (NRL) allergy have concentrated on the prevalance using skin prick test (SPT) and specific IgE assay. The objective of this study is to examine the target organ (skin, nasal mucosa) responses in patients with positive SPT to NRL using the nasal provacation test (NPT) and glove use test (GUT).
Methods: Four thousand four hundred and twenty patients presented to our polyclinic between July 2003 and January 2007 were evaluated. One thousand six hundred and ninety-nine patients had positive SPT to one or more allergens (NRL and other inhaler allergens). Twenty-nine patients with positive SPT to NRL comprised the NRL sensitive group (group 1). Thirty-five randomized patients with positive SPT to an inhaler allergen other than NRL and negative NRL-specific IgE comprised atopic control group (group 2). Thirty healthy individuals who had no allergic diseases and had negative SPT and NRL-specific IgE comprised the healthy control group (group 3).
Results: The lowest NRL allergen concentration leading to NPT positiveness was 0.05 μg/mL. NPT was negative in groups 2 and 3. NPT was found to have a sensitivity of 96%, specificity of 100%, negative predictive value of 98% and positive predictive value of 100%. GUT was found to have a sensitivity of 81%, specificity of 90%, negative predictive value of 75% and positive predictive value of 93%.
Conclusions: Nasal provocation test was successfully used for the first time in the diagnosis of NRL allergy. NPT is a more sensitive method as compared to GUT.

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Natural rubber latex (NRL) allergy is recognized as a significant health problem. The tests used in the diagnosis of NRL allergy include specific IgE analysis and skin prick test (SPT). However, neither of these diagnostic methods has 100% sensitivity and predictive value (1–4). Moreover, the history has a limited diagnostic value in the diagnosis of NRL allergy (5–7). Therefore, provocation tests examining target organ responses are needed for an accurate diagnosis of NRL. A standard NRL provocation method has not been established yet. The objective of the present study is to examine the target organ (skin, nasal mucosa) responses in patients with positive SPT to NRL using the nasal provocation test (NPT) and glove use test (GUT).

Material and methods

Subjects

In this study, a total of 4420 patients presented to Ege University Medical Faculty Allergy Polyclinic between July 2003 and January 2007 were evaluated. 1699 of these patients had positive SPT responses to one or more allergens (NRL, pollens, dust mites, molds, animal epithelia). 29 of these patients with positive SPT to NRL were enrolled in the study as the NRL sensitive group (group 1). 35 randomized patients with positive SPT to any common inhaler allergen other than NRL comprised the atopic control (group 2). During the first visit, a medical history form questioning type 1 hypersensitivity reactions (contact urticaria, rhinitis, asthma, and anaphylaxis) stemming from NRL exposure was filled out. SPT to NRL and common inhaler allergens was repeated. NRL specific IgE levels were analysed. Test results were assessed during the second visit. Five patients from group 2 with positive NRL specific IgE (3 with +1 and 2 with +2) were excluded from the study. In addition to group 1 and 2, 30 healthy individuals outside the health sector who did not have any respiratory, allergic and serious systemic diseases participated in the study as healthy control group (group 3). The other inclusion criteria for this group were as follows: a negative SPT and a negative specific IgE test to NRL and common inhaler allergens.

NPT and GUT were applied to all groups on two different days. First, NPT was administered followed by GUT no sooner than a week after performing NPT. NPT was applied to the patients with pollen allergy outside pollen season. Respiratory function tests were evaluated before and after NPT. The study was approved by Ege

University Ethics Commission and written consent were obtained from individuals participating in the study.

Skin prick test

Skin prick test (SPT) was performed using commercial allergen extracts (ALK-Abello, Madrid, Spain). NRL SPT material contained 500 μg/ml NRL protein. Physiological saline was used as negative control and histamine (10 mg/ml) for positive control. SPT results were assessed after 20 min. Presence of an enduration 3 mm or greater than the negative control accompanied by an erythema was considered positive.

Specific IgE assay

In the NRL specific IgE analysis (CAP system; Pharmacia, Uppsala, Sweden) values higher than 0.35 kU/l were considered positive. The results were graded on a 6-point scale as recommended by the manufacturing firm.

Nasal provocation test

Nasal Provocation Test (NPT) was applied to groups 1, 2 and 3 to determine rhinitis symptoms associated with NRL. Three patients in group 1 were excluded from the study as NPT could not be performed due to a history of anaphylaxis, inability to discontinue nasal steroids and nasal deviation, respectively. The test was conducted according to NPT principles using the active anterior rhinomanometry technique (8). A no.5 vaccination flacon (ALK-Abello, Madrid, Spain) produced for NRL-specific sublingual immunotherapy was used as an allergen. One milliliter of this flacon contains 500 μg NRL protein, 0.5 ml glycerol, 3 mg phenol, 9 mg sodium chloride. The diluent portion of this flacon containing no NRL protein was used as placebo. The diluent was produced at Ege University Pharmacology Laboratories. The allergen was diluted 10, 100, 1000, 10 000 times corresponding to 50, 5, 0.5, 0.05 μg/ml NRL protein, respectively and placebo was diluted 10 times with physiological saline prior to NPT. The placebo and allergen were applied to all groups using nasal applicators spraying 0.1 ml each time. Nasal and eye symptoms were recorded during the 15 min observation, and the changes in the nasal flow rate were measured by rhinomanometry. First, the nasal provocation was started with placebo. Individuals who had no symptoms and did not show decrease in the nasal flow rate above 20% following placebo application were then exposed to allergen provocation test. The allergen provocation was started with 0.05 μg/ml NRL protein and then the applied protein concentration was increased 10, 100, 1000 times (0.5, 5, 50 μg/ml NRL protein, respectively). In all patients and healthy controls when the nasal provocation test was found to be positive or the maximum allergen concentration (50 μg/ml NRL protein) was reached, the test was discontinued. In order to find the lowest allergen dose leading to NPT positiveness, NPT was repeated on a different day by using the 10, 100, 1000, 10 000 times diluted concentrations of 0.05 μg allergen on patients who had positive NPTs with 0.05 μg/ml.

Symptom score

Symptoms observed during the NPT were scored (9). Sneezing: 0–2 times, 0 point; 3–4 times, 1 point; ≥5 times, 3 points. Itching:1 point for itching of the nose, ear or palate, total 3 points. Rhinorrhea: none, 0 point; mild, 1 point; moderate, 2 points; severe, 3 points. Nasal block: none, 0 point; mild, 1 point; moderate, 2 points; severe, 3 points. Eye symptoms (watering of the eyes, itching, redness): 1 point, total 1 point.

Discontinuing the NPT

The test was discontinued when the symptom score reached or exceeded 5 (9) or reached 4 with the decrease in the nasal flow rate of 40% according to the basal value (10).

Respiratory function test

A respiratory function test was administered before and after NPT. FEV1s (forced expiratory volume in 1 s percentage) was measured 5 min after the test.

Glove use test

The test was used to determine contact urticaria symptoms associated with NRL. GUT was applied to all groups. First, all participants were asked to damp their hands, and then to put a powdered latex glove on their right hands and a non-latex vinyl glove on their left hands (negative control). The gloves were removed after 15 min. Symptoms and findings on both hands after 15 and 60 min were recorded. The symptom score was graded on a scale of 1 to 4 points (itching: 1 point; itching and erythema: 2 points; itching, erythema and induration: 3 points; systemic complaints such as rhinitis and asthma: 4 points) (11). In the present study, GUT was considered to be positive in individuals whose symptom scores reached 3 points.

Statistics

Mann–Whitney *U*-test and Spearman's rank correlation coefficient were used to evaluate the data. The difference among groups was found to be statistically significant at $P < 0.05$.

Results

Subjects

Three patients in group 1 were excluded from the study as NPT could not be performed due to a history of anaphylaxis, inability to discontinue nasal steroids and nasal deviation, respectively. Of the remaining 26 patients, four (14.8%) were male and 22 (85.2%) were female. The patients' ages ranged between 19 and 45 (mean of 30.6 ± 6.8). In this group all patients except four (patients 15, 17, 18, 26) were health care personnel. Three patients (14th, 17th and 18th patients) did not define type 1 hypersensitivity reactions when exposed to NRL. One of them (14th patient) was a health care personnel and the other two (17th and 18th patients) were students but not in medicine or dentistry. The remaining 23 patients described at least one of the diseases such as rhinitis, contact urticaria, angioedema and asthma after exposure to NRL (Table 1).

Group 2 comprised seven (30.5%) male and 23 (69.5%) female patients. The patients' ages ranged between 17 and 46 (mean of 28.8 ± 10.2). Group 3 comprised eight

(26.7%) male and 22 (73.3%) female patients and ages ranged between 18 and 49 (mean of 31.9 ± 8.1). There were no health care personnel among the members of groups 2 and 3. There was no statistically significant difference among these groups with respect to gender and age.

Skin prick test

In group 1, induration diameter in SPT with NRL ranged between 3 and 22 mm. Fifteen (57.7%) patients were sensitive only to NRL, while 11 (42.3%) were also sensitive to the inhaler allergens other then NRL.

Specific IgE assay

Two (11th and 13th patients) out of all (92.4%) patients in group 1 had a positive NRL-specific IgE. Measurements were within a range of +1 and +6 (Table 1).

Nasal provocation test

In group 1, NPT was positive in 22 (84.6%) out of 26, and negative in four (15.4%) (5th, 14th, 17th, and 18th patients). A history of a NRL related rhinitis was positive in a great majority of the patients (95.6%) with positive NPT. NPT caused itching of the nose, rhinorrhea, nasal block, watering and itching of the eyes, decrease in nasal flow rate of 20% in the 5th patient, however, the symptom score and decrease in the nasal flow rate failed to meet the the positiveness criterion.There was no change in the nasal provocation test symptom score (NPTSS) and nasal flow rate of the other three patients (14th, 17th, and 18th patients) who did not describe type 1 hypersensitivity reaction with NRL exposure. The symptom scores ranged between 4 and 10 in NPT-positive patients (Table 1). The mean NPTSS was 5.6 ± 1.8. A positive correlation (Fig. 1) was found between the NPTSS and the induration diameter of the SPT with NRL ($r = 0.48$, $P = 0.041$). The lowest NRL allergen concentration leading to NPT positiveness was determined as 0.05 μg/ml. NPT results were negative and the NPTSS was 0 in all members of the group 2. Only one patient had a decrease in the nasal flow rate in excess of 40% but this did not meet the positiveness criterion. NPT was negative in all members of the group 3. NPTSS was found to be 0 except for four patients in this group. The NPTSS was 1 point in two of them and 2 points in the other two patients. None of them had a decrease in their nasal flow rates in excess of 40%. Unlike these four patients, two patients showed decrease in nasal flow rate more than 40%, however, since their NPTSS was zero, their NPT tests were considered negative. When coexistence of SPT positiveness to NRL with a history of NRL-associated rhinitis was accepted as the 'Gold Standard' in the diagnosis of NRL allergy, NPT was found to have a sensitivity of 96%, specificity of 100%,

Table 1. Demographic, clinical and laboratory specifications of group 1

Patient	Gender	Age	HCP	NSI	Clinic	Prick (mm)	sIgE	NPTSS	R40%	AC (μg/ml)	GUTSS
1	F	30	+	1	R	7	+3	6	+	50	0
2	F	29	+	0	R,A,CD	6	+2	4	+	5	0
3	F	33	+	0	R,CU	12	+3	6	+	50	3
4	F	35	+	4	R,CU	10	+3	5	–	0.05	3
5	F	32	+	1	R	5	+1	4	–	50	0
6	F	39	+	3	R,CD	6	+1	4	+	50	1
7	F	26	+	0	R,A,CU	6	+5	6	+	5	2
8	F	25	+	0	R,A,CU	10	+3	4	+	0.5	3
9	F	25	+	1	R,A,CU	10	+5	9	–	5	3
10	M	39	+	1	R,CU, CD	11	+4	7	–	0.05	3
11	F	42	+	0	R,CU	5	0	4	+	50	3
12	F	29	+	0	R,A,CU	5	+3	4	+	5	3
13	F	26	+	0	R,CU	8	0	6	+	0.05	1
14	F	24	+	0	CD	4	+2	0	–	50	0
15	F	45	–	2	R,AE	13	+3	5	+	0.5	3
16	F	30	+	2	R,CU	7	+2	4	+	0.5	3
17	F	23	–	1	Ø	4	+2	0	–	50	0
18	M	20	–	0	Ø	3	+2	0	–	50	0
19	F	27	+	0	R,A,CU,CD	7	+6	4	+	50	3
20	F	39	+	3	R,A,CU,CD	10	+3	7	+	0.5	3
21	M	36	+	1	R,CD	13	+4	8	+	0.5	2
22	F	30	+	2	R,CU	9	+3	10	+	0.5	3
23	F	35	+	3	R,CU,CD	5	+3	4	+	0.5	3
24	F	29	+	2	R,CU	11	+3	6	–	5	3
25	F	28	+	1	R,CU	10	+4	9	+	50	1
26	M	19	–	4	R	22	+1	5	–	50	1

HCP, health care personnel; NSI, number of surgical interventions; R, rhinitis; A, asthma; AE, angioedema; CU, contact urticaria; CD, contact dermatitis; splgE, latex specific IgE; NPTSS, nasal provocation test symptom score; GUTSS, glove use test symptom score, AC, allergen concentration used in the nasal provocation test; R40%, more than 40% decrease in rhinomanometry, +, yes; –, no; F, female, M, male; Ø, none.

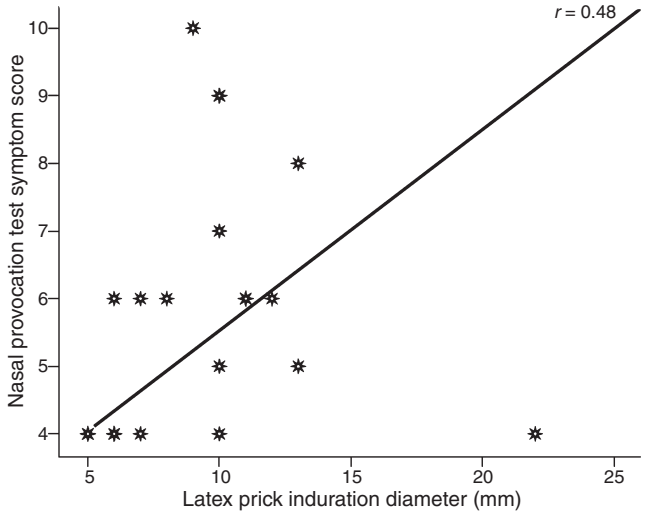

Figure 1. A positive correlation was found between patients' nasal provocation symptom scores and prick test induration diameter to latex allergen ($r = 0.48$, $P = 0.041$, Spearman's rank correlation test). Each asterisk represents a patient. *Y*-axis shows patient's nasal provocation test symptom score and *X*-axis shows patients' prick test induration diameter to latex allergen.

Table 2. NPT and GUT performances

Test	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
GUT	81	90	75	93
NPT	96	100	98	100

NPV, negative predictive value; PPV, positive predictive value.

negative predictive value of 98% and positive predictive value of 100% (Table 2).

Respiratory function test

In all three groups, there was no decrease in excess of 15% in FEV1s following NPT compared to FEV1s prior to NPT.

Glove use test

Glove use test was found to be positive in 13 (50%) of the 26 patients in group 1. Sixteen (61.5%) of them had a history of contact urticaria. The glove use test symptom score (GUTSS) was found to be 3 in 13 (81.3%) of the 16 patients. The other three patients (7th, 13th and 25th patients) had GUT scores of 2, 1, and 1, respectively. Three (33%) of the nine patients (6th, 21st and 26th) who did not describe contact urticaria had the scores of 1, 2, 1 points, respectively (Table 1). History of a contact urticaria could not be sought in one patient (15th) as he did not use NRL gloves and the GUTSS was found to be 3 in this patient. The GUTSS performed by using vinyl gloves was 0 in all members of the group 1. None of the patients in group 1 experienced systemic symptoms. GUTSS was also found to be 0 by using NRL and vinyl gloves in all patients of the groups 2 and 3. When coexistence of a positive SPT to NRL with a positive history of a contact urticaria with NRL exposure was considered as a 'Gold Standard' in the diagnosis of NRL allergy, GUT was found to have a sensitivity of 81%, specificity of 90%, negative predictive value of 75% and positive predictive value of 93% (Table 2).

Discussion

In this study we investigated the target organ responses of NRL sensitive patients by using NPT and GUT. So far different NRL provacation tests have been used in the diagnosis of NRL allergy. Hamilton et al. applied a two-stage NRL GUT on 31 NRL-sensitive patients. During the first stage, the patients had been asked to put NRL gloves on their hands while the conjunctivial and inhaler exposure was prevented by means of an eye and nasal respiration mask. During the second stage, after removal of the eye and respiration masks, the patients were asked to puff the air of the powdered NRL glove which they inflated through their faces. The skin and respiratory symptoms have been recorded and peak expiratory flow (PEF) changes have been measured (6).

Niggemann et al. performed similar NRL glove provocation test in 88 spina bifida patients with positive SPT and/or specific IgE to NRL. The symptoms while the patients put on and blew the gloves were recorded (7). During the NRL glove provocation methods aforementioned above, the effects of NRL on the skin were examined in detail but these methods failed in investigating the effects of NRL on the respiratory tract. The amount of the allergen applied in these methods is not known.

Pisati et al. performed a bronchial provocation test on patients with NRL-induced occupational asthma history. Increasing doses of allergen isolated from powdered NRL gloves was administered to the patients by using a nebulizer inside a 7 m^3 room. The test was discontinued when the decrease in FEV1s reached 15%. All the patients in this study developed bronchoconstriction (12). Vandenplas et al. applied an inhaler provocation test to patients suspected of having NRL-induced occupational asthma using powdered NRL gloves in a 5 m^3 exposure room (5). Kurtz et al. developed a novel device called Hooded Exposure Chamber (HEC). The patients were made to inhale an allergen isolated from powdered NRL gloves by a hood placed on each patient's head (13).

The provocation methods applied in the last three studies were time-consuming and required use of special equipment. Furthermore, the allergen used in these tests is not standardized and causes serious side effects such as bronchoconstriction. In the diagnosis of NRL-induced respiratory tract allergy, more reliable, more easily applied and standardized tests are needed. In NRL provocation methods, nasally administered allergens produce allergic inflammations in a more restricted area when compared to allergens administered through inhalation. Moreover, the patient has a lower risk of developing bronchoconstriction and the allergic inflammation can be taken under control without causing any harm to the patient. Therefore, we investigated the effects of NRL on the respiratory tract using the NPT.

In present study 22 out of 23 (95.6%) patients in group 1 who described NRL induced rhinitis (except 5th patient) had positive NPT. The 5th patient developed nose and eye symptoms along with a 20% decrease in the nasal flow rate; however, neither the symptoms developed nor the decrease in the nasal flow rate met the positiveness criterion. If this patient had been exposed to a higher dose of NRL he could most probably fulfill the positiveness criterion. The other NPT negative patients (14th, 17th, and 18th patients) had a NPTSS of 0 and did not have any type 1 hypersensitivity reaction history. In this study, it has been shown that NPT is a good method in the diagnosis of NRL allergy by means of the sensitivity, specificity and predictive value rates (Table 2). As can be seen in Table 1, positive SPT with NRL does not necessarily provide any information on the type of the reaction as a result of exposure to NRL. In this

study a correlation was found between the diameter of the enduration recorded by latex SPT and the symptom score obtained by NPT shown in Fig. 1. This result may indicate that the rhinitis is likely to follow a more severe course as the induration diameter with SPT to NRL increases.

There is only a single study using NPT in the diagnosis of NRL allergy. Palczynski et al. applied NPT to 16 nurses who described rhinitis or rhinitis and asthma associated with NRL. Three different groups consisting of nine healthy nurses exposed to NRL, six atopic patients not exposed to NRL and six healthy individuals not exposed to NRL constituted the control group of this study. Although the nasal symptom score in the group with NRL allergy was higher, the mean symptom scores in all groups were close to one another. This has been explained by the possibility that the prepared material was not clean enough and therefore caused nonspecific nasal irritation (14). In this study some dirtiness problems were experienced and high concentrations of allergens (1000 μg/ml latex protein) were used. Whereas, in present study, standardized latex protein was used; moreover, NPT was applied at much lower concentrations and to a bigger patient and control groups. In order to prevent false positive reactions that may be stemming from phenol and glycerol, the test was discontinued when the allergen concentration reached 50 μg/ml.

Patriarca et al. used sublingual and conjunctival provocation tests to assess the NRL specific immunotherapy responses. The highest allergen concentration was determined as 500 μg/ml NRL protein (ALK-Abello, Madrid, Spain), for the sublingual provocation test and 50 μg/ml NRL protein (ALK-Abello) for the conjunctival provocation test, and both tests were safely used (15). In our study, the lowest allergen concentration causing NPT positiveness was determined as 0.05 μg/ml.

The fact that no systemic reaction except for a rhinoconjunctival symptom was observed in any of the patients including the eight patients describing asthma with NRL exposure and that the decrease in FEV1s was not above 15% showed that this test was indeed a reliable method in the diagnosis of NRL allergy. Negative NPT results in groups 2 and 3 have increased the diagnostic value of the test.

Several previous researchers reported that there was a cross reaction between NRL and plant pollens (wormwood, Kentucky Bluegrass, Timothy-grass and American pellitory) (16). The prick tests of the three patients with negative NPT (14th, 17th, and 18th patients) in group 1 were found to be positive with Timothy-grass in addition to NRL. As a risk factor, the 17th patient had undergone a scoliosis operation and had a history of using NRL gloves. The negative NPT results in these patients can be explained by the fact that the NRL epitope, cross-reacting with pollens, is not responsible for NRL allergy.

NRL-specific immunotherapy has become increasingly widespread in late years. NRL provocation tests are used in determining immunotherapy candidates and assessing immunotherapy responses (15, 17). We believe that the NPT method used in our study will be a practical and reliable method of diagnosis that can serve this purpose.

In the present study, the more than half of the group 1 (62%) described a positive history of contact urticaria episodes and contact urticaria diagnosis was verified by means of GUT in most of them (81%). One patient (15th patient), who had not used NRL gloves before, developed redness, swelling and itching during the GUT. This patient was atopic, had sensitivity to pollens along with NRL and had a history of major surgical intervention twice. The development of contact urticaria on the GUT can be explained by the previous sensitization to NRL on an atopic bases during the operations. This will lead to a decrease in the negative predictive value of GUT (75%). In GUT, the NRL content of the glove and the amount of the NRL protein that penetrates into the skin are not known. It could be difficult for NRL to penetrate through healthy skin surfaces, or the exposure time of the skin to NRL while the glove is on may not be sufficient for the penetration. All these factors restrict the diagnostic value, sensitivity and specificity of the GUT. In this sense, these disadvantages observed in GUT are not true for NPT. In our study, the sensitivity, specificity and predictive value of the glove use test was found to be lower as compared to NPT (Table 2).Therefore, NPT can be said to be a more sensitive provocation method than GUT.

The allergen used in NPT is a suitable test material to provoke rhinitis symptoms. The amounts of phenol and glycerol in the allergen may restrict performing nasal provocation at greater concentrations. If the amounts of phenol and glycerol decrease, NPT can be performed with greater concentrations of NRL protein. GUT is a sensitive provocation method in the diagnosis of NRL allergy. Better results can be obtained if the 15-min exposure time is lengthened.

In brief, we investigated the target organ responses of NRL-sensitive individuals in the present study. We used the NPT, one of the diagnostic methods for respiratory tract allergy, successfully for the first time in the diagnosis of NRL-related allergic rhinitis. The NPT we devised carries the specifications of a standard nasal provocation test in that a reliable diluent was used as placebo, specified and increasing concentrations of NRL were applied, symptoms were scored, and nasal flow rates were recorded. Furthermore, it can also be used as a dependable method of provocation in assessing the effectiveness of NRL-specific immunotherapy. The fact that all the patients including those who described asthma episodes associated with NRL exposure did not have a decrease in excess of 15% in FEV1s with respect to the basal value during NPT confirmed that NPT is in fact a reliable diagnostic method.

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