

LATEX ALLERGY

JOLANTA STANKIEWICZ, URSZULA RUTA
and PAWEŁ GÓRSKI

Department of Occupational Diseases,
The Nofer Institute of Occupational Medicine
Lodz, Poland

Key words: Latex, Allergy, Occupational diseases, Nasal challenge

Abstract: Over the last ten years allergy to latex has become a serious, life-threatening medical problem. Exposure to latex may result in immediate hypersensitivity reactions such as urticaria, dyspnoea, rhinitis, angioedema and anaphylactic shock in sensitized individuals. People occupationally exposed to latex – health care and rubber industry workers and children suffering from spina bifida – are the most important risk groups.

Clinical manifestations, immunological mechanisms, trials for identifying latex allergens and laboratory testing are reviewed here. Moreover, the authors present two cases of latex allergy diagnosed with the use of a nasal challenge test. 0.0005% latex solution (Stallergen) and latex extract prepared at the Clinic were used. Nasal washings were performed before, 30 minutes, 3 and 24 hours after provocation. The test evaluation was based on changes in the number and type of cells present in the washings. As there is no laboratory test to be used in latex allergy diagnosis approved by the Food and Drug Administration (FDA) the nasal provocation test seems to be worthy of further investigation.

Ways of reducing of the allergenicity of latex products and preventing hypersensitivity reactions are also presented.

INTRODUCTION

Latex allergy is an emerging public-health problem and causes significant morbidity and mortality. Since the first cases of hypersensitivity reactions to latex were recorded (Germany, 1927, Nutter 1979, Slater 1989, Spanner et al. 1989) over 1,100 anaphylactic episodes have to date been reported to the US Food and Drug Administration (FDA) (28).

Most of these allergies occur in individuals who frequently use latex products. Health care workers, rubber industry workers and children with spina bifida are therefore the most important risk groups (27) (Table 1). The prevalence of latex allergy has been estimated to be 10% in surgeons and operating theatre nurses

Table 1. Risk factors for latex allergy

High-risk populations (health care workers, rubber industry workers, spina bifida/urogenital anomalies)
Female sex
Age (young people)
Predisposing skin injuries (contact dermatitis) atopic status
Food allergy (banana, chestnut)
History of multiple surgery

(but 23.7% in atopic health care workers), 8.8% in dental professionals, and 2.8% in laboratory assistants (8, 16). Occupational asthma was noted in 6–11% of workers in a latex supply company (5, 8). In Tarlo's et al.' study 3/81 workers in a Canadian surgical glove factory had occupational asthma and 7/81 complained of urticaria (29). Pediatric patients with spina bifida show a 500 times greater risk of intraoperative anaphylaxis than the general population (4) and 12–67% of children suffering from meningomyelocele experience latex allergy (13, 23).

CLINICAL MANIFESTATIONS

Immediate hypersensitivity to latex may occur as a result of exposure through cutaneous, percutaneous, mucosal and parenteral routes. Direct contact evokes clinical manifestations as does exposure to aerosols (28). What is more, mucosal and parenteral contact to the allergen pose the greatest risk of anaphylaxis (21).

Clinical symptoms of latex allergy can be divided into the following groups:

1. Contact urticaria

This seems to be the most common complaint of patients. In Jeager's et al. studies 100% of patients allergic to latex experienced urticaria (16), Pecquet observed the same in 92% of patients (16).

Nevertheless, pruritus alone is usually not predictive of latex allergy and only some patients suffering from pruritus appear to show a positive prick test to latex (16).

2. Respiratory symptoms

Manifestations such as acute rhinitis or/and asthma may occur as a result of the inhalation of a latex aerosol, or as a part of a generalized anaphylactic reaction (5, 8, 15). These symptoms are not surprising, if one remembers that the concentration of airborne latex allergens in the personal breathing zone of health care workers can be very high. It ranges from 8 to 136 ng/m³ (21) and the highest reported latex level in an area sample taken from a biochemical laboratory was 311 ng/m³ (28).



3. Systemic manifestations

Systemic anaphylaxis due to latex was presented, for the first time, by Axelsson et al. in 1987 in Sweden (4). Since then many severe systemic reactions have been described, which result predominantly from mucosal or parenteral allergen exposure. The most dangerous allergic reactions such as anaphylactic shock, angioedema, generalized urticaria, usually happen intraoperatively in patients and are induced by contact with a surgeon's gloves, catheter, tracheal intubation tube, barium enema examination (16, 21). Unfortunately, such symptoms may also occur after contact with rubber balloons and balls, adhesive bandages, a baby pacifier, a diving mask, etc. (21). All the deaths related to latex allergy reported to FDA took place during barium enemas, while applying latex catheters (7).

CHARACTERISTICS OF LATEX ALLERGENS AND IMMUNOLOGIC MECHANISMS

The lactiferous cells of the rubber tree — *Hevea brasiliensis* are the source of "natural latex". They are able to convert sucrose into *cis*-1,4-polyisoprene, which congregates into droplets stabilized by lipid and protein coatings (8, 10, 31). Three major proteins are involved in this synthesis: phenyltransferase (38 kD), rubber elongation factor (14.5 kD) and hevein protein (10 kD) (28). Latex is collected by the periodic incision of the inner bark of the tree (tapping) (10). Then, to prevent autocoagulation, ammonia and other preservatives are added, and this solution is concentrated to produce a high — ammonia solution (1.6%) and a low — ammonia solution (0.15%) (28). Natural rubber latex contains approximately 60% water, 35% rubber, 4.5% proteins and hydrocarbon (31).

The identification of the latex antigens responsible for inducing hypersensitivity has been the aim of many studies. Morales et al. demonstrated that latex allergens are soluble proteins and range in molecular weight from 10 to 100 kD (4). Slater determined 14 kD peptide to be main protein in latex allergy (4), while Fuchs et al. considered the 28 kD protein a latex antigen (4, 31). Further investigations made by Czuppon et al. revealed that the rubber elongation factor may be the major allergen of latex, as it blocked specific IgE antibodies in the serum of latex-sensitized subject (6). It is a noncovalent homotetramer 58 kD molecule, in which the 14.6 kD monomer was identified. In the most recent study, Alenius et al. demonstrated at least 30 protein bands, with molecular weights ranging from 14 to 200 kD (2). Using the sera of 27 patients and 30 controls as the source of IgE antibodies, the investigators managed to identify 19 allergenic rubber proteins. Out of 27 patients, the sera of 22 (82%), and one of the controls, showed positive immunoblot test results. In the sera of 17 of these 27 patients, a 20 kD protein was detected. This may be a major rubber allergen in adult patients allergic to latex.

It has been also observed that in about half of individuals allergic to latex, bananas, chestnuts, avocados and other fruits evoke allergic reactions such as urticaria, asthma, rhinitis, coughing, anaphylaxis, etc. (18). On the other hand, subjects with a banana allergy can experience adverse reactions after contact with latex products. Cross reactivity of the IgE antibodies was demonstrated in several inhibition assays, and the existence of a cross-reacting antigen and

allergen has been confirmed by immunoelectrophoretic and autoradiographic analyses (25).

Latex allergy can be observed as immediate hypersensitivity reactions (type I) mediated by IgE or IgG₄, delayed type allergy (type IV) or as a combination of both types of hypersensitivity. Contact allergy to rubber products has been known for many years and it probably causes 1/3 of all allergic reactions to latex (26), but immediate hypersensitivity has become a new problem, discovered during the last 10 years. It is often life-threatening and therefore requires thorough investigation. As is mentioned above, two types of antibodies can mediate a type I latex allergy. Alenius et al. found the parallel occurrence of IgE and IgG₄ in sera from four patients allergic to latex. The IgG₄ antibodies are bound to 12 rubber protein antigens with molecular weights ranging from 14 kD to 53 kD, while IgE antibodies are bound to 9 antigens. The major antigen for IgE and IgG₄ seemed to be a 21 kD protein (1).

LABORATORY TESTING IN THE DIAGNOSIS OF LATEX ALLERGY

The main difficulty in confirming latex allergy by laboratory testing lies in great number (not known precisely) of possible latex antigens. Moreover, latex extracts are prepared using different techniques and by different laboratories. This often means that there are many differences in their potency, reactivity and dependability, and therefore the results obtained may not be comparable (26). There is no satisfactory testing extract available to date and tests are largely carried out with unstandardized materials (30). Due to this, two-way studies have been performed: namely, research into the allergen in latex, responsible for inducing hypersensitivity reactions (described above), and evaluation of the sensitivity, specificity and safety of diagnostic tests. At present, the following tests can be applied in latex allergy diagnosis:

1. skin prick test (SPT) — sensitive and specific for identifying patients with latex sensitivity. The largest evaluation of SPT was performed by Moneret-Vautrin and Laxenaire (20). SPT was found to be 100% sensitive and 99% specific. The predictive value of a positive test was 80% and of a negative test 100%. However, one problem is that SPT may be associated with adverse reactions (anaphylaxis) and should be carried out very carefully, starting with a low concentration of latex antigen (30). SPT is performed with: a) an ammoniated natural rubber emulsion (60% of rubber particles, 0.5% of ammonia), b) a commercial extract of ammoniated latex, and c) by pricking through a latex surgical glove (31). There is no latex skin test extract approved by the Food and Drug Administration (13).

2. latex — specific IgE levels (RAST, ELISA) — unfortunately, the lack of defined antigens makes the results of the test not completely reliable and often not reproducible (26). For example, the commercial latex RAST (Pharmacia, Uppsala, Sweden) detects IgE antibodies in about 50% to 70% of patients allergic to latex (11, 14).

3. bronchial provocation test — performed with a solution used as a spray, made by rinsing a latex glove with a quantity of distilled water. It very quickly evokes



a bronchospasm in patients with latex-induced asthma, after, for instance, 2 minutes, which means that such a test must be carried out with extreme caution and may be dangerous to a patient's health (12, 16).

4. nasal provocation — described only by Jager et al. (11) and Czuppon et al. (6), and consisted of a nasal challenge with a suspension of powder from latex glove or a glove extract. In all cases examined it was positive and latex rhinitis was proved only by rhinamometry.

5. wearing of a latex glove by a patient for 15 minutes — in Turjanmaa's et al. studies it gave positive results in 12/13 cases (16). Wrangsjo et al. tested patients by placing 1 cm² pieces of latex glove on the skin of the forearm or by having them wear one glove finger for 20 minutes (16). They observed positive reactions in 9/10 patients. According to some authors the risk of anaphylaxis must be taken into account during this test (3, 16).

6. basophil histamine release test (BHTR) — so far it is more sensitive than commercial latex RAST. This test yields positive results in 93% of patients with contact urticaria (30).

7. lymphocyte proliferation test (LPT) — positive in 20% of patients suffering from contact urticaria, what means that cell-mediated immune reactions may also play a part in latex allergy (30).

8. patch tests — may be positive in cases of contact urticaria. For example Sanmartin-Jimenez et al. found positive patch tests to rubber accelerators in 33% of patients with contact urticaria (25).

As can be seen, a very sensitive, specific and safe laboratory test to confirm latex allergy is not yet available. Nasal provocation with challenge evaluation seems worthy of testing, because it has been shown to be a very reliable method in allergy diagnosis. So far this test has not been very popular in the evaluation of latex allergy. Other provocation tests such as bronchial provocation can be too dangerous to a patient. Nasal provocation is not only safer but also provides more information about the course of the hypersensitivity reaction than other tests. This is why we decided to perform this test in our two patients allergic to latex.

CASES PRESENTATION

Case 1

A 44-year old atopic technician, with a 6-year history of hand swelling, itching and facial swelling also accompanied by urticaria when wearing latex gloves. She also complained of mouth swelling during dental procedures and local urticaria induced by condoms. In addition, she reported rhinitis, dyspnea and a dry cough which started 4 weeks before admission to the Clinic. Twenty years earlier she had anaphylactic shock after a penicillin injection.

The percentage cell composition

	albumin		The number of cells $\times 10^3$						The percentage cell composition												
	total protein		leucocytes	eosinophils	basophils	epithelium	neutrophils	eosinophils	basophils	lymphocytes	monocytes										
case	1	2	1	2	1	2	1	2	1	2	1	2	1	2							
before	latex	19.1	12.5	137.2	21.91	6.26	0	3.13	6.26	65	0	28	0	3	0	1	0	0			
	PBS	—	—	10.1	20.4	0	0	0	0	55	0	32	0	1	0	0	11	0	1	0	
30'	latex	26.8	15.4	150.2	53.21	18.78	9.39	6.26	21.91	9	66	80	15	9	9	2	7	0	3	0	0
after	PBS	—	—	22.95	42.7	0	0.71	0	0.71	43	86	46	7	2	2	1	1	8	0	0	0
	3 h latex	21.8	7.6	266.0	75.12	44.43	9.39	9.39	15.65	26	62	52	11	14	10	3	11	3	6	2	0
after	PBS	—	—	29.87	36.4	0	0	0	0	30	70	52	27	2	2	0	1	16	0	0	0
	24 h latex	13.5	72.2	845.1	90.77	100.1	25.0	18.7	15.65	27	36	50	31	12	20	3	8	5	4	2	1
after	PBS	—	—	76.3	54.2	0	0	0	0	31	35	67	62	1	2	0	0	1	1	0	0

Latex skin prick testing (Stallergen, Pasteur) was performed and resulted in a 7 mm wheal and a 40 mm erythema from the appropriate control tests. The provocation test in which patient wore a latex glove for 30 minutes was negative and, so with the patient's required consent, it was decided to perform nasal challenge. Before provocation each nostril was washed 10 times with 10 cm³ of saline. A volume of 6 cm³ of 0.0005% latex solution (Stallergen, Pasteur) in neutral saline was inserted into the nasal cavity for 10 minutes. Nasal washings with saline were performed before and 30 minutes, 3 and 24 hours after provocation. Afterwards, centrifugation (10 minutes at 100 rpm) of the nasal washings was performed to isolate the cells from the supernatant. The sediment was washed with sterile phosphate buffered saline (PBS, Sigma) and 0.1% human serum albumin (HSA, Behringwerke A.G) and then suspended in 1 ml PBS and 0.1% HSA. Subsequently, the cells were stained: with the Turk method for leucocytes, the Dunger method for eosinophils and 0.06% toluidine blue in 30% ethanol for basophils. The total number of cells was counted in a Fuchs-Rosenthal chamber. In addition, the supernatant protein content and the albumin content were evaluated with the Lowry method and the Laurell method, respectively.

During the test and within 24 hours the patient complained of nasal obstruction and sneezing. To ensure that the observed changes were really induced by latex, a provocation test with PBS as a placebo was performed. The procedure was exactly the same as described above. After an evaluation of the latex-induced changes in the number and type of cells in the washings induced by latex and a comparison with the placebo test, the provocation test was found to be positive. The results of the test assessment are presented in Table 2.

Case 2

A 36-year-old atopic female, not occupationally exposed to latex, was admitted to the Clinic because of face angioedema and urticaria which had appeared 4 months earlier, initially after a course of antibiotics (Doxycycline, Cefradine), which had then occurred without any known reason. Patch tests resulted in dermatitis induced by adhesive tape and she also reported hand pruritus when wearing rubber gloves. All prick tests, including latex and histamine ones, were negative, probably due to Hismanal taken 3 weeks earlier. The patient gave her consent to a nasal challenge test.

In this case the latex solution was prepared at the Clinic by washing latex gloves, catheters and drains with PBS at 37°C for 2.5 hours. It was next decanted, filtrated and the protein content was estimated. It was found that the protein concentration in this extract was 55 µg/ml (0.0055 g/dl) and the pH was 7.4. The nasal provocation test was performed as described above. During the provocation the patient complained of nasal obstruction and 3 hours later rhinitis occurred. A test with a placebo (PBS) was also performed. The test with latex was also found to be positive (the results are shown in Table 2).

The nasal challenge test turned out to be positive in both cases — either when applying a commercial latex extract or one prepared at the Clinic. Two positive results are certainly too few to fully evaluate the advantages and disadvantages of using this method in latex allergy diagnosis, but our experience in diagnosing other allergies using this test has proved it to be very useful and it is better

tolerated and less invasive than a bronchial provocation test or a broncho-alveolar lavage (BAL). A nasal lavage has a low risk of harmful side effects, we never observed anaphylaxis when performing it with many allergens, but we have insufficient experience with latex provocation to assess its safety. What is more, since the inflammatory mechanisms involved in bronchial asthma and rhinitis are similar, it may be more convenient to perform a nasal challenge instead of BAL (24). This non-traumatic method permits quantitative and qualitative studies of the nasal mucosa cells together with the simultaneous determination of biochemical parameters. At our Clinic a nasal challenge is often used in diagnosing occupational and non-occupational allergies to many different allergens, in pharmacological studies and in the differentiation of irritant and allergic reactions (9, 22).

PREVENTION OF LATEX-INDUCED ANAPHYLAXIS AND SUPPRESSION OF THE ALLERGENICITY OF LATEX

There are few ways of preventing hypersensitivity reactions induced by latex. An essential part of such a project should be to increase a clinician's awareness of latex allergy and latex-exposed health care workers. Questions about latex allergy are not yet a routine part of a patient's history and most patients do not realize that they are allergic to latex. Special attention should be given to high-risk groups, and ideally offer them diagnostic testing, especially before latex exposure. It is also worth remembering that latex may be responsible for symptoms such as urticaria, rhinitis, conjunctivitis, asthma in health care and rubber industry workers. The American Academy of Allergy and Immunology and the American College of Allergy and Immunology has also recommended the availability of non-latex devices and latex-free areas in health care institutions (29).

As latex gloves, condoms etc. are the best prevention against HIV infection, and as synthetic neoprene surgical gloves may be unacceptable to some surgeons and vinyl plastic gloves are not always watertight and thus permeable to the *herpes simplex* virus (3, 17) studies on reducing allergenicity of latex are being performed. Leynadier et al. investigated ways of reducing the allergenicity of the latex glove and found that a longer washing period during production decreased the protein content, allergenic material (RAST inhibition) and frequency of positive skin tests. Moreover, the usual method of steam sterilization of gloves yielded similar results (17). Yunginger et al. proved that much less allergen and protein could be extracted from powder-free examination gloves than from powdered ones. Cornstarch used to powder gloves is not usually allergenic by itself, but latex allergens may be absorbed by the powder after contact with the glove (32).

In conclusion, although there are many studies investigating ways of reducing the quantity of latex allergen and, searching for the best methods of latex allergy diagnosis, neither a satisfactory latex allergenicity reduction method nor a reliable diagnostic test have yet been found. More research into these problems is urgently needed. One possible answer to diagnostic problems seems to be the nasal provocation test, but it requires further investigation.



REFERENCES

1. Alenius H, Reunala T, Turjanmaa K, Palosuo T. Detection of IgG₄ and IgE antibodies to rubber proteins by immunoblotting in latex allergy. *Allergy Proc* 13 (2): 75–77, 1992.
2. Alenius H, Turjanmaa K, Makinen-Kiljunen, Reunala T, Palosuo T. IgE immune response to rubber proteins in adult patient with latex allergy. *J Allergy Clin Immunol* 93 (5): 859–63, 1994.
3. Autegarden JE. Measuring reduction of the allergenicity of latex gloves. *Clin Rev Allergy* 11: 403–412, 1993.
4. Blaiss MS. Latex allergy in children: a review. *Pediatric Asthma. Allergy Immunol* 6 (2): 71–75, 1992.
5. Charpin D, Vervloet D. Epidemiology of immediate-type allergic reaction to latex. *Clin Rev Allergy* 11: 385–390, 1993.
6. Czuppon AB, Chen Z, Rennert S et al. The rubber elongation factor of rubber trees (*Hevea brasiliensis*) is the major allergen in latex. *J Allergy Clin Immunol* 92 (5): 690–697, 1993.
7. Gelfand DW. Barium enemas, latex balloons, and anaphylactic reactions. *AM J Roentgenol* 156: 1–2, 1991.
8. Gold M, Sussman GL. Latex allergy. *Practical Allergy Immunol* 8 (3): 101–105, 1993.
9. Górski P, Pazdrak K, Pałczyński C, Ruta U. Inhibitory effect of cetirizine and terfenadine on histamine-induced changes in nasal secretion. *Intern Rev Allergol Clin Immunol* 1 (1): 7–10, 1994.
10. Jacob JL, d'Auzac J, Prevot JC. The composition of natural latex from *Hevea brasiliensis*. *Clin Rev Allergy* 11: 325–337, 1993.
11. Jager D, Engelke T, Rennert S, Czuppon AB, Baur X. Stepwise diagnosis of respiratory latex allergy. *Pneumologie* 47 (8): 491–496, 1993.
12. Kanny G, Prestat F, Moneret-Vautrin DA. Allergic asthma to latex, proven by a bronchial provocation test. *Allerg Immunol Paris* 24 (9): 329–332, 1992.
13. Kelly KJ, Kurup VP, Reijula KE, Fink JN. The diagnosis of natural rubber latex allergy. *J Allergy Clin Immunol* 93 (5): 813–816, 1994.
14. Kelly KJ, Kurup V, Zachrisen M, Resnick A, Fink JN. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 91 (6): 1140–1145, 1993.
15. Kurup VP, Kumar A, Kelly KJ, Fink JN. Characterization of a monoclonal antibody against latex protein associated with latex allergy. *J Allergy Clin Immunol* 92 (5): 638–643, 1993.
16. Levy DA, Charpin L, Pecquet C, Leynadier F, Verloet D. Allergy to latex. *Allergy* 47: 579–587, 1992.
17. Leynadier F, Tran Xuan T, Dry J. Allergenicity suppression in natural latex surgical gloves. *Allergy* 46: 619–625, 1991.
18. Makinen-Kiljunen S. Banana allergy in patients with immediate-type hypersensitivity to natural rubber latex: characterization of cross-reacting antibodies and allergens. *J Allergy Clin Immunol* 93 (6): 990–996, 1994.
19. Moneret-Vautrin DA, Beaudouin E, Widmer S et al. Prospective study of risk factors in natural rubber latex hypersensitivity. *J Allergy Clin Immunol*, 92 (5): 668–677, 1993.
20. Moneret-Vautrin DA, Laxenaire MC. Routine testing for latex allergy in patients with spina bifida is not recommended (reply). *Anesthesiology* 74: 391–392, 1991.
21. Ownby DR, Tomlanovich M, Sammons N, McCullough J. Anaphylaxis associated with latex allergy during barium enema examinations. *AM J Roentgenol* 156 (5): 903–908, 1991.
22. Pazdrak K, Górski P, Krakowiak A, Ruta U. Changes in nasal lavage fluid due to formaldehyde inhalation. *Int Arch Environ Health* 64: 515–519, 1993.
23. Pearson ML, Cole JS, Jarvis WR. How common is latex allergy? A survey of children with myelodysplasia. *Develop Med Child Neurol*, 36: 64–69, 1994.
24. Prat J, Xaubet A, Mullol J, Plaza V, Picado C. Cell content and albumin concentration in nasal lavage from patients with rhinitis. *Ann Allergy* 70: 175–178, 1993.
25. Sanmartin-Jimenez O, Botella-Estrada R, de-la-Cuadra-Oyanguren J, Aliaga-Boniche A. Contact urticaria and latex anaphylaxis. A review of 15 cases. *Med Clin Barc* 100 (9): 321–324, 1993.
26. Sussman GL, Tarlo S, Dolovich J. The spectrum of IgE-mediated responses to latex. *JAMA* 265 (21): 2844–2847, 1991.

27. Task Force on Allergic Reactions to Latex. Committee report. *J Allergy Clin Immunol* 92: 16–18, 1993.
28. Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 93 (6): 985–989, 1994.
29. Tarlo SM, Wong L, Roos J, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol* 85: 626–631, 1990.
30. Turjanmaa K, Rasanen L, Lehto M, Makinen-Kiljunen S, Reunala T. Basophil histamine release and lymphocyte proliferation tests in latex contact urticaria. *In vitro* tests in latex contact urticaria. *Allergy* 44 (3): 181–186, 1989.
31. Yassin MS, Sanyurah S, Lierl MB et al. Evaluation of latex allergy in patients with meningo-myelocoele. *Ann Allergy* 69: 207–211, 1992.
32. Yunginger JW, Jones RT, Fransway AF, Kelso JM, Warner MA, Hunt LW. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. *J Allergy Clin Immunol* 93 (5): 836–842, 1994.

Received for publication: October 7, 1994

Approved for publication: April 3, 1995

