



Latex allergy: prevalence, risk factors, and cross-reactivity

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Abstract

There are few little exact epidemiological data on the prevalence and incidence of latex allergy, partly because the diagnostic tools are unsatisfactory and partly because the epidemiological study planning often does not fulfill criteria of good praxis. On the basis of present data, latex allergy in normal population is low, under 1%. Known risk groups such as health care workers, atopic subjects, people with hand dermatitis, and especially spina bifida patients show higher prevalence numbers. The common serological cross-reactivity between latex and a great number of different fruits and vegetables is bound to common plant pathogenesis-related proteins and storage proteins. Despite positive serological tests, only about half of NRL-allergic subjects have clinical symptoms after eating cross-reacting foods. © 2002 Elsevier Science (USA). All rights reserved.

1. Introduction

The relevance of studies on the prevalence, incidence, and occurrence of allergy to natural rubber latex (NRL) is closely connected to the definition of the diagnosis. In different countries and on different continents the criteria employed for positivity and negativity of tests are not uniform, which has led to many controversies in published papers (Table 1). A positive skin prick test (SPT) and IgE antibodies to NRL indicate sensitization. Allergy can be diagnosed only on the basis of symptoms in a sensitized person either with a positive challenge test or with evidently positive clinical symptoms. All these facts must be considered with respect to the prevalence of allergy to NRL. In addition to IgE-mediated allergy to NRL there is probably also a delayed-type, cell-mediated allergy to NRL proteins [1]. So far only a few case reports exist on this topic, making it too early to speak about its prevalence [2].

Since the first study on the prevalence of NRL allergy in 1987 several studies have been published on health care workers and spina bifida patients. The numbers vary between 2.7 and 12% in health care workers depending on the methodology and selection of patient

material used [3], and up to 60% in children with spina bifida [4]. In some papers only the numbers of sensitized subjects have been given based either on SPTs or estimation of latex-specific IgE either with AlaSTAT (Diagnostic Products, Los Angeles, CA) or RAST/CAP RAST (Pharmacia, Uppsala, Sweden). In the United States, Ownby et al. [5] studied 1000 volunteer Red Cross blood donors using AlaSTAT and found 6.4% of them to have antilatelax IgE. The US Centers for Disease Control and Prevention conducted an estimation of IgE antibodies to latex with AlaSTAT using serum samples obtained during the third National Health and Nutritional Examination Survey (NHANES III) and reported positive results in 17.6% [6]. The prevalence of antilatelax antibodies (AlaSTAT) in 741 registered nurses in the United States was found to be 8.9%. The samples from 27 nurses were strongly positive (3.6%). Of the seropositive nurses, 86.2% reported in a questionnaire at least one symptom associated with latex allergy, whereas 58% of the seronegative nurses also reported at least one symptom suggestive of allergy to latex products. They also found that nurses reporting certain food allergies (banana, avocado, peanut, and tree nut) were more likely to have positive antilatelax IgE test results. In addition, a reported history of allergy to penicillin appeared to be related to antilatelax IgE. Nurses using only vinyl gloves more often had positive IgE antibodies to latex than those using only latex gloves [7]. Liebke et al.

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Table 1
Factors hindering the comparison of figures for prevalence of allergy to NRL

1. Differences in methodology
Different types of skin prick test devices
Different limits for positivity of skin prick test reactions
Small positive SPT reactions not always repeatable
Standardized SPT material not available in all countries
Challenge tests not standardized
Methods used not clearly described in text
2. Sensitivity and specificity of SPT and serological tests (AlaSTAT, RAST) not known exactly
False positivity, e.g., in atopic patients with allergy to cross-reacting fruits, vegetables, and pollens
3. Terms used imprecisely
Sensitization and allergy to NRL are not the same
Numbers of sensitized patients often directly compared to number of allergic patients
Term “only sensitized” used for nonsymptomatic patients who have not been challenged
4. Proper challenge test material not commercially available
Low-allergenic latex glove material may give false-negative result
Latex gloves containing casein may give false-positive results in milk-allergic patients

[8] screened 609 atopic and nonatopic children in Germany for latex allergy with commercial latex RAST and found elevated IgE values in as many as 61 (10%) of the children. Latex glove challenge tests confirmed latex allergy in only 12 of these children, which gives a prevalence of 2%.

At the Department of Dermatology, Tampere University Hospital, which is the only dermatological clinic for the 450,000 inhabitants of a region in southern Finland, NRL allergen has been included in the routine series for inhalant allergens since 1988 and in the food series used for diagnosing food allergy especially in children, since 1990. Between 1988 and 2000 the routine inhalant series was performed on 1416 ± 364 subjects annually. At the beginning tests were performed with glove eluants (1:5, w/v) and later together with a standardized, commercially available SPT allergen [9]. Diagnosis of latex allergy has been based on positive SPT and/or positive IgE antibodies to NRL using RAST/CAP RAST and evident symptoms anamnesticly or a positive challenge test. From 1992 to 1995 a total of 3269 children were skin prick tested and 55 (1.7%) were positive. On reexamination, 37 (1.1%) still had a positive SPT, and 33 (1.0%) were RAST-positive and confirmed as having latex allergy by means of the latex glove use test [10]. Only one-third of the latex-allergic children were referred because of symptoms; the others were identified at routine SPT screening for latex allergy. An important finding in that study was that even after a careful history from the patients or their parents at reexamination, 37 and 25% of the two groups studied had never noticed any kind of symptoms suggesting NRL allergy. This is contrary to what is described in questionnaire studies where

several symptoms suggested an allergy to NRL that could not be confirmed by testing [7].

In Tampere, results on a total of 4702 patients tested in four different groups because of suspicion of atopy have been reported. Allergy to NRL was found in 0.7–1.1%, and according to the local practice, all patients with any kind of discrepancy between anamnestic data and SPT results were challenged with glove on skin. Among 804 consecutive unselected adult patients tested before surgery only one had allergy to NRL (0.12%) [3]. In accordance with these results, Gautrin et al. [11] skin prick tested, with a commercially available standardized SPT material, 758 apprentices starting careers in animal health, pastry making, and dental hygiene and 0.7% tested positive. Another Canadian study on dental students gives concordant results. Two hundred and three dental students and staff members completed a questionnaire and 131 subjects underwent SPTs. The sensitization was 0% the first year and positive tests were reported since the second year of glove use. The numbers of sensitized persons rose yearly, finally reaching 10% [12].

The outcome of 160 adult NRL-allergic subjects diagnosed in 1982–1994 was analyzed in Tampere [13]. Health care workers were the largest single occupational group (71/160); 63 of them were considered to have an occupational disease. Further occupational diseases were reported in 19 patients comprising farmers, farmers' wives, kitchen workers, cleaners, textile workers, workers in a rubber band factory, paper mill workers, and private caretakers. All others were people using protecting gloves or other rubber articles at home or in hobbies. In one US study, no difference could be found in the prevalence among health care workers and the general population [14]. However, this finding was based on the analysis of the NHANES III data, which were subsequently declared inconclusive due to analytical flaws and inconsistencies (<http://www.fda.gov/cdrh/ocd/latexcrada.html>).

There seems to be agreement based on published results that the prevalence of NRL allergy among nonatopics is low, 0–0.7% (clearly under 1%), in atopics 0.7–2%, and highest in health care workers with the greatest use of latex products. It remains to be seen whether the US results change once a SPT material is licensed there and challenge tests are in use. Preliminary results with SPT materials made from two highly allergenic gloves showed that among 2166 dental workers tested as a part of the American Dental Association's Annual Health Screening Program, 6.2% were SPT-positive [15]. This is in agreement with the European and Canadian numbers.

2. Risk groups

The degree of exposure to NRL allergens seems to be an important factor in sensitization for both children

with spina bifida and health care workers. Atopy and hand dermatitis are commonly accepted risk factors [16]. Traffic exposure has been regarded as a risk factor, but in a recent publication from Germany this could not be confirmed. Latex-specific IgE was estimated with CAP RAST in 2505 children and the sensitization rates measured did not correlate with exposure to road traffic [17]. This is in agreement with the Tampere patient material where NRL-allergic patients with earlier anaphylaxis have not reported any inconvenience in the traffic.

3. Changing picture of NRL allergy

Minimization of allergen concentration in NRL products as a preventive measure in health care has been launched and the results already look promising. At Tampere University Hospital, where low-allergenic gloves have been in use since 1990, the prevalence of NRL allergy among glove-using hospital employees decreased from 2.9% in 1987 to 1% in 1999 [18]. Outside the health care sector things may look different, because no regulations exist or are even forthcoming to reduce the allergenicity in NRL consumer products.

Two cases of severe anaphylaxis have been recently described in Italy, where children were playing in a ball pit, the bottom of which was found to be lined by a layer of NRL foam covered with a PVC sheet [19]. Fatal latex anaphylaxis was described in a 28-year-old woman, earlier known to be NRL-allergic. She suffered from asthma, had severe allergy to nuts and scalp eczema, and was trained to use self-injected epinephrine. She had hair extensions bonded with an adhesive that was later confirmed to contain NRL. The reaction began in 5 min with itching of the scalp and although the woven hairs were removed and the adhesive was partially removed, the reaction rapidly progressed to generalized urticaria, facial edema, and asthma. Antihistamine and salbutamol did not help and she collapsed. The patient did not use the epinephrine injector in her handbag [20]. Unexpected side effects may occur when NRL-allergic persons consume food prepared by personnel using latex gloves. NRL allergens are very water soluble and easily contaminate food [21,22].

Numerous consumer products are made from NRL, like balloons, condoms, and pacifiers, for which the allergenicity has not been studied and no regulatory actions have been introduced to control their allergenicity. Therefore reactions such as those described above are possible, and currently the only countermeasures remain testing risk groups on a regular basis and informing sensitized persons about prophylaxis and the dangers associated with the use of NRL products.

4. Cross-reactivity

Latex allergy has been reported to be associated with hypersensitivity to a number of food and other allergens. A latex–fruit syndrome has been postulated based on clear evidence of a significant clinical association between allergies to latex and certain fruits.

The first report to suggest allergen cross-reactivity between NRL and banana was published in 1991 by M'Raihi et al. [23], after which a number of studies dealing with cross-reactivity between NRL and various foods and other allergens have been published. Several inhibition studies have verified cross-reacting IgE antibodies to latex and foods such as avocado, banana, chestnut, kiwi, melon, pineapple, peach, papaya, potato, tomato, almond, buckwheat, cantaloupe, carrot, celery, condurango bark, dill, ficus, fig, grapefruit, mango, oregano, papain, passion fruit, peanut, pear, pepper, pineapple, sage, soybean, Swedish turnip, wheat germ agglutinin, and breadfruit [16,24–46]. However, a cross-reaction between NRL and mango has not always been demonstrated [47]. The most prevalent cross-reacting foods may vary due to differences in nutritional habits between different countries.

In addition to serologic cross-reactivity, several studies have demonstrated that about one-half of NRL-allergic patients have clinical symptoms after eating cross-reacting food [28,35,48,49]. Among 47 latex-allergic adults, 17 (40%) had clinical reactivity to at least one food [49]. Clinical manifestation may vary, and result in mild oral symptoms that in some cases may lead to severe anaphylactic reactions [48].

The proteins involved in rubber synthesis are considered latex specific, but several of the enzymes, such as chitinases, glucanases, lysozymes, and papain, are also present in fruits and may account for the symptoms of latex–fruit cross-reactivity. An extensive cross-reactivity of NRL and plant allergens is bound to plant pathogenesis-related (PR) proteins such as chitinases against insects and lysozyme against bacteria and fungi [50]. Important cross-reacting allergens in fruits are class I chitinases with an N-terminal domain homologous to latex hevein [51–53]. In inhibition studies, hevein (Hev b 6.02) has been demonstrated to be an important cross-reactive allergen between NRL and avocado [40,52]. Because of their wide distribution in plants and foods such as fruits and legumes, class I chitinase protein enzymes are considered panallergens [34,35,53–56]. Class I chitinases are easily inactivated by heat and induced by ethylene treatment used to hasten ripening of fruits and vegetables. In addition, avocado endochitinases have been shown to resist simulated gastric fluid, a prerequisite for proteins to act as food allergens [52].

Apart from PR proteins, other proteins such as storage proteins in potato (patatin, Sola t 1) and tomato have been shown to cross-react with NRL [44,46]. IgE

reactivity to patatin-like protein in NRL (Hev b 7) has been demonstrated in 49% of latex-allergic adults, 43% of whom had IgE antibodies to Sola t 1 [44]. Moreover, 73% of these patients had a positive skin prick test to raw potato, but none of them had clinical symptoms from potato. Cross-reactivity between NRL and potato has not always been confirmed [57,58].

In addition to foods, latex cross-reacting allergens have been reported in pollen such as ragweed, mugwort, Kentucky blue grass, timothy grass, oilseed rape pollens, and *Ficus benjamina* [32,59–61]. Concomitant allergy to pollen has been suggested as an important risk factor in determining which plant-derived foods sensitize latex-allergic patients [62].

Profilins, well-known panallergens in several pollens and plant species, are also present in NRL [63]. Recombinant latex profilin (rHev b 8) has been suggested to represent a minor allergen in NRL and to have IgE-binding epitopes different from Bet v 2 [64]. However, another study suggested cross-reactivities between profilins of latex, pollen, and plant food based on their ability to inhibit IgE binding to rHev b 8 [65]. Even though profilin is a labile allergen and hardly detectable in latex-glove extracts, cross-reactivity should be taken into account when interpreting test results for NRL and banana in food-allergic children.

In addition to proteins, carbohydrate determinants have also been suggested to be cross-reactive determinants between latex and pollens. This, however, could not always be confirmed [59,66].

A latex–mold syndrome has been postulated on the findings that two important allergens in molds, manganese superoxide dismutase (MnSOD) in *Aspergillus fumigatus* (Asp f 6) and 2-phosphoglycerate dehydratase (enolase) in *Cladosporium herbarum* (Cla h 6), show clear sequence similarities to their latex counterparts, Hev b 10 and Hev b 9 [34,67]. These allergens and rHev b 10, however, are considered minor allergens in NRL since only two sera from 20 patients with spina bifida and none from 20 health care workers showed specific IgE to recombinant latex MnSOD [68]. The cross-reactivity between NRL and several food allergens has been confirmed in several molecular biological studies.

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