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NATURAL RUBBER LATEX ALLERGY: ANTIGEN SPECIFIC IgE IN POLISH BLOOD DONORS, PREVALENCE AND RISK FACTORS – PRELIMINARY DATA

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Abstract

Objectives: There is insufficient data on the prevalence of latex allergy in the general population in Poland. The aim of the study was to evaluate natural rubber latex (NRL) sensitization and its risk factors among Polish blood donors. **Materials and Methods:** The study group comprised 1000 consecutive blood donors attending the Regional Centre for Transfusion Medicine. Total IgE and allergen specific IgE to NRL (asNRL-IgE) were assayed using the EIA (enzyme immunoassay) test. In the subjects with asNRL-IgE equal to or above Class II further surveys were performed: questionnaire, skin prick tests (SPT) to common allergens, NRL and food allergens cross reactive to NRL, asNRL-IgE with FDA (Food and Drug Administration) approved FEIA (fluorescent enzyme immunoassay) test and antigen profile of asNRL-IgE. **Results:** asNRL-IgE (EIA) was observed in 17.9% of blood donors. Only 10% of positive results equal to or above Class II were confirmed with the FEIA test. The positive FEIA results were confirmed with SPT to NRL in 60% and the negative FEIA results in 5.4% of cases. The specific IgE to Hev b 3,5,6 and 13 were observed in the subjects with occupational exposure to NRL. The highest concentration of Hev b 8 was observed in the subjects not symptomatic to NRL with positive SPT to grass and tree pollens. **Conclusion:** The EIA test showed the high prevalence of antigen specific IgE to NRL among Polish blood donors. There was low concordance between EIA and FEIA tests. Therefore, the EIA test should be used only for screening purposes along with the establishment of sensitivity and specificity of the method. Elevated total IgE level, active tobacco smoking, and history of atopic disease symptoms were revealed to be risk factors for the presence of asNRL-IgE.

Key words:

Natural rubber latex, Latex allergy, Antigen specific IgE, Blood donors

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INTRODUCTION

From the 1980s, allergy to natural rubber latex (NRL) has become a serious medical problem [1]. Health care workers and subjects with spina bifida are well documented risk groups [2–5]. Owing to the insufficient data on the prevalence of latex allergy in the general population and some methodological deficiencies (inappropriate controls), it is difficult to identify the risk factors of allergy to NRL [6]. Cross sectional studies are very difficult and expensive to conduct mostly due to low participation rates, especially when such procedures as blood samples collection and skin prick tests (SPT) performance are involved. Therefore, blood donors are a very suitable group of population to study the prevalence of latex sensitization. In Poland, blood donors are mainly occasional family donors, not honorary ones and it is thought that this group can provide an approximate model of the general population. There are some studies on the prevalence of antigen specific IgE to natural rubber latex (asNRL-IgE) in sera of blood donors in the USA and Europe, where it varies from 4.6% to 7.6% [7–10]. However, no study of this kind has as yet been undertaken in Poland.

MATERIALS AND METHODS

Study design

The blood samples were collected from 1000 consecutive blood donors attending the Regional Centre for Transfusion Medicine. The study was divided in two phases. At phase I, total IgE and asNRL-IgE were assayed in sera of all subjects with the EIA test. At phase II, additional assays of all sera with asNRL-IgE equal to or above Class II were conducted with the FEIA test approved by FDA (Food and Drug Administration) and antigen profile of asNRL-IgE was determined. The subjects qualified for the second stage of the study underwent, upon their consent, further surveys: questionnaire and skin prick tests to common allergens, latex, and food allergens known to be cross reactive to NRL (Fig. 1).

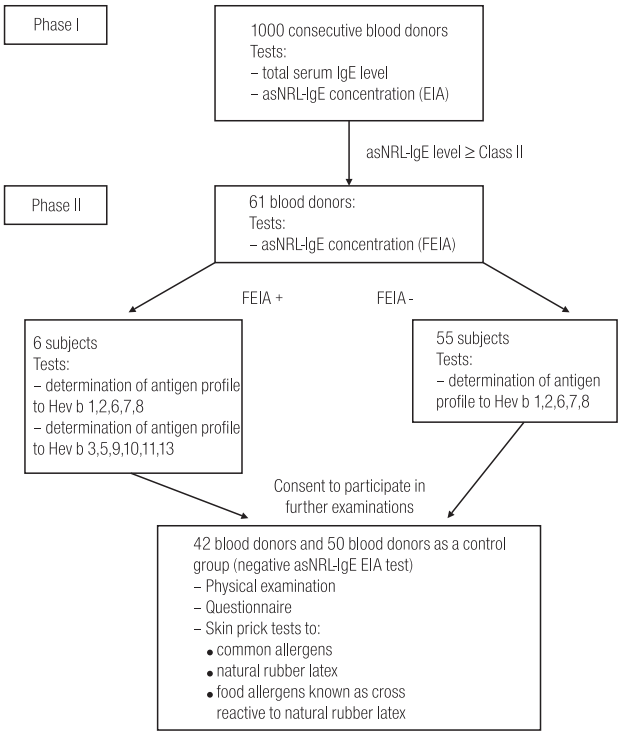

Fig. 1. Scheme of the study.

Questionnaire

The questionnaire included history of atopy and allergic diseases (including diagnosis of hay fever, allergic rhinitis and conjunctivitis, bronchial asthma, atopic dermatitis), family history of atopy, tobacco smoking habit, exposure to pet allergens at home, sexual behavior (condom usage), medical history (including surgery procedures involving NRL, current or previous food allergy), detailed work history, occupational exposure to NRL, and self-reported symptoms associated with NRL exposure.

Skin prick test

Skin prick test was performed using latex, common allergens and food allergens (including kiwi, banana, avocado, mango, hazelnut, walnut, celery) (Allergopharma, Germany). The negative control was allergen diluent and the positive one, histamine solution. All the tested sites were examined after 20 min: a wheal 3 mm larger than control and a flare 5 mm larger than control were considered positive.

Table 1. Results of study phase II – the questionnaire survey and additional tests performed in the group of 42 subjects with high levels of asNRL-IgE (Class II or more) and the control group

No. of subjects	42	50 (control group)
Female:Male, No. (%)	15 (35.7%):27 (64.3%)	19 (38%):31(62%)
Occupational exposure to NRL, No. (%)	4 (9.5%)	3 (6%)
Positive history of atopic diseases No. (%)	7 (16.7%)	5 (10%)
Asthma	2	0
Asthma and allergic rhinitis	1	2
Allergic rhinitis	4	3
Conjunctivitis	0	0
Habits, No. (%)		
Using condoms	20 (47.6%)	27 (54%)
Smoking	29 (69%)	17 (34%)
Environmental allergen exposure, No.(%)		
Domestic pets:	33 (78.6%)	37 (74%)
dogs	20 (47.6%)	27 (54%)
cats	8 (19%)	7 (14%)
birds	1 (2.4%)	2 (4%)
rodents	4 (9.5%)	2 (4%)
others	3 (7.1%)	1 (2%)
Medical history, No. (%)		
Surgery procedures with NRL exposure	18 (42.8%)	20 (40%)
Symptoms after NRL exposure	2 (4.8%)	0 (0%)
Symptoms after eating fruits	1 (2.4%)	1 (2%)
Allergic symptoms reported including:	27 (64.3%)	20 (40%)
cough	8 (19%)	7 (14%)
dyspnea	3 (7.1%)	2 (4%)
rhinitis	16 (38%)	14 (28%)
urticaria	7 (16.7%)	6 (12%)
other skin symptoms	6 (14.3%)	9 (18%)
Family history, No.(%)		
Having siblings	26 (61.9%)	35 (70%)
Positive family history for allergic diseases	5 (11.9%)	7 (14%)
Delivered through natural passages	40 (95.2%)	46 (92%)
Breastfed	33 (78.6%)	37 (74%)
Positive results of SPT, No. (%)		
Common allergens	8 (19%)	11 (22%)
including pollens	6 (14.3%)	7 (14%)
NRL	5 (11.9%)	1 (2%)
Allergens cross reactive to NRL	0 (0%)	1 (2%)
Mean total IgE serum level [kU/L±SD]	117.26 ± 184.08	94.08 ±1 35.01

Serological tests

Total serum IgE and asNRL-IgE level were measured using the EIA (enzyme immunoassay) test (Allergopharma, Germany). Total IgE levels higher than 100 kU/L were considered elevated; asNRL-IgE above 0.35 kU/L level was considered positive and that above Class II (0.7 kU/L) significant positive.

To verify significant positive results the FDA approved FEIA (fluorescent enzyme immunoassay) test was used (UniCAP, Pharmacia, Sweden). AsNRL-IgE level above 0.35 kU/L was considered positive.

To determine antigen profile of NRLs-IgE, a panel of single recombinant latex allergens was coupled with ImmunoCAPs. This panel comprised rHev b 1, rHev b 2, rHev b 3, rHev b 5, rHev b 6, rHev b 8, rHev b 9, rHev b 10, rHev b 11**,** and rHev b 13. All of them were produced in *E. coli* in fusion with the maltose binding protein (MBP as fusion component). The maltose binding protein coupled with ImmunoCAPs served as a negative control. The individual latex allergen profile was determined with sera and the ImmunoCAPs using the Pharmacia UniCAP-System. Results over 0.35 kU/L were considered positive [11–13].

Statistical analysis

To evaluate the risk factors for latex sensitization, based on the presence of asNRL-IgE, odds ratios (ORs)**,** and their 95% confidence intervals were calculated with Epi-Info 6.0 program. The analysis covered two groups of cases: 42 subjects with the sera containing asNRL-IgE and 50 subjects of the control group (blood donors with the sera not containing asNRL-IgE).

RESULTS

Serum samples were collected from 1000 consecutive volunteer blood donors (312 females and 688 males). Mean age in this group was 29.64 ± 8.73 years (26.23 ± 7.37 for females and 31.18 ± 9.35 for males). Total serum IgE level was 104.84 ± 173.27 kU/L (86.56 ± 165.59 for females and 111.85 ± 175.75 for males); 216 subjects had elevated total IgE serum level (21.6%). Antigen specific IgE to NRL was found in sera of 179 (17.9%) subjects, 47 women (15.06% of all women) and 132 men (19.2% of all men). Table 1 gives the results of the questionnaire and additional tests preformed in the group of 42 subjects from phase II and in the control group of 50 subjects with no presence of latex-specific antibodies.

The EIA test verified against the FEIA revealed very low concordance between this two methods. In only 6 sera samples the prevalence of antigen specific antibodies to NRL was confirmed with the FDA approved FEIA test. The positive FEIA results were confirmed with SPT to NRL in 60% and negative in 5.4% of cases (Table 2).

In all negative FEIA tests**,** the antigen profile of asNRL-IgE determination revealed no presence of any specific IgE. Table 3 presents the results of cases I to VI of the positive FEIA verification. The specific IgE to Hev b 3,5,6 and 13 were observed in the subjects with occupational exposure to NRL. The highest concentration of Hev b 8 was observed in the subjects not symptomatic to NRL with positive SPT to grass and tree pollens. In one case with the lowest concentration of asNRL-IgE confirmed by the FEIA test, Hev b profile was negative (Table 3).

The statistical analysis revealed that the elevated total IgE serum level is the risk factor for the presence of antigen specific IgE to NRL determined by both, the EIA and FEIA methods. The two other risk factors were active tobacco smoking and positive history of atopy (Table 4).

Table 2. Results of the EIA test against the FDA approved FEIA test

	FEIA (+)	FEIA (–)
No. of subjects with EIA ≥ class II	6	55
No. of subjects who agreed to participate in additional tests	5	37
Positive SPT to common allergens	2	6
Positive SPT to NRL	3	2
Positive SPT to allergens cross reactive to NRL	0	0
Symptoms with NRL	1	1

Table 3. Results of antigen profile determination of asNRL-IgE

	Case I Occupational exposure to NRL	Case II Without occupational exposure to NRL	Case III Occupational exposure to NRL	Case IV Without occupational exposure to NRL	Case V Occupational exposure to NRL	Case VI Did not agree to participate in the study
ELISA (EIA)[kU/L]	0.71	1.04	1.03	1.04	1.51	1.23
ImmunoCAP (FEIA) [kU/L]	10.0	1.52	2.38	1.57	1.74	0.5
Hev b 1 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 2 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 3 [kU/L]	4.55*	0.58*	1.53*	< 0.35	< 0.35	< 0.35
Hev b 5 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	3.55*	< 0.35
Hev b 6 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	0.91*	< 0.35
Hev b 7 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 8 [kU/L]	6.72*	1.41*	< 0.35	1.14*	< 0.35	< 0.35
Hev b 9 [kU/L]	0.5*	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 10 [kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 11[kU/L]	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35	< 0.35
Hev b 13 [kU/L]	1.82*	0.38*	1.78*	< 0.35	< 0.35	< 0.35
SPT to NRL	Positive	Negative	Positive	Negative	Positive	No data
SPT to common allergens	Negative	Positive: – tree pollens – grass pollens	Negative	Positive – tree pollens – grass pollens	Negative	No data
Symptoms with NRL	Yes	No	No	No	No	No data

* Positive results.

Table 4. Statistical analysis of factors influencing the presence of antigen specific IgE to natural rubber latex

Factor	Odd ratio (OR) CI 95%
Elevated total serum IgE level [for EIA]*	1.66 (1.11 < OR < 2.47)*
Elevated total serum IgE level [for FEIA]*	17.5 (3.31 < OR < 169.76)*
Occupational exposure to NRL	1.65 (0.26 < OR < 11.89)
History of atopic disease	1.8 (0.44 < OR < 7.8)
Condom usage	0.77 (0.31 < OR < 1.91)
Domestic pets	1.29 (0.44 < OR < 3.8)
Active tobacco smoking*	4.33 (1.65 < OR < 11.53)*
History of surgical procedures with NRL	1.13 (0.68 < OR < 1.67)
Symptoms suggested allergic disease*	2.7 (1.07 < OR < 2.79)*
Having siblings	0.7 (0.27 < OR < 1.81)
Positive family history for allergic disease	0.83 (0.19 < OR < 3.34)
Breastfed	1.74 (0.23 < OR < 20.07)
Positive SPT to common allergens	0.83 (0.27 < OR < 2.58)
Gender	0.75 (0.51 < OR < 1.09)

* Risk factors.

DISCUSSION

Epidemiological data have not yet provided sufficient information on the prevalence of latex allergy in the general population. Therefore, it is very difficult to find hard evidence that risk factors of latex allergy do exist [6]. Some studies pointed out that the prevalence of latex allergy in the non-occupationally exposed population is extremely low.

Cross sectional studies are very difficult to conduct due to high costs and low participation rates, especially when such procedures as blood samples collection or SPT performance is involved. Therefore, blood donors are a very suitable group of population for such a kind of study and its results, with some limitations, can be projected on the general population. It is commonly known that the presence of antigen specific IgE is required to diagnose atopic disease. Two most common methods for testing the presence of such antibodies are serological tests to determine the presence of antigen specific IgE in serum and skin

prick test. In our study we used both methods to confirm sensitization. First, serum asNRLs-IgE was assayed then the results were verified by skin prick tests. Antigen profile of asNRL-IgE was also determined. Antigen profile is very important for the sensitization analysis because the presence of particular antigens is of different sensitization origin. For example, the subjects with spina bifida often show IgE to Hev b 1 and 7, whereas for occupationally exposed health care workers profile containing Hev b 2,5,6 and 13 is most characteristic. Antigens Hev b 8 and 11 are bound up with cross reactivity to pollens and exotic fruits.

Two studies of latex allergy among non-occupationally exposed groups have been performed in Poland. Nitecka et al. [14] studied the prevalence of positive SPT to latex among 434 consecutive patients of an out-patient clinic for allergy. This study revealed that 7% of patients had positive SPT to latex, but none of them showed antigen specific IgE to NRL. Only 2.5% of patients reported symptoms associated with NRL. There were no data on occupational exposure available in this group. In the group with positive SPT to latex, atopy was more common than in the negative SPT group, 81% and 52%, respectively. Cudowska et al. [15] studied a population of 507 atopic children. Five (0.98%) of them had positive SPT to NRL and only two (0.4%) had reported symptoms associated with NRL. It should be noted that the aforesaid studies are of no reliable value from the epidemiological point of view. They only signal the problem of latex allergy, but do not tackle the problem of its prevalence in the general population. What is even more important, according to those studies the high prevalence of atopy among the subjects might influence the frequency of latex sensitization.

Todate, four studies have demonstrated the prevalence of antigen specific IgE to NRL among blood donors. In 1996, Merret et al. [7] published the results of their study among British blood donors. They report that the prevalence of latex specific IgE vary from 4% to 7% and the variance depended on the time of the year the serum was collected. The higher level was observed when the concentration of pollens was higher in the air, which indicates that the higher concentration values may depend on the higher level of cross reactive IgE to pollens. Our study was conducted from August to November so it is not possible to refer to the results obtained by Merret et al. [7].

Also in 1996, Ownby et al. [8] published results of their study on the prevalence of latex specific IgE in 1000 U.S. volunteered blood donors, using the FDA approved AlaSTAT test twice to confirm the results. They showed a 6.4% prevalence of allergen specific IgE in the population of blood donors. All positive results were verified with ImmunoCAP test and only a 61% concordance was revealed. They also observed twofold higher values of prevalence of allergen specific IgE in males than in females (8.7% and 4.1%, respectively). Our study also indicates higher prevalence of latex sensitization in the group of males, but the difference is not as high.

In 1999 Senna et al. [10] analyzed the prevalence of latex specific IgE in a group of 1025 Italian volunteered blood donors. In 3.5% of blood donors, the positive ImmunoCAP results of latex specific IgE in serum were observed. That was the first study with positive results verified with SPT to NRL. SPT confirmed latex sensitization in only 6 cases, i.e. 0.5% of the study group. Only one subject reported symptoms associated with products containing NRL.

In 2000, Saxon et al. [9] reported a study performed among U.S. blood donors to check the agreement between the same test methods used in different laboratories and to compare differences in the AlaSTAT results depending on the laboratory. The prevalence of latex specific IgE in this study varied from 5.4 to 7.6%, depending on the laboratory and confirmed only a 90% concordance of the method. In our study the prevalence of antigen specific IgE to NRL was much higher and amounted to 17.9%.

It is important to stress that we used the EIA test (Allergopharma, Germany), not the FDA approved test, to determine the presence of asNRL-IgE in serum. This test is widely used in Europe, but its specificity and sensitivity in the determination of latex specific IgE have not yet been described. In 61 cases, we determined concentration of latex specific IgE equal to and above Class II. In only 6 cases, the verification with the FDA approved test (UniCAP) was positive. The concordance between this two tests is very low – 9.8%. The concordance between positive FEIA and SPT to NRL is over tenfold higher than that

between negative FEIA and SPT to NRL, 60% and 5.4%, respectively. The antigen profile determination gives positive results only in the group of positive FEIA and it is not observed in the negative FEIA. The data indicate that in the subjects occupationally exposed to NRL, IgE to Hev b 3,5,6 and 13 is observed. The highest level of IgE to Hev b 8 is present in subjects non-symptomatic to NRL, with sensitization to grass and tree pollens, which may be associated with cross reactivity of IgE specific to pollens and NRL. These results indicate that the FEIA test is much more accurate in the recognition of NRL sensitization than the EIA, which seems to produce too many false positive results. Therefore, the FEIA test should be applied for diagnosis of latex allergy and the EIA test only for screening purposes. It is also important to point out that only subjects with occupational exposure to natural rubber latex reported symptoms of latex allergy. In view of the above, the opinion of some authors that non-occupational latex allergy is extremely rare seems to correspond with our results [15]. Subjects with spina bifida and patients with positive history for multiple surgical procedures are the only non-occupational well documented groups of risk for latex allergy [3,4,16]. The mean total IgE level in blood donors was 104.84 ± 173.27Ku/L; 21.6% of the subjects showed elevated levels of total serum IgE which corresponds with the prevalence of atopy in the general population. This indicates that our study group does not differ significantly from the general population in the prevalence of atopy.

The statistical analysis revealed that elevated total serum IgE is a risk factor of specific IgE to NRL determined by both the EIA and FEIA methods. This corresponds with observations made by other authors [17]. Active tobacco smoking and history of atopic disease symptoms are the other two risk factors of allergen specific IgE to NRL. Interestingly, some authors report that tobacco smoking is a risk factor for atopic disease [18,19]. For example, Jarvis et al. [20] observed that smoking is associated with an increased risk of sensitization to house dust mites.

The above data indicate that determination of antigen specific antibodies cannot directly lead to final diagnosis. The presence of asNRL-IgE may indicate sensitization as well as misdiagnosis with cross reactivity. According to some authors, clinical history of latex allergy symptoms can also be inadequate and highly depends on the physician who takes patient's history [21,22]. For example, in occupational airway allergy, sensitivity of clinical history, according to different authors, varies from 87 to 92% and specificity only from 14 to 32% [23,24]. Therefore, to maximize the diagnostic reliability we should not rely on asNRL-IgE tests and clinical history, but rather concentrate on specific challenge tests.

CONCLUSIONS

1. The prevalence of antigen specific IgE to natural rubber latex among Polish blood donors assessed with the EIA test is high and was estimated at about 18%.
2. Concordance between the EIA and FEIA tests is very low, approximately about 10%.
3. The prevalence of atopy among blood donors is similar to that found in the general population.
4. In case of latex allergy, the EIA test should be used only for screening purposes, but not for diagnosis.
5. Elevated total serum IgE, tobacco smoking, and history of allergic symptoms are the risk factors for the presence of antigen specific IgE to natural rubber latex.

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