

Natural rubber latex allergy in children: a follow-up study

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Summary

Background Natural rubber latex (NRL) allergy occurs frequently in children with spina bifida and other children with disorders requiring multiple operations. Also atopic children who have not undergone surgery can be sensitized to NRL, but the outcome of these children has not been studied.

Objective To study how NRL-allergic children manage at home and whether their skin prick test (SPT) reactivity, latex RAST or IgE antibody levels to NRL allergens change during the follow-up.

Methods Twenty-four NRL-allergic children who had not undergone surgery and eight children with histories of multiple operations were followed up for a mean of 2.8 years. Clinical symptoms were recorded and all children were re-examined with SPT, latex RAST and ELISA for IgE antibodies to prohevein (Hev b 6.01), hevein (Hev b 6.02) and rubber elongation factor (REF, Hev b 1).

Results Nineteen of the 24 NRL-allergic children (79%) who had not undergone surgery had occasional contacts to balloons and other NRL products at home, and 10 of them experienced symptoms ranging from contact urticaria to systemic reactions. Three of the eight NRL-allergic children with a history of multiple operations had contacts to rubber balloons without any symptoms, and five children underwent 1–8 uneventful operations in a latex-free environment. SPT reactivity to NRL allergens, latex-RAST or IgE antibody levels to prohevein or hevein did not change in either group of NRL-allergic children during the follow-up.

Conclusions Occurrence of clinical symptoms and no decrease in SPT reactivity or IgE levels to NRL allergens in the course of the present follow-up study imply that more attention should be paid to the protection of NRL-allergic children from rubber contacts in the home environment.

Keywords: latex allergens, fruit allergy, skin prick test, IgE antibodies, RAST, ELISA

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Introduction

Sensitization to natural rubber latex (NRL) is an important cause of allergy in children with spina bifida and other children requiring multiple operations [1–3]. These children are repeatedly exposed to gloves and other NRL-containing medical devices, and the frequency of NRL allergy ranges from 29% to 65% [2–5]. Several authors have noticed that especially atopic children may become sensitized to NRL

although they have not been subjected to multiple operations [6–8]. When screening 3269 children admitted for inhalant or food allergy testing by skin prick testing we found NRL allergy in 1%, and two thirds of these children had no disorders requiring multiple operations [9].

The outcome of NRL-allergic children with spina bifida and other children requiring multiple operations has been evaluated in some studies showing that if operations are performed in an allergen-free environment, systemic reactions can be avoided [10,11]. The outcome of NRL-allergic children outside the hospital environment has not been well documented.

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Table 1. NRL contacts, number of surgical operations and type of symptoms during the follow-up of 32 NRL allergic children

Group of children	No surgery (<i>n</i> = 24)	Multiple operations (<i>n</i> = 8)
Mean age at diagnosis, years (range)	5.9 (0.6–13.7)	7.1 (0.7–13.1)
Mean follow-up time, years (range)	2.8 (2.3–3.1)	2.9 (2.7–3.1)
Number of children having NRL contacts at home	19 (79%)*	3 (38%)**
of which with symptoms	10 (53%)*	0
Number of children with surgical operations	2 with adenotomy	5 with 1–8 major operations
of which with symptoms	0	0

*15 with balloons, 2 with boots, 2 with household gloves, **all with balloons, ***6 with contact urticaria, 2 with lip swelling, 2 with facial oedema, generalized urticaria and asthmatic attack.

The purpose of the present prospective study was to determine how NRL-allergic children with or without histories of multiple operations manage to avoid allergic reactions at home. We also studied whether SPT reactivity, latex RAST or IgE antibody levels to specific NRL allergens decrease during the follow-up of these children.

Methods

Patients

In 1995–96, we diagnosed 30 children who had not undergone surgery and 12 children with spina bifida or other malformations to have NRL allergy by using three diagnostic criteria: a positive skin prick test to a commercial NRL allergen (Stallergènes SPT reagent, Fresnes, France) and/or to a NRL glove extract (Triflex, Baxter, Valencia, CA, USA), a positive latex RAST (>0.4 kU/L; Pharmacia, Uppsala, Sweden) and a positive NRL glove (Triflex) use test [9]. Eleven of the children who had not undergone surgery and three of the children with a history of multiple operations had no previous history of symptoms from NRL allergy. At diagnosis the parents of all children were carefully advised orally and in writing how to avoid gloves, balloons and other NRL products at home and in a hospital environment. This information was forwarded also to the kindergarten or school, and to the dentist and physician taking care of each of these children. In addition, a warning sign of NRL allergy was attached to the hospital records, and all surgical procedures were advised to be performed in a latex-free environment. The parents and the children were advised to contact our department if any problems arose with protection or symptoms of NRL allergy. No particular recommendations were given for avoidance of any fruits or other possible NRL cross-reactive foods for these children. Seven NRL-allergic children visited our

department regularly because of atopic dermatitis or food allergies.

Twenty-four children who had not undergone surgery and eight children with a history of multiple operations, including six children with spina bifida, participating in the follow-up study were re-examined in June–August 1998 (Table 1). The mean follow-up times of the two groups of children were 2.8 and 2.9 years, respectively. During the follow-up eight parents contacted our department owing to their children's allergic reaction at home. At re-examination, all children and/or their parents were personally interviewed by using a structured questionnaire which included questions about exposure to and symptoms from NRL products, their treatment and presence or absence of atopic symptoms. The number of surgical operations and their outcome were also checked from hospital records.

Sera were obtained from NRL-allergic children at diagnosis and at re-examination for RAST and ELISA studies. Control sera were from 17 atopic children (mean age 5.9 years; range 1.5–12.8 years) with negative SPT to NRL but positive SPT to inhalant or food allergens [12].

The study was approved by the Ethical Committee of Tampere University Hospital, and the children and/or their parents gave their informed consent for participation.

Skin prick test

On re-examination, SPTs were performed with the same two NRL allergens (Stallergènes SPT reagent, Triflex glove extract) as at diagnosis. Banana, kiwi fruit and avocado SPTs were performed with freshly peeled fruit by the prick-prick method as described previously [9]. Histamine dihydrochloride (10 mg/mL, ALK) served as a positive control and physiological saline as a negative control. A weal half the size of that of histamine and 3 mm or larger was regarded as positive.

RAST and total IgE

Blood was drawn for latex RAST and total IgE measurements (Pharmacia, Uppsala, Sweden). Specific IgE values greater than 0.4 kU/L were regarded as positive. Total IgE levels greater than 110 kU/L (age group 2–3 years), 130 kU/L (age 4–7 years), 320 kU/L (age 8–14 years), and 160 kU/L (age 15–17 years) were regarded as elevated values.

Purification of NRL allergens and ELISA

Prohevein (Hev b 6.01) and hevein (Hev b 6.02) were purified from the bottom (lutoid) fraction and REF (Hev b 1) from the rubber particle fraction of NRL as described previously [12]. IgE-ELISA using these allergens as the solid phase was performed as described previously [12,13]. In brief, prohevein (2 µg/mL in 50 mM carbonate buffer, pH 9.6), hevein (2.0 µg/mL) or REF (1.5 µg/mL) were applied to 96-well polystyrene microtiter plates (100 µL/well; Nunc, Roskilde, Denmark) and incubated for 3 h at room temperature and overnight at 4°C. The wells were then post-coated with 100 µL of 1% human serum albumin in 50 mM carbonate buffer, pH 9.6, washed with phosphate-buffered saline and incubated for 2 h with 100 µL of patient or control serum (diluted 1/10). After washing, biotinylated antihuman IgE (Vector, Burlingame, CA, USA; diluted 1/1000), streptavidin-conjugated alkaline phosphatase (Bio-Rad; diluted 1/3000) and the substrate development solution (Sigma Chemical Co., St. Louis, Mo, USA) were added, and the optical density was read at 405 nm using an automated ELISA reader (Titertek Multiskan, Eflab, Espoo, Finland). The patient sera taken at diagnosis and on re-examination were measured at the same ELISA runs. The mean OD + 3 SD of the 17 control sera was chosen as the cut-off limit for positivity.

Statistics

Wilcoxon matched-pair test was used to compare the results of SPTs, latex RAST and the IgE antibody levels to purified NRL allergens at diagnosis and re-examination. The children who had not undergone surgery and the children with a history of multiple operations were analysed separately. Fischer's exact test was used to compare the occurrence of NRL contacts and symptoms and the Mann-Whitney *U*-test to compare the SPT reactivity, latex RAST, and the IgE antibody levels to purified NRL allergens in symptomatic and asymptomatic children at the end of the follow-up. Probability (*P*) values below 0.05 were considered significant.

Results

NRL exposure and symptoms during the follow-up

Nineteen of the 24 NRL-allergic children (79%) who had not undergone surgery had occasional contacts with rubber balloons, boots and household NRL gloves (Table 1). Ten of these children (53%) experienced NRL allergy symptoms such as contact urticaria and lip swelling (Table 1). Two of these children had, in addition, generalized urticaria, facial oedema and asthmatic attacks from balloons which required a visit to the emergency care. Of the 10 children who experienced symptoms during the follow-up, two had previously been totally asymptomatic. Two children underwent adenotomy in a latex-free environment without any symptoms.

Three of the eight children with a history of multiple operations had a few contacts with rubber balloons, but they remained free of symptoms. Five of these eight children underwent 1–8 operations uneventfully in a latex-free environment.

Eighteen (56%) of the 32 children had presented with symptoms before the diagnosis of NRL allergy. During the follow-up the NRL contacts occurred in 13 (72%) symptomatic and in nine (64%) asymptomatic children (*P* = 0.458). Eight (62%) of the symptomatic, and two (22%) of the asymptomatic children experienced symptoms during the follow-up (*P* = 0.07).

Skin prick test and RAST

On re-examination, SPT reactivity to NRL allergens did not show any decrease in the mean weal diameters in the children who had not undergone surgery or in the children with a history of multiple operations. (Table 2a,b). At diagnosis, 23 of the 24 NRL-allergic children (96%) who had not undergone surgery had positive SPTs to NRL glove extract and 21 (88%) to the commercial latex allergen. On re-examination, the frequencies were 92% and 79%, respectively. At diagnosis, all eight children with a history of multiple operations had positive SPTs, on re-examination six children showed positive SPTs to both NRL allergens but the mean weal diameters remained unchanged (Table 2b). The SPT reactivity to NRL glove extract and to the commercial latex allergen did not differ between the symptomatic and the asymptomatic children at the end of the follow-up (*P* = 0.154 and *P* = 0.084, respectively).

Twenty (83%) of the children who had not undergone surgery showed positive SPTs to banana, avocado and kiwi fruit both at diagnosis and at re-examination. The same was true of five children (63%) with a history of multiple operations. In more detail, 15 children (63%) who had not undergone surgery had positive SPTs to banana at diagnosis and 10 children (42%) on re-examination. The frequencies to kiwi

Table 2a. Skin prick test results to NRL allergens, latex-RAST and IgE antibody levels to specific NRL allergens in ELISA at diagnosis and after the follow-up in 24 NRL allergic children who had not undergone surgery

	At diagnosis		At follow-up		<i>P</i> -value*
	Mean (range)	Number of positive	Mean (range)	Number of positive	
Skin prick test (diameter in mm)					
Triflex glove‡	6.5 (1–11)	23	6.9 (0–11)	22	0.417
Stallergènes	5.8 (0–10)	21	6.0 (0–13)	19	0.532
Latex-RAST(kU/L)	6.3 (0.4–28.4)	24	5.7 (<0.4–20.2)	23	0.291
Total IgE (kU/L)	582 (27–3300)	19	605 (55–1868)	18	0.116
IgE-ELISA§					
Prohevein	0.317 (0.001–1.170)	16†	0.229 (0–1.388)	14	0.052
Hevein	0.102 (0–0.693)	16	0.129 (0–1.219)	15	0.171
REF	0.008 (0–0.095)	7	0.001 (0–0.020)	4	0.002

*Wilcoxon matched-pair test at diagnosis and at the end of follow-up. †Bigger than the mean + 3 SD of the 17 control sera. ‡Extract 1 : 5 w/vol. §OD units.

Table 2b. Skin prick test results to NRL allergens, latex RAST and IgE antibody levels to specific NRL allergens in ELISA at diagnosis and after the follow-up in 8 children with with spina bifida and other children requiring multiple operations

	At diagnosis		At follow-up		<i>P</i> -value*
	Mean (range)	Number of positive	Mean (range)	Number of positive	
Skin prick test (diameter in mm)					
Triflex glove‡	6.9 (3–13)	8	6.4 (0–13)	6	0.463
Stallergènes	6.0 (3–10)	8	5.6 (0–10)	6	0.447
Latex-RAST(kU/L)	12.0 (0.7–74.2)	8	12.9 (<0.4–79.1)	7	0.575
Total IgE (kU/L)	549 (24–2036)	5	256 (18–627)	4	0.161
IgE-ELISA§					
Prohevein	0.303 (0–1.374)	5†	0.242 (0–1.422)	3	0.208
Hevein	0.163 (0–1.021)	5	0.159 (0–1.141)	5	0.612
REF	0.280 (0–1.449)	7	0.208 (0–1.295)	5	0.063

*Wilcoxon matched-pair test at diagnosis and at the end of follow-up. †Bigger than the mean + 3 SD of the 17 control sera. ‡extract 1 : 5 w/vol. §OD units.

fruit was 63% at diagnosis and 67% on re-examination, to avocado 50% and 54%, respectively. In the children with a history of multiple operations, positive SPTs to banana were seen in three children at diagnosis and in four children at re-examination, and to kiwi fruit in four and four children and to avocado in two and three children, respectively.

RAST and total IgE

The mean latex RAST levels did not show any significant change during the follow-up in the children who had not

undergone surgery or in the children with a history of multiple operations (Table 2 a,b). Similarly, the mean total IgE levels remained unchanged in these groups. The mean latex RAST or total IgE levels did not differ between the symptomatic and the asymptomatic children at the end of the follow-up ($P = 0.820$ and $P = 0.254$, respectively).

ELISA

The mean IgE antibody levels to prohevein and hevein did not show any significant changes during the follow-up in the

children who had not undergone surgery or in the children with a history of multiple operations (Table 2 a,b). The mean IgE antibody level to REF decreased from 0.008 to 0.001 ($P=0.002$) in the children who had not undergone surgery and from 0.280 to 0.208 ($P=0.063$) in the children with a history of multiple operations (Table 2a,b). The mean IgE antibody levels to prohevein, hevein and REF did not differ between the symptomatic and the asymptomatic children at the end of the follow-up ($P=0.436$, $P=0.138$, and $P=0.595$, respectively).

When the children were analysed individually, 16 of the 24 children (67%) who had not undergone multiple surgery showed IgE antibodies to prohevein at diagnosis and 12 of them also at re-examination. In addition, two children showed IgE antibodies to prohevein only at re-examination. Sixteen children (67%) had IgE antibodies to hevein at diagnosis, and 14 of them and another child also at re-examination. Seven of these children (29%) had IgE antibodies to REF at diagnosis, three of them and another child became also positive at re-examination.

In the eight children with a history of multiple operations, IgE antibodies were found at diagnosis to prohevein in five, to hevein in five and to REF in seven children. At re-examination three, five and five children had these IgE antibodies, respectively.

Discussion

In spite of careful NRL precautions, two thirds of the present 32 children had contacts with balloons, rubber boots or household gloves during the follow-up. One third of the NRL-allergic children, none of whom had histories of multiple operations, experienced symptoms ranging from contact urticaria to systemic reactions. This shows that it is rather difficult for children to completely avoid NRL products at home. In contrast, all five children with a history of multiple operations and two children from the other group remained free of symptoms although they were operated 1–8 times in a hospital. This is not unexpected because the operations were performed in a latex-free environment as recommended by several authors [4–14]. It was a surprise, however, that the children with a history of multiple operations showed no decrease in the SPT reactivity, latex RAST or IgE antibody levels in ELISA. Recently, Harrigan *et al.* [15] measured latex-specific IgE by ELISA in 16 spina bifida patients before and after being operated in a latex-free environment and found decreased IgE levels in 11 (69%) patients. One reason for the unchanged latex RAST IgE levels in our children could be a somewhat shorter follow-up time or also NRL exposure at home. This was documented in three children with a history of multiple operations and in as many as 19 children (79%) who had not undergone surgery. The children in the latter group did not show any

marked change in the SPT reactivity, latex RAST or in the IgE antibody levels to the prohevein or hevein in ELISA either. The only change during a follow-up was a slight decrease of the mean IgE antibody levels to REF, a finding which did not reach statistical significance in the children with history of multiple operations. In the children who had not undergone surgery, the IgE antibodies to REF were very low already at diagnosis and the decrease of the mean IgE level, although significant, seems not to be of clinical relevance.

To analyse possible relationship between the outcome and occurrence of symptoms during the follow-up, the 32 NRL-allergic children were divided in two groups, i.e. on those who had presented with symptoms before the diagnosis (18 children) or not (14 children). The NRL contacts occurred during the follow-up in both groups in similar frequencies, but symptomatic children experienced symptoms more frequently than the asymptomatic ones, but this difference did not reach statistical significance ($P=0.07$). Among the latter group were two previously asymptomatic, nonoperated children who experienced symptoms from balloon or household NRL gloves. This shows that also previously asymptomatic but NRL glove challenge-positive children are at risk for NRL allergy symptoms due to which they should carefully avoid NRL contacts at home environment. Interestingly, at end of the follow-up the SPT reactivity and IgE levels to NRL allergens did not differ between the symptomatic and asymptomatic groups of the NRL allergic children. Our results based mainly on the outcome of the nonoperated NRL-allergic children do not support the findings of Mazon *et al.* [16] and Bernardini *et al.* [17] in children with spina bifida. They studied the risk factors of NRL allergy and found that symptomatic children with spina bifida were more likely to have positive SPTs and higher IgE antibody levels to NRL than the asymptomatic ones. One reason for the discrepant results could be that in the present study the NRL allergy diagnosis was confirmed with NRL glove use test, whereas no challenges were performed in the studies of Mazon *et al.* [16] and Bernardini *et al.* [17].

The NRL contacts in the present NRL-allergic children were rather infrequent at home, suggesting that exposure to latex aeroallergens could also maintain positive IgE antibody levels. Allmers *et al.* [18] showed recently that IgE antibody levels to NRL decreased significantly when latex aeroallergens were removed from the working environment of health care workers. To our knowledge there is, however, no information on the effect of NRL aeroallergen concentrations on NRL-specific IgE levels when using household gloves, balloons or other NRL products at home.

NRL allergy is frequently associated with hypersensitivity to foods, such as banana, avocado, kiwi fruit, papaya and chestnut [19–22]. This 'latex–fruit' syndrome could also be

one explanation for the persisting SPT reactivity to NRL and IgE antibody levels to hevein in the present NRL-allergic children. Class I chitinases in avocado, banana and chestnut are known to contain hevein-like domains, and IgE antibodies to hevein from NRL allergic subjects crossreact with these plant proteins [23–25]. Interestingly, 83% of the present children who had not undergone surgery and 63% of the children with multiple operations showed positive SPTs to cross-reacting fruits, banana, kiwi-fruit and avocado at diagnosis, and no major change occurred in the SPT reactivity to these fruits during the follow-up. It is therefore possible that exposure to these fruits and the cross-reactivity between class I chitinases and hevein could also maintain the persisting high IgE antibody levels to NRL and especially to hevein. We did not, however, find evidence that cross-reacting fruits caused any marked allergic reactions in our NRL-allergic children during the follow-up. Further studies are obviously needed to clarify the role of plant class I chitinases in the outcome of latex–fruit syndrome in NRL-allergic children.

In conclusion, the present study on NRL allergic children showed that exposure to NRL products continues easily at home. This contention is supported by stable SPT reactivity and latex RAST and rather constant specific IgE antibody levels during the follow-up. NRL-allergic children, asymptomatic or not at diagnosis, may get even serious allergic symptoms in the home environment. Therefore, latex avoidance instructions should be addressed, not only to hospital environment, but also carefully to families, kindergarten and other places where children were exposed to NRL.

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