

Sensitivity and allergy to latex in atopic and non-atopic children

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To study the sensitivity and allergy to latex in children, we investigated sera of 306 atopic and 303 non-atopic children (median age 4.5 years) for specific IgE to latex. In patients with specific IgE to latex, a questionnaire was sent to families and provocation tests were carried out. 60/306 atopic children (20.8 %) and 1/303 non-atopic children (0.3 %) showed specific IgE to latex in serum. The proportion of atopic, latex-sensitized and provocation positive children was 12/48 (25 %). Specific IgE to latex was significantly higher ($p < 0.03$) in symptomatic compared to non-symptomatic patients. Specificity of a positive history was 92 %, sensitivity 50 %. Atopic dermatitis tended to be more prevalent among the 12 provocation positive atopic children (75 %) compared to 36 provocation negative children (58 %). There was a tendency that children of the symptomatic group underwent surgical interventions more frequently compared to non-symptomatic children. In conclusion, latex sensitization and latex allergy seem to have occurred more often in atopic children than previously known. Risk factors for the development of a sensitization to latex are atopy and the clinical diagnosis of atopic dermatitis; risk factors for a clinically manifest allergy to latex are an elevated specific IgE to latex, a positive history upon contact to material containing latex and probably frequent operations. Provocation tests should be performed to plan avoidance measures in latex-allergic children especially before surgical interventions.

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Allergy to latex has become an increasing and clinically important problem during the last years. While delayed type clinical reactions to latex (e.g. hand-eczema) have been known for a long time, immediate type allergic reactions have only been reported in recent years. Many case-reports about fatal and near-fatal incidents (mainly during surgery) have been published recently (1–3). Groups known to be at risk for latex sensitivity include healthcare professionals (4, 5) and children with spina bifida (6). Recent estimates of the prevalence of sensitization to latex range from 34 % (7) up to 73% (8).

Little is known about the prevalence and clinical relevance of latex sensitization and allergy in the general population. There is evidence that the incidence of latex allergy is increasing in children (9). One of the proposed risk factors is an atopic disposition (1, 6). The aim of our study was therefore to study the sensitization and allergy to latex in atopic and non-atopic children.

Material and methods

Patients

We investigated two groups of children: 306 atopic and 303 non-atopic children. In total, 609 patients (261 girls, 348 boys) were studied. Ages ranged from 1 month to 18 years (median age 4.5 years). Sera were sent to our laboratory for diagnosing or excluding sensitization. Children were defined as atopic if they showed specific IgE to common inhalant and/or nutritional allergens, as well as typical clinical symptoms (such as bronchial asthma, allergic rhinitis or atopic dermatitis). Children were defined as non-atopic if total IgE was within the age-related normal range, specific IgE was not detectable and clinical symptoms were not suggesting allergic disease.

Study design

Sera from the two groups were investigated for total IgE and for specific IgE to latex, inhalant and nutri-

tional allergens. If patients were positive for specific IgE to latex, a questionnaire was sent to families and sequential provocation tests (see below) were carried out. Parents gave their written consent. The study protocol was approved by the local ethics committee.

Specific IgE

Total IgE and specific IgE to latex was determined from sera by the solidphase immunoassay (FEIA), the Pharmacia CAP-system (PCS) (KabiPharmacia, Uppsala, Sweden) (10). Inhalant (SX1) and nutritional (fx5) allergens were investigated by screening tests using the same automated IgE assay (11). SX1 contains the allergens timothy, birch, mugwort, house-dust mite, cat, dog and *Cladosporium herbarum*. Fx5 contains the foods milk, egg, fish, soy, wheat and peanut. None of these allergens is known to cross-react with latex.

Questionnaire

The questionnaire sent to latex-sensitized children included questions of clinical symptoms upon contact to latex in the daily environment (e.g. to balloons) and to medical equipment (e.g. during surgery).

Skin prick testing

SPT was performed in children who showed specific IgE to latex in serum. As allergen extracts, two different sources were used: 1) low ammoniated natural rubber latex milk (Ansell, Munich, Germany); and 2) high ammoniated natural rubber latex milk (Regent, Monchengladbach, Germany). Skin test was assessed as positive if the maximum wheal diameter was ≥ 3 mm without reaction of negative control.

Glove wearing test

After having washed their hands, children put one wet hand into a latex glove (Sempermed® classic, Semperit, Vienna, Austria) and, as a control, the other wet hand into a neoprene glove (Dermaprene®,

Ansell, Munich, Germany). After wearing these gloves for 30 min (or in case of clinical symptoms), gloves were taken off and possible clinical reactions were assessed by a physician. Hands were washed again. The single blind test was assessed as positive if typical immediate-type clinical reactions (e.g. urticaria, Quincke edema) occurred. If test was negative, a glove was blown up as an additional test.

Blowing up a glove

The open end of a latex glove was turned inside out for about 3 cm and the children took a deep breath, put the glove onto their lips and blew up the glove. In order to avoid inspiration of latex particles, great care was taken that the children took their mouth away from the glove while inhaling. In case of infants ($n = 6$), we turned the glove inside out and rubbed part of it smoothly on the lips for one min. In children from about 5 years on, lung function was monitored by measuring peak expiratory flow (PEF) before and every 10 min after the test up to 30 min. Possible clinical reactions were monitored continuously by a physician. The test was assessed as positive if typical immediate-type clinical reactions occurred (e.g. swelling of lips).

Statistical analysis

The Wilcoxon Rank-Sum test was used for continuous and ordered data, and the Chi-Square test for categorical data.

Sensitivity was defined as the fraction of true positives among symptomatic individuals, specificity as the fraction of true negatives among non-symptomatic individuals, positive predictive value as the fraction of symptomatic individuals among test positives, negative predictive value as the fraction of non-symptomatic individuals among test negatives and efficiency as the fraction of tested individuals correctly classified by the test.

Results

We studied two groups of children: 303 non-atopic and 306 atopic children (Table 1). As expected, total IgE in serum was significantly higher ($p < 0.0001$) in atopic children. Atopic children (median 5.6 years) were older than non-atopic ones (median 3.3 years). In the atopic group, boys were found more often than girls. The atopic children suffered from typical allergic diseases such as bronchial asthma ($n = 149$), atopic dermatitis ($n = 144$) or allergic rhinoconjunctivitis ($n = 60$); 47 children had two or three of these diagnoses.

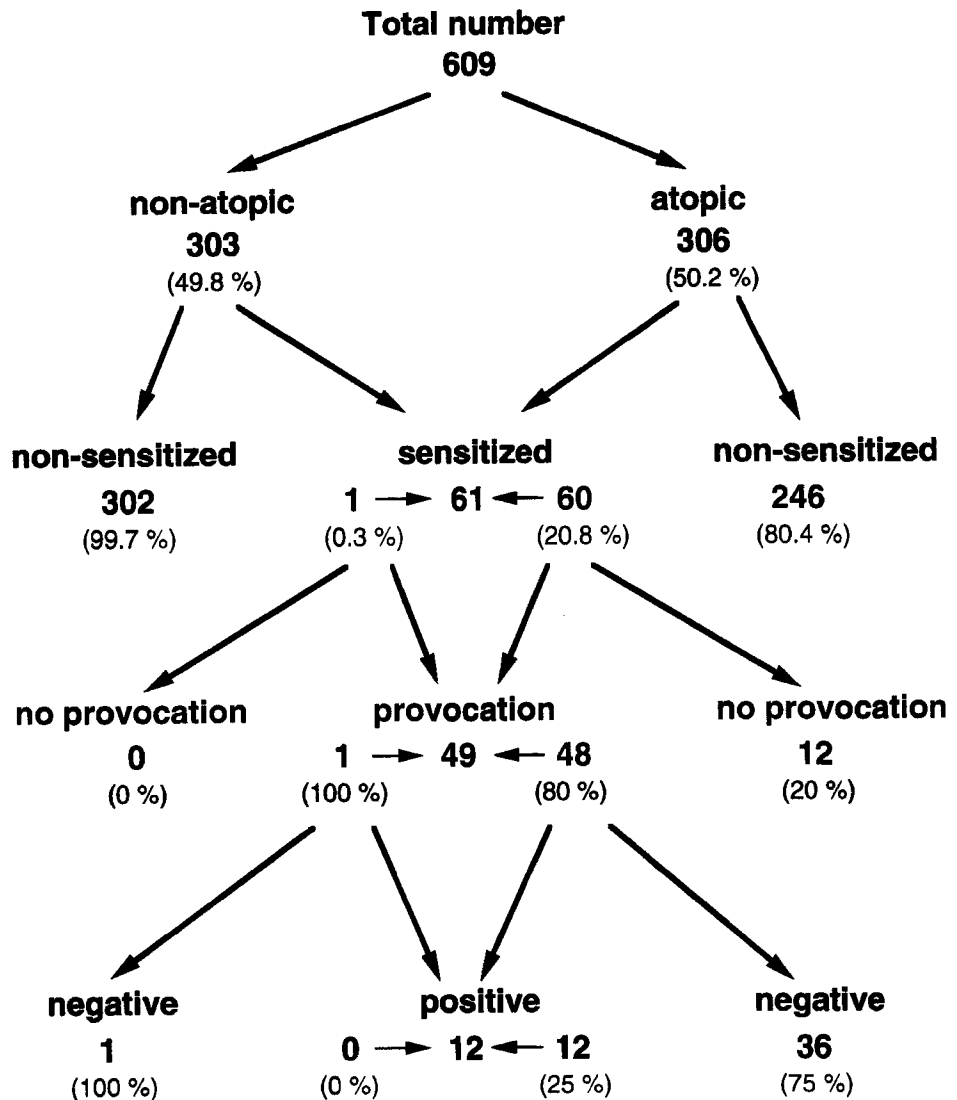
The outcome for the 303 non-atopic and 306 atopic children is shown as a synopsis in Fig. 1. 20.8

Table 1. Comparison of the two study populations.

	non-atopic	atopic	p
number	303	306	n.s.
age (years)	0.1 - 16.7 (3.3*)	0.4 - 18.0 (5.6*)	$p < 0.0001$
sex (f/m)	144 / 159	118 / 188	$p < 0.04$
Total IgE (kU/l)	$<0.35 - 232$ (15*)	$4 - 16\ 620$ (219*)	$p < 0.0001$

* represents median values.

Fig. 1: Synopsis of the outcome for non-atopic and atopic children



% (60/306) atopic children and 0.3 % (1/303) non-atopic children were sensitized to latex in terms of specific IgE to latex in serum.

The 60 latex-sensitized atopic children showed higher total IgE values (median 872 kU/l) than the 246 atopic children without sensitization to latex (median 149 kU/l, $p < 0.0001$). Male gender was represented more often in this patient group than female ($p < 0.04$).

Skin prick tests and provocation tests could be performed in 49/61 children (80 %). Twelve families refused the provocation procedure. Skin prick tests were positive in 16 (high ammoniated milk) and 17 (low ammoniated milk) of 48 children, respectively. In 9 tests there was a discrepancy between the two extracts used for skin prick testing. By combining both skin tests, sensitivity concerning the outcome of provocation tests was 75 %, specificity 67 %, positive predictive value 43 %, negative predictive value 89 %. 12/48 (25 %) children were

atopic, latex-sensitized and provocation positive. The single non-atopic latex-sensitized child showed a negative reaction to provocation with latex. Specific IgE to latex was significantly higher ($p < 0.03$) in provocation test positive compared to provocation test negative children (Fig. 2). No patient showed a significant decrease of peak-flow during the first hour after provocation or to the neoprene control glove.

53/61 families (87 %) sent questionnaires back. Nine of these families (17 %) reported that the child showed clinical symptoms upon contact to material containing latex. Symptoms consisted mainly of local swelling or urticaria; for one child typical asthmatic symptoms were reported when visiting his mother at her dental surgery.

History of symptoms upon contact with latex was positive in 6/12 children with positive provocation (50 %) compared to 3/36 children in the negative provocation group (8.3 %). Therefore, specificity of

Table 2. Data of children who underwent surgery: Total number of operations and age of first operation in provocation positive (5/12) and provocation negative children (12/36).

	Provocation positive						Provocation negative												
Age at first OP (years)	2	2	5	3	0.2	mean 2.4 median 2.0	0.5	2	2	3	5	6	7	2	3	3	2	3	mean 3.2 median 3.0
No of OP	1	1	1	6	8	mean 3.4 median 1.0	1	1	1	1	1	1	1	2	2	2	3	3	mean 1.6 median 1.0

a positive history was 92 %, sensitivity was 50 %, positive predictive value was 67 %, negative predictive value was 85 %.

Atopic dermatitis tended to be more prevalent among the 12 provocation positive atopic children (75 %) compared to 36 provocation negative children (58 %); however, this difference failed to reach statistical significance.

Looking at surgical interventions as a risk factor, children of the symptomatic group were younger at time of their first operation (mean age 2.4 years) and had been operated on more frequently (mean 3.4 OP) compared to non-symptomatic children (mean age 3.2 years, mean 1.6 OP) (Table 2).

Discussion

21 % of our atopic children with typical allergic diseases such as bronchial asthma or atopic dermatitis showed specific IgE to latex. In the literature, 19 % of children suspected of having allergic diseases were reported (12) and 7 % for adults (13). In a smaller study on 80 children, latex sensitization for only 7 % atopic children was found (14).

Unfortunately, provocations tests were not performed in most of these studies so that no statement can be made about clinically relevant latex allergy. In our latex sensitized children, 25 % were symptomatic in terms of a positive provocation test with latex gloves. The single non-atopic latex-sensitized child showed a negative reaction to provocation with latex. Therefore, no non-atopic child had any clinically relevant latex allergy.

A possible bias could be inherited in our study design due to the inclusion criteria of a positive proof of specific IgE to latex; however, for practical reasons provocation tests were performed in the group of sensitized atopic children and not in the additional 246 non-sensitized atopic children. This procedure is justifiable, because only very few not-latex-sensitized patients had a positive history in the literature (15, 16) and none of our 36 non-atopic children had a positive latex skin-test (14).

The provocation procedure used in our study differed from that of Sorva et al. (17): The main difference was that we exposed the whole hand instead of initially only a single finger. 8/48 children showed positive reactions to the glove wearing test (and therefore did not have to inflate a balloon). Skin symptoms could easily be handled by treatment with local antihistamines. We accordingly think that an over-cautious procedure is not mandatory.

Four children could only be detected when mucosa of the lips was also exposed (in case of a negative glove wearing test). Again, no severe clinical reactions were seen in the study population. Our data indicates that the sequential provocation represents a safe and efficient procedure to identify clinically allergic patients. Certainly, persons with a previous history of anaphylaxis must be excluded from use tests (18).

Of the non-atopic group ($n = 303$), only one child (0.33 %) showed a sensitization to latex; however, this child did not react clinically upon provocation. In the literature, 1/272 (0.37 %) non-atopic individuals was sensitized according to a positive skin prick test (19). Therefore, non-atopic children do not seem to be at risk for clinically relevant latex allergy.

Atopic dermatitis tended to be more prevalent among the provocation positive atopic children (75%) compared to provocation negative children -

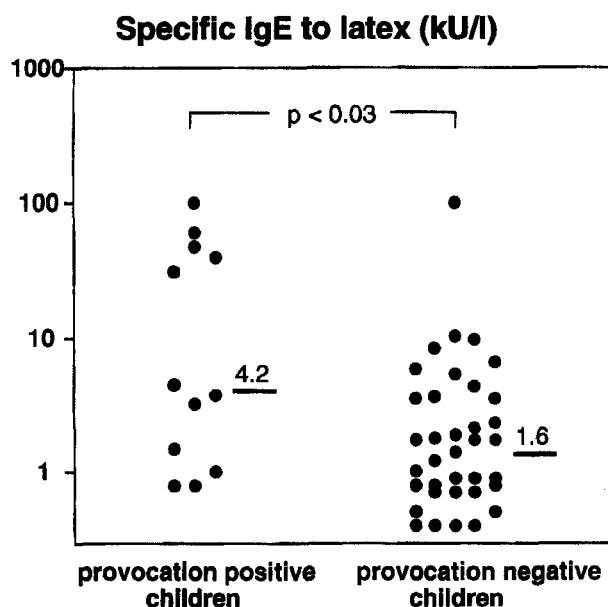


Fig. 2: Specific IgE to latex in symptomatic ($n = 12$) and non-symptomatic ($n = 36$) patients. Bars represent median values.

especially when compared to the distribution of diagnoses among the total group of 306 atopic children; however, this difference failed to reach statistical significance. Atopic dermatitis - due to the excessive production of total and specific IgE to environmental allergens - may also predispose to sensitization to latex (20, 21). Our data is supported by an observation in atopic children with symptomatic latex allergy, highlighting the need for determination of specific IgE against latex even in children with no known risk factor for latex allergy, but with e.g. severe atopic dermatitis (17).

There was a tendency that children of the symptomatic group were younger at time of their first operation and underwent surgical interventions more frequently than non-symptomatic children (Tab. 2). However, the difference was statistically not significant if median values were taken into account. Interestingly, 12/36 (33 %) latex sensitized children, who did not show a positive clinical reaction upon provocation, had already undergone at least one operation. These children may have been sensitized during the previous operations and may be at risk for clinically manifest allergy in the future.

In conclusion, latex sensitization and latex allergy seem to occur more often in atopic children than previously known. This is worth mentioning, because these children had had less extensive contact to latex than well known riskgroups (e.g. children with spina bifida). Risk factors for the development of a sensitization to latex are atopy and the clinical diagnosis of atopic dermatitis; risk factors for a clinically manifest allergy to latex are an elevated specific IgE to latex, a positive history upon contact to material containing latex and probably frequent operations. Due to the low sensitivity of the history, children with allergic diseases, especially with atopic dermatitis, should be screened for sensitization to latex. For sensitized children, provocation tests should be added. In positive cases, avoidance measures should be adopted, e.g. when planning operations. Generally, total protein levels of latex rubber material should be reduced (22) to prevent sensitization in persons at risk - such as atopic children.

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