

Determination of independent risk factors and comparative analysis of diagnostic methods for immediate type latex allergy in spina bifida patients

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Summary

Background Development of allergy to natural rubber latex in spina bifida patients is determined by several risk factors, such as age, number of interventions and atopic disease that are, however, interdependent. Furthermore, several diagnostic procedures have been analysed, but a comprehensive analysis of their diagnostic significance is lacking.

Objective To determine the independent major risk factor(s) for development of natural rubber latex allergy and the most valuable diagnostic procedure.

Methods In aselectively collected spina bifida patients, we correlated existing natural rubber latex allergy with age, sex, atopy and the number of hospitalizations and of surgical interventions in appropriately matched subgroups. Allergy to natural rubber latex was established by application of a latex glove fragment on the skin. Skin-prick tests with glove eluate, a natural latex extract and a commercial latex extract were carried out as were specific IgE measurements by radioimmuno assay (RAST-CAP). The results of the latex application test are compared with the other diagnostic methods.

Results Out of 74 fully evaluated patients, 17 had a positive application test. The number of surgical interventions correlates strongly with the presence of natural rubber latex allergy ($P < 0.0002$), independent of age, sex and presence of atopy. Skin-prick tests with unstandardized allergens made from known high allergenic latex gloves represent the most sensitive diagnostic method, with the highest negative predictive value and a specificity of 0.95. RAST-CAP was the next best method with a specificity of 0.93, a sensitivity of 0.89 and a negative predictive value of 0.97.

Conclusion The number of surgical interventions is the major independent determining factor for allergy to natural rubber latex in spina bifida patients. Unstandardized skin-prick tests are the most sensitive and specific diagnostic tool, but RAST-CAP is almost equally performant and therefore a valid alternative.

Keywords: natural rubber latex allergy, spina bifida, risk factors, skin-prick tests, RAST-CAP, application test

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Introduction

Children and adults with spina bifida are at highest risk of developing natural rubber latex (NRL) allergy: in the last 7

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years prevalences varying from 18% [1] to 64.5% [2] have been reported. Other risk groups for development of NRL allergy are health care workers [3], rubber industry workers [4] and patients other than spina bifida patients with multiple surgery [5,6].

A previous history of atopic disease [5], handeczema [3]

and recurrent exposure to latex [5] have been shown to be predisposing factors for NRL allergy. Allergy to latex crossreacting fruits is a risk factor that may be cause or consequence of latex allergy [7–9]. Frequent surgical interventions [2,10–13], regular use of latex products [5,11] and atopy [2,5,12,13] have been suggested as predisposing factors specifically for spina bifida patients. The level of exposure to latex is probably the major factor determining latex sensitization [14].

NRL allergy causes a large variety of symptoms: urticaria, eczema, conjunctivitis, rhinitis, bronchospasm, angio-oedema and anaphylaxis [3]. Anaphylactic reactions mostly occurred during diagnostic [15] or surgical [6,16] interventions. Fatal accidents have been reported [15].

Specifications on age [11,17], sex [11], atopy [2,5,11–13] and the number of surgical interventions [5,11–13] in the study population are given in several publications on NRL allergy. However, all these variables are interdependent. Consequently, any of them may be evaluated only in a patient group that is carefully matched for the other variables. In the present study we establish which of these variables are independent determinants for NRL allergy in spina bifida patients.

The diagnostic procedures for NRL allergy are still heavily debated [18–20]. According to most American authors, we can — at this moment — only rely on a careful history and measurement of latex specific IgE, until standardized extracts for skin-prick testing become available [18,19,21]. In other countries skin-prick tests [5,20,22] and uetests [22] are advocated. Skin-prick tests with extracts of latex and with latex glove eluate were shown to have a higher specificity [18,23] and sensitivity [22,23,24] than specific serum IgE. Clinically useful commercial extracts are available, but they are not yet standardized [25].

Skin-prick tests with latex glove extracts [3] or commercial extracts [5], application tests [3], measurements of specific IgE for latex [11,12,13,18], and combinations [12,13,18] of some of these techniques have been described in many papers. In the present study we make a comprehensive comparative analysis of all these diagnostic methods in a well defined aselectively collected population at risk.

Materials and methods

Patients

This study was authorized by the ethics committee and all patients and/or parents gave their informed consent to participate in the study. From April 1994 to May 1995, 101 spina bifida patients from the out-patient clinic of the paediatric neurology department, entered aselectively in the study: 45 boys, 56 girls, from 2 months to 36 years old. A

standardized patient file was completed by means of an interview of the parents and/or the patient and data from the medical record of the patient. Age, sex and type of spina bifida were noted. The frequency of contacts with latex products outside the hospital, specifically latex catheters, gloves, balloons, other rubber toys, elastics, mattress cover, wheel-chair and pacifier was recorded as daily, weekly or monthly. The number of surgical interventions and hospitalizations and the age at which they took place were recorded. The type of allergic reactions to rubber products was noted when occurring: conjunctivitis, rhinitis, asthma, urticaria, angio-oedema or anaphylaxis, and also the age at which such reactions were first observed. Allergic reactions to banana, kiwi, avocado and chestnut were recorded as well as reactions during local or general anaesthesia or dental surgery. Other past or present non latex related symptoms of eczema, rhinitis, asthma, urticaria, angio-oedema or anaphylaxis were noted. Respiratory allergy and food allergy were recorded according to a questionnaire for specific allergens.

Skin-prick test

Skin-prick tests were performed with an eluate of sterile latex gloves (Triflex^R, Baxter, lot number 90J10A0A1), prepared according to the method of Turjanmaa [22], undiluted and diluted 1/10, with a commercial extract of latex (Stallergènes) and with an extract of natural latex, prepared by centrifugation of raw latex at 15 000 tpm for 20 min and stored at –20°C. The supernatant, with protein content 3.5 mg/mL, was freshly diluted (1/100 000, 1/10 000, 1/1000) in saline every month and stored at 4°C. Patients with a history of clinical reaction to rubber products were initially tested with a lower concentration of the eluate (1/1000 and 1/100) and of the natural latex extract (1.10^{-7}). Skin-prick tests were performed with a microlance (Becton Dickinson, Canada) and read after 15 min. The maximal diameter and orthogonal diameter of the weal reaction were recorded and mean diameters were calculated.

Histaminediphosphate 1 mg/mL (HAL, The Netherlands) was used as a positive control and Coca's solution in 50% glycerol and physiological saline as a negative control. Results were expressed as mean orthogonal diameter of the weal reaction; then, the mean diameter of the negative control was subtracted. A skin-prick test then was considered positive when its mean diameter was minimum 3 mm and when it was equal to or larger than half the histamine mean diameter.

Application test

An application test was performed by means of a latex band, cut from a surgical latex glove (Triflex^R, Baxter,

90J10A0A1). The band was 4 cm for children older than 11 years, 3 cm for children aged 6–11 years and 2 cm for children younger than 6 years. It was fixed around the wrists, at one wrist dry, at the other one wetted, and removed after 15 min. Local urticaria, reactions on distance or systemic reactions were considered positive. Patients with a positive application test were defined as having NRL allergy. A negative control with a vinyl band was carried out in those patients who had only one positive skin-prick test.

Immunoblot

We have evaluated the antigen content of Baxter Triflex gloves before using them as a source material for skin testing and application test. The proteins in the glove eluate were separated by SDS-PAGE in a 14% polyacrylamide gel, according to Laemmli [26]. They were next electroblotted onto a PVDF membrane (Immobilon, Millipore, Bedford, Massachusetts, USA) in transfer buffer (25 mM Tris, 192 mM glycine and 20% methanol). The membrane then was cut in two parts. One part, including molecular weight markers, was extensively washed with distilled water and dried overnight between filter papers to be stained with sulforhodamine B (Sigma, St. Louis, Missouri, USA), according to Coull and Pappin [27]. The second part of the membrane was saturated for 1 h in phosphate-buffered saline containing 0.2% non-fat dried milk (PBS-NFDM 0.2%) before strips were cut and incubated overnight in 1 mL of a serum pool 1/5 in PBS-NFDM 0.1%. The serum pool consisted of a mixture of latex-sensitive patients' sera. The latex RAST-CAP value (Pharmacia, Uppsala, Sweden) of the pool was 19.6. The serum of a patient monosensitized to house dust mite (*Dermatophagoides pteronyssinus*) was used as a control. Bound IgE was detected by monoclonal mouse anti-human IgE antibodies (CLB, Amsterdam, The Netherlands), 1/100 in PBS-NFDM 0.1% followed by peroxidase-conjugated rat anti-mouse light-chain-kappa antibodies (CLB, Amsterdam, The Netherlands), 1/2000 in PBS-NFDM 0.1%. TMB (KPL, Gaithersburg, Maryland) was used as a substrate for the peroxidase. Figure 1 shows that the glove eluate displays a pattern of protein bands ranging from 14 to more than 100 kDa. The highest IgE reactivity is seen in the region between 30 and 67 kDa.

Total IgE

Total serum IgE was determined on all serum samples simultaneously by CAP (Pharmacia, Sweden).

RAST-CAP

Specific serum IgE for latex was determined by RAST-CAP

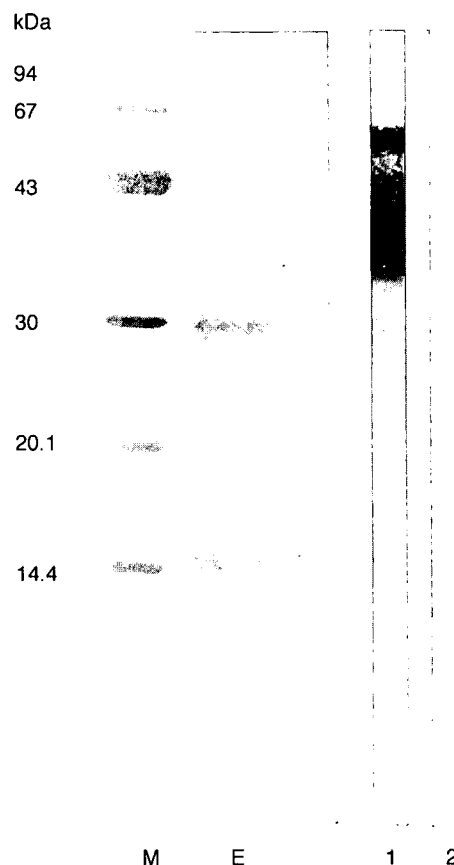


Fig. 1. SDS-PAGE pattern of Baxter-Triflex glove eluate stained with sulforhodamine B (lane E), and corresponding IgE immunoblot strips probed with a latex-positive serum pool (lane 1) and a control serum (lane 2). Molecular weight markers are on lane M.

(Pharmacia, Sweden). All serum samples were examined simultaneously and the results were expressed in RAST-CAP units or scores, according to the manufacturer's scoring system.

We determined specific IgE for the most common allergens in our region, namely house dust mite, cat, dog and *Lolium perenne*. Those allergens are responsible for allergic reactions in at least 0.5% of the patients in the age range studied. Because NRL allergy and allergy for ethylene oxide can be confounded and because spina bifida patients who have specific IgE against ethylene oxide are more likely to have specific IgE against NRL, we also determined specific IgE for ethylene oxide [28].

Specific IgE for three latex crossreacting foods, namely kiwi, avocado and banana was determined in two groups of age and sex matched patients, one group with positive application test and one group with negative application test. Specific IgE for all those allergens was determined by RAST-CAP and expressed as RAST-CAP units.

Atopy

Atopy was defined as a history of asthma or rhinitis or eczema and a positive RAST-CAP for one of the common allergens in our region. Atopic disposition was defined as sensitization to one or more allergens, investigated by RAST-CAP for the most common allergens in our region. Allergy to fruits was based on an unequivocal history.

Statistical analysis

Chi-square, Fisher's exact test, Spearman rank and Mann-Whitney *U*-test were used as indicated.

Results

Study population

Hundred and one patients entered the study. The first 27 patients served the purpose to determine adequate concentrations for skin-prick testing. Seventy-four patients, 31 boys and 43 girls, mean age 8.2 years, were fully evaluated by patient file, skin testing and determination of total serum IgE and specific IgE for latex. From them, 60 patients had an open and 14 a closed neural tube defect, five patients had a previous history of reaction to rubber products, and 14 patients were atopic: nine had eczema, six allergic rhinitis, four asthma and seven urticaria or angio-oedema.

According to the definition that patients with a positive application test were considered to be allergic to NRL, the study population was divided into two groups. The group with positive application test consisted of 17 patients, 11 boys and six girls, and the negative group of 57 patients, 20 boys and 37 girls. Boys were predominant in the positive group ($P < 0.06$) (Table 1). All patients with a positive

application test were 3 years of age or older, while in the negative group 13 patients were younger, which reflects in the mean age: 10 years in the application test positive group and 7.7 years in the application test negative group ($P < 0.05$). There was no significant difference in the percentage of open spina bifida between both groups.

Use of rubber material outside the hospital

For all patients repetitive contact with rubber products, mostly balloons, elastics, rubber toys was noted without significant difference (Fisher's exact test, NS) between both groups. Two patients in the positive group were using latex catheters regularly, but none in the negative group. Latex gloves were regularly used at home for five patients in the positive application test group and for 11 patients in the negative application test group (χ^2 , NS).

Hospitalizations and surgical interventions

The hospitalizations that were recorded, all had a relation to spina bifida or to a spina bifida related disease. Patients in the positive application test group had a total of 77 hospitalizations without surgery, mean 4.5 per patient. In the negative group 159 hospitalizations were recorded, mean 2.8 per patient ($P < 0.03$). Patients with a positive application test underwent a total of 173 surgical procedures, six intra-abdominal, 167 extra-abdominal, mean 10 per patient. In the negative group 277 surgical interventions were noted, 12 intra-abdominal and 255 extra-abdominal, mean 4.9 per patient ($P < 0.0002$).

To investigate whether the age and sex difference between the older positive application test group and the younger negative application test group determines the difference in hospitalization and intervention frequency,

Table 1. Demographic data and number of patients with open spina bifida, with history of latex allergy and with atopy in a group of 74 patients with a positive or a negative latex application test

	Application test		<i>P</i> -value*
	positive <i>n</i> = 17	negative <i>n</i> = 57	
	<i>n</i>	<i>n</i>	
Boys	11	20	<0.06
Open spina bifida	16	44	<0.2
Positive history of latex allergy	5	0	<0.007
Atopy	6	8	<0.12
Mean age in years	10	7.7	<0.05

* Fisher's exact test, two-tailed.

Table 2. Mean number of hospitalizations and of surgical interventions in 18 age- and sex-matched pairs of patients with a positive or a negative latex application test

	Application test		<i>P</i> -value*
	positive <i>n</i> = 18	negative <i>n</i> = 18	
Hospitalizations			
without surgery	4.27	2.11	<0.13
with surgery	9.4	4.3	<0.003
intra-abdominal	0.44	0.22	NS
extra-abdominal	8.94	4.33	<0.004

* Mann-Whitney *U*.

we compared 18 age- and sex-matched pairs. The number of surgical interventions was significantly higher in the positive application test group ($P < 0.003$) (Table 2). Hospitalization frequency was not significantly different in these groups, nor was the age at first intervention and that at first hospitalization.

In order to investigate if the number of surgical interventions determines whether the patients react to the application test, independently of the presence of atopy, we compared six age- and sex-matched pairs of atopic patients, six patients with a positive and six with a negative application test. The number of surgical interventions was significantly higher in the patients with a positive application test (Mann-Whitney U , $P < 0.04$).

Clinical history of latex allergy

In the group with positive application test five patients had a clinical history of reaction to rubber products. They all mentioned reactions to balloons: four of them had local urticarial reactions, two experienced conjunctivitis and one also rhinitis. Two patients reacted to latex gloves: one patient with local urticaria, another with conjunctivitis. Three patients mentioned oedema of the penis when using

latex catheters. Two of those patients experienced severe oedema of the penis after cystometry with a latex catheter; they were from then on treated with latex-free catheters and gloves. None of the patients in the negative group had a history of latex allergy. The mean age at which a first allergic reaction to latex was recorded, was 6.7 years; the youngest age was 1 year.

Atopy

Six patients in the positive application test group had a history of atopy: three had eczema, four rhinitis, one asthma; two of them experienced urticaria and angio-oedema immediately after the ingestion of bananas. In the negative application test group eight patients were atopic: six had eczema, two rhinitis and three had asthma; there were no patients with a history of allergy to foods in this group. Six patients in the positive application test group and 10 patients in the negative application test group were RAST-CAP positive for one or more common allergens (NS). In the 18 age- and sex-matched pairs six patients in the positive application test group and one patient in the negative application test group had an atopic disease ($P < 0.09$). RAST-CAP for one or more common allergens

Table 3. Results of skin-prick tests with glove eluate, natural latex extract and commercial latex extract in 74 patients with a positive or a negative latex application test

	Application test				<i>P</i> -value*
	positive <i>n</i> = 17		negative <i>n</i> = 57		
Skin-prick test	<i>n</i> positive	<i>n</i> tested	<i>n</i> positive	<i>n</i> tested	
Glove eluate					
1/1000	2	8	0	14	
1/100	3	8	0	14	
1/10	10	16	0	57	
1/1	10	10	3	57	
1/1000 to 1/10	12	17	0	57	<1.10 ⁻⁸
Glove eluate positive <u>and</u> commercial extract positive	11	17	3	57	<1.10 ⁻⁵
Glove eluate positive <u>or</u> commercial extract positive	17	17	5	57	<1.10 ⁻⁵
Natural latex extract					
1/10 000	1	16	0	57	
1/1000	4	15	0	57	<1.10 ⁻³
Commercial extract**	11	17	5	57	<1.10 ⁻⁵

* Fisher's exact test, two-tailed.

** Stallergènes®.

was positive in six patients in the positive application test group and in four patients in the negative application test group.

In order to know if atopy determines a positive application test, independently of the number of surgical interventions, we matched 12 patients with a positive application test with 12 patients with a negative application test as to sex, age and number of surgical interventions. Clinical atopy was not significantly more frequent in the patients with a positive application test, nor was mean serum IgE significantly different. However, the number of positive RAST-CAP tests per patient for four inhalation allergens was trendwise higher (Mann-Whitney U , $P=0.06$) in the patients with positive application test.

Latex skin-prick tests

In the study group of 74 patients, 22 patients (30%) had a positive skin-prick test with one or more latex extracts: 17/17 in the positive application test group and 5/57 in the negative application test group (Table 3).

Skin-prick tests with glove eluate were positive in all the patients with a positive application test; 12 of them were positive for a dilution 1/10 or lower, and five had a positive test for the undiluted eluate only. Of the patients with a negative application test 3/57 had a positive skin-prick test with undiluted glove eluate and none reacted to diluted extracts. Only five patients in the positive application test group had a positive skin-prick test with the dilutions of natural latex extract, whereas all patients in the negative application test group were negative. Eleven patients in the group with positive application test and five in the group

with negative application test had a positive skin-prick test for the commercial extract.

Application test

In the study group of 74 patients 17 patients had a positive application test. Four of them showed a local reaction to the dry and 15 to the wet latex band. Two patients experienced conjunctivitis and one had moderate wheezing, disappearing a few minutes after administration of salbutamol by inhalation. All the controls performed with a vinyl band were negative.

Latex RAST-CAP

Latex RAST-CAP was positive in 22 out of 92 patients tested (Fig. 2); 17 of them were in the positive application test group. All patients with a clinical history of latex allergy had a positive RAST-CAP. Five patients with a negative application test had a positive latex RAST-CAP and scores were significantly lower (Mann-Whitney U , $P<0.00001$).

Other RAST-CAPs

Nine out of 22 patients with a positive latex RAST-CAP and 13 out of 52 patients with a negative latex RAST-CAP had a positive RAST-CAP for one or more common allergens (NS).

RAST-CAP for food allergens and ethylene oxide was determined in 16 age- and sex-matched pairs (Table 4). All patients who had a positive RAST-CAP for fruits also had a positive RAST-CAP for latex. In these 16 pairs of patients,

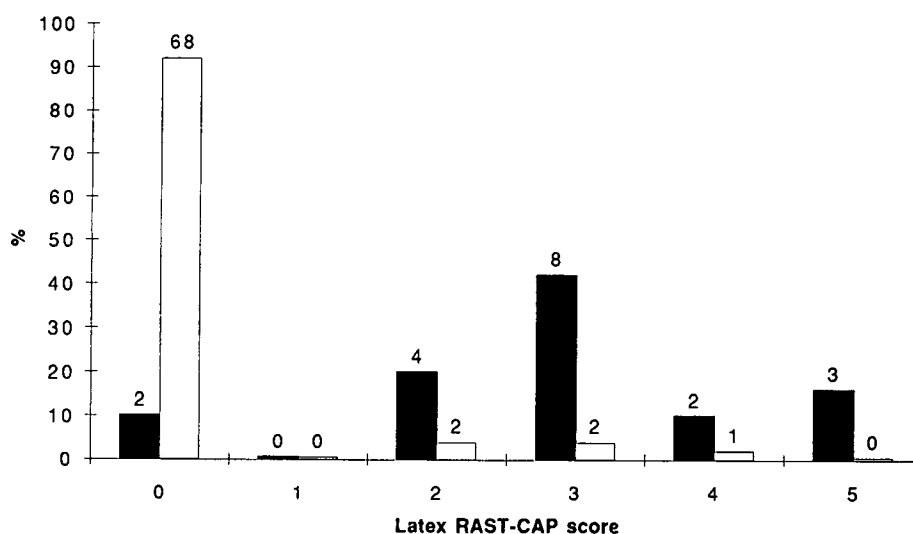


Fig. 2. Latex RAST-CAP in two groups of patients: 19 patients with a positive application test (■), 73 patients with a negative application test (□), expressed in RAST-CAP score; absolute numbers are indicated on top of the bars (Mann-Whitney U , $P<0.00001$).

Table 4. Positive RAST-CAPs for latex, avocado, banana and kiwi and for ethylene oxide in 16 age- and sex-matched pairs of patients with a positive or a negative latex application test

	Application test		<i>P</i> -value*
	positive <i>n</i> = 16	negative <i>n</i> = 16	
RAST-CAP for latex	15	1	<0.001
avocado	6	1	<0.08
banana	4	0	<0.1
kiwi	2	0	NS
either fruit	6	1	<0.08
ethylene oxide	2	0	NS

* Fisher's exact test, two-tailed.

RAST-CAP units for latex correlated strongly with RAST-CAP units for avocado (Mann-Whitney *U*, *P* < 0.01) and for banana (Mann-Whitney *U*, *P* < 0.05).

Total serum IgE

Total serum IgE was measured in 12 pairs of application test positive and negative patients, who were matched as to age, sex and number of surgical interventions. In the positive

group the geometric mean was 102.8 kU/L, and in the negative group 39.2 kU/L (Mann-Whitney *U*, *P* < 0.12).

Sensitivity, specificity and predictive value for skin-prick test and RAST-CAP

Sensitivity, specificity, positive and negative predictive values for skin-prick tests with different concentrations of glove eluate and of natural latex extract and with the commercial extract and for the combination of glove eluate and the commercial extract, as well as for latex RAST-CAP are given in Table 5.

Discussion

We calculated the prevalence of NRL allergy in a group of spina bifida patients, according to a positive application test. Prevalence was 23%. Some authors reported a much higher prevalence of NRL allergy: in those studies all patients with a positive skin-prick test for one or more latex extracts or with serum specific IgE for latex were considered to be allergic [2,10]. However, we, in this study, considered a positive rubber application test as a more valid criterium for latex allergy because, as a usetest with the latex gloves used in the hospital where our patients were regularly hospitalized and had their surgical interventions, an application test comes closer to the clinical reaction than non

Table 5. Sensitivity, specificity and predictive value of skin-prick tests with latex extracts and of latex RAST-CAP

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Glove eluate				
1/1000 to 1/1	1	0.95	0.85	1
Natural latex extract				
1/10 000 and 1/1000	0.31	1	1	0.83
Commercial extract*	0.64	0.91	0.68	0.83
Glove eluate positive and commercial extract positive	0.65	0.95	0.79	0.9
Glove eluate positive or commercial extract positive	1	0.91	0.77	1
RAST-CAP	0.89	0.93	0.77	0.97
Commercial extract* and RAST-CAP	0.65	0.95	0.78	0.9
Commercial extract* or RAST-CAP	0.88	0.88	0.68	0.96

* Stallergènes®.

standardized skin tests or specific IgE measurements with latex from various sources. The allergenicity of latex gloves may vary greatly [29] even among brands produced by the same manufacturer. The brand of latex gloves we used proved to have a high allergenicity.

For the application test a latex band of different width, according to the age of the patient, was used, because a whole glove might constitute a too high challenging dose [30], and as such, it would not fit well in small children. We only used a 15 min exposure procedure. In some studies the time of exposure was prolonged in patients with a positive clinical history when the usetest was still negative after that time [3], while in our patient group all patients with a clinical history of latex allergy had a positive application test after 15 min. However, in the former studies patients suffered from occupational natural latex allergy and most of them had contact urticaria and/or hand eczema, which is a different pathology, that was not present in our study population.

Five patients with a negative application test had a positive RAST-CAP for latex. However latex RAST-CAP in these patients was only weakly to moderately positive, which suggests that the sensitivity of latex RAST-CAP may at times exceed clinical symptoms. At those low values we never found positive RAST-CAP tests for crossreacting fruits, and also in those five patients RAST-CAP for kiwi, avocado and banana remained negative. Two of the five patients with positive latex RAST-CAP and negative application test were atopic: one had allergic rhinitis and the other suffered from atopic dermatitis; it has been claimed in a recent study on inadequately matched study groups of atopic and non-atopic children, that atopy is a risk factor for latex sensitization in children [31]. In those five children with positive latex RAST-CAP and negative application test a prolonged usetest might give supplementary information. We did not study this question because prolonged observation of children with spina bifida would require observation in a hospital setting which we could not achieve. Furthermore it is very difficult to interpret the results of such late reactions in terms of IgE-mediated pathology.

We found wetting of the latex band, as also is regularly used by other authors [22], to be of primary importance since only 4/17 positive patients reacted to the dry material. The prevalence of latex sensitization, as defined by the presence of latex specific IgE, was 24%, which is much lower than what is found in American studies [10,19], but comparable with the results of another European study [13]. This difference may be explained by differences in the frequency of latex contacts in domestic and surgical situations as well as by methodological differences in specific IgE measurements.

Mean age was significantly higher in the group of NRL allergic patients than in the non-allergic group. All patients

with a history of NRL allergy, except one, were older than 3 years at the time of their first reaction to latex. This is in agreement with another study where latex allergy was not reported before the age of 4 [17]. Probably this reflects a crucial sensitization period, as in our age- and sex-matched pairs we could not detect any significant difference regarding the youngest age at hospitalization or surgical intervention (data not shown).

The number of surgical interventions is significantly higher in the latex allergic group. This is in agreement with other studies [2,11–13]. However, as age, sex ($P < 0.06$) as well as the number of interventions correlated with latex allergy, we had to analyse whether the number of interventions is an independent determining factor. This proved to be the case in 18 age and sex-matched pairs. As there was also a significant difference in the number of surgical interventions in age- and sex-matched atopic pairs, we conclude that the number of surgical interventions is the major risk factor for NRL allergy in spina bifida patients independent of the presence of atopy.

The hospitalization rate without surgery was trendwise higher in the application test positive patients in age- and sex-matched pairs. Whereas rubber gloves are seldom used at home, they were till now almost regularly used in our hospitals for daily care. In some studies it was stated that the main sensitizing factor in children with spina bifida would be the contact of skin and mucous membranes with latex catheters and with latex gloves [5]. In our study, only two patients had regular contact with latex catheters and only 16 children had been using latex gloves at home for catheterization of the bladder. Therefore, we cannot evaluate this factor in the sensitization process.

The number of open spina bifida is higher in the latex allergic group. However, the number of surgical interventions and hospitalizations was also significantly higher in this group (data not shown). Therefore, the type of spina bifida cannot be evaluated for its facilitating effect on latex allergy development. The same applies for a significantly higher use of wheel-chairs with rubber tires in the positive application test group of age- and sex-matched pairs (data not shown). Wheel-chair users underwent significantly more surgical interventions ($P < 0.03$).

Atopy has been shown to be one of the risk factors for developing latex allergy [2,5,13]. The frequency of atopic disease in the positive application test group was only trendwise higher ($P < 0.12$) in the whole study group. When we matched for age and sex 18 positive application test patients with 18 negative application test patients it was found indeed that atopic disease was significantly more frequent in the application test positive group. When we compared 12 patients with positive application test with 12 patients with negative application test, matched as to age, sex and number of surgical interventions, there was no

significant difference in the frequency of atopic disease between both groups and the number of positive RAST-CAPs for inhalation allergens was only trendwise higher in the application test group. As in two groups of patients, who are matched as to sex, age and atopy, the influence of the number of surgical interventions remains highly significant in the application test positive group, we conclude that atopy is a risk factor for development of NRL allergy in spina bifida patients, but that the number of interventions is more important than the atopic state; this is in agreement with the conclusions of another recent study [13] on the subject. It is also striking that out of five children with a clinical history of NRL allergy only one child was atopic.

In our study group only two patients had a history of food allergy: they were allergic to banana and also had a clinical history of latex allergy; both were RAST-CAP-positive for banana. This is consistent with the findings of other authors that patients who are allergic to banana and some other fruits, can be sensitive for crossreacting allergens in latex and run a higher risk to present allergic reactions to latex [7–11]. However, in contrast to another study [11], history of clinical allergy for foods was not a sensitive marker for latex allergy in our study, as only two out of 17 latex allergic patients had a history of food allergy. Food-specific IgE did not provide complementary diagnostic information for our patients, as positive RAST-CAPs for banana, kiwi or avocado were found only at high RAST-CAP tests for latex of more than 11.8 Ua/mL that are found only in the application positive group. None of our patients with a positive RAST-CAP for avocado had a history of clinical allergy to avocado, which suggests that the presence of IgE-antibodies to common epitopes with latex is more associated with latex allergy rather than with clinical allergy to avocado. This is in agreement with the findings of another author [32].

Only 30% of our patients with latex allergy had a clinical history of reaction to rubber products. Another author found 49% of latex allergic patients to have a positive clinical history for latex [2]. Consequently, we do not agree that the diagnosis of latex allergy should be based primarily on clinical history [16,17]. Indeed, this criterium is highly dependent on occasional contacts of varying intensity with rubber devices. In our study group 70% of latex allergic children would have been diagnosed faulty negative if diagnosis would have been based on clinical history only. For those children a forthcoming contact with latex during a surgical intervention or a diagnostic procedure might have dramatic consequences, as the first presentation of latex allergy can be life-threatening [15].

The 30% prevalence of positive skin-prick tests in our study group is comparable with the 32% in spina bifida patients, studied by Moneret-Vautrin [5]. Skin-prick tests with several dilutions of different latex extracts all proved to

have a high specificity. The high specificity obtained with glove eluate could not be improved by using a combination of results of glove eluate and the commercial extract. A 100% sensitivity and a 100% negative predictive value were reached with the combined results of diluted and non-diluted glove eluate. This is in accordance with the results of another author [22]. In accordance with other studies a 100% specificity was noted for the raw latex extract [24]. The sensitivity of skin-prick tests with dilutions of raw latex was very low, but doubled when blanks were used as a negative reference instead of histamine as a positive reference. This suggests that, using a higher concentration of raw natural latex, the skin-prick tests might become more sensitive. In contrast with another author [25,33] we did not find a good sensitivity for skin-prick test with a commercial extract. Here we want to emphasize that, in contrast with findings of others [18], we did not register any systemic side reactions using commercial or raw latex extracts. Further analysis of an appropriate natural latex extract for skin-prick tests should be considered, because such an extract is more suitable for standardization than glove eluate or ammoniated latex.

Latex RAST-CAP has been quoted as less reliable in a recent review article [33]. However, the referenced publications in this article do not seem to give straightforward evidence in favour of that opinion. In contrast, we found that latex RAST-CAP has a good specificity and sensitivity and a high negative predictive value for the detection of latex sensitization in spina bifida patients and that it scored better than skin-prick tests with a commercial extract. Specificity and positive predictive value improved only slightly when the combination of a positive RAST-CAP and a positive skin-prick test with a commercial extract was considered. Results obtained hitherto for sensitivity and specificity of latex RAST-CAP in food allergic children and health care workers, cannot be applied for spina bifida patients.

Conclusions

We have demonstrated that frequent exposure to latex during repetitive surgical interventions is the major independent risk factor for developing latex allergy in spina bifida patients. Atopy is another risk factor, but less important, as was demonstrated by analysis after matching of our patients. Consequently direct contact with latex material, including gloves, during surgery should be avoided in spina bifida patients from birth on. Only one-third of patients with latex allergy has a history of a clinical reaction to latex; consequently we cannot rely on history as the sole criterium for diagnosis, as has been proposed elsewhere [17,19,21].

The skin-prick test with glove extract is a sensitive and specific tool for the diagnosis of latex allergy and proved to be safe in our study. Furthermore, as this skin-prick test has

the highest sensitivity and negative predictive value, it should be performed in every patient at risk, provided the quality of the test material can be guaranteed. As this is not the case until now, further attempts should be made to develop sensitive and standardized extracts. In the meantime, RAST-CAP for latex can routinely be used as a screening method, as its specificity, sensitivity and positive and negative predictive value are only slightly lower than that of our glove extract for skin testing.

References

- Meeropol E, Kelleher R, Bell S, Leger R. Allergic reactions to rubber in patients with myelodysplasia. *N Engl J Med (Letter)* 1990; 323:1072.
- Yassin M, Sanyurah S, Lierl M et al. Evaluation of latex allergy in patients with meningomyelocele. *Ann Allergy* 1992; 69: 207–11.
- Turjanmaa K. Update on occupational natural rubber latex allergy. *Dermatol Clin* 1994; :561–67.
- Tarlo SM, Wong L, Roos J, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol* 1990; 85:626–31.
- Moneret-Vautrin DA, Beaudouin E, Widmer S et al. Prospective study of risk factors in natural rubber latex hypersensitivity. *J Allergy Clin Immunol* 1993; 92:668–77.
- Gold M, Swartz J, Braude B, Dolovich J, Shandling B, Gilmour R. Intraoperative anaphylaxis: An association with latex sensitivity. *J Allergy Clin Immunol* 1991; 87:662–6.
- Fernández de Corres L, Moneo I, Muñoz D et al. Sensitization from chestnuts and bananas in patients with urticaria and anaphylaxis from contact with latex. *Ann Allergy* 1993; 70: 35–9.
- Ceuppens J, Van Durme P, Dooms-Goossens A. Latex allergy in patients with allergy to fruit. *Lancet (Letter)* 1992;339: 493.
- Rodriguez M, Vega F, Garcia M et al. Hypersensitivity to latex, chestnut, and banana. *Ann Allergy* 1993; 70:31–4.
- Ellsworth P, Merguerian P, Klein R, Rozycki A. Evaluation and risk factors of latex allergy in spina bifida patients: is it preventable? *J Urol* 1993; 150:691–3.
- Kelly K, Pearson M, Kurup V et al. A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: Epidemiologic features, risk factors, and latex hypersensitivity. *J Allergy Clin Immunol* 1994; 94:53–61.
- Michael T, Niggemann B, Moers A et al. Risk factors for latex allergy in patients with spina bifida. *Clin Exp Allergy* 1996; 26:934–9.
- Nieto A, Estornell F, Mazon A et al. Allergy to latex in spina bifida: A multivariate study of associated factors in 100 consecutive patients. *J Allergy Clin Immunol* 1996; 98:501–7.
- Capriles-Hulett A, Sánchez-Borges M, Von-Scanzoni C, Medina J. Very low frequency of latex and fruit allergy in patients with spina bifida from Venezuela: influence of socio-economic factors. *Ann Allergy Asthma Immunol* 1994; 75: 62–4.
- Ownby D, Tomlanovich M, Sammons N, McCullough J. Anaphylaxis associated with latex allergy during barium enema examinations. *Am J Roentgenol* 1991; 156:903–8.
- Leynadier F, Pecquet C, Dry J. Anaphylaxis to latex during surgery. *Anaesthesia* 1989; 44:547–50.
- Pearson M, Stilwell Cole J, Jarvis W. How common is latex allergy? A survey of children with myelodysplasia. *Dev Med Child Neurol* 1994; 36:64–9.
- Kelly K, Kurup V, Zacharisen M, Resnick A, Fink J. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 1993; 91:1140–5.
- Slater J. Allergic reactions to natural rubber. *Ann Allergy* 1992; 68:203–9.
- Levy D, Charpin D, Pecquet C, Leynadier F, Vervloet D. Allergy to latex. *Allergy* 1992; 47:579–87.
- Slater J. *Ann Allergy* 1993; 70:1–2.
- Turjanmaa K, Reunala T, Räsänen L. Comparison of diagnostic methods in latex surgical glove contact urticaria. *Contact Dermatitis* 1988; 19:241–7.
- Mathew S, Melton A, Wagner W. Latex hypersensitivity: a case study. *Ann Allergy* 1993; 70:483–6.
- Wrangsjö K, Wahlberg J, Axelsson I. IgE-mediated allergy to natural rubber in 30 patients with contact urticaria. *Contact Dermatitis* 1988; 19:264–71.
- Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, Palosuo T, Reunala T. Commercial skin prick test preparations in the diagnosis of rubber latex allergy. *J Allergy Clin Immunol (Abstract)* 1993; 93:299.
- Laemmli UK. Cleavage of structural proteins during the assembly of the head of the bacteriophage T4. *Nature* 1970; 227:680–5.
- Coull JM, Pappin DJC. A rapid fluorescent staining procedure for proteins electro-blotted onto PVDF membranes. *J Protein Chem* 1990; 9:259–60.
- Pittman T, Kiburz J, Steinhardt G, Krock J, Gabriel K. Ethylene oxide allergy in children with spina bifida. *J Allergy Clin Immunol* 1995; 96:486–8.
- Yunginger JW, Jones RT, Fransway AF et al. Extractable latex allergens and proteins in disposable medical gloves and other rubber products. *J Allergy Clin Immunol* 1994; 93:836–42.
- Turjanmaa K, Reunala T. Contact urticaria from rubber gloves. *Dermatologic Clinics* 1988; 6:47–51.
- Liebke C, Niggemann B, Wahn U. Sensitivity and allergy to latex in atopic and non-atopic children. *Pediatr Allergy Immunol* 1996; 7:103–7.
- Ahlroth M, Alenius H, Mäkinen-Kiljunen S, Turjanmaa K, Reunala T, Palosuo T. Cross-reacting allergens in natural rubber latex and avocado. *J Allergy Clin Immunol (Abstract)* 1993; 93:299.
- Turjanmaa K, Alenius H, Mäkinen-Kiljunen S, Reunala T, Palosuo T. Natural rubber latex allergy. *Allergy* 1996; 51: 593–602.

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