

Original article

Increased prevalence of latex-sensitization among children with chronic renal failure

Background: Type-I-allergy to natural rubber latex (NRL) has been shown to be more prevalent among certain groups of patients. Children suffering from chronic renal failure (CRF) could be a suspected risk group because of their intense exposure to latex through catheters, gloves and anesthetic equipment during frequent hospitalizations from early life on. We investigated the prevalence of latex-sensitization among this group of patients and sought to identify risk factors.

Methods: Ninety-three patients (mean age 10.5 years) suffering from CRF were assessed by questionnaire-based history (details on renal disease, number and kind of surgical procedures, family and personal history of atopic diseases, allergic reactions to NRL, and the use of pacifiers) and by measurement of total and latex-specific serum immunoglobulin (Ig)E.

Results: Ten of 93 (10.8%) patients showed elevated latex-specific IgE-levels. One of 10 patients reported clinical symptoms to latex-allergen, but no allergic reactions to NRL during medical care were reported. Sensitized patients were significantly more likely to be atopic, reflected by a positive history of other allergies as well as elevated total serum IgE-levels, and had a significantly higher number of urogenital surgeries ($P = 0.02$ in all cases, Fisher's exact and Wilcoxon test, respectively).

Conclusion: This study demonstrates that children with CRF are at increased risk of latex-hypersensitivity. Significant associations with atopy and repeated surgeries were observed. Larger studies are required to elucidate whether these children are also at increased risk of anaphylaxis and therefore deserve preventive measures.

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Up to 72% of children with spina bifida (1–3), 20.8% of atopic children (4) and two-thirds of children with bladder extrophy (5) are sensitized to natural rubber latex (NRL). Atopy (4, 6) and repeated exposure to latex-allergen through multiple surgical procedures (7, 8) have been ascertained as the major determinants for the development of latex-specific immunoglobulin E (IgE) antibodies. As allergic reactions to latex can be life threatening, the identification of risk groups has been a major concern over the last years. Children suffering from chronic renal failure (CRF), who are undergoing multiple surgical procedures, long-term dialysis and/or renal transplantations, might be a suspected risk group due to their high exposure to latex-containing medical devices. We therefore sought to determine the prevalence of latex sensitization in this group of patients and its association with the mentioned risk factors and determinants of renal disease (sex, age on enrolment, age at onset of disease, number of renal transplantations and other surgeries, age at first urogenital procedure, as well as the period of

hemodialysis, family and personal history of allergies, and the use of pacifiers).

Materials and methods

From 1997 to 2000, a total of ninety-three consecutive patients (44 boys, 49 girls, mean age on enrolment 10.5 ± 6.02 years) presenting to the nephrology outpatient clinic of the University of Vienna Children's Hospital with CRF was evaluated in this study.

Patients' histories were checked for details on renal disease (age at onset and etiology of renal failure, period of hemodialysis, number of renal transplantations) and surgeries (numbers and dates of other surgical procedures and period of hemodialysis, respectively).

During the second period of the study (in 2000), subjects and their parents respectively completed a questionnaire concerning etiology of renal failure, age at onset of disease, number and dates of renal transplantations and urological surgeries, as well as total number and kinds of other surgical procedures and period of hemodialysis. Questions on clinical symptoms of latex allergy, family and personal history of allergies and the use of pacifiers were posed as well.

Both sources of data (medical histories and questionnaires) were consistent.

In 1997 and 2000, sera were investigated for total and latex-specific IgE by solid phase immunoassay (CAP-System; Pharmacia Uppsala, Sweden). Patients were designated latex sensitized if their latex-specific serum IgE was ≥ 0.35 kUA/l at either times. Screening tests for inhalant and nutritional allergens were performed using the same assay-system. Standardized panels tested in all patients comprised timothy grass-, rye-, birch-, and mugwort-pollen, house dust mite, cat and dog dander, and *Cladosporium herbarum* for inhalant allergens, hen's egg white, cow's milk, codfish, wheat flour, soy bean, peanut, hazelnut, Brazil nut, almond, and coconut for nutritional allergens. To account for age, total serum IgE-levels were converted into z-units according to the values published by Kjellman et al. (9).

Data were analyzed with SAS for Windows (SAS Institute Inc., Cary, NC, USA). Categorical variables were compared by Chi-square test or Fisher's exact test when indicated. Wilcoxon rank sum test was used to analyze numeric variables. To evaluate independent risk factors a multiple logistic regression analysis (Enter-method) was performed using the presence of latex-sensitization as dependent variable and sex, age on enrolment, age at onset of disease, number of renal transplantations, urogenital and general surgical interventions, duration of hemodialysis, as well as personal and family history of allergies, the use of pacifiers, and the total serum-IgE levels (given in z-units) as independent variables. A p-value of < 0.05 was considered significant.

Results

A total of ninety-three patients presenting to our nephrology outpatient unit between 1997 and 2000 were consecutively enrolled in this study; although, nine cases had to be excluded from statistical analysis because of missing values. All excluded patients were latex-IgE negative. The etiology of renal failure of the remaining eighty-four children (39 boys and 45 girls, mean age 10.7 ± 6.1 years) is presented in Table 1. Patients' characteristics and results of statistical analysis are shown in Table 2.

Of the ninety-three patients studied, 10 (10.8%) were found to be latex-sensitized showing latex-specific serum IgE-levels from 0.35 to 9.44 kUA/l (radioallergosorbent test classes 1–3) (Table 3). Among them, only one reported clinical symptoms upon contact with NRL

(itching, swelling of the lids, and respiratory symptoms when blowing up a balloon), whereas four other patients reporting reactions to latex (redness and itching) did not show elevated latex-specific IgE-antibodies and were therefore designated 'not latex-sensitized'. No allergic reactions to NRL during medical care were reported. As no scientifically based recommendations for patients with CRF were yet established, no latex-avoidance measures were undertaken during the whole period of the study.

When analyzing the etiology of CRF, the diagnosis 'urethral valve' turned out to be significantly more prevalent among latex-sensitized patients ($P = 0.02$, Fisher's exact test, data not shown).

The median age at onset of renal disease was 0.04 years in sensitized patients vs 2.63 years in non-sensitized children ($P = 0.06$, Wilcoxon test). Sensitized patients were significantly more likely to be atopic, reflected by a personal history of allergy (50% vs 14.9%, $P = 0.02$, Fisher's exact test) and higher values of total serum IgE (median 1.36 vs 0.44 z-units, $P = 0.02$, Wilcoxon test). Family history of allergy was positive in 40% of latex-sensitized patients vs 13.5% of nonsensitized children ($P = 0.06$, Fisher's exact test). They had a significantly higher number of urogenital surgeries (median 4 vs 1.5, $P = 0.02$, Wilcoxon test) than their nonsensitized counterparts. More patients sensitized to NRL underwent hemodialysis (70% vs 59.5%) with the median period of this treatment being longer among sensitized patients (12 months vs 4 months), but this difference was not statistically significant. The percentage of patients having had renal transplantations was comparable in both groups (60% vs 66.2%), as well as median numbers of renal transplantations and other surgeries (median 1 in all cases). Sex, the age on enrolment to the study and at the first urogenital surgery, as well as the use of pacifiers did not significantly differ between the two groups of patients either (Table 2).

However, when trying to identify independent risk factors for sensitization to NRL, multiple logistic regression analysis did not reveal significant associations between latex-sensitization and any of the independent variables (sex, age on enrolment, age at onset of disease, duration of hemodialysis, number of renal transplantations, urogenital and general surgical interventions, as well as personal and family history of allergies, the use of pacifiers, and total serum IgE, Table 2).

Discussion

Although the prevalence of latex-allergy in the general pediatric population is low, distinct groups are known to be at greater risk to develop IgE-antibodies to NRL (10).

The major finding of the present study is the increased prevalence of latex-sensitization among children suffering from CRF compared with the general pediatric population (ten of 93 or 10.8% vs eight of 1175 or 0.68% (11),

Table 1. Etiology of renal failure ($n = 84$)

Etiology of renal failure	<i>n</i>
Renal malformation	16
Vesicourethral reflux	14
Glomerulonephritis	13
Urethral valve	11
Juvenile nephrophtisis	8
Complex syndromes (Prune Belly, Joubert,...)	7
Nephrotic syndrome	3
Metabolic disease (Cystinosis, Methylmalonicaciduria,...)	5
Congenital Nephroblastoma	1
Nephropathy for different reasons (infectious, toxic, HUS,...)	6

Table 2. Patients' characteristics and results of statistical analysis (univariate tests and multiple logistic regression analysis, $n = 84$)

	Latex sensitized ($n = 10$)	Not latex sensitized ($n = 74$)	Univariate analysis		Multivariate analysis P -value
			Test	P -value	
Sex (m/f)	6/4	33/41	F	0.5	0.83
Median age on enrolment (range)	13.29 years (8 months–21.83 years)	11.71 years (2 months–23.08 years)	W	0.43	0.4
Median age at onset of disease (range)	0.04 years (first day of life–7.67 years)	2.63 years (first day of life–14 years)	W	0.06	0.07
Renal transplantation	6 (60%)	49 (66.2%)			
Median number of renal transplantations (range)	1 (0–5)	1 (0–3)	W	1.0	0.22
Median number of urogenital surgeries (range)	4 (0–9)	1.5 (0–14)	W	0.02	0.49
Median age at first urogenital surgery (range)*	2.25 years (2 months–16.9 years)	6 years (first day of life–16.6 years)	W	0.32	
Median number of other surgeries (range)	1 (0–3)	1 (0–5)	W	0.55	0.95
Hemodialysis	7 (70%)	44 (59.5%)			
Median period of hemodialysis (range)	12 (0–104 months)	4 (0–76 months)	W	0.19	0.15
Latex-related symptoms	1 (10%)	4 (5.4%)			
Use of pacifiers	3 (30%)	43 (58.1%)	F	0.17	0.1
Other allergies	5 (50%)	11 (14.9%)	F	0.02	0.37
Family history of allergy	4 (40%)	10 (13.5%)	F	0.06	0.28
Median total serum IgE in kU/ml range	115.25 (13–1638)	23.78 (2–790)			
Median total serum IgE in z-units (range)	1.36 (–0.08–3.75)	0.44 (–2.03–3.23)	W	0.02	0.08

* $n = 68$.

m, Male; f, female; F, Fisher's exact test; W, Wilcoxon rank sum test.

Table 3. Characteristics of latex-sensitized patients

ID	1	7	17	18	23	24	34	45	75	90
Sex	f	f	m	m	m	m	m	m	f	f
Age on enrolment (years)	9	11.25	17.25	21.83	4.58	15.33	15.92	17.75	6.33	0.67
Etiology of renal failure	GN	RM	VUR	UV	UV	RM	UV	UV	GN	NS
Age at onset of disease (years)	1st doL	0.08	7.67	1st doL	1st doL	0.33	1st doL	6.92	0.67	1st doL
Latex-specific IgE (kUA/l) 1997	0.58	2.06	1.40	1.76	n.d.	9.44	0.85	1.96	8.26	n.d.
Total serum IgE (kU/l) 1997	22.2	1638	189	533	n.d.	276	18.3	127	13	n.d.
Total serum IgE (z-units) 1997	0.07	2.97	1.97	2.88	n.d.	2.3	–0.08	1.62	0.07	n.d.
Latex-specific IgE (kUA/l) 2000	1.63	0.69	n.d.	n.d.	1.39	1.58	n.d.	0.35	0.35	0.69
Total serum IgE (kU/l) 2000	20.5	1424	n.d.	n.d.	136	36.7	n.d.	62	21.7	25.1
Total serum IgE (z-units) 2000	–0.05	3.75	n.d.	n.d.	1.66	0.53	n.d.	0.99	0.02	1.26
Number of NTX	1	–	5	1	–	1	–	–	2	1
Number of urogenital surgeries	3	–	4	6	4	3	7	9	6	1
Age at first urogenital surgery (months)	99	–	203	2	3	16	6	82	31	27
Number of other surgeries	1	1	1	1	2	–	–	–	3	1
Period of hemodialysis (months)	4	–	104	12	–	12	–	68	39	13
Latex-related symptoms	–	–	–	–	Yes	–	–	–	–	–
Pacifier	–	–	–	–	Yes	Yes	–	–	–	Yes
Other allergies*	–	Yes	Yes	–	Yes	Yes	–	–	Yes	–
Family history of allergies	Yes	–	Yes	–	–	Yes	–	–	Yes	–

* History of any atopic disease (bronchial asthma, allergic rhinoconjunctivitis, atopic eczema) and/or elevated specific IgE to any inhalant or nutritional allergen.

m, Male; f, female; GN, glomerulonephritis; RM, renal malformation; VUR, vesico-urethral reflux; UV, urethral valve; NS, nephrotic syndrome; NTX, renal transplantation; 1st doL, first day of life; n.d., not determined.

respectively). Interestingly, in adult patients with CRF this prevalence was found to be three in 268 subjects, or 1.1%, which is not elevated compared with the general adult population (3.5%) (12, 13). Thus, based on findings of Konz et al. reporting a remarkably higher prevalence of latex-hypersensitivity among patients with (inborn) spina bifida in comparison with patients with spinal cord injuries (72% and 4%, respectively), although both groups were exposed to latex to a comparable extent

(1), we hypothesized that the age at exposure to NRL-allergen might be crucial.

Indeed, in eight of the ten sensitized subjects renal disease and therefore frequent exposure to latex-containing medical devices commenced in their first year of life (median onset 0.04 years *vs* 2.63 years), but values achieved only borderline-significance ($P = 0.06$, Wilcoxon test). Degenhardt et al. (14) reported that particularly procedures during the first year of life appear to

predispose to developing hypersensitivity to NRL. However, as for our patients, the age at the first urogenital surgery did not vary significantly between the two groups of patients. Although, as 16 of the analyzed 84 patients did not have any urogenital surgery and were therefore not included in the analysis of this variable, the sample size tested might have been too small to reveal differences ($n = 68$, thereof nine patients sensitized to NRL). To prevent a loss of sample size, this variable was not included in multivariate logistic regression analysis.

In our study, the 10 patients sensitized to NRL were significantly more likely to have a personal history of allergy as well as elevated total serum IgE-levels ($P = 0.02$ for both variables, Fisher's exact and Wilcoxon test, respectively), and they had significantly more urogenital procedures compared with nonsensitized patients ($P = 0.02$, Wilcoxon test). Both variables, atopy and multiple surgical procedures standing for repeated exposure to latex-allergen, are known to be the major risk factors for developing latex-hypersensitivity (4, 6–8, 11, 15, 16). Regarding the use of pacifiers, our results contribute to previous studies finding no influence on the development of latex sensitization (15, 16). The same applies to the period of hemodialysis, which has been shown not to be associated with latex-hypersensitivity in adult patients with CRF (12).

Surprisingly, when investigating associations between specific sensitization and each of the other independent variables (sex, age on enrolment, age at onset of disease, duration of hemodialysis, number of renal transplantations, urogenital and general surgical interventions, as well as personal and family history of allergies, the use of pacifiers, and total serum IgE) by multiple logistic regression analysis, no significant results were found (Table 2). This might be attributable to the rather small-sized sample of $n = 84$.

In the latex-sensitized group, one patient reported clinical symptoms upon contact with NRL-allergen (itching, swelling of the lids, and respiratory symptoms when blowing up a balloon) and can therefore be designated latex-allergic. There were four patients reporting symptoms upon contact with NRL without having elevated latex-specific IgE-levels, hence they were assigned to the 'not latex-sensitized' group. As we did not perform skin prick tests or provocation tests, these patients could have been false negative in the CAP test (17) and might confound statistical analysis. However, excluding the four subjects did not alter results of univariate and multivariate tests (data not shown).

The diagnosis 'urethral valve' was significantly more frequent among the group of patients with elevated latex-specific IgE when compared with the latex-IgE negative group (four of 10 vs seven of 74 patients, $P = 0.02$, Fisher's exact test). However, this seems to be a surrogate

for the higher number of urogenital surgeries in the four sensitized patients rather than disease-associated (median number of urogenital surgeries in sensitized patients 6.5 vs 3 in nonsensitized patients).

'Chronic renal failure' was the unifying diagnosis of our study population, but of course the etiology of renal failure was miscellaneous (Table 1). Broadly speaking, it can be divided into 'structural' and 'immunologically driven' diseases. The latter are usually classed Th1-dominated and might counterbalance the Th2-driven pathway of allergy. To account for this possible confounder we repeated statistical analysis excluding subjects with potentially immunologically driven primary diseases (glomerulonephritis, nephrotic syndrome, complex syndromes, metabolic diseases, nephroblastoma, and nephropathy for different reasons), but univariate tests in patients with structurally caused CRF ($n = 49$) revealed the same results as in the complete study-sample. The seven latex-sensitized subjects were significantly more likely to have additional allergies ($P = 0.02$, Fisher's exact test), had significantly higher total IgE levels, and significantly more urogenital surgeries ($P = 0.01$ and $P = 0.04$, respectively, Wilcoxon test). In the same way we considered subjects with renal transplantations, as organ-transplanted patients usually receive immuno-suppressive treatment, which in turn could limit the development of sensitization to NRL. Fifty-five patients had at least one renal transplantation, and were therefore excluded from analysis. Four of the remaining twenty-nine patients without renal transplantations had elevated latex-specific IgE. Statistical analysis did not reveal any significant differences between sensitized and non-sensitized children in this subgroup, which can be explained by the extremely small sample size. Multivariate logistic regression could not be calculated in either of the two models as the maximum likelihood ratio did not exist.

In conclusion, our data clearly indicate that in contrast to adult patients, children with CRF are at increased risk of latex-hypersensitivity. Sensitized patients were significantly more likely to be atopic and had significantly more urogenital procedures when compared with nonsensitized subjects. However, investigating quite a small sample, multiple logistic regression analysis did not figure out significant associations with any determinants of renal disease or any definite risk factor. Larger studies are required to elucidate whether these children, like patients with spina bifida, are at increased risk of anaphylaxis (18) and therefore deserve preventive measures.

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