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Effects of latex avoidance on latex sensitization, atopy and allergic diseases in patients with spina bifida

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Abstract

Background: Ten years ago, avoidance measures such as the performance of latex-free operations were implemented in children with spina bifida. Since then, latex sensitization and latex allergy have decreased in this high-risk group.

Objective: To study the effect of primary latex-free prophylaxis on the prevalence of allergic diseases and atopy as a marker for sensitization spreading in children with spina bifida.

Methods: One hundred and twenty children with spina bifida born after the introduction of latex-free prophylaxis and operated on under latex-free conditions ('current group') were examined for latex sensitization, latex allergy, sensitization to aero- and food allergens and allergic diseases. Results were compared to a 'historic' (not latex-free operated) group of children with spina bifida and comparable age ($n = 87$) and to a recent sample of children from the general population ($n = 12\,403$).

Results: In comparison with the 'historic group', latex sensitization (55% *vs* 5%, $P < 0.001$) and latex allergy (37% *vs* 0.8%, $P < 0.001$) were significantly reduced in the 'current group'. Furthermore, a significant reduction could be demonstrated for sensitization to aeroallergens (41.4% *vs* 20.8%, $P = 0.001$) and for allergic diseases (35% *vs* 15%, $P = 0.001$). The prevalence for atopy, sensitization to aero-/foodallergens and for allergic diseases in children of the 'current group' was similar to those in children of the weighted population sample.

Conclusions: Latex avoidance in children with spina bifida prevents latex sensitization and latex allergy. Additionally, it also seems to prevent sensitization to other allergens and allergic diseases which might be explained by the prevention of sensitization spreading.

Patients with spina bifida belong to the highest risk group of becoming sensitized and allergic to latex allergens: About 10 years ago, half of the children with spina bifida were sensitized to latex (1–4). One-third suffered from clinically relevant latex allergy (1, 5). Since that time, most of the centers treating patients with spina bifida have implemented a primary prevention program with a focus on latex-free surgical procedures as well as avoidance of latex in the general environment of these children. Only a few studies with small numbers of patients have been published in recent years. These have shown that prevention is effective in reducing latex sensitization (6–8).

Before a latex-free prophylaxis was introduced, the prevalence for atopy was almost twice as high in children with spina bifida (34–45%) (1, 3, 4) when compared to the normal

Abbreviations
CD, Cluster of differentiation; CI, Confidence interval; fx5, Screening test for specific IgE to the most common food allergens; HRP, Horseradish peroxidase; IgE, Immunoglobulin E; IL-4, Interleukin-4; OR, Odds ratio; SPT, Skin-prick test; SX1, Screening test for specific IgE to aeroallergens; Th2, T helper 2.

pediatric population at that time (25%) (4, 9). Thus it seemed that children with spina bifida were prone not only to become sensitized to latex but sensitized also to other allergens. This could be explained either by a general genetic predisposition within the disease spina bifida or by the phenomenon of 'sensitization spreading' where a primary allergen sensitization influences subsequent immune responses of e.g. naive T cells and enhances differentiation towards Th2-type cells with specificity against other allergens (10–12).

The aim of this study was to investigate the effect of primary latex-free prophylaxis on the prevalence of atopy, allergic diseases and latex sensitization in patients with spina bifida born after the introduction of latex prophylaxis. Results were compared to historic data from children with spina bifida born before 1994, when primary prevention was not yet established in German centers. Results were also compared to a recent sample of children from the general population. Our hypothesis was that primary prevention of latex sensitization reduced the risk of sensitization to other allergens and the development of allergic diseases.

Methods

Study population

From September 2005 to October 2006, one hundred and twenty patients (67 women, 53 men) with spina bifida, aged 6 months to 12.5 years (mean age 6.3 years), were recruited from five German centers treating patients with spina bifida (Berlin, Cologne, Hamburg, Hannover, Mainz). Patients had to be born after 1994, after the introduction of latex-free prophylaxis in Germany, to be included in this study. They had to have at least one neurosurgical operation (primary correction during their first days of life), which had to be conducted under strict latex-free conditions. The accuracy of a latex-free surgical procedure was either confirmed by a note in the patients' files or by personal consultation with the surgical or neuropediatric team. Patients were excluded when it was unclear whether the surgical procedure was really conducted under latex-free conditions. This study population is further referred to as the 'current group'.

Study design

In a structured questionnaire, all parents were asked about any clinical symptoms of their child (hives, asthma, rhinoconjunctivitis and angioedema) owing to latex exposure. They were also asked whether the child had wheeze (ever in life), doctors-diagnosed allergic rhinitis and doctors-diagnosed atopic dermatitis, following the ISAAC questionnaire (13). Parents themselves were asked whether they suffered from doctors-diagnosed asthma, allergic rhinitis and atopic dermatitis. A positive family history for atopy was defined as at least one atopic parent positive for any of these diseases. Data also was collected on the presence of a shunt system, the number of total operations as well as shunt operations and the need for regular urethral catheterization. Parents were also asked whether they knew about the risk for latex sensitization in patients with spina bifida and about recommendations for latex avoidance. Additionally, skin-prick test and latex glove provocation tests were performed. Blood samples were taken. Local ethics committees approved the study. Parents gave their signed informed consent.

In vitro testing for sensitization

Latex-specific immunoglobulin E (IgE) was analyzed from sera of all patients at the time of recruitment by the Phadia ImmunoCAP-System (Phadia, Uppsala, Sweden) [reviewed in (14)] and defined as positive when above the detection limit of >0.35 kU/l. The screening tests for aero-(SX1) and food (fx5) allergens were performed by the same system at the same time. SX1 contained the allergens birch, timothy grass, mugwort, house dust mite (*Dermatophagoides pteronyssinus*), cat dander, dog dander and mold (*Cladosporium herbarum*). This includes 90% of all relevant aeroallergens in Central Europe (15). Fx5 contained cow's milk, hen's egg, cod, soy, wheat and peanut. None of these are known to cross-react with latex. They are the most common food allergens in the pediatric population. Children were regarded as atopic if SX1 and/or fx5 was above the detection limit (>0.35 kU/l). A more specific definition for sensitization to at least one aeroallergen was also established: patients with positive SX1 were further investigated by skin-prick (birch, timothy grass, *D. pteronyssinus*, dog and cat). If results were incongruent to SX1, serum was further tested for specific IgE against birch, timothy, mugwort, *D. pteronyssinus*, dog, cat and *C. herbarum*.

In some patients (current group and sensitized to latex), serum was further analyzed for the presence of Hev b1-, Hev b3-, Hev b5-, Hev b6.01 and for horseradish peroxidase (HRP, Ro 400)-IgE using the Phadia ImmunoCAP-System.

Skin-prick testing

Skin-prick tests (SPT) were performed with latex extract (Stallergenes, Kamp-Lintfort, Germany) and commercial antigens for birch, timothy grass, *D. pteronyssinus*, dog and cat (ALK-Abelló, Wedel, Germany). SPT responses were defined as positive if the maximum wheal diameter was ≥ 3 mm without reaction to the negative control and the skin index was >0.6 (1). The skin index was calculated as the ratio of diameter of the allergen wheal to the histamine wheal. Three of 120 patients refused a skin-prick test.

Glove-wearing provocation test

Patients with latex sensitization underwent a provocation test according to standard procedures (1): The patient slipped a latex glove (Sempermed classic, Lot YE5F7; Semperit, Vienna, Austria) onto one of his wet hands. As a negative control, the other hand slipped on a neoprene glove (Dermaprene; Ansell, Munich, Germany). After the gloves were worn for 30 min, they were taken off, and possible allergic reactions were assessed. Of six latex-sensitized patients, one received a provocation, as five patients refused the provoca-

tion. Therefore, clinically relevant latex allergy was defined in all patients sensitized to latex as either latex provocation test positive or a convincing history for allergic symptoms after latex contact.

Historic group

The previously mentioned study group (current group) was compared to a 'historic group' of eighty-seven patients (42 women, 45 men) with spina bifida, aged 3 months to 11.4 years (mean age 7.6 years) who were recruited from the neuropediatric department in Berlin in 1997 (1, 5). This group was part of a larger study where 159 patients with spina bifida of all ages were recruited between May 1997 and October 1997. To match by age the current group of patients with spina bifida, we selected only patients who were born before 1994 and operated on in our department. Thus, we could be certain that surgical procedures were not conducted in a latex-free condition at that time, and the age range was also similar to the current group. In the selected 87 patients, the questionnaire was comparable to the one of the current group. Latex-specific IgE and SPT were examined at that time following exactly the same protocols as mentioned earlier. Three children of the 87 patients of the historic group refused a SPT at that time. Except for two patients who refused provocation, all of the children with latex-specific IgE and/or a positive latex-SPT test were challenged by a glove-wearing test. Furthermore, sera of these children were screened for SX1 and fx5 as well as single sensitization to birch, timothy, mugwort, *D. pteronyssinus*, dog, cat and *C. herbarum* in the same manner at the time of recruitment as described previously.

Sample of children from the general population

To compare our present data on atopy and allergies in patients with spina bifida to a large population-based sample, we performed a specially weighted analysis of data from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), performed by the Robert Koch Institute in Berlin, Germany (16, 17). Between May 2003 and May 2006, 17 641 children, aged 0–17 , from 167 communities all over Germany were enrolled in the KiGGS study. The survey involved a computer-assisted personal interview with the accompanying parent, asking whether a doctor had ever diagnosed asthma, atopic dermatitis or allergic rhinoconjunctivitis in the child. Data on parental allergies were obtained by parent-administered questionnaire. SX1 (Phadia ImmunoCAP-System) was measured in all children above the age of 1. Fx5 was not measured in the KiGGs study, but sensitization to single allergens such as cow's milk, hen's egg, soy, wheat and peanut was measured in blood samples of children aged ≥3.

To allow comparison to our current data, the KiGGS data were restricted to 0- to 12-year-olds. Special weights were constructed to reach the same distribution of age, sex and parental atopic status as present in our study population. Finally, data from 12 403 children of the KiGGS study (further referred to as the 'KiGGS reference group') were compared to our current data of children with spina bifida born after 1994 having a known family history. For this purpose, a positive SX1 was defined as >0.35 kU/l. Because the serum was available only from children above 1 year of age in the KiGGS reference group, this data could be compared to only 114 children of the current group. A 'positive fx5' in the KiGGS group was defined as sensitization to at least one of the food allergens (cow's milk, hen's egg, soy, wheat and peanut), available from children above 2 years of age. Atopy was defined as either SX1 $>$ 0.35 kU/l and/or sensitization to at least one of the food allergens, available only from children above 2 years of age in the KiGGS reference group. This data could be compared to only 97 children of the current group.

Statistical analysis

We calculated median, mean and standard deviation (SD) for continuous variables such as age, number of total operations and number of shunt operations. Differences between the current and the historic group were tested by Mann–Whitney *U*-test or *t*-test for continuous variables (nonparametric or parametric distribution respectively) and chi-squared test for categorical variables. Statistical significance was defined by a two-sided alpha-level of 0.05.

We calculated crude odds ratios (OR) with 95% confidence intervals (CI) as a measure of uncertainty to estimate the association between the type of operation (latex-free *vs* not latex-free) and allergic sensitization, allergic diseases, latex sensitization and latex allergy. In multiple regression analyses, we calculated ORs and 95%CIs adjusting for potential confounders. The adjusted models included sex, age (in years), number of shunt operations, allergic family history (yes *vs* no) and urethral catheterization (yes *vs* no). All calculations were performed using the statistical software package SPSS versions 14.0 and 15.0 (SPSS Inc., Chicago, IL, USA).

Prevalence estimates and their 95% CIs of the KiGGS reference group were calculated with the special weights applied, by using the SPSS procedure Complex Samples, thus accounting for the stratified and clustered sample design of the survey.

Results

One hundred and twenty patients with spina bifida (mean ± SD age: 6.3 ± 3.1 years) were recruited for this study. The current group and the historic group were similar in distribution of sex, presence of a shunt system, frequency of bladder catheterization and atopic family history. The historic group was significantly older (mean ± SD age: 7.6 ± 2.4 years) and was exposed to a higher number of shunt operations than the current group (Table 1).

Latex sensitization and latex allergy

In the current group, only 5% of the 120 children with spina bifida showed a specific latex-IgE above the detection limit, whereas the historic group showed with 55% ($P < 0.001$) a

Table 1 Baseline characteristics of study participants comparing children with spina bifida operated latex-free *vs* those operated not latex-free (statistically significant results are bold)

	Latex-free operated group (current group)	Not latex-free operated group (historic group)	*P*-value
Patients (*n*)	120	87	
Age: mean (years ± SD)	**6.3 (±3.1)**	**7.6 (± 2.4)**	**0.002**
median (years)	6.0	7.9	
Sex (male)	44.2%	51.7%	0.282
Patients with ventricular shunt	74.2%	75.6%	0.818
Mean number of total operations (±SD)	**5.2 (±3.5)**	**6.3 (±3.9)**	**0.044**
Mean number of shunt operations (±SD)	**1.8 (±1.7)**	**2.6 (±2.9)**	**0.018**
Regular urethral catheterization	55.0%	65.1%	0.145
Patients with positive atopic family history	46.2%	39.5%	0.347

ten times higher prevalence of latex sensitization. This markedly significant difference in latex sensitization was also confirmed by SPT (latex-positive SPT: 1/117 of current group *vs* 43/84 of the historic group, $P < 0.001$) (Fig. 1). The magnitude of latex sensitization was lower in the current than in the historic group (mean latex-specific IgE 3.0 ± 3.7 kU/l *vs* 15.5 ± 22.7 kU/l, $P = 0.054$). Furthermore, the prevalence of clinically relevant latex allergy was also markedly lower in the current group (1/120) than in the historic group (32/86, $P < 0.001$) (Fig. 1): Of the six patients sensitized to latex in the current group, one patient was negative in the provocation. Five patients did not undergo a provocation test. Of these, one had a convincing history of immediate type allergic symptoms and four did not report on any allergic events.

After adjusting for potential confounders, effects remained statistically significant for latex sensitization of the current compared to the historic group (crude OR 0.04, 95%CI 0.02–0.11; adjusted OR 0.05, 95%CI 0.02–0.13; $P < 0.001$) and latex allergy (crude OR 0.01, 95%CI 0.02–0.11; adjusted OR 0.02, 95%CI 0.002–0.15; $P < 0.001$).

Sensitization to aero- and food allergens

There was no significant reduction in prevalence of atopy (SX1 and/or fx5 positive) in the current group in comparison with the historic group (35% *vs* 48.3%, $P = 0.055$, Fig. 2). Similar to the univariate analysis, the adjusted analysis also showed no significant reduced odds for atopy in children of the current group (data not shown).

Looking at the prevalence of sensitization to common food allergens (fx5) separately, the prevalence of sensitization to food allergens in both groups was comparable (18.3% *vs* 25.3%, $P = 0.227$, Fig. 2). The results did not change considerably after adjusting for potential confounders (data not shown). Therefore, analysis of separate nutritional sensitization to the single allergens was not further investigated. However, children of the current group had a significantly lower prevalence of sensitization to aeroallergens measured by SX1 when compared to those of the historic group (28/120 *vs* 38/

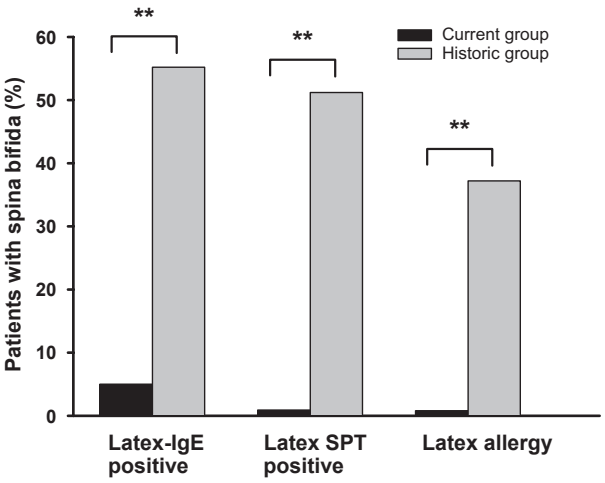

Figure 1 Comparison of latex sensitization (latex-specific immunoglobulin E >0.35 kU/l or positive latex-skin-prick test, SPT) and latex allergy in children with spina bifida operated latex-free (current group) *vs* those operated not latex-free (historic group). $^{**}P < 0.001$ (Chi-squared test, univariate analyses).

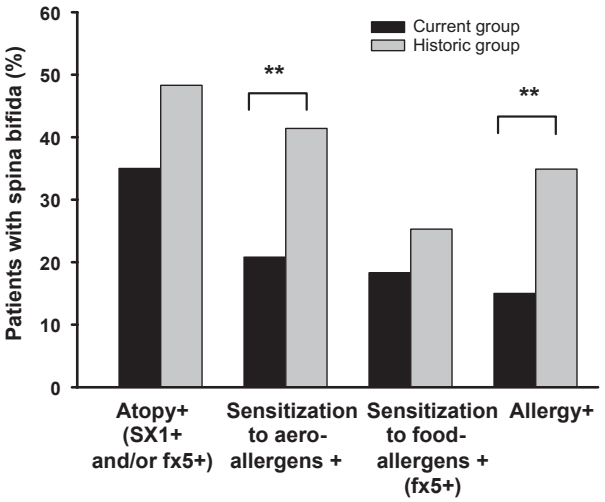

Figure 2 Comparison of allergic sensitization and clinical allergy in children with spina bifida operated latex-free (current group) *vs* those operated not latex-free (historic group). atopy +: either SX1 and/or fx5 positive; sensitization to aeroallergens: Immunoglobulin E >0.35k U/l to ≥1 of the aeroallergens: birch, timothy, mugwort, *Dermatophagoides pteronyssinus*, dog, cat or *Cladosporium herbarum*; sensitization to foodallergens: fx5 positive; allergy: history of 'wheeze', doctors-diagnosed allergic rhinitis and/or atopic dermatitis. $^{**}P < 0.001$ (Chi-squared test, univariate analysis).

87, $P = 0.002$). After adjusting for possible confounders, the odds of a positive SX1 in the current group were still reduced, but this effect was no longer statistically significant (crude OR 0.39, 95%CI 0.22–0.71; adjusted OR 0.59, 95%CI 0.3–1.31; $P < 0.11$).

However, further differentiating aeroallergens of the SX1 on single allergen basis, only 20.8% of children of the current group were sensitized to either birch, timothy grass, mugwort, house dust mite, dog, cat or *C. herbarum*. In contrast, the prevalence of sensitization to at least one of these aeroallergens in children of the historic group was twice as high (historic group 41.4%, $P = 0.001$) (Fig. 2). In the adjusted analysis, this effect was slightly less pronounced but remained statistically significant (Table 2). Furthermore, catheterization, male sex and increasing age of the study participants were also significantly associated with a sensitization to these aeroallergens (Table 2). When sensitization to the tested aeroallergens was further investigated separately and compared between both groups, a significantly lower prevalence of single sensitization was seen for birch, timothy and dog allergen in the current group (data not presented).

Allergic diseases

The prevalence of allergic diseases in the current group was significantly lower when compared to the historic group. In answering a questionnaire, 18 parents of 120 children of the current group reported that either 'wheeze' and/or doctors-diagnosed allergic rhinitis and/or doctors-diagnosed atopic dermatitis had at some time been present in their child. In comparison, 30 parents of 86 children of the historic group indicated that their child was suffering from an atopic disease (Fig. 2, allergy: 15% *vs* 35%, $P = 0.001$). This remained statistically significant in the adjusted analysis (Table 2).

Comparison of the current study group with a weighted population sample of children

The prevalence proportions of atopy and allergic diseases in patients with spina bifida who were operated on in a latex-free environment were comparable to those of the weighted population sample of children (KiGGS reference group). Confidence intervals were overlapping: The prevalence of atopy (sensitization to ≥1 aero-/foodallergen = SX1 and/or fx5 positive) was comparable in both groups. The prevalence of sensitization to at least one aero- (SX1+) and at least one food allergen (fx5+) was almost identical. Also the prevalence of wheeze (ever), atopic dermatitis or allergic rhinoconjunctivitis was similar in both groups (Table 3).

Characterization of the six patients of the 'current group' sensitized to latex

The latex-specific IgE recognition pattern was further analyzed (Table 4) in the six patients of the 'current group' who showed a latex-IgE above the detection limit and were operated latex free. Only one patient (#24) showed sensitization towards a specific Hev b tested within the study. He showed a sensitization towards Hev b1 and Hev b6.01, characteristic for the specific sensitization pattern seen in patients with spina bifida before latex avoidance measures were implemented (18–20). This was also the only patient suffering from clinical relevant latex allergy in the 'current group'. For all of the other patients (5/6), no specific Hev b-recognition pattern could be identified within the Hev-b-spectrum tested. Of the six patients sensitized to latex, three were identified with a positive SX1. Of these two showed a sensitization to grass pollen in combination with HRP as a marker for sensitization to cross-reactive carbohydrate determinants (CCDs) (20).

Table 2 Crude and adjusted odds for developing sensitization and clinical allergy in children with spina bifida regarding the use of latex materials during operations and potential confounders (statistically significant results are bold)

	Sensitization to ≥1 aeroallergen*				Allergic diseases†			
	Crude OR (95%CI)	*P*	Adjusted OR‡ (95%CI)	*P*	Crude OR (95%CI)	*P*	Adjusted OR‡ (95%CI)	*P*
Latex-free *vs* not-latex free operation	**0.37 (0.2–0.69)**	**0.002**	**0.51 (0.26–0.99)**	**0.048**	**0.33 (0.17–0.64)**	**0.001**	**0.39 (0.19–0.79)**	**0.009**
Male *vs* female	1.61 (0.88–2.95)	0.119	**2.36 (1.18–4.73)**	**0.016**	1.62 (0.84–3.1)	0.148	1.85 (0.9–3.79)	0.093
Age	**1.21 (1.08–1.35)**	**0.001**	**1.2 (1.05–1.36)**	**0.006**	**1.15 (1.02–1.3)**	**0.020**	**1.15 (1.01–1.32)**	**0.042**
Number of shunt operations	1.04 (0.92–1.18)	0.545	0.95 (0.82–1.1)	0.501	1.07 (0.94–1.22)	0.323	0.99 (0.86–1.15)	0.940
Atopic *vs* nonatopic family history	0.91 (0.49–1.67)	0.754	1.18 (0.6–2.32)	0.638	1.42 (0.74–2.72)	0.288	1.71 (0.84–3.49)	0.141
Urethral catheterization *vs* no catheterization	**2.4 (1.24–4.63)**	**0.009**	**2.53 (1.2–5.31)**	**0.014**	1.2 (0.62–2.32)	0.598	1.12 (0.53–2.37)	0.764

*Sensitization to ≥1 aeroallergen: birch, timothy, mugwort, house dust mite (*Dermatophagoides pteronyssinus*), dog, cat and *Cladosporium herbarum*.

†Allergic diseases ('wheeze' and/or doctors-diagnosed allergic rhinitis and/or atopic dermatitis)

‡Adjusted for all other variables that are presented in this table.

Table 3 Prevalence of allergic sensitization and allergic diseases in children with spina bifida operated on latex free compared to participants of the German Child Health Survey 'KiGGS' as a reference group

	Latex-free operated children with spina bifida (current group) prevalence in % (95% CI)	Weighted population sample of children (KiGGS reference group) prevalence in % (95% CI)
Atopy+ (SX1+ and/or fx5+)	37.1 (27.5–46.7)*	33.1 (31.9–34.4)*
Sensitization to ≥1 aeroallergen (SX1+)	24.6 (16.7–32.5)	25.1 (24.0–26.2)
Sensitization to ≥1 food allergen (fx5+)	16.5 (9.1–23.9)*	16.9 (15.9–18.1)*
Allergy+	15.4 (8.9–21.9)	18.7 (17.8–19.7)

*Sensitization to ≥1 food allergen: defined in current group as fx5 +, defined in KiGGS reference group as sensitization to either cow milk, egg, soy, wheat or peanut.

Table 4 Laboratory and clinical characterization of the six patients with spina bifida of the current group, sensitized to latex and being operated latex free

Patients	#7	#24	#27	#46	#62	#114
Latex-IgE	+	+	+	+	+	+
Hev b1-IgE	–	+	–	–	–	–
Hev b3-IgE	–	–	–	–	–	–
Hev b5-IgE	–	–	–	–	–	–
Hev b6.01-IgE	–	+	–	–	–	–
Latex allergy	–	+	–	–	–	–
Knowledge about risk for latex sensitization*	+	–	+	+	+	+
Number of shunt operations	0	2	10	2	1	0
SX1	+	–	–	–	+	+
Timothy grass- SPT	+	–	–	–	–	+
Birch-SPT	–	–	–	–	+	+
HRP-IgE	+	–	–	–	–	+

*Parents/children were asked via a questionnaire whether they knew about the high risk for latex sensitization in patients with spina bifida and whether they knew about recommendations for latex avoidance (especially during operations). SPT, Skin-prick test; HRP, horseradish peroxidase; IgE, Immunoglobulin E.

Discussion

This study shows a dramatic reduction in prevalence of latex sensitization in children with spina bifida over the last decade (55–5%). This suggests that implementing a primary latex-free environment in children with spina bifida is an effective example for primary prevention because of allergen avoidance. Previous studies have shown similar results, with a reduction in prevalence of latex sensitization from 27–42% to 4.5–7% (6–8). The advantage of this study is the large number of patients included.

Studies analyzing the prevalence for latex sensitization in the normal pediatric population (4, 21–23) showed a wide range of prevalence – from 0.2% in unselected population samples (4, 21, 24) up to 3–10% in biased atopic population samples (22, 23). Assuming that the prevalence for latex sensitization in the 'normal' population of 6-to 7- year-olds is about 1%, patients with spina bifida of our current group showed nearly the same prevalence as the normal population.

This study also showed a dramatic reduction in prevalence of latex allergy in children with spina bifida over the last decade. Before latex-free prevention measures were introduced, 37% of children with spina bifida of the historic group suffered from challenge-test positive latex allergy. Similarly, high prevalence estimates for latex allergy were reported 10 years ago, ranging from 12% when based only on self/ parent reported symptoms (2, 4) up to 35% (1) when latex challenge tests were conducted for proof of diagnosis. After introducing a primary latex prophylaxis, only 0.8% of children with spina bifida suffered from latex allergy in our current group. This finding is comparable to other recently published results for children with spina bifida after introduction of prophylaxis (6, 7) as well as to rates of prevalence for latex allergy in the 'normal' pediatric population (21, 24, 25).

Up to now, a specific Hev b-recognition pattern has been identified for patients with spina bifida : In contrast to the sensitization pattern in health care workers (mainly Hev b 2, 5, 6.01 and 13 (18, 20), patients with spina bifida showed sensitization mainly to Hev b 1, 3 and 6.01 (18–20). This can be explained by the different sensitization routes (airborne allergens and sensitization via inhalation in health care workers versus insoluble thus not-airborne allergens and sensitization by direct tissue contact in patients with spina bifida (26)). However, it seems that patients with spina bifida being operated latex free and thus not being sensitized via direct tissue contact, no longer show the typical sensitization pattern (Table 4). Only one of six patients sensitized to latex displayed the typical sensitization pattern. Interestingly, this patient was the only one suffering from clinical latex allergy. The parents of this non-German-speaking family had no knowledge about the risk for latex sensitization in spina bifida and thus did not avoid latex. Except for the first neurosurgical operation, it is not clear whether all further operations (e.g. the two shunt operations, Table 4) were also conducted latex free. Thus, sensitization could have happened during surgeries outside the spina bifida center. Interestingly, only 32% of non-German-speaking families *vs* 87% of German-speaking families knew about the risk for latex sensitization in the current group (data not shown). This data might strengthen the fact that not only latex-free operations but also information given to the parents is important to reduce the risk for latex allergy.

The reduction in latex sensitization and latex allergy in the current group can be attributed to the primary latex-free prevention which was introduced in German centers dealing with patients with spina bifida, around 1994. However, comparing the historic group (not latex-free operated on) with the current group (latex-free operated on), we can also see a statistically significant reduction in numbers of shunt operations (Table 1). After adjusting the analysis for possible confounders, this effect was still relevant although not as strong as the one seen for latex-free operations (data not presented). With the development of better neurosurgical devices, such as better shunt valves, it is apparent that the number of shunt operations is also reduced in our current study group. Obviously, this also influences the lesser likelihood of latex exposure during operations. But this effect would certainly not account for such an enormous reduction in latex sensitization as seen in our current study group. Furthermore, the number of shunt operations was not associated with the likelihood of sensitization to ≥1 aeroallergen, even after adjusting for the influence of being operated latex free or not (Table 2).

Before introducing a latex-free prophylaxis, children with spina bifida had a very high prevalence of atopy, ranging from 34% (3) to 45% (1, 4), whereas healthy children of the same age showed an atopic disposition of only 25% at that time (4, 9). Thus, children with spina bifida were regarded as having a higher predisposition for atopy, generally. With a prevalence of atopy of 48%, the historic group of our study can be compared to the published data. We have demonstrated for the first time, however, that after the introduction of a primary latex-free prevention, the prevalence of sensitization to other allergens was reduced when compared to children with spina bifida 10 years ago. This effect was mainly attributed to a reduction in prevalence of sensitization to aeroallergens, mainly to birch, timothy grass and dog. Even after adjusting for possible confounders such as sex, age, number of shunt operations, family history for atopy and urethral catheterization, this effect was still prominent. The prevalence of sensitization to food allergens was not altered in both groups. Comparing our present data with a recently ascertained weighted sample from the German population of similar age, children with spina bifida showed the same prevalence of atopy, sensitization to food- and sensitization to aeroallergens as the average pediatric population today.

One-third of children with spina bifida of the historic group had wheeze (ever), doctor-diagnosed atopic eczema or allergic rhinoconjunctivitis, whereas our current group showed a marked reduction in prevalence of these conditions to 15%. This was comparable to the prevalence in the weighted German population sample. Therefore, patients with spina bifida are not likely to have a genetic predisposition for atopy or for the development of atopic diseases, generally, as was postulated for the higher prevalence of latex sensitization (27–29). We think it is more likely that degree, route and early exposure to latex in children with spina bifida favored latex sensitization in early life with multiple booster effects owing to further operations. This might have established a general T helper 2 (Th2) cytokine-milieu which favored subsequent further sensitization to other allergens ('sensitization spreading') and the development of allergic diseases as was demonstrated in recent *in vitro* and murine data (10–12, 30). Our data might suggest that prevention of a sensitization to latex reduces the risk of sensitization spreading and development of atopic diseases. This hypothesis of prevention of 'sensitization spreading' was also demonstrated in studies where specific immunotherapy in patients with allergic rhinitis prevents sensitization to other allergens and the development of asthma (31–33).

The hypothesis might be challenged by the argument that the high prevalence for sensitization to aeroallergens in the 'historic group' might only result from cross-reactivity between glycosylated latex and grass pollen-proteins mediated by CCDs (34, 35). However, inhibition studies showed that cross-reactivity is more important in patients primarily sensitized to grass pollen and subsequently sensitized to latex, whereas patients, such as spina bifida, who were primarily sensitized to latex show low cross-reactivity to grass pollen (35). We were not able to test the sera of the 'historic group' for the presence of CCDs and to conduct inhibition tests. However, Raulf-Heimsoth et al. (20) showed an absence of detectable IgE to HRP (marker for CCDs) in patients with spina bifida before the implementation of latex avoidance measures. These patients with spina bifida were mainly sensitized to not-glycosylated Hev b- proteins (Hev b 1, 3, 6.01) (20). Also, looking at sensitization to CCDs and aeroallergens in the six latex-sensitized patients of the 'current group' (Table 4), the detection of CCDs is associated with the sensitization to grass pollen as only the two patients with positive IgE to CCDs were also sensitized to grass pollen. Furthermore, in combination with a reduction in sensitization to grass pollen in the 'current group' we could demonstrate a reduction in sensitization to birch pollen and dog protein – both allergens are not known to cross-react with latex. However, the strongest argument to strengthen our hypothesis of prevention of 'sensitization spreading' is that there is not only a reduction in sensitization to aeroallergens but also a reduction in prevalence for clinical relevant atopic diseases when latex avoidance measures were implemented.

The question still remains why a reduction in prevalence of sensitization was only seen to aeroallergens and not to foods: The prevalence of sensitization to food allergens was similar in all three groups ('current', 'historic'- and 'KiGGS'-reference group). Therefore, a reduction in prevalence of food sensitization was not expected because children of the historic group did not have an increased prevalence for sensitization to foods compared to the normal pediatric population. Furthermore, the foods tested in our study are also not known to cross-react to latex. Finally, it maybe tempting to speculate that oral tolerance mechanisms may be responsible for the fact that food sensitization was not affected. Early oral tolerance is achieved by high doses of (food) allergens in the gastro-intestinal tract, involving many immunological tolerogenic mechanisms which might overrule the more subtle effect of latex sensitization and 'sensitization spreading' to foods.

In conclusion, implementing a latex-free environment for children with spina bifida from the first day of life prevents not only allergic sensitization and clinically relevant allergy

to latex but also seems to prevent sensitization to other allergens and even allergic diseases.

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