

Early exposure to latex products mediates latex sensitization in spina bifida but not in other diseases with comparable latex exposure rates

T. Eiwegger*, E. Dehlink*, J. Schwindt*, G. Pomberger†, N. Reider‡, E. Frigo†, A. M. Rokitansky†, R. Urbanek* and Z. Szépfalusi*

*Department of Paediatrics, Medical University of Vienna, Vienna, Austria, †Department of Paediatric Surgery and Department of Paediatric Surgical Research, Donauspital, Vienna, Austria and ‡Department of Dermatology, Medical University of Innsbruck, Innsbruck, Austria

Clinical and Experimental Allergy

Summary

Background The high prevalence of latex sensitization in patients with spina bifida (SB) has been attributed to repeated and early exposure to latex products. Other diseases such as gastroschisis/omphalocele and post-haemorrhagic/congenital hydrocephalus are also associated with repeated and early latex exposure.

Objective The aim of the study was to evaluate whether the high prevalence of latex sensitization in patients with SB is rather related to the underlying disease itself than to disease-associated known risk factors.

Methods We compared children with SB ($n = 35$), children with gastroschisis/omphalocele (G/O, $n = 20$) and children with post-haemorrhagic/congenital hydrocephalus (PH, $n = 45$). All children with SB and PH had a ventriculo-peritoneal shunt since a very young age. Patients who underwent three or less surgical procedures matched in terms of age, number of operations, atopy and gender distribution, and were analysed for IgE sensitization rates to latex.

Results In the SB group, 16 of 35 patients (46%) showed elevated latex-specific IgE antibodies in contrast to one of 20 patients (5%) in the G/O group and four of 45 patients (8.9%) in the PH group ($P < 0.0005$ and $P < 0.005$, Fisher's exact test). Comparing matched control groups (≤ 3 operations), the effects remained significant ($P < 0.05$ and $P < 0.01$).

Conclusion This study suggests that the SB population bears a disease-associated propensity for latex sensitization. This effect cannot be explained exclusively by a higher number of operations and differences related to atopy, age or gender.

Keywords gastroschisis, latex allergy, latex-specific IgE antibodies, omphalocele, ventriculo-peritoneal shunt

Submitted 7 February 2006; revised 27 June 2006; accepted 2 August 2006

Correspondence:

Zsolt Szépfalusi, Department of Paediatrics and Juvenile Medicine, Medical University of Vienna, Währinger Gürtel 18-20, A-1090 Vienna, Austria.
E-mail: zsolt.szepfalusi@meduniwien.ac.at

Introduction

Allergy to latex represents a serious health problem in several distinct populations [1–6]. Patients with spina bifida are particularly vulnerable to develop IgE-mediated latex sensitization and hypersensitivity reactions [7–11].

Although the association between latex sensitization and spina bifida is well documented and many risk factors leading to latex allergy have been described [1, 2, 8, 11–14], it is still unclear whether the increased prevalence of latex sensitization in spina bifida is disease-associated or more a surrogate of the disease-related treatment procedures [2, 7, 15–17]. As a major risk factor to develop latex-specific IgE, a family history of atopy and repeated exposure to latex

allergens through multiple surgical procedures has been ascertained [5, 8, 9, 13, 18]. Fortunately, the presence of a ventriculo-peritoneal shunt has not proved to be an independent risk factor [19, 20]. Moreover, the time-point of first exposure and the route of exposure have been linked to a higher probability of developing latex sensitization and latex allergy [12, 19]. In spina bifida patients, most of these risk factors are combined (latex exposure within the first days of life, repeated surgeries, latex exposure via the cerebrospinal fluid). It is difficult to define patient groups with different underlying diseases but comparable risk factors to evaluate whether the increased incidence of latex sensitization in spina bifida patients is associated with a disease-related propensity or not.

A potential genetic contribution is supported by the association of the HLA-DRB1*0701 (DR7) phenotype with Hev b1-IgE responsiveness (rubber elongation factor) and the HLA-DRB4 and HLA-DQB8 phenotype with hevein-specific IgE antibody production in SB patients [18, 19]. The fact that latex-sensitized patients with SB recognize other latex allergens (rubber elongation factor = Hev b1, a 23 kDa protein) as health care workers with latex allergy may reflect the possibility of two different subgroups within the same clinical disease [20]. To unravel this question, we designed the present study by comparing three groups of patients undergoing early and repeated surgical procedures. Exposure to latex was assumed to occur randomly through these procedures as latex avoidance strategies were not implemented at the time of patient recruitment. The first group with spina bifida and the second group with post-haemorrhagic/congenital hydrocephalus were sharing a comparable place of latex contact (ventriculo-peritoneal shunt). The third group with gastroschisis/omphalocele was chosen because the first latex exposure via surgery may have occurred immediately after birth in a similar way as in the management procedure used for spina bifida patients.

Methods

Patient selection

Thirty-five children with spina bifida, 20 children with gastroschisis or omphalocele and 45 children with post-haemorrhagic hydrocephalus were evaluated. Patients were enrolled prospectively in order of appearance in the outpatient wards from 1996 to 2001 in three different centres in Austria. All children with G/O and SB underwent surgical correction within the first days of life, whereas children with PH had surgery within the first 4–6 weeks post-partum. None of the surgical procedures occurred in a preventative latex-free environment until latex allergy was diagnosed. For blood analysis, informed consent was obtained from the patients' guardian as approved by the local ethical committee. As blood donation represented a part of the routine control procedure, none of the included patients refused to be included in the present study.

Questionnaire

The patients' guardian was interviewed concerning a clinical history indicative of latex hypersensitivity in a face-to-face interview via an experienced medical doctor. These questions pertained to: type of latex hypersensitivity (e.g. contact urticaria, bronchospasm, rhinitis, anaphylaxis) and total number of surgical procedures. Also, questions regarding a history of allergies, asthma and urticaria were posed.

Immunological studies

The levels of total IgE- and latex-specific IgE antibodies were determined by the ImmunoCAP System (Phadia, Uppsala, Sweden). The values were expressed in kU/L. The cut-off level was defined as 0.35 kU/L for latex-specific IgE antibodies. Atopy was assessed by means of elevated total IgE antibodies. Elevated total IgE has been shown to correlate with increased latex-specific IgE-antibodies [20, 21].

Statistical analysis

Fisher's exact test was applied to analyse the frequencies of latex sensitization in the three groups of patients. A P -value < 0.05 was considered to be significant. Matching of subgroups was controlled via univariant tests (Mann-Whitney U -test) for the possible confounders age, number of operations, total IgE and gender (Fisher's exact test).

Results

One hundred patients were recruited in this study. The characteristics of the study groups are shown in Table 1. For the purpose of simplification, we denoted the group with PH for post-haemorrhagic hydrocephalus, with SB for spina bifida and with G/O for gastroschisis/omphalocele. The three groups were analysed with regard to number of operations, age and the latex sensitization rate.

The latex sensitization rate was significantly higher in the SB group (46%) as in the groups PH (8.9%; $P < 0.0005$) and G/O (5%; $P < 0.05$). Owing to the fact that the SB group had patients with higher number of surgical interventions, this subgroup was excluded and statistical analysis was performed exclusively with patients who underwent three or less surgical interventions (Fig. 1, Table 1). The subgroups generated thereof were comparable with respect to number of operations, age and sex (Table 1). None of the above-mentioned variables differed significantly between the respective control group (PH or G/O) and the spina bifida group. However, as shown in Fig. 1, the frequency of latex sensitization differed significantly in the SB group (38%) as compared with the G/O group (5%, $P < 0.05$) and the PH group (5.9%, $P < 0.01$).

Discussion

This study demonstrates that patients with spina bifida (congenital spinal cleft) have, in addition to their high latex exposure rates, a disease-associated propensity to mount latex-specific IgE antibodies upon latex contact. This particular association was delineated in our study by the use of control groups who matched with respect to

Table 1. Study group characteristics

	Ventriculo-peritoneal shunt		
	Spina bifida	Post-haemorrhagic hydrocephalus (PH)	Gastroschisis omphalocele (G/O)
All patients			
Number	35	45	20
Mean age (month)	80	67	69
Age range (month)	1–264	1–192	5–156
Duration of neurologic disorder	Birth	First month of life	–
Male : female ratio	22 : 16	23 : 22	11 : 9
Mean # of operations (range)	5.1 (1–30) [‡] vs. PH, G/O	2.6 (1–8)	1.7 (1–3)
History of allergic reaction to latex	4/35 (11.4) [†] vs. PH	0/45	0/20
Elevated total IgE	20/35 (57%)	11/44* (25%)	10/20 (50%)
Prevalence of latex-specific IgE	16/35 (46%) [†] vs. PH, G/O	4/45 (8.9%)	1/20 (5%)
Matched groups (≤ 3 operations)			
Number	21	34	20
Mean age (month)	54	60	69
Age range (month)	1–180	1–180	5–156
Male : female ratio	12 : 11	15 : 19	11 : 9
Mean # of operations	1.9	1.7	1.7
History of allergic reaction to latex	1/21 (4.8%)	0/34	0/20
Elevated total IgE	12/21 (57%)	8/33 (24.7%)*	10/20 (50%)
Prevalence of latex-specific IgE	8/21 (38%) [†] vs. PH, G/O	2/34 (5.9%)	1/20 (5%)

*Data from one patient missing.

[†] $P < 0.05$ (Fisher's exact test).

[‡] $P < 0.05$ (Mann-Whitney U -test).

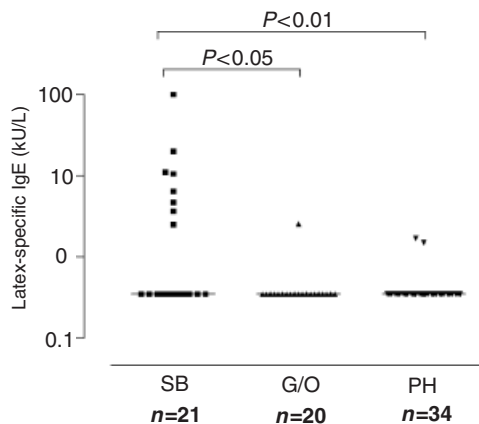


Fig. 1. Latex sensitization rates of patients with spina bifida (SB, $n = 21$), gastroschisis/omphalocele (G/O, $n = 20$) and post-haemorrhagic/congenital hydrocephalus (PH, $n = 34$) who underwent three or less surgical procedures. Groups are matched according to age and number of operations. Points represent data from individual patients, while bars show median values.

age, number of operations, atopy and gender. Patients with gastroschisis and/or omphalocele are exposed to latex at birth as do children with spina bifida. Patients with post-haemorrhagic hydrocephalus or congenital hydrocephalus were sharing with the spina bifida group the anatomic location of repeated surgical latex exposures, i.e. spinal fluid. We have carefully generated the data

acquisition in order to eliminate the confounder factor of multiple surgeries as a well-documented risk factor for latex sensitization. Our findings suggest that the particular propensity of spina bifida patients to mount latex-specific IgE antibodies appears primarily related to the disease of spina bifida itself and only secondarily to the number of exposures to latex products. Thus, it seems likely that spina bifida is an independent risk factor to develop latex sensitization.

Numerous publications assessed additional risk factors and underlying mechanisms of latex sensitization/allergy in spina bifida [8, 11, 20, 22, 23]. Atopy and number of surgical interventions were found to be the major risk factors. However, some contradictory points remained. Most prominent is the assumption that the increased prevalence of latex sensitization in the spina bifida patients is rather a surrogate marker for the disease associated risk factors than related to the disease itself [7, 15, 16]. Our results strongly support the hypothesis that spina bifida represents an independent risk factor for latex sensitization via inclusion of patients with more than one of the documented risk factors.

One of the most prominent confounders is the number of operations that is abundant in spina bifida patients, making an independent analysis of this factor complicated. The association between the number of surgeries and latex allergy has been described by many surveys and

Table 2. Characteristics of latex-sensitized patients

ID	P3	Z1	Z2	S18	S4	S15	S16	S8	S12	S6	S17
Disease	G/O	PH	PH	SB	SB	SB	SB	SB	SB	SB	SB
Sex	M	M	M	M	M	M	M	F	M	F	M
Age	13	1.5	5	6	9	8	9	13	4	3	4
Age of first surgical intervention (days)	1	40	42	1	1	1	1	1	1	1	1
Latex specific IgE (kU/L)	2.56	1.7	1.5	10.6	2.5	4.71	20	> 100	6.46	11.1	3.68
Total serum IgE (kU/L)	1049	8.46	76.2	409	103	91	176	1197	71.2	45.6	61.5
Total serum IgE (z-units)	3.13	1.02	1.82	3.01	1.33	1.24	1.71	3.23	2.03	3.34	1.89
Latex related symptoms	neg	neg	neg	neg	neg	neg	neg	A	neg	neg	neg
Number of surgeries	1	1	3	3	2	3	1	3	3	3	1
Catheterization	neg	neg	neg	neg	neg	neg	neg	pos	pos	neg	pos

A, anaphylaxis; G/O, gastroschisis/omphalocele; PH, post-haemorrhagic/congenital hydrocephalus; SB, spina bifida; M, male; F, female; neg, negative; pos, positive.

independent investigations [8, 17, 18, 23, 24]. We thus included only patients with a low number of surgical interventions ($n = 1, 2$ or 3) in order to minimize the influence of this factor. It is also important to mention that all included patients in the matched groups did undergo surgical intervention before the age of 6 months and that all these interventions were disease-associated. Using this approach, the spina bifida group still differed significantly from the other groups with respect to the prevalence of latex sensitization (Fig. 1). Furthermore, most of the published investigations recruited patient groups with a high number of surgical interventions, thus needing matched groups of patients who underwent the same high number of surgical operations [18, 19]. This proper matching of groups was mostly not achievable. In our study, the number of surgical interventions, atopic status (total IgE) and age were comparable in all three groups after correcting for the number of surgical interventions in the range of three or less. Therefore, we concluded that these factors might not be of primary importance for the increased latex sensitization rate in the SB group.

Primary preventative measures to reduce early latex sensitization have been implemented in many countries in the last few years. The recruitment of all patients included in the present study was performed before these primary preventative measures for spina bifida patients took place. First international long-term studies [25–27] with SB patients treated in a latex-free/reduced environment provide evidence that an early latex avoidance strategy initiated at birth is the mainstay of a long-lasting tolerance to latex products and is part of the standard procedure in the care of SB patients in Austria.

The results of our study with a particular group sampling strengthen the possibility that latex sensitization/allergy in spina bifida patients might be related to an as yet undefined genetic association. A potential genetic contribution is supported by the association of the HLA-DRB1*0701 (DR7) phenotype with Hev b1-IgE responsive-

ness and the HLA-DRB4 and HLA-DQB8 phenotype with hevein-specific IgE-antibody production in SB patients [28, 29]. The fact that latex-sensitized patients with SB recognize preferentially certain latex allergens (Hev b1, Hev b3) may also reflect the particularity of spina bifida patients in being susceptible to latex sensitization [30].

Despite careful matching, limitations have to be considered. The potential confounder catheterization cannot be eliminated due to frequent co-occurring paraplegia in many cases of spina bifida. However, in our SB group only three of the eight latex-sensitized spina bifida patients underwent repeated catheterization (Table 2). Although not in the focus of our investigation, increased sensitization to other allergens in SB patients has to be considered.

Our data further support the fact that the first contact of SB patients with latex products may trigger latex sensitization and is in accordance with numerous studies [12, 15, 16, 25]. As a consequence of both findings, our study strongly supports the recommendation that patients with SB should at no time of life be exposed to latex products (in particular at surgical operations).

In summary, this study suggests that the spina bifida population bears a disease-associated propensity for latex sensitization. This effect cannot be explained exclusively by a higher number of operations and differences related to atopy, age or gender.

Acknowledgement

This work was supported by the Austrian Science Foundation (FWF) P14659-PAT, SFB F1817-B13.

References

- 1 Kelly KJ, Kurup VP, Reijula KE, Fink JN. The diagnosis of natural rubber latex allergy. *J Allergy Clin Immunol* 1994; 93:813–6.
- 2 Niggemann B. Atopy and latex allergy in spina bifida: what's chicken, what's egg? *Pediatr Allergy Immunol* 1997; 8:51.

- 3 Dehlink E, Prandstetter C, Eiwegger T, Putschogl B, Urbanek R, Szeffalusi Z. Increased prevalence of latex-sensitization among children with chronic renal failure. *Allergy* 2004; **59**:734–8.
- 4 Ricci G, Gentili A, Di Lorenzo F *et al*. Latex allergy in subjects who had undergone multiple surgical procedures for bladder exstrophy: relationship with clinical intervention and atopic diseases. *BJU Int* 1999; **84**:1058–62.
- 5 Porri F, Pradal M, Lemiere C *et al*. Association between latex sensitization and repeated latex exposure in children. *Anesthesiology* 1997; **86**:599–602.
- 6 Roberts G, Lack G, Northstone K, Golding J. Prevalence of latex allergy in the community at age 7 years. *Clin Exp Allergy* 2005; **35**:299–300.
- 7 Konz KR, Chia JK, Kurup VP, Resnick A, Kelly KJ, Fink JN. Comparison of latex hypersensitivity among patients with neurologic defects. *J Allergy Clin Immunol* 1995; **95**:950–4.
- 8 Nieto A, Estornell F, Mazon A, Reig C, Garcia-Ibarra F. Allergy to latex in spina bifida: a multivariate study of associated factors in 100 consecutive patients. *J Allergy Clin Immunol* 1996; **98**:501–7.
- 9 Mazon A, Nieto A, Estornell F, Reig C, Garcia-Ibarra F. Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida. *J Allergy Clin Immunol* 1997; **99**:600–4.
- 10 Bernardini R, Novembre E, Lombardi E *et al*. Prevalence of and risk factors for latex sensitization in patients with spina bifida. *J Urol* 1998; **160**:1775–8.
- 11 Bernardini R, Novembre E, Lombardi E *et al*. Risk factors for latex allergy in patients with spina bifida and latex sensitization. *Clin Exp Allergy* 1999; **29**:681–6.
- 12 Degenhardt P, Golla S, Wahn F, Niggemann B. Latex allergy in pediatric surgery is dependent on repeated operations in the first year of life. *J Pediatr Surg* 2001; **36**:1535–9.
- 13 Cremer R, Hoppe A, Kleine-Diepenbruck U, Blaker F. Longitudinal study on latex sensitization in children with spina bifida. *Pediatr Allergy Immunol* 1998; **9**:40–3.
- 14 Gentili A, Ricci G, Di Lorenzo FP, Pigna A, Masi M, Baroncini S. Latex allergy in children with oesophageal atresia. *Paediatr Anaesth* 2003; **13**:668–75.
- 15 Szeffalusi Z, Seidl R, Bernert G, Dietrich W, Spitzauer S, Urbanek R. Latex sensitization in spina bifida appears disease-associated. *J Pediatr* 1999; **134**:344–8.
- 16 Hochleitner BW, Menardi G, Haussler B, Ulmer H, Kofler H, Reider N. Spina bifida as an independent risk factor for sensitization to latex. *J Urol* 2001; **166**:2370–3; discussion 2373–4.
- 17 Niggemann B, Buck D, Michael T, Wahn U. Latex provocation tests in patients with spina bifida: who is at risk of becoming symptomatic? *J Allergy Clin Immunol* 1998; **102**:665–70.
- 18 Hourihane JO, Allard JM, Wade AM, McEwan AI, Strobel S. Impact of repeated surgical procedures on the incidence and prevalence of latex allergy: a prospective study of 1263 children. *J Pediatr* 2002; **140**:479–82.
- 19 Buck D, Michael T, Wahn U, Niggemann B. Ventricular shunts and the prevalence of sensitization and clinically relevant allergy to latex in patients with spina bifida. *Pediatr Allergy Immunol* 2000; **11**:111–5.
- 20 Mazon A, Nieto A, Pamies R *et al*. Influence of the type of operations on the development of latex sensitization in children with myelomeningocele. *J Pediatr Surg* 2005; **40**:688–92.
- 21 Niggemann B, Breiteneder H. Latex allergy in children. *Int Arch Allergy Immunol* 2000; **121**:98–107.
- 22 Cremer R, Hoppe A, Korsch E, Kleine-Diepenbruck U, Blaker F. Natural rubber latex allergy: prevalence and risk factors in patients with spina bifida compared with atopic children and controls. *Eur J Pediatr* 1998; **157**:13–6.
- 23 Shah S, Cawley M, Gleeson R, O'Connor J, McGeady S. Latex allergy and latex sensitization in children and adolescents with meningomyelocele. *J Allergy Clin Immunol* 1998; **101**:741–6.
- 24 Chen Z, Cremer R, Posch A, Raulf-Heimsoth M, Rihs HP, Baur X. On the allergenicity of Hev b 1 among health care workers and patients with spina bifida allergic to natural rubber latex. *J Allergy Clin Immunol* 1997; **100**:684–93.
- 25 Cremer R, Kleine-Diepenbruck U, Hoppe A, Blaker F. Latex allergy in spina bifida patients – prevention by primary prophylaxis. *Allergy* 1998; **53**:709–11.
- 26 Cremer R, Kleine-Diepenbruck U, Hering F, Holschneider AM. Reduction of latex sensitisation in spina bifida patients by a primary prophylaxis programme (five years experience). *Eur J Pediatr Surg* 2002; **12** (Suppl.1):S19–21.
- 27 Nieto A, Mazon A, Pamies R *et al*. Efficacy of latex avoidance for primary prevention of latex sensitization in children with spina bifida. *J Pediatr* 2002; **140**:370–2.
- 28 Rihs HP, Chen Z, Rueff F *et al*. HLA-DQ8 and the HLA-DQ8-DR4 haplotype are positively associated with the hevein-specific IgE immune response in health care workers with latex allergy. *J Allergy Clin Immunol* 2002; **110**:507–14.
- 29 Rihs HP, Cremer R, Chen Z, Baur X. Molecular analysis of DRB and DQB1 alleles in German spina bifida patients with and without IgE responsiveness to the latex major allergen Hev b 1. *Clin Exp Allergy* 1998; **28**:175–80.
- 30 Bohle B, Wagner B, Vollmann U *et al*. Characterization of T cell responses to Hev b 3, an allergen associated with latex allergy in spina bifida patients. *J Immunol* 2000; **164**:4393–8.