

Risk factors for latex allergy in patients with spina bifida and latex sensitization

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Summary

Background Some subjects with spina bifida (SB) and latex sensitization (cutaneous and/or serum IgE) can have clinical reactions, while others may have no symptoms after the exposure to latex products.

Objective This study was carried out to determine the risk factors associated with latex allergy in patients affected with SB and latex sensitization.

Methods Fifty-nine consecutive subjects affected with SB, besides answering a questionnaire, underwent a skin-prick test (SPT) to latex and the determination of the specific serum IgE (RAST CAP) to latex. The total serum IgE concentration was determined and SPT to common aero- and food-allergens, skin tests (prick + prick) with fresh foods (kiwi, pear, orange, pineapple, tomato, banana) and RAST CAP to the same foods tested by the prick + prick technique, were also performed.

Results Fifteen out of the 59 subjects (25%) were sensitized to latex according to the presence of IgE to latex detected by SPT (nine patients) and/or RAST CAP (13 patients). Five out of the 15 sensitized patients (33%) suffered from clinical reactions to latex (urticaria, conjunctivitis, angioedema, rhinitis, bronchial asthma) while they were using latex gloves and while inflating latex balloons. In the 15 sensitized patients, the presence of specific latex serum IgE > 3.5 kU/L ($\geq$ class 3), a positive latex SPT, an elevated total serum IgE, and a positive prick + prick and/or a positive RAST CAP to foods, were significant ($P < 0.05$) risk factors associated with latex symptoms. The other factors tested (age, gender, months of intermittent bladder catheterization, surgical procedures, SPT reactivity and clinical reactions to aero-allergens and food-allergens, skin tests for fresh foods, positive RAST CAP to foods) were not significantly different in symptomatic and asymptomatic patients.

Conclusion Significant risk factors for symptoms to latex in patients with SB and latex sensitization were a presence of specific IgE to latex > 3.5 kU/L, a more frequent positive latex SPT, elevated total IgE, and one or more positive prick + prick and/or RAST CAP to fresh foods.

Keywords: latex, risk factors, sensitization, spina bifida

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Introduction

Patients with spina bifida (SB) are at high risk of latex sensitization (presence of cutaneous and/or serum latex

specific IgE) [1]. Some sensitized subjects may present clinical reactions to latex while others have no symptoms after exposure to products containing latex proteins. Several factors may be relevant to a high risk of latex symptoms in subjects with SB and latex sensitization. Some authors showed that high levels of serum-specific IgE to latex, positive responses to latex skin prick test (SPT), a high number of operations, and a personal history of atopy were

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significantly associated with symptoms to latex in patients with SB and latex sensitization [2].

An association between latex sensitivity and foods is well known and has been reported at the clinical level [1,2] (e.g. buckwheat [3]; banana and avocado [4]; oregano [5]; dill [5]; kiwi [6]), the level of skin sensitization [3] (e.g. milk, egg white, wheat), the level of RAST and/or immunoblotting inhibition (e.g. pear [8]; papaya, avocado, banana and chestnut [9]; passion fruit [4]; fig, melon, mango, kiwi, pineapple, peach and tomato [9]). *In vitro* studies are important to confirm a cross-reaction between latex and food [10]. However, specific IgEs for food allergens have never been studied because of possible risk factors for clinical reactions to latex in patients with SB and latex sensitization.

The aim of this investigation was to evaluate the possible risk factors for symptoms to latex in subjects with latex sensitization affected with SB.

Materials and methods

Fifty-nine patients (42 females and 17 males, mean age $\pm$ SD: 14.3 ± 9.3 years, age range 2–40 years) were studied. These subjects represented an entire population of patients with SB in our area and had been referred to the Allergy and Clinical Immunology Unit, Department of Paediatrics, Florence, Italy to evaluate a possible latex sensitization and/or allergy. All patients or their parents answered a questionnaire (under the supervision of an allergist) revealing any current or previous presence of IgE-mediated diseases, clinical reactions to rubber, the number and dates of previous surgical procedures, and the number and duration of intermittent bladder catheterizations. The patients also underwent latex SPT with a commercial extract (Laboratorio Lofarma, Milan, Italy), as previously reported [7,8]. For the purpose of this investigation only subjects with latex sensitization (i.e. with specific cutaneous and/or seric IgE to latex) were studied.

Specific serum IgE to latex (RAST CAP System, Pharmacia, Uppsala, Sweden) as well as total serum IgE (PRIST, Sanofi Diagnostics Pasteur, Chaska MN, USA) were determined according to the manufacturer's instructions. The reference values for RAST CAP and PRIST were provided by the manufacturers. The latex-specific IgE results were graded as class 0 for values lower than 0.35 kilounits per litre (kU/L), class 1 for values between 0.35 and 0.7 kU/L, class 2 for values between 0.7 and 3.5 kU/L, class 3 for values between 3.5 and 17.5 kU/L, class 4 for values between 17.5 and 50 kU/L, class 5 for values between 50 and 100 kU/L, and class 6 for values greater than 100 kU/L. Results >0.35 kU/L for RAST CAP and >2 SD for age for PRIST [international units per millilitre (IU/mL)] were considered positive.

SPTs to the most common sensitizing aero-allergens (*Dermatophagoides pteronyssinus* and *D. farinae*, horse,

cat and dog dander, *Alternaria tenuis* and *Cladosporium herbatum*, grass pollen, *Parietaria officinalis*, *Artemisia vulgaris*, olive pollen, cypress pollen, plane-tree pollen) and food-allergens (milk, egg white, tomato, peanut, codfish, wheat, soybean) in Italy were performed (Bayrofarm, Milan, Italy). Skin tests (prick + prick according to Dreborg and Foucard [11]) with some fresh foods reported to cross-react with latex proteins (kiwi, pear, orange, pineapple, tomato, banana) [9], and RAST (CAP System, Pharmacia) to the foods tested by the prick + prick technique were also carried out. Skin tests were done on the volar side of the forearm with a lancet from Dome Hollister Stier (Slough, UK; 1 mm tip). The skin test results (commercial extracts and fresh foods) were considered to be positive if the weal was ≥ 3 mm without any reaction to the negative control solution [12].

For statistical analysis Fisher's exact test and Wilcoxon Rank Sum-test were used (Intercooled Stata 4.0 for Windows). A *P*-value <0.05 was considered significant for both tests.

Results

Fifteen (25%) subjects (mean age $\pm$ SD: 13 ± 7.8 years, age range 2–28 years) were sensitized to latex as shown by the presence of IgE to latex detected by either SPT or RAST CAP (two patients had only a positive SPT, six patients had only a positive RAST CAP, and seven patients were positive to both tests) (Table 1). Of the 13 RAST CAP positive patients, three presented a class 1 RAST CAP, four had a class 2, one presented a class 3, three had a class 4, one had a class 5 and one patient presented a class 6 RAST CAP. No side-effects to the SPT were noted.

Five patients (8%) reported clinical reactions to latex (urticaria in four subjects, conjunctivitis in four, angioedema in two, rhinitis in two and bronchial asthma in two subjects) which were substantiated both by the clinical history and by the reports of the physicians responsible for these patients. No anaphylactic reactions were reported. Both the latex RAST CAP and SPT were positive in the five patients. All patients affected with latex allergy reported clinical symptoms while using latex gloves and while inflating latex balloons. A positive latex SPT was more likely in symptomatic than in asymptomatic patients (5/5 vs 4/10, *P* = 0.04; Table 2). In the 15 subjects sensitized to latex, the mean of specific serum IgE to latex was significantly higher in the group of symptomatic patients as compared with the asymptomatic group (*P* = 0.005; Table 2). The proportion of subjects with specific serum IgE to latex >3.5 kU/L was significantly higher in the symptomatic group (5/5 subjects) than in the asymptomatic group (1/10 subjects) (*P* = 0.002; Table 2).

The presence of elevated total serum IgE was significantly more likely in symptomatic than in asymptomatic patients (5/5 vs 4/10, *P* = 0.04; Table 2).

Table 1. Clinical and immunological features in 15 patients sensitized to latex

No.	Sex	Age (years)	Symptoms to latex	Latex SPT*	Latex RAST CAP (kU/L)	Prick + prick positive foods	RAST CAP positive foods (kU/L)	Total IgE (IU/mL)
1	F	5	No	0	0.587	None	Orange (0.733) Tomato (0.879) Banana (1.06)	40
2	F	6	No	6	29.7	Pear Banana	Pear (2.95) Banana (1.24)	82
3	F	18	No	0	0.647	Pear	Pear (0.894)	42
4	F	15	No	3	<0.35	None	None	448
5	F	9	Yes	7	46.4	Kiwi Pear Orange Tomato	None	1940
6	M	21	No	3	<0.35	None	None	346
7	M	6	No	0	1.03	None	None	2700
8	F	10	Yes	8	76.1	Kiwi	None	710
9	M	10	No	0	1.99	None	None	22
10	F	23	No	3	2.87	None	Tomato (0.419) Banana (0.467)	513
11	F	28	No	0	0.406	None	None	33
12	F	16	Yes	3	12.0	Kiwi Tomato	None	627
13	F	20	Yes	6	27.3	Kiwi Pear Orange	None	446
14	F	5	Yes	8	185	None	Pear (0.555) Tomato (0.586) Banana (0.657)	263
15	M	2	No	0	0.703	None	None	12

*size of the skin weal in mm.

Nine out of the 15 (60%) patients presented one or more positive skin tests (prick + prick) and/or RAST CAP to foods (four patients had only a positive prick + prick, three patients had only a positive RAST CAP, and two patients were positive to both tests) (Table 1). By prick + prick kiwi was positive in four subjects, pear in four, orange in two, tomato in two, banana in one, whereas pineapple was negative in all subjects. By RAST CAP banana was positive in four subjects, pear in three, tomato in three, orange in one, whereas kiwi and pineapple were negative in all subjects.

In patients sensitized to latex a positive prick + prick and/or a positive RAST CAP to foods were statistically associated with latex symptoms ($P = 0.04$; Table 2).

In the 15 latex-sensitized patients, there was no statistical difference between symptomatic and asymptomatic subjects in gender, age at the time of study, number of operations, duration in months of intermittent bladder catheterizations,

presence of one or more positive SPT to aero-allergens and one or more positive SPT to food allergens, presence of one or more positive food RAST CAP, presence of one or more positive prick + prick, clinical reactions to aero-allergens and clinical reactions to food-allergens (Table 2).

Discussion

We found a prevalence of latex sensitization equal to 25% (15/59) in subjects affected with SB. Only five out of the 15 patients (33%) with latex sensitization had clinical reactions to latex. No subjects presented severe systemic clinical reactions to latex: the most frequent clinical reactions were urticaria and conjunctivitis. Symptoms arose shortly after patients had used latex gloves and inflated latex balloons.

	Latex symptomatic subjects (n = 5)	Latex asymptomatic subjects (n = 10)	P-value
Sex (F)	5	6	0.231†
Age (median years [range])	10 (5–20)	12.5 (2–28)	0.806§
Intermittent bladder catheterization (median months [range])	84 (36–216)	63 (0–276)	0.355§
Surgical procedures n (range)	6 (5–14)	5 (2–10)	0.238§
Presence of total serum IgE > 2SD for age	5	4	0.04†
Presence of ≥ 1 positive SPT to aero-allergens (commercial extracts)	4	5	0.580†
Presence of ≥ 1 positive SPT to food allergens (commercial extracts)	0	2	0.524†
Presence of ≥ 1 positive RAST for foods	1	4	0.600†
Presence of ≥ 1 positive prick + prick for foods	4	2	0.089†
Presence of ≥ 1 positive RAST and/or prick + prick for foods	5	4	0.04†
Clinical reactions to aero- allergens	2	2	0.560†
Clinical reactions to food allergens	1	0	0.333†
RAST CAP to latex (median kU/L [range])	46.4 (12–185)	0.7 (0.3–29.7)	0.005§
RAST CAP to latex > 3.5 kU/L	5	1	0.002†
Size of skin weal to latex (median mm [range])	7 (3–8)	0 (0–6)	0.005§
% positive SPT to latex	100	40	0.04†

Statistical tests: † = Fisher exact test two tailed; § = Wilcoxon rank sum test.

Patients with SB are usually, but not always, told to avoid contacts with latex products to prevent latex sensitization [13]. Cremer and coworkers showed that primary latex prophylaxis during surgery can prevent latex sensitization in young SB patients [14]. These authors found that the risk of latex sensitization in patients with SB exposed to latex was 38%, while this risk was reduced to 0 when latex exposure was avoided. The advice of avoiding latex exposure is especially given to latex-sensitized patients, because they are more likely to develop symptoms to latex [1]. Identifying the risk factors for latex symptoms among subjects sensitized to latex might be important for predicting the appearance of symptoms to latex.

In this study the mean RAST CAP value for latex was

Table 2. Comparisons of variables between five symptomatic and 10 asymptomatic latex-sensitized subjects

significantly higher among symptomatic than asymptomatic patients (69.4 vs 3.9 kU/L) confirming the data of Mazon and coworkers [2], who found that high mean RAST CAP values for latex were a significant risk factor for symptoms to latex. However, in our study the mean value of specific latex IgE in symptomatic subjects was more than twice that found by Mazon and colleagues (32.8 U/mL). We think that identifying a threshold level of specific IgE for latex could be a suitable tool for use in clinical practice. For this reason we assessed the association between the presence of latex symptoms and the concentrations of specific IgE to latex and found that a value of RAST CAP for latex > 3.5 kU/L was a significant risk factor for the onset of latex symptoms. The presence of a positive latex SPT was significantly

associated with latex symptoms as shown by Mazon. Moreover, the skin weal for latex was significantly larger in subjects with symptoms to latex than in asymptomatic subjects (Table 2). Therefore, in subjects with SB and latex sensitization, finding either a positive latex SPT (especially with a large skin weal) or a RAST CAP to latex >3.5 kU/L is a risk factor for the appearance of latex symptoms. Having a small sample size just makes this finding stronger, because a larger sample size would increase the statistical significance of the difference between the two proportions. These data show that high levels of specific IgE to latex are necessary to cause latex symptoms.

In this report elevated levels of total IgE were significantly associated with latex symptoms. This association was not reported in a previous study [2], in which the authors found that a personal history of atopy was more frequent in symptomatic than in asymptomatic patients. This observation was not confirmed in our study, in which an atopic status (elevated levels of total IgE) favoured the appearance of latex symptoms even when a personal history of atopy (clinical manifestations to aero- or food allergens) was absent. One might observe that, in subjects symptomatic to latex, high levels of total IgE might be caused by the presence of high levels of specific IgE for latex. However, an association between atopic status and allergy to latex is usually acknowledged [8,13].

Latex exposure is an important risk factor for latex sensitization and/or allergy [7,13]. In our study the number of previous operations was not recognized as a risk factor for symptoms to latex, while in another report, regarding latex-sensitized SB patients, there was a significantly higher number of operations in symptomatic than in asymptomatic patients [2]. There are two possible explanations for this discrepancy. Firstly, the duration and the amount of exposure to latex, as well as the kind of operation, more than the number of operations *per se*, could be associated with symptoms in latex-sensitized patients. It is possible that some form of latex avoidance was performed during repetitive operations in these subjects. Unfortunately, we were not able to collect data to confirm this hypothesis. A second possible explanation is that our study might lack the statistical power to detect a significant difference in the mean number of operations between symptomatic and asymptomatic patients.

Patients affected with allergy to latex often present clinical symptoms after eating fruit. It is well known that natural rubber products may cross-react (at the clinical level, at the level of skin sensitization, at the level of RAST and/or immunoblotting inhibition) to various foods such as avocado, banana, buckwheat, egg white, papaya, *Ficus* spp., mango, melon, milk, passion fruit, chestnut, kiwi, pineapple, peach, tomato, pear, oregano, dill, sage, and carrot [3–10,15]. We found a high prevalence of specific

IgE to foods (60%), although only one patient with symptoms to latex had reactions (oral allergic syndrome [OAS]) after eating tomato and kiwi. The presence of specific IgE to fresh foods was significantly associated to latex symptoms, confirming the importance of food sensitization as a risk factor for latex allergy in patients with SB and latex sensitization. We decided not to study the sensitization to single foods (assessed with a prick + prick and/or RAST CAP) because a comparison between patients with and without latex symptoms on the basis of single foods would not be statistically reliable due to the small proportions of subjects with cutaneous and/or seric IgE to the single food allergens.

In conclusion, this study revealed that only 33% of patients with SB and latex sensitization had symptoms to latex: only five out of the 15 sensitized patients presented clinical reactions to latex. In patients with SB and latex sensitization symptoms to latex were associated to the presence of specific IgE to latex >3.5 kU/L, more frequent positive latex SPT, elevated total IgE, and one or more positive prick + prick and/or RAST CAP to fresh foods.

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