Latex allergy and associated risk factors in a group of Turkish patients with spina bifida

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Allergic reactions to latex are common in patients with spina bifida. Its incidence varies between 28% and 67%. The aim of this study was to investigate the incidence of latex allergy and its risk factors in patients with spina bifida in İzmir, Turkey.

Forty-six patients (24 male, mean age 10 years) were included in the study. A questionnaire was completed and skin prick tests with latex solution and cross-reacting foods were performed. Total IgE levels, specific IgE to common aeroallergens (Phadiotop), and latex specific IgE levels were measured. Patients with positive skin test reaction and/or who had specific IgE to latex without clinical symptoms were considered as sensitive to latex. The patients who also had clinical symptoms with latex exposure were diagnosed as allergic to latex.

Latex sensitivity was found in 5/46 patients (10.8%). Only two patients had latex allergy (4.3%). Total IgE levels were higher (median 157 vs. 40 kU/L, p=0.012) and the duration of clean intermittent catheterization was longer insensitized patients when compared to non-sensitized patients (median 8 vs. 3 years, p=0.015). Specific IgE to common aeroallergens and positive skin prick test to cross-reacting foods were more prevalent in sensitized than in non-sensitized patients (p=0.02 and 0.015, respectively).

The incidence of latex allergy in our group was lower than reported in the literature. This result may be due to the low number of surgical interventions. High levels of total IgE, positive Phadiotop, positive skin prick test to cross-reacting foods and the duration of clean intermittent catheterization are the risk factors for latex sensitivity in patients with spina bifida.

Key words: latex allergy, spina bifida, risk factors.

Although the first report that established a relationship between anaphylaxis and exposure to latex was published in 1927, latex allergy remained an undiscovered issue until the 1980's[1,2]. In the last 20 years, allergy to latex has become one of the most important allergies, and its risk groups, diagnostic tools and prevention terms are well defined[3]. While most of the reactions are delayed type hyperreactivity reactions that can cause irritant or allergic contract dermatitis, IgE-mediated immediate type reactions ranging from rhinoconjunctivitis, urticaria, angioedema and asthma to fatal anaphylactic reactions constitute the most important problem in latex allergy. Sensitization rates to latex differ in various populations, ranging from 0.1% to 1% in the normal population, and 2.6% to 16.9% in health care workers, to 28% to 67% in patients with spina bifida[4-8]. Since there is limited data on the prevalence of latex allergy and its associated risk factors in Turkey, we aimed to examine the prevalence of IgE-mediated allergy to latex in a group of Turkish patients with spina bifida living in İzmir, and to determine factors that may play a role in the sensitization.

Material and Methods

Patients

Fifty-four patients with spina bifida, members of the Spina Bifida Association in İzmir, were invited to investigate their latex sensitivity; 46 (24 male and 22 female) of them (85%) accepted

to be included in the study. The remaining eight patients refused to be a part of the study mainly because of difficulty in coming to the hospital. Their ages ranged from 1 year to 31 years (median age 10 years). The patients or their parents gave their written consent and the study was conducted in our outpatient clinic between February 2001 and March 2001.

Questionnaire

The questionnaire included questions about sex, age, personal history of atopy (allergic rhinitis asthma, atopic dermatitis) the presence of atopy in first-degree relatives, history of clean intermittent bladder catheterization (CIC: an accepted mode of management for chronic retention of urine, the aim of which is to keep the bladder completely empty at regular intervals to prevent urinary infections), number of operations and cystourethrograms, the presence of ventriculoperitoneal (VP) shunt, symptoms on contact with latex in the daily environment (e.g. balloons) and medical devices, and also symptoms related to known cros-reacting foods with latex such as avocado, kiwi, banana, etc.

Skin prick tests (SPT) with commercial latex antigen and cross-reacting foods such as banana, kiwi, melon, peach, celery root, carrot, tomato, and apple (Stallergenes, France) were applied to the volar side of the forearm in all the patients with Stallerpoint (Stallergens, France). Histamine phosphate (10 mg/ml histamine based) was the positive control and glycerinated saline the negative control. Skin test responses were regarded as positive if the maximum wheal diameter was 3 mm or greater than negative control[9].

In vitro tests

Serum total and latex-specific IgE (Pharmacia CAP system, Uppsala, Sweden) were measured in all patients, according to the manufacturer's instructions. Total serum IgE was evaluated in KU/L. The latex-specific IgE results were graded as follow: (class 0: <0.35 U/ml, class 1: 035-0.7 U/ml, class 2: 0.7-3.5 U/ml, class 3: 3.5-17.5 U/ml, class 4: 17.5-50 U/ml, class 5: 50-100 U/ml, and class 6 for values above 100 U/ml). Specific IgE to common aeroallergens such as grasses, weeds, tree pollens, molds, and house dust mites was investigated by Phadiotop.

Classification of patients

Patients were classified according to responses to both in vivo and in vitro tests. Patients with wheal diameter 3 mm greater than negative control and/or CAP class ≥3 were considered sensitized to latex. Patients who had symptoms on contacts with latex and had positive test were regarded as allergic to latex.

All statistical analyses were performed using SPSS for Windows 9.05 (SPSS Inc). Fisher's exact test was used for comparison of frequencies between groups (e.g., latex sensitive and non-sensitive). Odds ratios (OR) with 95% confidence intervals (CI) were also presented. Non-parametric tests (Mann-Whitney U) were used for comparisons between latex sensitive and non-sensitive patients for total IgE levels, number of operations, first operation age, duration of VP shunt and clean intermittent catheterization. Result were expressed as median, 1st-3rd quartiles. A P value <0.05 was considered significant.

Results

Patient characteristics are given in Table I.

Table I. Patient Characteristics

Males (n)	24 (52.2%)
Females (n)	22 (47.8%)
Age (years)	10.1±0.9 (1-31)
Personal history of atopy	5 (10.8%)
Family history of atopy	11 (23.9%)
Phadiotop positive patients (n)	9 (20.5%)
Number of operations	3.8±0.3 (1-10)
First operation age (months)	9.8±3 (0-84)
Number of cystourethrograms	3±0.4 (0-15)
Number of urodynamic investigations	2.5±0.3 (0-8)
Number of cystoscopies	1±0.3 (0-6)
Ventriculoperitoneal shunt (n)	19 (41.3%)
Clean intermittent catheterization (n)	36 (78.3%)

Data are presented as means ± standard error and range (n=46).

Seven of 46 patients (15.2%) had either positive prick test or specific IgE to latex. One patient was SPT negative, but had specific IgE to latex in serum (CAP Class 3), while three patients were SPT positive, but showed no specific IgE to latex (Table II). According to the aforementioned criteria we classified five patients as sensitized (10.8%), two patients as allergic (4.3%) and 39 patients as non-sensitized to latex. Among the seven patients classified as sensitized, two (28.5%) reported adverse reactions in relation to latex. Symptoms included

urticarial lesions and angioedema of the penis while undergoing bladder catheterization. These two patients with clinical reaction to latex in their history had higher reactivity in SPT or had a CAP class ≥3. The other five sensitized patients and patients classified as non-sensitized did not report any clinical reactions to latex (Table II).

Four of seven patients (57.1%) who were sensitized to latex also had positive specific IgE to common environmental allergens based on Phadiotop, while only five of 39 (12.8%) non-sensitized patients were Phadiotop positive (p=0.02). Total serum IgE levels were significantly higher in sensitized than in non-sensitized patients (median 157 kU/L vs. 40 kU/L, p=0.012, Fig. 1). Six of 46 patients (13%) had symptoms with cross-reacting foods. The main symptom was itching at the oral mucosa while eating these foods. Otherwise 19 patients (41.3%) presented one or more positive SPT to foods. The presence of positive prick tests to foods was significantly more likely in sensitized than in non-sensitized patients (p=0.015; OR 12.000; 95% CI: 1.304-110.402, Table III).

Table II. Data of the Patients with Latex Sensitivity and Allergy

No.	Sex	Age (years)	Symptoms to latex	SPT* to latex (mm)	Latex RAST U/ml	SPT* to foods	Total IgE (kU/L)	Phadiotop
1	M	15	No	5	0.7	Apple, peach, melon celery	992	Positive
2	F	6	No	3	17.5	Banana	148	Negative
3	M	13	No	5	0	Apple, melon, carrot	892	Positive
4	M	8	No	4	0	Apple, peach	53	Negative
5	F	7	No	3	0	Tomato, kiwi	49	Negative
6	M	9	Yes*	10	50	Kiwi, carrot	157	Positive
7	M	5	Yes*	0	17.5	None	3718	Positive

* Pruritus, hyperemia and swelling of penis with bladder catheterization.
* SPT: Skin prick test.

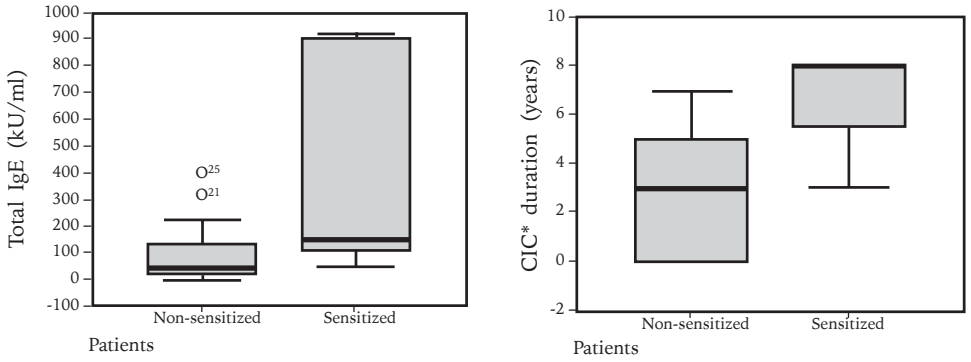

Fig. 1. Total IgE levels and the duration of CIC* in sensitized and non-sensitized patients.
Total IgE levels were higher (median 157 vs. 40 kU/ml, p=0.012) and the duration of CIC was longer (median 8 vs. 3 years, p=0.015) in sensitized patients when compared to non-sensitized patients. Boxplot shows median 1st-3rd quartiles of total IgE levels and the duration in years of CIC.
*CIC: Clean intermittent catheterization.

Table III. Comparison of Variables Between Sensitized and Non-sensitized Patients

	Sensitized patients (n=7)	Non-sensitized patients (n=39)	P-value	OR; 95% CI
Sex (F/M)	2/5	20/19	ns	0.380; 0.066-2.200
Age (years) (median, 1st-3rd quartile)	88 (6-13)	9 (6-13)	ns	—
Personal atopy (yes/no)	0/7	5/34	ns	0.872; 0.773-0.983
Family atopy (yes/no)	1/6	10/29	ns	0.483; 0.052-4.521
Total IgE (kU/ml) (median, 1st-3rd quartile)	157 (53-922)	40 (21.5-138.5)	0.012	—
Phadiotop (positive/negative)	4/3	5/34	0.020	9.067; 1.549-53.067
Reaction to foods (yes/no)	0/7	6/33	ns	0.842; 0.734-0.966
SPT to foods (positive/negative)	6/1	13/26	0.015	12.000; 1.304-110.402

SPT: Skin prick tests; OR: odds ratio, CI: confidence intervals; NS: not significant.

There was no significant difference between test positive and negative groups regarding sex, personal or family atopy history, symptoms with cross-reacting foods and VP shunt ($p>0.05$). There were also no differences between the two groups according to age, number of operations (median 3 vs. 3), the first operation age, cystoscopies, cystourethrograms and urodynamic investigations ($p>0.05$). However, the duration in years of clean intermittent catheterization was significantly longer in sensitized than non-sensitized patients (median 8 years vs. 3 years, $p=0.015$, Tables III-IV, Fig. 1).

well protected against latex. Indeed, in well-controlled studies, the main risk factor that leads to sensitivity to latex in patients with spina bifida is the number of surgical operations[13-14]. Michael et al.[10] reported that operation number greater than five was an independent risk factor. Moreover, if the number of surgical procedures exceeds nine, the patient may be at risk of developing anaphylaxis[15]. In our patients the median operation number was only three, and the number of operations was not a risk factor for latex sensitivity. On the other hand, the number

Table IV. Comparison of Medical Procedures Between Senisitized and Non-sensitized Patients

	Sensitized patients (n=7)	Non-sensitized patients (n=39)	P-value
Cystourethrograms (yes/no)	4/3	28/11	ns
Cystoscopy (yes/no)	2/3	12/19	ns
Urodynamic (yes/no) investigations	5/0	28/5	ns
CIC* (yes/no	7/0	29/10	ns
CIC duration (years) (median 1st-3rd quartile)	8 (4.25-8)	3 (0-5.25)	0.015
VP[8] shunt (yes/no)	3/4	16/23	ns
VP shunt (years) (median, 1st-3rd quartile)	0 (0-8)	0 (0-6)	ns
Number of operations (median, 1st-3rd quartile)	3 (2-5)	3 (2-5)	ns
First operation age (month) (median, 1st-3rd quartile)	4 (0-7)	2 (0-6)	ns
Number of cystourethrograms (median, 1st-3rd quartile)	1 (1-3)	2 (1-4)	ns
Number of cystoscopies (median, 1st-3rd quartile)	0.5 (0-1.75)	0 (0-2)	ns
Number of urodynamic investigations (median, 1st-3rd quartile)	2.5 (1.25-3)	2 (1-3)	ns

CIC: clean intermittent catheterization; VP: ventriculoperitoneal, NS: not significant.

Discussion

The prevalence of latex sensitivity was 10.8% (7/46) and of latex allergy 4.3% (2/46) in our patients affected by spina bifida. None of the cases had severe clinic reactions to latex; the main symptom was urticarial-like lesions occurring just after the use of intravesical catheters. These allergic patients had larger skin test reactivity and/or higher CAP class than asymptomatic patients (Table II). Thus patients highly sensitive to latex according to their tests may be at a higher risk of developing allergic symptoms. As reported before[10-12].

Our latex sensitivity rates were lower than seen in other study groups (28-67%[5,8] vs. 10.8%). Akçakaya et al.[8] reported that 30.5% of children with neural tube defects had positive prick tests to latex. They found that latex allergy was present 3.5 times more frequently in operated patients. Lower prevalence of latex sensitivity in our group may be due to the low number of surgical interventions, rather than to being

of previous operations was not recognized as a risk factor for latex allergy in other studies[11,16]. Furthermore, Szepfalusi et al.[17] found a disease-associated propensity for latex sensitization in patients with spina bifida. These findings support the interpretation that spina bifida per se represents the primary risk factor for latex sensitization, and the number of operations represents only the second risk factor. The duration of operation, the amount of exposure to latex during surgery, and the route of sensitization are other risk factors to be evaluated for sensitization.

Genetically determined susceptibility is an important factor regulating type I allergy. Latex-sensitized patients with spina bifida with hevein-specific IgE antibodies showed an increased but not significant DQB1*0302 frequency compared with that seen in those without hevein-specific IgE antibodies[18]. In a small group of individuals with latex allergy, there was a strong association between the IgE responsiveness to hevein and the HLA class II

antigens DR4 and DQ8[19]. We do not know whether there was an association between sensitization to latex allergens and HLA class II genes in our group of patients, which may be another possible explanation for lower latex sensitivity prevalence in our cohort.

It is argued that atopy can lower the threshold of latex sensitivity as well as latex allergy[10,12,13,15,20,21]. But there are also some report against the influence of atopy on latex allergy in patients with spina bifida[11,22]. In our cohort we found that high levels of total IgE which may reflect the presence of an atopic status, were associated with higher prevalence of latex sensitivity, as observed in other studies[13]. Sensitivity to common aeroallergens such as pollens of grasses, weeds and trees; molds; house-dust mite; and animal dander was found in 57.1% of our latex-sensitized subjects and in 12.8% of non-sensitized subjects (OR: 9.067; 95% CI: 1.549-53.067, Table III). We concluded that high levels of total IgE and positive Phadiotop were significant risk factors for latex sensitivity in our patients.

Whether symptomatic or not, patients with positive SPT to foods that cross-react with latex were 12 times more at risk of becoming sensitive to latex than those with negative tests (Table III). There are other reports which suggest allergy to foods is also another risk factor for latex sensitivity[15]. Moreover, patients who are at risk of developing latex sensitivity, like patients with spina bifida, should be warned about the cross-reacting foods and these foods should be strictly eliminated from their diet as prophylaxis[23].

We could not find any relation between sensitivity to latex and age at first operation and the number of urodynamic investigations, cystoscopies and cystourethrograms. Although other authors reported VP shunt as an important risk factor[13,20,21], its existence and duration were not associated with sensitivity to latex in our cohort. One simple explanation for this is that the materials used for this procedure do not contain latex but rather silicone, and the duration of this procedure is relatively short.

Finally, the duration in years of clean intermittent bladder catheterization was a risk factor for latex sensitivity (Table IV). To our knowledge this procedure was not previously recognized as a risk factor for patients with spina bifida. Ricci et al.[24] reported that in patients with bladder exstrophy, another group of patients who undergo multiple surgical interventions, the years of intermittent catheterization were significantly greater in latex allergic patients. The reason for this remains unclear because this procedure is often performed with latex-free devices. Nevertheless, patients who will require CIC should also be kept away from latex from the beginning.

In summary, latex sensitivity and latex allergy rates in our cohort were lower than reported in the literature. This result may be due to the low number of surgical interventions in this group of patients. High levels of total IgE, positive Phadiotop, positive skin prick test to cross-reacting foods and the duration of clean intermittent catheterization are the risk factors for latex sensitivity in patients with spina bifida.

REFERENCES

1. Niggemann B, Breitender H. Latex allergy in children. Int Arch Allergy Immunol 2000; 121: 98-107.
2. Nutter AF. Contact urticaria to rubber. Br J Dermatol 1979; 101: 597-598.
3. Poley G, Slater J. Latex allergy. J Allergy Clin Immunol 2000; 105: 1054-1062.
4. Barton EC. Latex allergy: recognition and management of a modern problem. Nurse Pract 1993; 18: 54-58.
5. Randolph C, Fraser B. Latex hypersensitivity in a horse farmer. Allergy Asthma Proc 1996; 17: 89-91.
6. Saraçlar Y, Çetinkaya F, Tuncer A, Sekeral B, Hovanec-Burns D, Unver E. Latex sensitivity among hospital employees and atopic children. Turk J Pediatr 1998; 40: 61-68.
7. Sener O, Taşkapan O, Ozangüç N. Latex allergy among operating room personnel in Turkey. J Investig Allergol Clin Immunol 2000; 10: 30-35.
8. Akçakaya N, Kulak K, Hassanzadeh A, Camcıoğlu Y, Çokuğraş H. Latex allergy: the incidence among Turkish children with atopic disease with neural tube defects. Allergol Immunopathol (Madr) 1999; 27: 141-144.
9. Dreborg S, Backman A, Basomba A, Bousquet J, Digies P, Malling HI. Skin tests used in type I allergy testing. Position paper prepared by the Subcommittee on Skin Tests of the EAACI. Allergy 1989; 44 (Suppl) 1-69.
10. Michael T, Niggemann B, Moers A. Risk factors for latex allergy in patients with spina bifida. Clin Exp Allergy 1996; 26: 934-939.
11. Bernardini R, Novembre E, Lombardi E. Risk factors for latex allergy in patients with spina bifida and latex sensitization. Clin Exp Allergy 1999; 29: 681-686.
12. Mazon A, Nieto A, Estornell F. Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida. J Allergy Clin Immunol 1997; 99: 600-604.

13. Turjanmaa K, Makiner-Kiljunen S, Ruendo T, Alenius H, Palosuo T. Natural rubber latex allergy. The European experience. Immunol Allergy Clin North Am 1995; 15: 71-88.

14. De Swert LF, Van Laer KM, Verpoorten CM, Van Hoevveld EM, Cadot P, Stevens EA. Determination of independent risk factors and comparative analysis of diagnostic methods for immediate type latex allergy in spina bifida patients. Clin Exp Allergy 1997; 27: 1067-1076.

15. Kelly KJ, Pearson ML, Kurup VP. A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: epidemiologic factors, risk factors and latex hypersensitivity. J Allergy Clin Immunol 1994; 94: 53-61.

16. Ziylan OH, Ander AH, Alp T, et al. Latex allergy in patients with spinal dysraphism: the role of multiple surgery. Br J Urol 1996; 78: 777-779.

17. Szepfalusi Z, Seidl R, Bernert G, Dietrich W, Spitzauer S, Urbauek R. Latex sensitization in spina bifida appears disease-associated. J Pediatr 1999; 134: 344-348.

18. 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: 507-514.

19. Rihs HP, Chen Z, Cremer R, Baur X. HLA class II antigens DR4 and DQ8 are associated with allergy to hevein, a major allergen of Hevea latex. Tissue Antigens 1997; 49: 92-95.

20. Niggemann Bb, Bauer A, Jendroska K, Wahn U. Latex allergy as a cause of eosionphilia in cerebrospinal fluid in a child with a ventricular shunt. J Allergy Clin Immunol 1997; 100: 849-850.

21. Nieto A, Estornell F, Mazon A, Reigh C, Garcia-Ibarra F. Allergy to late in spina bifida: a multivariate study of associated factors in 100 consecutive patients. J Allergy Clin Immunol 1996; 98: 501-507.

22. Capriles-Hulett A, Sanchez-Borges M, Von-Scanzoni C. Very low frequency of latex and fruit allergy in patients with spina bifida from Venezuela: influence of socioeconomic factors.Ann Allergy Asthma Immunol 1995; 75: 62-64.

23. Ferreira MB, Carlos Ag. Latex: a complex allergy. Allergy Immunol (Paris) 1999; 31: 18-21.

24. 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 International 1999; 84: 1058-1062.