Factors that influence the presence of symptoms caused by latex allergy in children with spina bifida

Angel Mazón, MD,[a] Antonio Nieto, MD,[a] Francisco Estornell, MD,[b] Alicia Nieto, MD,[a] Carlos Reig, MD,[b] and Fernando García-Ibarra, MD[b]
Valencia, Spain

Background: Some children with spina bifida who are sensitized to latex can have severe reactions, whereas others remain free of symptoms.
Objective: Our aim was to study the differences between these two groups of patients.
Material and methods: In 110 consecutive children with spina bifida, we identified by means of skin prick tests and serum latex-specific IgE 32 patients sensitized to latex. In these 32 patients, data were collected for sex, age, personal and familial history of atopy, number of cystourethrograms and number of operations, history of intermittent bladder catheterization, serum levels of total IgE in units per milliliter and in z units, levels of latex-specific IgE, and results of skin prick tests.
Results: Sixteen patients (50%) had clinical symptoms related to latex. These patients had significantly higher levels of serum specific IgE (32.8 ± 30.7 U/ml vs. 12.8 ± 16.5 U/ml), were more likely to have positive responses on skin tests (100% vs. 75%), had a higher number of operations (10.5 ± 6.9 vs. 5.8 ± 2.7), and were more likely to have a personal history of atopy (44% vs. 6%) in comparison with findings for patients who did not have symptoms ($p < 0.05$ in all cases). A multivariate logistic regression analysis identified the latter two factors as independent synergistic variables to predict symptoms.
Conclusions: The number of operations is the main risk factor for latex-related symptoms in sensitized children. Atopy seems to lower the threshold both for sensitization and for the presentation of clinical reactions. (J Allergy Clin Immunol 1997;99:600-4.)

Key words: Latex, spina bifida, hypersensitivity, atopy, exposure, symptoms, risk factors

Latex allergy has emerged as a problem in the past 15 years, since latex-related urticaria was described by Nutter.[1] Severe IgE-mediated reactions to latex appear in the course of surgical manipulations or roentgenologic explorations as a result of the direct contact with latex. These reactions may be life threatening and they often are the first symptom in sensitized patients.[2-5] Recent studies on anaphylactic reactions during operation have identified latex as the responsible agent in most cases,[2] and some reactions formerly attributed to anesthetic drugs have been demonstrated to be caused by latex.[5]

One of the risk groups for hypersensitivity to latex is that of children with spina bifida, who have been repeatedly exposed to contact with latex, since the first day of life, through multiple therapeutic and diagnostic procedures. Sensitization in these children ranges from 18% to 72% depending mainly on the diagnostic criteria,[6-10] and it is known that some sensitized children have latex-related symptoms, whereas others do not exhibit clinical reactions. Some reports have identified risk factors associated with the development of latex hypersensitivity,[6, 8, 9, 11, 12] but the differences between sensitized children with and without symptoms have not been thoroughly studied. The aim of our work was to evaluate, in a large group of children with spina bifida, the differences between sensitized children who display symptoms in relation to latex and those sensitized patients who remain free of symptoms.

METHODS

A total of 110 children with spina bifida was entered into the study. The children were consecutively selected from the outpatient clinic of the Pediatric Urology Section of a tertiary referral center, where they had been receiving follow-up since birth. The following data were collected in all cases: age, sex, familial and personal history of atopy, history of intermittent bladder catheterization, history of untoward reactions to latex, number of operations and number of cystourethrograms, rate of operations per year of age, level of serum total IgE in absolute units per milliliter and in relative z units, latex-specific IgE in units per milliliter, and results of latex skin prick tests.

Clinical reactions to latex included urticaria, edema of face and lips, tongue itching, rhinitis, and cough related to contact with latex in balloons, gloves, or colostomy bags plus anaphylactic shock during a cystourethrogram in one patient. A positive familial or personal history of atopy was based on clinical grounds and included antecedents of atopic dermatitis, asthma, rhinoconjunctivitis, and urticaria/angioedema not related to latex.

In vivo tests

After informed consent was obtained from parents, skin prick tests with commercial latex antigen (ALK–Abello Labs, Spain) were done in all patients. This antigen is obtained from an ammoniated preparation of latex, but ammonium is eliminated during the process of extraction. The final product is a glycer-

From the Departments of [a]Pediatric Allergy and [b]Pediatric Urology, Children's Hospital La Fe, Valencia, Spain.
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Reprint requests: Antonio Nieto, MD, S. de Alergia Pediátrica, Hospital Infantil La Fe, Av. Campanar, 21, 46009-Valencia, Spain.
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TABLE I. Results in sensitized patients with and without symptoms sorted by latex-specific IgE levels in ascending order

Latex symptoms*	Specific IgE (U/ml)	Skin test result	No. of operations	Personal history of atopy	Total IgE (z units)
—	<0.35	4+	5	+	1.3
—	<0.35	4+	9	−	0.3
—	0.44	3+	3	−	2.1
—	1.23	4+	3	−	2.5
—	1.55	4+	12	−	0.2
—	1.64	4+	6	−	0.6
—	2.55	2+	4	−	1.6
—	4.52	3+	4	−	2.6
—	8.31	0+	8	−	1.9
—	9.40	1+	3	−	2.7
—	10.2	4+	4	−	1.4
—	13.7	0+	6	−	1.5
—	18.2	4+	9	−	1.5
—	38.8	4+	7	−	3.5
—	46.7	4+	3	−	1.6
—	47	4+	6	−	3.1
1	1.52	3+	7	−	2.3
1, 3	3.36	4+	3	+	0.8
1, 5	3.81	3+	5	+	2.8
1	5.64	4+	6	+	0.8
4	9.74	4+	10	−	1.3
1	12.3	4+	11	−	0.8
1	15.2	4+	8	+	1.4
1	18.3	4+	8	+	2.3
1, 2	21.7	3+	5	−	0.8
1	35.3	4+	25	−	−1.5
2	41.1	4+	8	+	2
1	45.7	4+	11	−	2.5
1	55.3	3+	19	−	−0.4
1	76.2	4+	6	+	3.7
1	86.3	4+	10	−	3.2
1	93.6	4+	26	−	2.3

*1, Urticaria/angioedema; 2, rhinitis; 3, cough; 4, tongue itching; 5, shock.

inated solution with a 2 mg/ml concentration of proteins, which include a 14 kD antigen, identified by amino acid sequence as the rubber elongation factor (information provided by the manufacturer). Skin test results were graded 0 to 4+ compared with results with saline solution and 1% glycerinated histamine, according to a method similar to that of Turjanmaa et al.[13] No wheal was graded as 0+; wheals with an area up to 25% of the wheal elicited by histamine were graded as 1+, those with the area between 25% and 50% were graded 2+, those with the area between 50% and 75% were graded 3+, and those that exceeded 75% were graded 4+. Skin tests caused no adverse reactions. No challenge or use tests were done.

In vitro tests

Serum total and latex-specific IgE levels were measured in all cases with the Pharmacia CAP System RAST Fluoroenzymoimmunoassay (Uppsala, Sweden) according to the manufacturer's instructions. Total serum IgE level was evaluated in absolute units per milliliter and, to account for age, it was also converted into standard deviations from the mean for age (z units), with use of the values published by Kjellman et al.[14] Values lower than 2 U/ml (sensitivity of the technique) were treated as 2 U/ml for analysis. Latex-specific IgE results were graded, as suggested by the manufacturer, as class 0 for values lower than 0.35 U/ml, class 1 for values between 0.35 and 0.7 U/ml, class 2 for values between 0.7 and 3.5 U/ml, class 3 for values between 3.5 and 17.5 U/ml, class 4 for values between 17.5 and 50 U/ml, class 5 for values between 50 and 100 U/ml, and class 6 for values greater than 100 U/ml.

Classification of patient results

Patient results were classified according to responses to both in vivo and in vitro tests. Patients with strong responses (skin test result ≥3+, CAP class ≥3) to any of the tests were considered to be sensitized to latex. One patient with a skin test result of 2+ and latex-specific IgE findings of class 2, concordant with each other, was also considered to be sensitized. Patients with both test results negative or with only one of them with a very weak response (skin test result 1+, CAP class 1) were considered to be nonsensitized. The remainder of the patients (with responses 0 and 2, 1 and 1, or 1 and 2 to the tests) were considered to have inconclusive or doubtful results.

Statistical study

Chi-square or Fisher's exact tests were used to compare categorical variables. Quantitative variables were studied with

TABLE II. Potential risk factors in latex-sensitized children with and without symptoms

	Symptomatic (n = 16)	Asymptomatic (n = 16)	Test	p Value
Sex (M/F)	10/6	8/8	Chi	0.47
Family history of atopy (yes/no)	7/9	5/11	Chi	0.46
Personal history of atopy (yes/no)	7/9	1/15	Fisher	0.03
IBC (yes/no)	12/4	9/7	Fisher	0.16
Age (yr)	12 ± 3.1	9 ± 5	F	0.051
No. of operations	10.5 ± 6.9	5.8 ± 2.7	K-W	0.014
Rate of operations/yr	1.05 ± 0.99	0.92 ± 0.74	F	0.68
No. of CUG	6.4 ± 2.5	4.8 ± 3	K-W	0.10
Total IgE (U/ml)	273 ± 336	179 ± 271	K-W	0.41
Total IgE (z units)	1.6 ± 1.3	1.8 ± 0.9	F	0.64
Specific IgE to latex (U/ml)	32.8 ± 30.7	12.8 ± 16.5	K-W	0.019
Skin test results (≥3+/<3+)	16/0	12/4	Fisher	0.05

M, Male; *F*, female; *Chi*, chi-square test; *Fisher*, Fisher's exact test; *IBC*, intermittent bladder catheterization; *F*, variance test; *K-W*, Kruskal-Wallis test; *CUG*, cystourethrograms.

the variance test or with its nonparametric equivalent Kruskal-Wallis test when indicated. A correlation test was used to study the relation between the number of operations and the levels of latex-specific IgE. A stepwise logistic regression analysis was done with the presence of latex-related symptoms used as the dependent variable and all the mentioned factors as independent variables. The statistical analysis was done with the commercial SPSS-PC package.

RESULTS

We considered 32 patients to be sensitized, 70 to be nonsensitized, and 8 to have inconclusive results. Among the sensitized patients, 16 (50%) had adverse reactions in relation to latex as shown in Table I, which ranged from mild urticaria during inflation of balloons to anaphylactic shock while undergoing a cystourethrogram. These patients were considered to have symptoms, and the remainder were considered free of symptoms. There were no patients with symptoms among those considered nonsensitized or those who had inconclusive results. Patients with a positive personal history of atopy were considered atopic and the rest as nonatopic.

In Table I we show the raw data of the 32 sensitized children, sorted by ascending levels of specific IgE. The levels were higher in patients with symptoms, but only values of more than 50 U/ml distinctly separated both groups. Among these sensitized children, there were 8 patients, none of them atopic, who had been operated on 10 or more times, and 7 (88%) of them had symptoms (Table I). Eight of the 32 patients were atopic, and 7 (88%) of them also had symptoms. There was a significant correlation between the number of operations and the levels of latex-specific IgE ($r = 0.52, p = 0.002$). All the operations in the analysis had been done before we had a latex-free operating room.

Table II displays the results of the variables in sensitized patients with and without symptoms. Patients with symptoms had significantly higher levels of serum specific IgE, were more likely to have a personal history of atopy and positive skin test results, and had a higher number of previous operations. We divided sensitized patients into four groups, nonatopic asymptomatic, atopic symptomatic, nonatopic symptomatic, and atopic asymptomatic, and the results by this categorization are shown in Table III. The patients in the third group had been operated on more often than those in the other groups and had significantly higher levels of specific IgE than those in the first but not the second group. The rate of operations per year was higher in the third group compared with that in the second, but not with that in the first. In the fourth group (atopic asymptomatic) there was only one patient, so no comparisons could be made.

A multiple logistic regression analysis that included all variables selected two factors, personal history of atopy (0 = no, 1 = yes) and number of operations, as synergistic to predict latex-related symptoms in sensitized children with spina bifida. Results of this analysis are shown in Table IV.

DISCUSSION

All children with spina bifida are currently recommended to avoid contact with latex to prevent sensitization.[15] This can sometimes be difficult, and patients may be exposed to inapparent sources of latex in household products. About 50% of children with spina bifida who are sensitized to latex will have clinical reactions to latex. These are usually mild, but the gradual progress from minor to severe reactions is possible and has been described in patients with spina bifida[16] and in adult patients in other risk groups.[4, 17, 18] The absence of clinical reactions is not a warranty, and children who do not have clinical reactions may also have a progression to severe reactions, inasmuch as the first symptom in some patients has been a life-threatening reaction.[2-5] Thus a latex-free environment must be used for all medical procedures in patients with spina bifida. Although the clinical management must be the same, little is known about the differences between sensitized patients with and without latex-related symptoms, and we have found only one work on this subject in the litera-

TABLE III. Univariate analysis according to atopic status and presence of latex-related symptoms

	A Non-atopic asymptomatic	B Atopic symptomatic	C Non-atopic symptomatic	D Atopic asymptomatic
No. of cases	15	7	9	1
Sex (M/F)	8/7	3/4	7/2	0/1
Family history of atopy (yes/no)	4/11	4/3	7/2	1/0
IBC (yes/no)	8/7	6/1	6/3	1/0
Age (yr)	8.9 ± 5.1	12.8 ± 2.1	11.4 ± 3.8	11
No. of operations	5.8 ± 2.8	6.3 ± 1.9	13.8 ± 7.7	5
Rate of oeprations/yr	0.95 ± 0.8	0.5 ± 0.1	1.5 ± 1.2	0.45
No. of CUG	4.8 ± 3.1	7 ± 3	5.9 ± 2.1	5
Total IgE (U/ml)	181 ± 280	387 ± 428	184 ± 234	152
Total IgE (z units)	1.79 ± 0.9	1.97 ± 1.1	1.26 ± 1.51	1.29
Specific IgE to latex (U/ml)	13.6 ± 16.7	23.4 ± 26.8	40.2 ± 33.2	<0.35
Skin test results (≥3+/<3+)	11/4	7/0	9/0	1/0

M, male; *F,* female; *IBC,* intermittent bladder catheterization; *CUG,* cystourethrogram.
Analysis results:
Age: A vs. B, $p = 0.07$.
No. of operations: A vs. C, $p = 0.002$; B vs. C, $p = 0.014$.
Rate of operations/yr: B vs. C, $p = 0.013$.
Specific IgE to latex: A vs. C, $p = 0.029$.
All other comparisons: $p > 0.10$.

ture, in which the patients were those who had had severe anaphylactic reactions during general anesthesia.[2]

In our study, 16 patients had symptoms related to latex. They were more likely to have positive skin test findings, had higher levels of serum specific IgE, were more likely to have a personal history of atopy, and had been operated on more often than the 16 patients who were free of symptoms. The latter two factors have been implied in the genesis of sensitization,[6, 8, 9, 11, 12] but as we have seen they are also important in the clinical expression of latex hypersensitivity. In the work by Kelly et al.[2] these two factors were also identified, along with others, as independent risk factors for the development of anaphylaxis during anesthesia.

The remaining factors were not statistically different. The rate of operations per year, as a measure of severity of spina bifida (Table II), was not different between patients with and without symptoms as a whole. The development of sensitization seems to depend on the absolute amount of latex antigen offered through successive exposures and not on the intrinsic characteristics of each case of spina bifida. Total serum IgE levels did not differ between patients with and without symptoms. Kelly et al.[2] found significant differences in this variable, but their control patients included sensitized and nonsensitized children, and because the latter tend to have lower levels of IgE,[11] inclusion of these children might be in part responsible for this result. Total IgE levels increase with age. Transformation of the levels into standard deviations from the mean for age (z units) gives us a better understanding of the atopic predisposition. Atopic predisposition as measured by serum total IgE in z units, which is a risk factor for latex hypersensitivity,[11] loses significance once the patients are sensitized.

In a multivariate logistic regression analysis, the variables whose differences reached statistical significance between patients with and without symptoms were the same two, number of operations and personal history of atopy. They are synergistic and give independent information, because, as shown in Table III, patients in the nonatopic asymptomatic group were operated on less often than those in the nonatopic symptomatic group, and specific IgE levels were higher in the latter (significant correlation between number of operations and specific IgE level). On the other hand, atopic patients had symptoms with half the absolute number of operations and one third the rate of operations per year of nonatopic patients with symptoms. The specific IgE levels in these patients were intermediate. The number of operations is a risk factor first for sensitization and second for that sensitization to be clinically expressed. The same happens with a personal history of atopy. Atopic patients sensitize faster, even if they have less severe spina bifida, and target organs respond to slightly lower levels of specific IgE. Differences in age were close to statistical significance. The number of operations and age were correlated, so age may be acting as a confounding factor. Should age have a determinant role by itself, we would expect to find more patients who were sensi-

TABLE IV. Logistic regression analysis to predict latex-related symptoms

	No. of operations	Personal history of atopy
Coefficients ± SE	0.45 ± 0.2	3.65 ± 1.37
Odds ratio (95% CI)	1.56 (1.06 ± 2.3)	38.6 (2.7 ± 562)

Number of operations and personal history of atopy were selected as synergistic variables. *SE,* Standard error; *CI,* confidence interval.
Constant: −4.23
Model chi square = 19.1, $p = 0.0001$.
Area under receiver-operating characteristic curve: 0.95.

tized and had symptoms among those who had been operated on only once or twice, which was not the case.

There were eight patients in whom results were inconclusive. Information on these patients is available elsewhere.[11] Most probably they are in the early stages of sensitization. Our diagnostic criteria were quite strict to avoid false-positive findings with certainty, and according to other authors' criteria these patients would be considered sensitized. None of them had clinical symptoms with latex, and including them in the asymptomatic sensitized group would have strengthened our findings about the differences between children with and without symptoms inasmuch as they had lower figures in all the potential risk factors.

We might describe the natural history of latex allergy in children with spina bifida as a process in which antigen exposure in successive operations gives rise to sensitization, with the development of specific IgE, levels of which increase with subsequent operations. When these levels are higher, clinical symptoms appear. If the patient has an atopic diathesis, with high levels of total IgE, the process of sensitization is shortened and sensitization appears earlier. When the patient has atopic symptoms, reflective of somewhat more sensitive target organs, hypersensitivity to latex causes allergic symptoms with a somewhat lower specific IgE level and a lower number of operations.

In a study by Konz et al.,[12] there was a low prevalence of hypersensitivity to latex in patients who had had multiple operations who had been operated on first at an adult age. The age of first exposure seems crucial for the development of sensitization, although an immunologic imbalance linked with spina bifida was suggested by the same authors. Nevertheless, children who have multiple operations other than those with spina bifida are also at risk.[19] In our personal experience (data not published), the prevalence of sensitization was 18% in a small group of 16 patients with urologic malformations. This figure, although not significantly different, is somewhat lower than that in patients with spina bifida. Children with other malformations, however, had been operated on less often than those with spina bifida. Further studies with comparable groups are needed to investigate whether spina bifida by itself carries an added risk for hypersensitivity to latex.

Latex allergy in children with spina bifida is not a frequent problem in everyday practice; however, it has served as a model in the investigation of the genesis of sensitization. The early and repeated exposure to a potent antigen seems enough, by itself, to induce sensitization even in nonatopic subjects not predisposed to allergy. The chances of sensitization are high when these conditions are present. The repeated exposure to antigen increases the level of specific IgE, and as this rises so does the probability of the occurrence of clinical symptoms. The atopic diathesis lowers the threshold both for sensitization and for clinical expression of that sensitization, but allergy can no longer be considered a problem exclusively of atopic subjects.

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