Allergy to latex in spina bifida: A multivariate study of associated factors in 100 consecutive patients

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Background: *Latex allergy is quite frequent in patients who have undergone multiple operations, such as children with spina bifida.*
Objective: *This investigation was carried to study the prevalence and risk factors associated with latex allergy in patients with spina bifida.*
Methods: *We studied 100 consecutive patients by skin prick tests and quantified specific IgE to latex with commercial antigens.*
Results: *Twenty-nine patients were sensitized to latex, although 14 (49%) did not report symptoms. There was a statistical association ($p < 0.05$) between sensitization and age, number of operations, number of cystourethrograms, antecedents of intermittent bladder catheterization, personal antecedents of atopy, the presence of a ventricular-peritoneal shunt, and levels of serum total IgE, the latter both in absolute units per milliliter and relative z-units. Through a forward stepwise multiple logistic regression analysis, the number of operations, serum total IgE in z-units, the presence of a ventricular-peritoneal shunt, and personal antecedents of atopy were selected as the synergistic variables that most contributed to identification of sensitized patients. The mathematical model so developed had an area under the receiver operating characteristic curve of 0.95. Alternative models always retained two variables, the number of operations and levels of IgE.*
Conclusion: *Allergy to latex is mainly related to the number of operations and to the atopic diathesis of patients. (J Allergy Clin Immunol 1996;98:501-7.)*

Key words: *Latex allergy, spina bifida, risk factors, atopy, exposure, multivariate analysis, logistic regression*

Allergy to latex is increasing. Although earliest reports date from 1927,[1] since 1979,[2] IgE-mediated allergy to latex has drawn much more attention. Symptoms of latex allergy range from mild urticaria to life-threatening events and death.[3-10]

Risk groups have been identified, and they include latex industry workers,[11, 12] health care workers,[13-15] and patients who have undergone multiple operations, such as those with spina bifida.[16-21] This has led to the publication of a Committee report on perioperative treatment of these patients.[22]

The aims of our study were, first, to examine the prevalence of IgE-mediated allergy to latex in children with spina bifida and, second, to identify factors that may be implicated in the process of sensitization.

METHODS

We studied 100 consecutive patients with spina bifida, whose cases were monitored from birth in the Pediatric Urology Section of a tertiary reference center. They were questioned about undue reactions to latex, and data were recorded about the factors listed in Table I. Patients who had experienced adverse reactions to latex were labeled as having symptomatic latex allergy, and the rest were labeled as free of symptoms.

In vivo tests

After informed consent was obtained from parents, skin prick tests with commercial latex antigen (ALK-

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TABLE I. Studied factors, codification of qualitative variables, and description of patients

Sex	0 = Male: 51, 1 = Female: 49
Intermittent bladder catheterization	0 = No: 55, 1 = Yes: 45
Ventricular-peritoneal shunt	0 = No: 12, 1 = Yes: 88
Familial antecedents of atopy	0 = No: 62, 1 = Yes: 38
Personal antecedents of atopy	0 = No: 89, 1 = Yes: 11
Age	
Mean ± SD (yr)	7.5 ± 4.9
Range	2 mo-17.5 yr
No. of operations	
Mean ± SD	5 ± 4.3
Range	1-26
No. of cystourethrograms	
Mean ± SD	3.9 ± 2.5
Range	0-11
Serum total IgE (U/ml)	
Mean ± SD	132 ± 223
Range	2-1289
Serum total IgE (z-units)	
Mean ± SD	1.2 ± 1.3
Range	−1.5-4.2

Abello Laboratories, 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 glycerinated solution with a 2 mg/ml concentration of proteins, which include a 14 kd antigen, corresponding to the rubber elongation factor (information provided by the manufacturer). Skin tests were graded 0 to 4+ compared with saline solution and 1% glycerinated histamine. No wheal was graded as 0+. When the area of a wheal was up to 25% of the wheal elicited by histamine, it was graded as 1+; when the area was between 25% and 50%, 2+; when the area was between 50% and 75%, 3+; and when it exceeded 75%, 4+.

In vitro tests

Serum total and latex-specific IgE (CAP System RAST FEIA; Pharmacia, Uppsala, Sweden) were measured in all cases according to the manufacturer's instructions and those in other reports.[21, 23] Total serum IgE 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), according to the values published by Kjellman et al.[24] Values lower than 2 U/ml (sensitivity of the technique) were treated as 2 U/ml for analysis. Latex-specific IgE was 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, class 2 for values between 0.7 and 3.5, class 3 for values between 3.5 and 17.5, class 4 for values between 17.5 and 50, class 5 for values between 50 and 100, and class 6 for values greater than 100 U/ml.

Classification of patients

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

Statistical study

Statistical analysis was performed with the commercial statistical program SPSS (SPSS Inc., Chicago, Ill.).

Univariate study. Chi square tests were used for categorical variables, the F variance test was used for normally distributed quantitative variables, and the Kruskal-Wallis test (a nonparametric test equivalent to the variance test) was used for those quantitative variables with a non-normal distribution.

Multivariate study. A forward stepwise logistic regression analysis, with the likelihood ratio method and with the criteria p in (0.05), p out (0.1), was performed with the SPSS statistical package. Sensitization (1 = yes/0 = no) was used as the dependent variable y; the sensitized group included patients who were free of symptoms and those with symptomatic latex allergy; doubtful cases were excluded.

This analysis allows the calculation of the probability (P(y=1)) of the dependent variable y equaling 1, which means, in our case, the probability that the patient is sensitized to latex. Its mathematical expression is the following formula:

$$P(y = 1) = \frac{1}{1 + EXP(-(a + b_1x_1 + b_2x_2 + \ldots + b_nx_n))}$$

where x_1, x_2, and x_n represent the values of the selected independent variables for a given patient; and a, b_1, b_2, and b_n are the calculated coefficients of the constant and of each variable. This mathematical model may be used as a diagnostic test to predict sensitivity to latex, and its area under the receiver operating characteristic curve was calculated by the maximum likelihood estimation method. The best cutoff point of the curve was chosen to calculate sensitivity, specificity, and the predictive values for our group of patients.

TABLE II. Comparison of qualitative variables between sensitized and nonsensitized patients

		Nonsensitized group	Sensitized group	OR (95% CI)*	Doubtful group
Sex	F	33	12	1.56 (0.64-3.79)	4
	M	30	17	p = NS	4
Familial antecedents	No	38	17	1.07 (0.44-2.63)	7
of atopy	Yes	25	12	p = NS	1
Personal antecedents	No	61	21	11.6 (2.28-59.12)	7
of atopy	Yes	2	8	p = 0.002	1
Intermittent bladder	No	43	10	4.1 (1.6-10.4)	2
catheterization	Yes	20	19	p = 0.002	6
Ventricular-peritoneal	No	12	0	∞	0
shunt	Yes	51	29	p = 0.03	8

Doubtful group values are shown but not included in the analysis.
OR, Odds ratio; *CI,* confidence interval; *NS,* not significant.
*Chi square, sensitized versus nonsensitized.

TABLE III. Comparison of quantitative variables between sensitized and nonsensitized patients

	Nonsensitized group	Sensitized group	Test p value	Doubtful group
Age (yr)	6.38 ± 4.75	10.47 ± 4.40	F = 15.4 0.0002	5.76 ± 2.31
No. of operations	3.57 ± 2.51	8.34 ± 5.91	K-W = 29.1 <0.0001	4.13 ± 0.83
No. of cystourethrograms	3.31 ± 2.23	5.52 ± 2.72	F = 16.8 0.0001	3.37 ± 1.06
Serum total IgE (U/mL)	74.7 ± 131.7	243.8 ± 315	K-W = 19.9 <0.0001	173.2 ± 260.3
Serum total IgE (z-units)	0.97 ± 1.30	1.72 ± 1.19	F = 7.06 0.009	1.76 ± 1.34

Values are expressed as mean ± SD. Doubtful group values are shown but not included in analysis.
F, Variance test; *K-W,* Kruskal-Wallis test (sensitized vs nonsensitized).

RESULTS

The study included 100 patients, whose description is shown in Table I. According to the aforementioned criteria, 29 patients were considered sensitized to latex, 63 nonsensitized, and eight doubtful. Among the 29 sensitized patients, 15 (51%) reported clinical reactions to latex, ranging from urticaria or angioedema on contact with balloons to shock while undergoing a cystourethrogram, formerly attributed to radiologic contrast material and later demonstrated to be caused by latex. The other 14 sensitized patients (49%) and patients classified as nonsensitized or doubtful did not report any clinical reactions to latex.

We found a statistical association between sensitization to latex and all but two of the factors studied. Results are shown in Tables II and III. Among the eight sensitized patients with other atopic diseases, seven (87.5%) had symptoms of latex allergy; whereas among the 21 latex-sensitized patients without any other atopic disease, only eight (38%) had clinical reactions to latex.

Patients were divided into four groups according to age. Sensitization increased with age, and the same was true for number of operations, number of cystourethrograms, number of patients receiving intermittent bladder catheterization, and levels of serum total IgE in units per milliliter (but not in z-units), as demonstrated in Fig. 1 (significance not shown). Thus some variables may be acting as confounding variables or may be giving redundant, not additive, information. This is managed by comparing variable-matched groups or, as we did, by using a multivariate statistical analysis, such as logistic regression.

A forward stepwise multiple logistic regression analysis was performed, in which variables are selected one by one, until the joining of a new variable does not add significance to the previous step. The first so developed model (Table IV), which

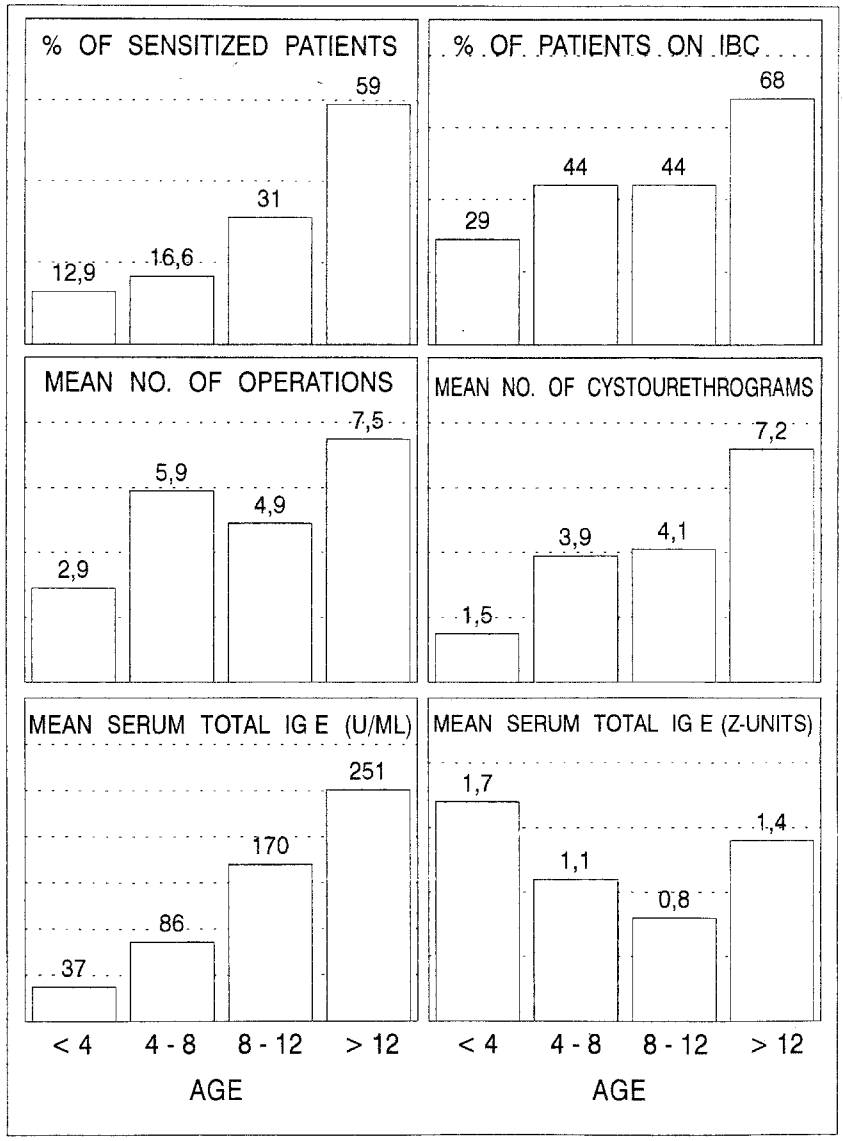

FIG. 1. Percentage of sensitization, number of diagnostic and therapeutic procedures, and levels of serum total IgE according to age. *IBC,* Intermittent bladder catheterization.

analyzes all variables, selected the variable "ventricular-peritoneal shunt." In the univariate analysis, no patient without this device was sensitized. This, in fact, made this variable behave like a distortion factor with a high coefficient and extremely high odds ratio. Therefore we analyzed the data of all patients again, excluding this variable, and two alternative mathematical models were developed. The selected variables, their respective coefficients, and their odds ratios are also shown in Table IV. In the first two models, the variable "serum total IgE" is expressed in z-units, and in the third it is expressed as units per milliliter.

The mathematical models built with these results permit the classification of patients and may be used as diagnostic tests, substituting x_1, x_2, and x_n for the value of each variable for a given patient. The equation $(a + b_1x_1 + b_2x_2 + ... + b_nx_n)$ in the denominator of the formula is the so-called "logit" (its preceding minus sign is omitted). The best cutoff point for the models was a logit value of -0.66, corresponding to a probability $P(y=1)$ of 34%. The area under the receiver operating characteristic curve and sensitivity, specificity, and predictive values for the chosen cutoff point are shown in Table V.

TABLE IV. Logistic regression analysis: Selected variables, their respective coefficients, odds ratios, and significance for each model

	Variable	Coefficient	OR (95% CI)	Model chi square (df) *p* value
Model 1	No. of operations	0.447	1.56 (1.23-1.99)	54.7 (4)
	Serum total IgE (in z-units)	0.871	2.39 (1.29-4, 4)	<0.0001
	Ventricular-peritoneal shunt (0 = No, 1 = Yes)	16.19	Incalculable	
	Personal antecedents of atopy (0 = No, 1 = Yes)	2.973	9.5 (1.8-215)	
	Constant	−20.62		
Model 2	No. of operations	0.404	1.49 (1.23-1.83)	43.7 (3)
	Serum total IgE (in z-units)	0.792	2.21 (1.29-3.79)	<0.0001
	IBC (0 = No, 1 = Yes)	1.470	4.35 (1.29-14.6)	
	Constant	−4.81		
Model 3	No. of operations	0.350	1.42 (1.17-1.72)	40 (3)
	Serum total IgE (in U/mL)	0.003	1.003 (1-1.006)	<0.0001
	IBC (0 = No, 1 = Yes)	1.317	3.73 (1.15-12.1)	
	Constant	−3.70		

OR, Odds ratio; *CI,* confidence interval; *df,* degrees of freedom; *IBC,* intermittent bladder catheterization.

DISCUSSION

Latex allergy has become a major problem in children with spina bifida, who must undergo many aggressive diagnostic and therapeutic procedures. We describe a systematic study on a group of 100 consecutive unselected children with spina bifida. We found a 29% prevalence of sensitization to latex, a figure in the lower range of those published by other authors.[20, 21, 25, 26] The reason for this may lie in the different selection and diagnostic criteria and the different allergen extracts used for testing. Ours were the first 100 unselected consecutive patients, including very young infants. The allergens used for diagnosis, both for in vivo and in vitro tests, were commercial, readily available products. Antigens used in most previous reports were prepared by the authors themselves,[19-21, 26] which is inconvenient for a routine clinical practice. The antigen we used for skin tests contains a 14 kd protein, identified as the major allergen in latex-sensitive children with spina bifida,[27, 28] although not in adults.[23] This antigen proved to be very sensitive, because all the patients with symptomatic latex allergy showed positive responses.

In our study we tried to identify those factors that may have a causal or predisposing role in the process of sensitization. Univariate analysis disclosed several significant variables, but some of them are directly related to one another; as age increases, so does the rate of sensitization, but there is also an increase in the number of operations and, in general, in the number of all diagnostic and therapeutic procedures, as well as in the absolute levels of serum total IgE (Fig. 1). The familial and personal antecedents of atopy and levels of relative serum total IgE (in z-units) remain fairly constant. As with age, there exists a correlation between other factors, so there is an overlap of information among many of the variables.

TABLE V. Logistic regression analysis: Area under ROC curve, sensitivity, specificity, and predictive values of each mathematical model for the chosen cutoff point

	Area under ROC curve	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Model 1	0.95	79	90	79	90
Model 2	0.91	82	82	69	91
Model 3	0.89	72	91	78	88

Cutoff point: logit = −0.66 (see text).
ROC, Receiver operating characteristic; *PPV,* positive predictive value; *NPV,* negative predictive value.

Multivariate analysis takes this into account and identifies variables that give redundant information or act as confounding variables. In this way the logistic regression analysis selected the variable "number of operations" as the one that most contributed to the process of sensitization, as previously described.[21, 29] Three other variables (serum total IgE levels, presence of a ventricular-peritoneal shunt, and personal antecedents of atopic disease in this order) were synergistic and

included to build the most parsimonious model. Other variables, such as "age" or "number of cystourethrograms," lost much of their significance when the number of operations and the other variables were considered and were left out of the model.

Among our patients with a ventricular-peritoneal shunt, sensitization to latex was present in 36%, but there was not a single case of sensitization among those patients without it. This device, made of silicone, does not contain latex, but its co-adjuvant role as a foreign body in the process of sensitization has been suggested.[30] Nevertheless, our group was small (12 patients), and later we found another patient (not included in the study) without a ventricular-peritoneal shunt who is sensitized to latex, so the apparently clear role of this device would need further confirmation. In view of the extremely high coefficient and odds ratio of this variable, we excluded it to perform a second logistic regression analysis. The variable "intermittent bladder catheterization" was then selected. Thus a variable that also implies further manipulation was included. Daily rectal disimpaction has been mentioned as a risk factor for anaphylactic reactions during anesthesia.[19] Unfortunately, we can offer no information about this point in relation to our patients.

Second to latex exposure in operations, atopy was proved to be the most important factor.[21, 27] There was no relation with familial antecedents of atopy, but a relation did exist in the case of personal antecedents of atopy, and with serum total IgE levels. There is a wide range of normal values of IgE with age, so we converted the absolute number of units into relative z-units, measured in standard deviations from the mean for age, by using those values published by Kjellman et al.[24] With this approach, we can evaluate a truer atopic predisposition and counterbalance the effect of age. In this way we found that sensitized patients had higher levels of serum total IgE, both in absolute units and in relative z-units. The latter, not related to age, were more meaningful than absolute units; and in fact, in the logistic regression analysis the relative IgE was selected to build the first two models, and the absolute IgE was rejected. We would recommend the use of the second model, but because absolute units per milliliter of IgE are easier to manage in a clinical setting, we performed a third logistic regression study in which the relative IgE was not included. In this case the absolute IgE was selected by the program, although its coefficient was very low. Ten patients had IgE values lower than 2 U/ml (sensitivity of the technique), and their data were processed as if they had a value of 2 U/ml. This might have altered the results. We made a parallel analysis without these 10 patients in the three models, and significance remained unchanged for all variables. There were small changes, less than 5%, in the values of the coefficients (data not shown), so we think that the error induced by these patients is negligible, and their data were included for the final results.

Among those 11 patients with other atopic diseases, eight were clearly sensitized to latex. Furthermore, seven of these eight had symptoms of latex allergy, compared with eight of 21 among nonatopic sensitized patients. Atopy behaves as a very important factor in the process of sensitization and also in the clinical expression of sensitization. This is in agreement with the higher number of atopic features of patients who experience anaphylactic reactions, when compared with control subjects.[19]

Because all patients with latex-related symptoms were sensitized and because most atopic subjects are sensitized, skin tests and RASTs would be especially indicated to identify sensitization in nonatopic patients who are free of symptoms. The mathematical model, apart from identifying variables, may be used in individual patients to predict their probability $P(y=1)$ of being sensitized. This attribute is most interesting in cases in which testing is difficult, or when there is a lack of appropriate antigens. When applying the formula to a patient, if the value of the logit is higher than -0.66, the patient might be considered to be sensitized to latex. This figure, corresponding to a probability of 34%, may seem low but was chosen as the best cutoff point to obtain an acceptably good sensitivity and specificity.

Doubtful cases were not included in the multivariate study, because this analysis accepts only two mutually excluding values, in our case, being or not being sensitized. Doubtful cases could not be assigned to either group. In fact, they tended to show an intermediate pattern in the variables studied, and it is reasonable to think that their natural evolution will be toward sensitization in the case of further exposure to latex. They had intermediate total IgE absolute units but higher z-units. This is because they were the youngest of the groups and had a low degree of exposure, so the presence of weak responses to the tests supports the idea that they would become sensitized with continuing exposure.

A considerable number of sensitized patients do not have an atopic diathesis. Why do these subjects become sensitized? Recently, Konz et al.[26] have suggested an attractive hypothesis about a neuroimmunologic imbalance, but the lack of an appropriate age-matched control group makes their results inconclusive. Rather, the initial exposure to latex at an early age and the massive and repeated exposure to a very potent allergen through the breakdown of natural barriers, along with associated factors (e.g., bladder catheterization, ventricular-peritoneal shunt), would cause sensitization to occur even in children not predisposed to allergy.

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