



Influence of the type of operations on the development of latex sensitization in children with myelomeningocele

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Abstract

Background: A genetic tendency to develop latex IgE responses in children with spina bifida has been suggested, but their degree of exposure to latex as well as the route and chronology for sensitization can be different from those of other children with multiple surgeries. The aim was to study the influence of the type of operation on the development of latex sensitization in children with myelomeningocele.

Methods: In 90 children with myelomeningocele operated with latex, data were collected about age, sex, family, and personal history of allergy, serum total IgE, presence of a ventricular-peritoneal (v-p) shunt, and number and duration of operations, classified as urological, orthopedic, on the v-p shunt, other neurosurgical, and others. A multivariate logistic regression analysis was performed, using the presence of latex sensitization as dependent variable.

Results: Serum total IgE, the number of urological and of orthopedic operations were synergistic variables to predict latex sensitization, together with the presence of a v-p shunt, but not the number of operations performed on this device. This seems to play an adjuvant role in the process of sensitization.

Conclusions: Not only the number, but also the type of operations, namely, of urological and orthopedic nature, is important in the development of latex sensitization in children with myelomeningocele.

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Since 1979 there is a growing concern about the increase of IgE-mediated allergy to latex. The patients at highest risk for sensitization to latex are by far the children with spina bifida [1]. The number of operations undergone by these

children is the most important factor implicated in the process both of sensitizing and of presenting latex-related clinical symptoms [2,3]. There is a correlation between the number of operations and the levels of latex-specific IgE: these are higher in patients with latex-related clinical symptoms [2] and, especially important, in those children with anaphylactic reactions during general anesthesia [4].

Because there are other groups of children in whom a high number of operations are also performed, we should expect latex allergy to be highly prevalent in these children

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Abbreviations: V-p shunt, Ventricular peritoneal shunt.

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Table 1 Number and percentage of patients sensitized to latex according to qualitative variables

		n	% Sensitized	P
Sex	Male	48	48	.54
	Female	42	54	
Personal history of allergy	No	79	49	.38
	Yes	11	64	
Family history of allergy	No	51	53	.69
	Yes	39	49	
v-p Shunt	No	12	0	<.001
	Yes	78	59	
Bladder catheterization	No	37	41	.09
	Yes	53	59	

too. There is conflicting evidence on this, with some reports of similar prevalence in patients without spina bifida who had multiple surgeries [5-9], whereas others have found a significantly higher prevalence of latex allergy in children with spina bifida compared to children with ventricular-peritoneal (v-p) shunt because of other causes and with a comparable number of operations [10,11]. It has been therefore suggested that spina bifida per se might be associated to a higher predisposition to develop allergic responses when compared with other diseases.

The aim of our work was to study the influence of the type of operations on the development of latex sensitization in children with myelomeningocele who had operations where latex exposure occurred before we could have a latex-free environment for these patients. Our a priori hypothesis was that differences in the aforementioned studies may be because of, among other causes, the type and duration of operations, which, in children with spina bifida, are commonly of orthopedic and urological nature, in addition to those for closing the neural defect and for the malfunctioning of the v-p shunt.

1. Materials and methods

1.1. Procedures

We studied 90 children with myelomeningocele who were at a follow-up program run by urologists, traumatologists, and neurosurgeons in a reference tertiary hospital. Data were collected from their medical records about age, sex, family and personal history of allergic diseases, presence of a v-p shunt, use of intermittent bladder catheterization, number of cystourethrograms, lapse of time since last operation to the date of the study, number of operations classified in the following types: urological, orthopedic, operations on the v-p shunt, neurosurgical operations besides those on the v-p shunt, and other operations not included in the preceding types. Operations after September 1994, performed in a latex-free operating room, were not included.

According to recommendations for high-risk patients [12], and after informed consent was obtained from parents, the

children underwent an allergologic study that included skin prick tests and serum total and latex-specific IgE (Pharmacia CAP test). Skin prick tests were performed on the volar surface of the forearm, with commercial latex extract (ALK-Abello Labs, Spain), control saline diluent, and histamine clorhydrate (0.1%). According to criteria previously published [13], children with skin prick tests with a wheal area more than 25% of that of histamine and/or CAP class 2 or higher (≥ 0.7 kU/L) were considered to be sensitized to latex.

1.2. Statistical study

1.2.1. Univariate study

The association of sensitization to latex with the qualitative variables was evaluated using the χ^2 test or the Fisher's Exact test when indicated. Comparison of quantitative variables between sensitized and nonsensitized patients was done using the Student's *t* test, or its nonparametric equivalent, the Mann-Whitney *U* test, when indicated.

1.2.2. Multivariate study

A logistic regression analysis was performed using the presence of sensitization to latex as the dependent variable. All variables that had a significance value of $P < .1$ in the univariate analysis were used as independent variables in the multivariate study to identify those which were synergistic cofactors.

2. Results

We studied 90 children with myelomeningocele who had undergone surgery with use of latex until September of 1994 when we could arrange a latex-free environment for treatment of these patients. Forty-six of them were sensitized to latex, and 16 of these had experienced clinical symptoms in relation to latex. Among qualitative variables, shown in Table 1, only the presence of a v-p shunt was significantly associated with latex sensitization.

Table 2 Univariate analysis of quantitative variables: comparison between patients with and without latex sensitization

	Sensitized (n = 46)	Non sensitized (n = 44)	P
Current age (y)	9.5 $\pm$ 4.6	8.9 $\pm$ 4.7	.58
Lapse last operation-evaluation (y)	2.7 $\pm$ 2.6	4 $\pm$ 2.7	.006
Serum total IgE (U/mL)	249 $\pm$ 363	76.5 $\pm$ 108	<.001
Serum total IgE (z units)	1.75 $\pm$ 1.15	0.79 $\pm$ 1.04	.001
No. of cystourethrograms	5.2 $\pm$ 3.2	3.7 $\pm$ 2.1	.06
No. of operations during first year	2.61 $\pm$ 1.34	2 $\pm$ 0.81	.01
No. of v-p shunt operations	2.35 $\pm$ 2.64	1.16 $\pm$ 1.26	.001
No. of neurosurgical operations	1 $\pm$ 0.54	1 $\pm$ 0.30	.99
No. of urological operations	0.83 $\pm$ 1.04	0.36 $\pm$ 0.61	.025
No. of orthopedic operations	1.65 $\pm$ 1.57	0.59 $\pm$ 1.06	<.001
No. of other operations	0.35 $\pm$ 0.74	0.16 $\pm$ 0.37	.21

Regarding quantitative variables, shown in Table 2, significantly higher values were found in the number of urological and orthopedic operations, in the number of surgeries on the v-p shunt, the number of operations during the first year of life, and in the levels of serum total IgE of sensitized patients. The interval between the last operation and the date of evaluation was longer for nonsensitized patients.

The mean duration of operations on the v-p shunt was 52 minutes. It was 115 minutes for other neurosurgical operations, 93 minutes for urological, 111 minutes for orthopedic, and 59 minutes for other operations. There was no difference for mean duration of operations between sensitized and nonsensitized children.

There is a correlation between some of the variables found to be significant in the univariate analysis; for instance, an association exists between the number of surgeries during the first year of life and the total number of operations, so one of them acts as a surrogate for the other and would offer no additional information. Multivariate analyses identify those variables that act as synergistic cofactors and discard the ones without additional information. In Table 3 we show the results of the multivariate logistic regression analysis. Model 1 was run using all patients and all variables that had reached a value of $P < .1$ in the univariate analysis. Four variables

were identified as synergistic; one of them was the presence of a v-p shunt, but not the number of operations on this device. The “v-p shunt” variable had a very high odds ratio; as none of the patients without a v-p shunt were sensitized, so a second analysis was performed. Model 2 was run using all patients, but the variable “v-p shunt” was excluded. The number of operations on the v-p shunt was then selected as synergistic variable. In model 3, patients without a v-p shunt were excluded. The value of the “v-p shunt” variable was the same for all of the 78 remaining patients, and it was therefore not selected. As in model 1, the number of operations on the v-p shunt was not selected either. The figures of coefficients and odds ratio were the same for models 1 and 3, except for the constant, whose value in model 3 was equal to that of the constant plus the coefficient of the “v-p shunt” variable in model 1.

3. Discussion

The avoidance of latex in children with spina bifida is the cornerstone for the treatment of latex allergy in these children [12] and has also proved efficacious for prevention of latex sensitization [14]. Until an evaluation of specific latex immunotherapy in sensitized children is available, from a practical point of view, it appears that not much more can be done, but these patients represent a unique human experimental natural model for the study of allergic diseases.

Allergic diseases appear because of the interaction of genes and environment. Much attention is being paid lately to the genetic factors, but it has been shown that, for instance, most of the children with asthma have no family history of allergy [15], and the increasing prevalence of allergic diseases in the last decades cannot be attributed to genetic changes. Concerning latex allergy and health care workers, it has been shown that the risk of sensitization is directly related to the degree of exposure [16]. In our study, only 7 of 46 latex-sensitized patients had a personal history of allergy other than to latex, and the family history of allergy was equally distributed among sensitized and non-sensitized children. Similar findings have been described [11,17]. Certainly, children with a personal history of allergy sensitize more easily to latex, as previously shown [2], but a genetic background is not present in most of the cases.

If the genetic factor acts rather as a regulating factor in the immune response against a heterologous substance, we might expect a high prevalence of sensitization to latex in children with multiple surgeries, other than spina bifida. Porri et al [8] found a prevalence of 59% in children with spina bifida and 55% in children with multiple surgeries for other causes, which seems to confirm this argument. Prevalences of latex sensitization in children without spina bifida ranging from 31% to 70% have also been described [6,7,9]. Nevertheless, recent studies by Szépfalusi et al [10] and by Hochleitner et al [11] offer conflicting results, with a very low prevalence of latex allergy in children with a high

Table 3 Logistic regression analysis: synergistic variables to predict sensitization to latex

		Coefficient	OR (95% CI)	P
Model 1 (n = 90)	Constant	-11.4		.68
	Serum total IgE in z units	0.99	2.7 (1.5-4.8)	.001
	No. of orthopedic operations	0.64	1.9 (1.1-3.2)	.015
	v-p Shunt	9.22	10,064 (0 to 5×10^{27})	.74
	No. of urological operations	1.26	3.5 (1.3-9.8)	.015
Model 2 (n = 90)	Constant	-3.37		<.001
	Serum total IgE in z units	1.08	2.9 (1.6-5.3)	<.001
	No. of orthopedic operations	0.77	2.2 (1.3-3.7)	.005
	No. of urological operations	0.98	2.7 (1.2-6)	.017
	No. of v-p shunt operations	0.48	1.6 (1.1-2.5)	.026
Model 3 (n = 78)	Constant	-2.18		.001
	Serum total IgE in z units	0.99	2.7 (1.5-4.8)	.001
	No. of orthopedic operations	0.64	1.9 (1.1-3.2)	.015
	No. of urological operations	1.26	3.5 (1.3-9.8)	.015

Model 1 was run using all variables and all patients. In model 2, the variable “v-p shunt” was excluded. In model 3, patients without a v-p shunt were excluded.

number of operations because of hydrocephalus of non-spina bifida origin, and all of them with a v-p shunt. Several causes have been proposed for this finding, with more stress placed on congenital causes, be it spina bifida itself, or the causes leading to spina bifida, which might confer a greater predisposition to develop IgE-mediated responses, particularly against latex.

We hypothesize that noncongenital causes such as the degree, the route, and the chronology of exposure to latex are more important. In our multivariate analysis, we identified 4 synergistic variables associated to latex sensitization: the level of serum total IgE, the number of urological and of orthopedic operations, and the fact of being a v-p shunt carrier, but not the number of operations on the v-p shunt. In a second multivariate study, we excluded the “v-p shunt” variable from the analysis (Table 3, model 2), and the number of operations on this device was then included as a synergistic variable. But this is in fact just an indication of the excluded variable, as the 12 patients without the v-p shunt had, logically, no operations on it, and all of them belonged to the nonsensitized group.

Therefore we run a third multivariate analysis, excluding the patients without a shunt. It yielded the same results as the first analysis; it selected the same factors, excluding the “v-p shunt” variable, as all remaining patients were carriers of the device, but it did not include the number of operations on the v-p shunt. Once a patient has this device, the number of operations because of its malfunctioning is no longer relevant [18], so it might be playing an adjuvant role in the process of sensitization to latex coming in through other type of operations, or through other routes, such as skin or the respiratory tract.

In urological operations, such as augmentation of bladder, latex comes often in direct contact with mucosas and peritoneum, which has the largest potential for sensitizing, and is the organ commonly used to sensitize laboratory animals. Orthopedic operations are also more sensitizing than the shorter and less aggressive operations performed on the v-p shunt, so, in the latter, the amount of latex entering the organism would be lower. The studies by Hochleitner et al [11] and by Szépfalusi et al [10] do not state if all the operations of their patients were on the v-p shunt or of other types, but in the comparative study of Porri et al [8] many of the operations were performed in the abdominal cavity.

Concerning chronology of exposure, the age at first operation might be important because the early period of life may direct immune responses toward the Th1 or toward the Th2 type. Children with spina bifida are usually first operated in the first 24 to 48 hours of life, but weeks may elapse before a child is operated because of hydrocephalus of other origin. In recent studies, there are also conflicting results about operations in the first year of life [7,18,19]. As in our study all children had myelomeningocele and were operated very soon after birth, we cannot draw any conclusions regarding this issue.

Likewise, the number of operations during the first year has been linked to latex sensitization in children with multiple surgeries [7]. In our group, this variable was significant in the univariate analysis, but it was not synergistic in the multivariate analysis, as it had a strong correlation with the total number of operations ($r = 0.53$, $P < .001$, data not shown).

In the univariate analysis the lapse since last operation to the date of allergologic evaluation was shorter in sensitized patients. This suggests that some patients lose their reactivity with time passing, but a confounding factor is that sensitized patients had more operations, so the chances that the last operation had been performed more recently are greater and, anyway, the multivariate analysis did not include this variable.

It is difficult to gather a large-enough and homogeneous group of children with multiple surgeries for causes other than spina bifida, and studies on them are sparse. For adequate comparisons, to elucidate if spina bifida is by itself a high risk for sensitizing to latex, the groups must be comparable not only in the whole number of operations, but also in their type and chronology. Our results prove that, although a genetic predisposition cannot be ruled out, environmental factors such as the type of operations have a role to be considered before conclusions can be drawn. Currently, latex avoidance is recommended for all children with spina bifida since birth [12], but latex avoidance measures should probably be implemented in all children in whom multiple surgeries are anticipated.

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