

Latex provocation tests in patients with spina bifida: Who is at risk of becoming symptomatic?

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Background: Although there is accepted information on the prevalence rates of sensitization to latex in patients with spina bifida, little is known about the clinical relevance of this sensitization.

Methods: We performed provocation tests with latex gloves in 159 patients with spina bifida (median age, 10 years).

Results: Eighty-eight patients (55.3%) were sensitized to latex in terms of a positive skin prick test response, specific IgE to latex in serum, or both. Fifty-five patients (34.6% of all patients or 62.5% of latex-sensitized patients) showed clinical symptoms on provocation. Specific IgE to latex was significantly higher in patients with a positive provocation test response ($P < .0001$). The total number of operations and degree of sensitization showed a significant correlation. More than 8 operations significantly increased the risk of sensitization ($P < .0001$), and more than 9 operations increased the risk of allergy to latex ($P < .0001$). One hundred seventeen (75%) patients had a ventricular shunt system. Specific IgE in these patients was significantly higher than in patients without ($P < .0001$), and the odds ratio for the existence of a shunt system in terms of a positive provocation was 3.9. Patients with a shunt system were significantly more often sensitized and had positive provocation results ($P < .0001$). Seventy-two patients (45.3%) were classified as atopic; they were significantly more often sensitized and clinically symptomatic ($P < .0001$), and the odds ratio for having a positive provocation response was 3.2 for atopic subjects. History of symptoms on contact with material containing latex had a sensitivity of 53.7% and specificity of 94.2%.

Conclusions: Our results indicate that an atopic disposition, number of operations, and presence of a shunt system increase the risk of becoming not only sensitized but also allergic to latex. Our results strongly support the necessity that patients with spina bifida as a high-risk group for latex allergy should remain latex-free from the first day of life. (*J Allergy Clin Immunol* 1998;102:665-70.)

Key words: Latex, provocation test, spina bifida

Patients with spina bifida belong to the highest risk group for becoming hypersensitive to natural rubber latex (NRL). Prevalence rates for sensitization range from 34% to 64.5%.¹⁻⁵ Several factors seem to be involved. First, the kind of exposure seems to be important. Sensitization

Abbreviation used

NRL: Natural rubber latex

rates seem to be enhanced by operations to a much greater extent than by skin contact. Second, operations early in life induce sensitization, such as in children with spina bifida or genitourinary malformations who undergo operations from the first day of life. Third, there may be a window of vulnerability early in life, with possibly only the first weeks of life being particularly important. Finally, frequent exposure is definitely a factor.⁶

Although there is accepted information on the prevalence rates of sensitization to latex, as well as clear evidence of the possible risks of a latex-sensitized patient with spina bifida exhibiting clinically relevant allergy (including life-threatening events), little is known so far about the rates of clinically relevant allergy among sensitized patients and the determinant risk factors involved. We therefore performed provocation tests in sensitized and nonsensitized patients with spina bifida to investigate to what extent sensitized patients are symptomatic and to look for risk factors for becoming symptomatic.

METHODS

Patients

Of 161 consecutive patients from the Berlin area with spina bifida visiting the neuropediatric department, 159 patients (85 male and 74 female subjects) were included in our study. Ages ranged from 6 months to 33 years (median, 10 years). Two patients were excluded because of known anaphylactic reactions to latex in their history.

Study design

In this prospective study a questionnaire was filled out by patients or parents while visiting the department of neuropediatrics as outpatients. Additionally, a blood sample was taken, a skin prick test was performed, and provocation tests were undertaken in 159 patients. The study protocol was approved by the local ethics committee, and parents or patients gave their written consent.

Questionnaire

The questionnaire included questions about known clinical symptoms on contact with latex in the daily environment (eg, to balloons) and medical equipment (eg, during surgical intervention).

Specific IgE

Total IgE and specific IgE to latex were determined from sera by the solid-phase immunoassay (FEIA) and the Pharmacia CAP-system (Pharmacia Upjohn, Uppsala, Sweden).⁷ To establish atopic status, inhalant (SX1) and nutritional (fx5) allergens were investigated by

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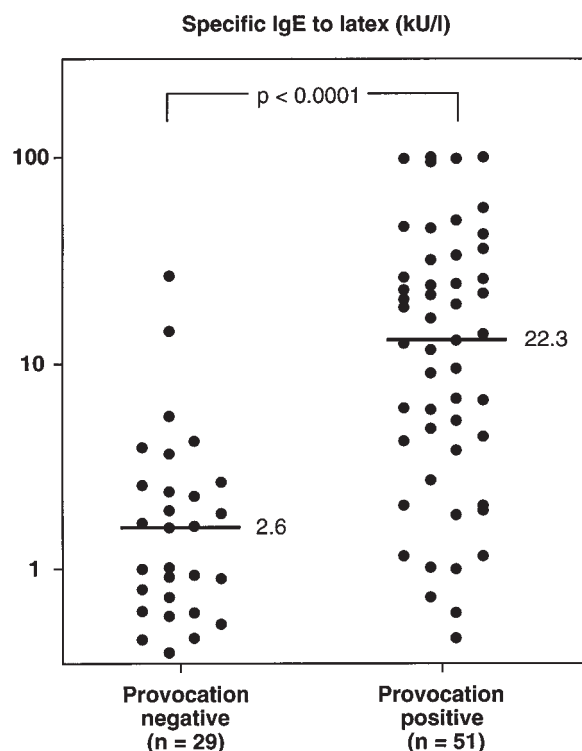


FIG 1. Specific IgE to latex in latex-sensitized patients with negative (n = 34) and positive provocation test responses (n = 54). Bars represent median values. For calculation of statistical significance, Mann-Whitney test was used.

TABLE I. Concordance of specific IgE to latex in serum and skin prick tests with NRL milk

	Specific IgE to latex (+)	Specific IgE to latex (-)	
SPT (+)	69	8	77
SPT (-)	11	71	82
	80	79	159

SPT, Skin prick test.

screening tests with the same automated IgE assay.⁸ SX1 contains the allergens timothy, birch, mugwort, house dust mite, cat, dog, and *Cladosporium herbarum*. Fx5 contains the foods milk, egg, fish, soy, wheat, and peanut. None of these allergens is known to cross-react with latex. Atopy was defined as a positive response to SX1, fx5, or both (>0.35 kU/L).

Skin prick testing

Two allergen sources were used: low ammoniated raw and unfinished NRL milk (Ansell, Munich, Germany) and latex skin prick test extract (Stallergen, Fresnes, France). Skin test responses were assessed as positive if the maximum wheal diameter was 3 mm or greater without reaction of negative control (saline), and the skin index was greater than 0.6. The skin index was calculated as the ratio of the diameter of the allergen wheal to the histamine wheal.

Glove wearing test

After having washed their hands, patients put 1 wet hand into a latex glove (Sempermed classic, Lot YE5F7; Semperit, Vienna,

Austria) and, as a control, put the other wet hand into a neoprene glove (Dermaprene; Ansell, Munich, Germany). After wearing these gloves for 30 minutes (or on showing clinical symptoms), the gloves were taken off, and possible clinical reactions were assessed by a physician. Hands were washed again. The single-blind test response was assessed as positive if typical immediate-type clinical reactions (eg, urticaria or Quincke's edema) occurred. If the test response was negative, a glove was inflated as an additional test.

Glove inflation test

The open end of a latex glove was turned inside out for about 3 cm, and the patients took a deep breath, put the glove to their lips, and inflated the glove. To avoid inspiration of latex particles, care was taken that the patients took their mouths away from the glove when inhaling. Possible clinical reactions were monitored continuously by a physician trained in treating allergies. In cases of children too small to cooperate (n = 11), we turned the glove inside out and rubbed part of it smoothly on the lips for 1 minute. The test response was assessed as positive if typical immediate-type clinical reactions occurred (eg, swelling of lips). Care was taken under continuous observation that children did not rub the glove onto other parts of the body. In patients with respiratory symptoms in their history and an age of at least 4 years, peak flow monitoring was performed.

Protein and allergen content of gloves

According to Baur et al,⁹ the protein content of the Sempermed classic latex glove (determined by a modified Lowry method with ovalbumin as a standard) was 1034 µg/g glove. The allergen content (measured by a competitive RAST-immunoinhibition with the Pharmacia CAP-system) was 626 µg/g.

Number of operations

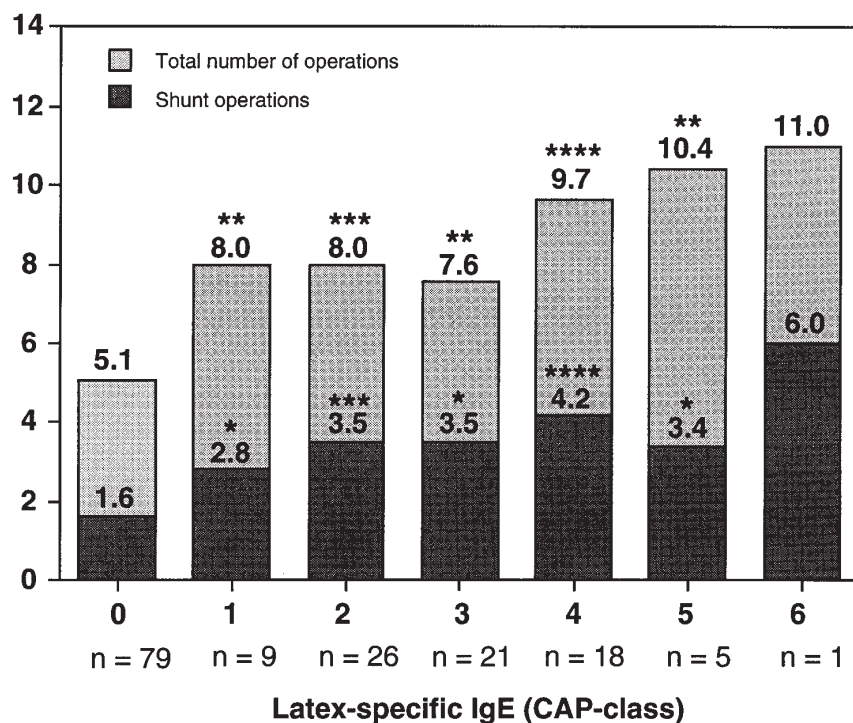


FIG 2. Relation of specific IgE to latex in serum and mean total and shunt operations. * $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$; values refer to patients without specific IgE to latex (CAP-class 0). For calculation of statistical significance, Mann-Whitney test was used.

Number of operations

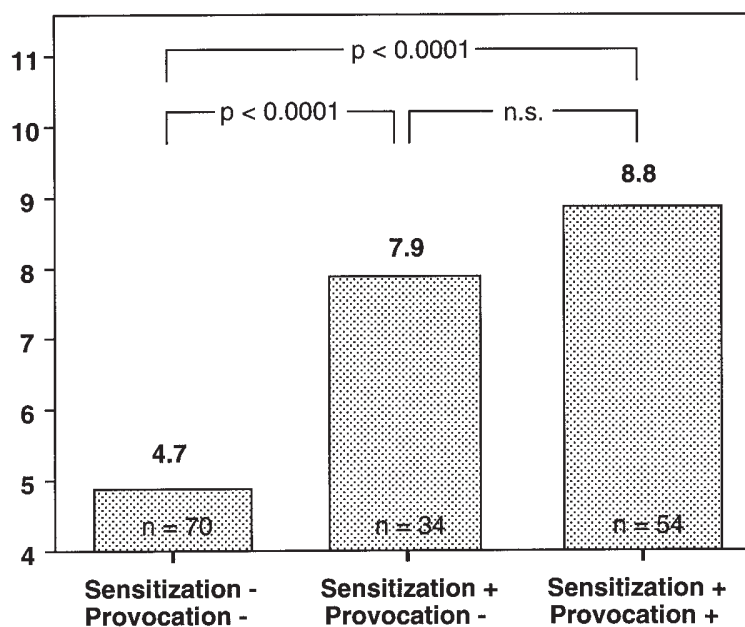


FIG 3. Mean number of operations, state of sensitization, and outcome of provocation tests. For calculation of statistical significance, Mann-Whitney test was used.

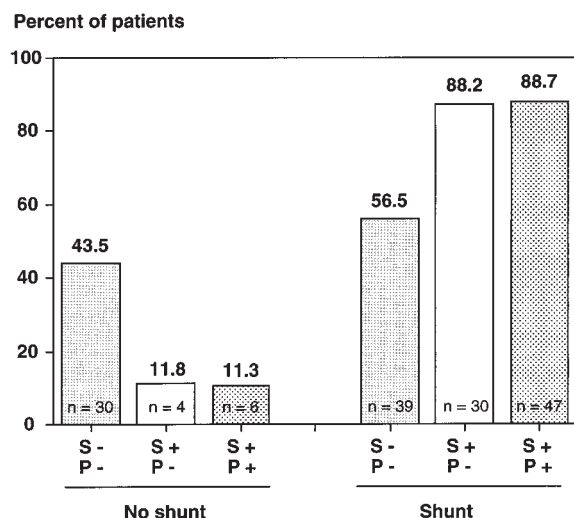


FIG 4. Percentage of patients according to the presence of a shunt system, state of sensitization to latex, and outcome of provocation tests (chi-square test, $P < .0001$). S, Sensitization; P, provocation.

TABLE II. Evaluation of the predictive capacity of risk factors for clinically relevant latex allergy

	Sensitivity	Specificity	PPV	NPV
Specific IgE in serum (%)	92.7	72.1	63.8	94.9
Skin prick test A (%)	96.4	76.9	68.8	97.6
Skin prick test B (%)	49.1	96.2	87.1	78.1
History of parents/patients (%)	53.7	94.2	82.9	79.7

PPV, Positive predictive value; NPV, negative predictive value; skin prick test A, NRL milk; skin prick test B, commercial extract.

Statistical analysis

For correlation of the number of operations and sensitization/provocation, the Mann-Whitney U test and Spearman's rank correlation test were used. For the atopic disposition and sensitization/provocation, the chi-square test was used. For calculation of odds ratios, the logistic regression and chi-square tests were used. Ninety-five percent confidence intervals are given in brackets. Differences associated with P values of less than .05 were considered significant.

Sensitivity was defined as the proportion of true positive results among symptomatic individuals, specificity as the proportion of true negative results among nonsymptomatic individuals, positive predictive value as the proportion of symptomatic individuals among those with positive test results, negative predictive value as the proportion of nonsymptomatic individuals among those with negative test results, and efficiency as the proportion of tested individuals correctly classified by the test.

RESULTS

Sensitization to latex

A questionnaire, skin prick test, IgE measurements, and provocation test could be applied for 159 patients. Total IgE ranged from less than 0.35 kU/L (detection

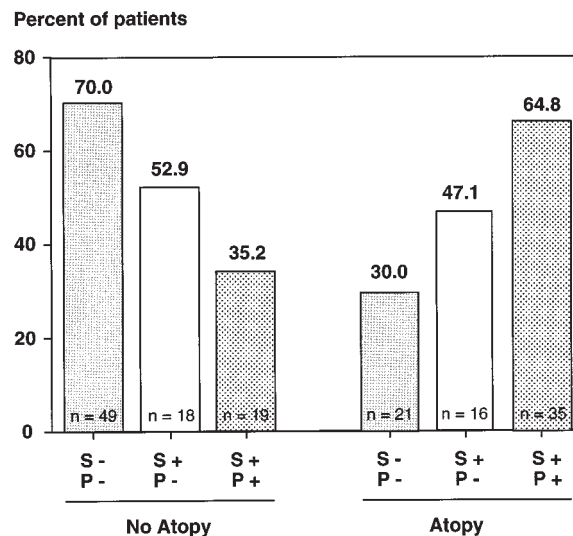


FIG 5. Percentage of patients according to atopic disposition, state of sensitization to latex, and outcome of provocation tests (chi-square test, $P < .0001$). S, Sensitization; P, provocation.

limit) to greater than 1865.0 kU/L (median, 52.6 kU/L). Latex-specific IgE in serum ranged from less than 0.35 kU/L to greater than 100.0 kU/L (median, 0.39 kU/L). Eighty patients (50.3%) showed specific IgE to latex in serum. Seventy-seven patients (48.4%) had positive skin prick test responses to NRL milk. However, only 31 patients (19.5%) had a positive response to the commercial latex skin prick test extract. Concordance between specific IgE to latex in serum and skin prick test with NRL milk was good (Table I). Patients were regarded as sensitized to latex if they were positive to either specific IgE in serum or in the skin prick test ($n = 88$ or 55.3%).

Provocation tests

One hundred fifty-nine patients were challenged; 2 patients with known anaphylactic reactions in their history had been excluded from provocation tests. Fifty-five patients (34.6% of all patients or 62.5% of the sensitized patients) had a positive response to the provocation test. Clinical symptoms were local urticaria, except for 1 patient who had mild generalized urticaria. Seven patients had additional symptoms of allergic conjunctivitis. No patient showed clinical reactions to the glove inflation test after a negative glove wearing test response.

Specific IgE values to latex were significantly higher in patients with a positive provocation test response compared with those with a negative provocation test response (Fig 1, $P < .0001$). An 11-year-old girl with a shunt system had a positive provocation response in the absence of specific IgE to latex in serum or a positive skin prick test response.

Surgical interventions

The total number of operations undergone ranged from 1 to 20 operations (median, 6 operations). The total number of operations and degree of sensitization showed a significant correlation (Fig 2). More than 8 operations significantly increased the risk of sensitization, and more than 9 operations increased the risk of allergy to latex ($P < .0001$) (Fig 3).

For the first year of life, the number of operations ranged from 1 to 13 operations (median, 3 operations). More than 3 operations in the first year of life significantly increased the risk of sensitization ($P < .005$), and more than 4 operations significantly increased the risk of allergy to latex ($P < .0001$).

Shunt system

One hundred seventeen (75%) patients with spina bifida had a ventriculo-atrial or ventriculo-peritoneal shunt system because of hydrocephalus. Specific IgE in patients with a shunt system (median, 0.91 kU/L) was significantly higher than in those without (median, <0.35 kU/L) ($P < .0001$). The number of shunt operations and degree of sensitization showed a significant correlation (Fig 2). Patients with a shunt system were significantly more often sensitized and more often had positive provocation responses compared with individuals without a shunt system (Fig 4, $P < .0001$). The odds ratio for the existence of a shunt system in terms of a positive provocation response is 3.9 (1.5 to 10.1; $P < .003$).

Atopic status

Seventy-two patients (45.3%) were classified as atopic. Atopic patients were significantly more often sensitized and more often had positive provocation responses compared with nonatopic individuals (Fig 5, $P < .0001$). The odds ratio for being atopic in terms of a positive provocation response is 3.2 (1.6 to 6.3; $P < .001$).

History of clinical reactions to latex

History of patients or their parents of symptoms on contact with material containing latex (excluding reactions to adhesive plasters) was positive in 35 patients (22.0%), of which 29 (82.9%) had positive provocation responses. Twenty-six of 55 patients (47%) had a negative history but a positive provocation test response. Table II summarizes data of sensitivity, specificity, positive predictive value, and negative predictive value for history, specific IgE in serum, and skin prick tests.

DISCUSSION

Our findings indicate that 55.3% of patients with spina bifida are sensitized to latex. Interestingly, 62.5% of sensitized patients had a positive response to the provocation test and may therefore be at risk of developing symptoms on contact with latex in daily life or during medical interventions.

A high number of surgical interventions were correlated with an increasing degree of sensitization. This confirms other investigations, which proved operations to be

one of the most important risk factors for sensitization to latex.^{2,10-18} In Fig 2 a statistical significance could not be calculated for CAP-class 6 because only 1 patient showed this high degree of sensitization. In other studies more than 8 and 9 operations^{2,15} have been reported to be an exceptional risk factor.

Because of the hypothesis that exposure early in life may facilitate early sensitization and allergy to latex, we looked separately at the number of operations during the first year of life and found a strong correlation between the number of operations during the first year and sensitization/allergy to latex. However, because the pattern was in the same range as for the number of operations beyond the first year, it is plausible that operations during the first year of life do not represent the determining risk factor.

In addition to the number of operations, the presence of a shunt system represents another important risk factor for sensitization and allergy to latex. Patients with a shunt system underwent significantly more operations (mean, 7.7) than patients without a shunt system (mean, 4.0; $P < .0001$). Thirty-eight percent of all operations were shunt operations, shunt revisions, or both. As seen in Fig 2, a greater number of shunt operations led to a higher degree of sensitization. Because shunt systems are latex-free, latex exposure is probably due to glove powder left on the meninge. Furthermore, the presence of latex allergy has been reported not to correlate with the number of intra-abdominal procedures,¹⁹ which indicates that a meningeal contact may be a predisposing factor. This hypothesis is supported by a recent case report providing evidence for local production of specific IgE to latex in the cerebrospinal fluid of a child with a ventricular shunt system.²⁰

During skin prick testing, no adverse reactions were noted. Although testing with the NRL milk showed a good sensitivity and specificity, the commercial skin prick test extract did not meet the demands for sensitivity at all (Table II). This may be because the commercial extract does not contain all clinically important major allergens or epitopes.

There were no significant side effects during 159 provocation tests, and glove tests may therefore be regarded as a safe diagnostic procedure. However, 2 patients with known anaphylactic reactions in their history had been excluded from provocation tests. The 1 patient who had a positive provocation response in absence of specific IgE to latex in serum or a positive skin prick test response was an 11-year-old nonatopic girl with 6 operations in her history, including a shunt system.

No patient who did not react to the glove wearing test showed a positive response to the subsequent glove inhalation test; that is, this additional test, which was performed as a mucosal and not a bronchial provocation test, does not seem to add information to the results of the glove wearing test. In contrast to our results, glove wearing tests have been reported in the literature as insensitive.²¹ This may be explained by the fact that the provocation tests were not performed on the high-risk group of patients with spina bifida.

A study of history of patients or parents for symptoms on contact with material containing latex (excluding reactions to adhesive plasters) revealed that 47% had a negative history despite a positive provocation test response. Therefore objective parameters of sensitization and provocation tests seem to be useful. Our findings indicate that an atopic disposition,²² the number of operations, and the presence of a shunt system increase the risk of becoming sensitized, and also allergic, to latex. Our results strongly support the necessity that patients with spina bifida as a high-risk group for latex allergy should remain latex-free from the first day of life.

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