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SPINA BIFIDA AS AN INDEPENDENT RISK FACTOR FOR SENSITIZATION TO LATEX

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ABSTRACT

Purpose: Patients with spina bifida are at a high risk for having an immediate type allergy to latex products. The number of surgical interventions, atopy and catheterization are well known responsible factors, whereas the condition of spina bifida per se has not been established as an independent risk factor.

Materials and Methods: A total of 131 patients with a shunted hydrocephalus (48 with spina bifida and 83 of other origin) were investigated for sensitization to latex by skin prick tests and determination of specific IgE. We hypothesized that the diagnosis of spina bifida will increase the risk for latex sensitization while considering potential confounding factors. Thus, we performed a multiple logistic regression analysis to determine independent risk factors.

Results: Whereas 56.3% (27/48) of children with spina bifida proved sensitized against latex, this result was the case in only 16.9% (14/83) with another cause of hydrocephalus ($p < 0.001$). The mean number of surgical interventions was 6.2 for patients with no latex sensitization and 9.3 for those with sensitization ($p = 0.02$). Of patient sensitized to latex 43.9% had a history of atopy compared to 15.5% of those not sensitized ($p = 0.02$). Sensitized and nonsensitized patients were comparable regarding gender and catheterization. In a multiple logistic regression analysis the cause of the hydrocephalus (odds ratio 6.76 for spina bifida), atopy (odds ratio 3.37) and the number of surgical interventions (odds ratio 1.14 per operation) were identified as independent risk factors.

Conclusions: The increased risk of latex sensitization in patients with spina bifida seems to be disease associated. Possible explanations for this finding may be genetic, antigen mediated, early latex exposure and immunological reasons.

KEY WORDS: latex allergy, risk factors, spinal dysraphism, spine

An anecdotal report in 1927 by Stern first established a link between anaphylaxis and exposure to natural rubber. About 50 years later the next case report on contact urticaria to rubber was published. In the last decade latex has been recognized as an important etiological agent in IgE mediated allergic reactions ranging from rhinoconjunctivitis, urticaria, angioedema and asthma to anaphylactic shock. Numerous studies have identified risk groups with an increased prevalence of latex sensitization, namely health care workers, rubber industry workers, individuals with history of atopy or self-catheterization and patients who have undergone multiple surgical procedures.[1–4] As an example of the latter group patients with shunted hydrocephalus require interventions for blocking of the ventricular catheter, tube disconnection and tube "shortening" due to physical growth which necessitates the conversion from ventriculoatrial to ventriculoperitoneal shunting.

Hydrocephalus may be associated with spina bifida or with other causes. The fact that sensitization against natural rubber latex occurs more often in subjects with spina bifida has been attributed to the higher number of neurological, orthopedic and urogenital operations, and to a higher rate of catheterization in this subgroup. The condition of spina bifida per se as a potential independent risk factor has not been investigated in most studies. Only a few have concluded from their data that there may be additional factors contributing to the development of latex hypersensitivity in spina bifida.[5–7] This possibility prompted us to screen our cohort of patients with shunted hydrocephalus (associated with spina bifida or of other origin) for latex sensitization and to analyze the data by multiple logistic regression analysis.

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PATIENTS AND METHODS

Within 1 year 131 patients underwent testing for latex sensitization by skin prick test and determination of specific IgE. The only inclusion criteria were the diagnosis of shunted hydrocephalus and oral or written informed consent from the patients or their parents. For skin prick testing the 2 different samples of latex containing material used were ammoniated natural latex milk (Regent Hospitalprodukte, Mönchengladbach, Germany) and Soluprick (ALK Abello, Copenhagen, Danmark), a latex prick test solution in 3 different concentrations (1, 10 and 100 histamine equivalent pricks per ml. The results obtained from both extracts had a correlation of 90%. In 10% Soluprick was negative when extract of the latex milk was positive. In 78% of these inconsistent cases sensitization was further supported by evidence of latex specific IgE. Thus, the overall correlation of skin prick and radioallergosorbent tests was 97.8%.

All skin prick tests were performed on the volar surface of the forearm. Normal saline and histamine hydrochloride (10 mg./ml.) were used as negative and positive controls. Results were read after 15 minutes, and reactions with a wheal size half or larger compared to histamine and 3 mm. or larger were regarded positive, according to the European Academy

of Allergology and Clinical Immunology guidelines. Total serum IgE and latex specific IgE were determined by the standard radioallergosorbent test technique. For specific IgE, results 0.70 KU/l. or greater (class 2) were considered positive.

Sensitization to latex was defined as a positive radioallergosorbent test (0.7 KU/l.) plus skin prick test to latex in at least 1 of the 2 samples used. Clinically manifest allergy was accepted when a specific history of anaphylactic reactions on contact with latex products was additionally given. In inconsistent cases a challenge test was started with a finger piece of latex glove on a wetted finger for 15 minutes. When negative a whole glove was applied to the wetted hand for another 15 minutes. For ethical reasons we did not perform challenge tests in all other patients, as most of them were severely physically and mentally disabled.

Atopy was defined as allergic rhinoconjunctivitis (due to pollen, house dust mites, animal dander and so forth), asthma or atopic dermatitis confirmed by increased IgE and positive skin prick tests. Skin prick tests to a panel of routine inhalative allergens were performed using commercially available extracts, including tree mix, grass mix, mugwort, horse, dog, cat and cow epithelia, and house dust mite. The medical and atopic history of all patients was reviewed with respect to possible anaphylactic reactions to latex containing products or to food and flowers known to cross-react with latex proteins.

As we hypothesized that the diagnosis of spina bifida will increase the risk for latex sensitization, we performed a statistical analysis where spina bifida was the primary target variable and potential confounding factors like age, gender, status of atopy, number of previous surgical interventions and catheterization were covariates, with the use of the t-test, chi-square test or Mann-Whitney U-rank sum test, as appropriate. A logistic regression model was fitted to evaluate independent risk factors. Odds ratios and 95% confidence intervals were calculated to represent the relative risk of these predictive variables, and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 131 children with shunted hydrocephalus were evaluated. Hydrocephalus was associated with spina bifida in 48 (37%) patients and with other causes (intraventricular hemorrhage, meningitis, congenital stenosis of the aqueduct of Sylvius) in 83 (63%). In 9 patients the etiology of the hydrocephalus was unknown. Latex-free management of high risk cases had not been established at the beginning of our study but was performed in all cases afterward, irrespective of the testing outcome.

Patients with spina bifida did not differ significantly from those with hydrocephalus of other pathogenesis with respect to number of surgical interventions (8.6 versus 6.2, $p = 0.07$) and mean age (18.8 versus 14.7 years, $p = 0.1$). Self-catheterization was performed in 25 patients with spina bifida. Urinary catheters used at the time of our study were usually made from latex but exchanged for silicone afterward. Atopy was more frequently associated with spina bifida than with other causes of hydrocephalus (39.6% versus 14.5%, $p = 0.03$).

Of the patients 41 (31%) proved to be sensitized against latex. They were comparable to the nonsensitized group in regard to age, gender, and catheterization (56% sensitized, 44% nonsensitized, $p = 0.403$). However, significant differences between sensitized and nonsensitized patients were observed regarding atopic status, mean number of surgical interventions and primary disease (spina bifida or not). A total of 18 (44%) patients with latex sensitization had a history of atopy compared to 14 of 90 (16%) not sensitized ($p = 0.05$). Patients sensitized to latex had undergone an average of 9.3 operations (range 3 to 24), which was significantly ($p = 0.02$) more than the nonsensitized group who had required 6.2 interventions (range 1 to 24) each. A significantly higher proportion of the latex sensitized patients had spina bifida associated hydrocephalus (56.3%) than those with no sensitization (16.9%, $p < 0.001$).

Of all patients with spina bifida 14.6% had experienced allergic symptoms after contact with latex products and 41.7% had an asymptomatic latex sensitization. In contrast, only 1.2% of patients without spina bifida had a manifest allergy to latex products and 15.7% were sensitized asymptomatically. Clinical symptoms ranged from contact urticaria (after exposure to air mattresses, balloons, catheters and other medical devices) and dyspnea (on inhalation of latex particles from balloons and powdered gloves) to anaphylactic shock during surgical interventions.

We tested our cohort for a possible statistical association between latex sensitization and all factors shown to be significantly different in univariate analysis, namely diagnosis (spina bifida or hydrocephalus of other origin), number of surgical interventions and history of atopy, using a logistic regression model. Age was also included as it had nearly reached statistical significance in univariate analysis. The table shows that diagnosis, atopy and number of operations were highly significant and independent risk factors for developing sensitization to latex. The odds ratios were 6.76 for the diagnosis of spina bifida per se, 3.37 for a positive history of atopy and 1.14 per surgical intervention. Interestingly, age, which was not a significant variable in univariate analysis, appeared as a weak negative risk factor with an odds ratio of 0.91.

DISCUSSION

The prevalence of sensitization to latex is higher in several groups in the population, including children with spina bifida.[1,2] In our cohort 31% of all patients were classified positive, which is in the range between 29% and 55%, as reported in several independent studies.[1,2,8,9] Although sensitization is not equivalent to manifest allergy, those patients may be regarded as being at high risk for anaphylactic reactions on further contact with latex products, since we defined sensitization rather strictly as a positive skin prick test plus positive specific IgE in a radioallergosorbent test 0.7 KU/l. or greater (class 2). As shown by Bernardini et al[3] and recently by Nieto et al,[9] this testing results in sufficient sensitivity and specificity. Furthermore, challenge tests were performed

Multiple logistic regression analysis for latex allergy

	Sensitization % (mean ± SD)	No Sensitization (%) (mean ± SD)	Adjusted Odds Ratio	Adjusted 95% CI	p Value
No. pts.	41 (31.2)	90 (68.8)			
Age (yrs.)	16.7 ± 6.6	16 ± 7	0.91/Yr. age	0.83–0.99	0.021
Hydrocephalus:					
Spina bifida	27/48 (56.3)	21/48 (43.7)	6.76	2.48–18.41	<0.001
Other	14/83 (16.9)	69/83 (83.1)	Reference		
Surgical interventions	9.3 ± 6.1	6.2 ± 4	1.14/Operation	1.02–1.27	0.02
History of atopy	18 (43.9)	14 (15.5)	3.37	0.98–8.30	0.02

in inconsistent cases. In the search for risk factors for latex hypersensitivity most conclude that increased exposure to latex products by a high number of surgical procedures or catheterization has a decisive role.[1,2] Others stress the importance of the number of operations in combination with atopic diathesis and self-catheterization[8,10,11] or with the presence of shunted hydrocephalus.[12]

In recent years studies expressing doubts on the exclusive role of these classical risk factors in patients with spina bifida have been published, the first in 1996.[5] By comparing skin prick test results in 3 groups of patients with different surgical histories, the authors concluded that repeated surgery alone could not be responsible for the higher incidence of latex hypersensitivity in patients with spina bifida. However, the mean number of operations was small (1.80), and spina bifida was not discussed as a possible risk factor. In another study spina bifida had a higher risk for latex sensitization compared to other diseases but the influence of the number of operations was not considered.[6] Another study suggests that the spina bifida population may bear a disease associated propensity for latex sensitization.[7] A total of 21 patients with spina bifida were compared to 32 with posthemorrhagic or congenital hydrocephalus. All patients had a ventriculoperitoneal shunt from a young age. The latex sensitization rate was significantly higher in the spina bifida group (43%) than in the nonspina bifida group (6%), while the mean number of operations was comparable in both and therefore not an independent risk factor.

Our study presents a large sample of patients with shunted hydrocephalus and histories of a high number of surgical interventions. The condition of spina bifida per se presented as the strongest independent risk factor for sensitization to latex, followed by atopy and the number of operations. Regarding the latter, patients with spina bifida usually undergo other surgical procedures besides shunt interventions, including urological and orthopedic operations. This consideration could imply a potential confounder. To our knowledge no studies have been performed to elucidate this question. Due to too small subgroup samples and resulting statistical problems, we were not able to investigate this further.

Atopy presented as an independent risk factor in univariate analysis and multiple logistic regression. Confounding factors like gender or catheterization could be ruled out. In contrast, age appeared to be weakly associated with decreased risk, which may be due to the fact that the majority of surgical interventions are performed in early childhood. In later years fewer operations may seemingly reduce the risk of a newly developed latex sensitization. This assumption could not be further evaluated because of too small subgroup samples but may be indicative of the importance of secondary preventive measurements in latex sensitized subjects. However, patients with were on average older than those without spina bifida. As a consequence, one would expect an even higher odds ratio for the diagnosis of spina bifida if the 2 groups were the same age. We can only speculate which mechanisms may be responsible for the apparent disease associated risk of sensitization to latex in spina bifida patients.

The majority of patients with spina bifida are exposed to latex products within 48 hours after birth for closure of the spinal cord, whereas those with other causes of hydrocephalus usually undergo surgery a few weeks later. The immune response of newborns is usually dominated by Th2 cells and thus "atopic."[13] Whereas the immune system in nonatopic children subsequently shifts to a Th1-mediated cytokine pattern, there is a further increase in Th2 cells in atopic subjects. This difference could explain the phenomenon of why atopic children are more susceptible to latex allergy and is in good agreement with our finding that atopy was observed more frequently in patients with spina bifida. Furthermore, it has been demonstrated that being born during pollen season increases the risk of pollinosis.[14] A similar situation, namely immediate and high exposure to latex products after birth, may occur in spina bifida. It is not known whether a delay in the first contact with latex products of several weeks or months would reduce the risk of latex sensitization. Also, for ethical reasons the natural course of latex sensitization over a lifelong period cannot be studied. However, the higher prevalence of sensitization to latex in our spina bifida group cannot be explained by a higher atopy rate or a later date of first surgical intervention in the nonspina bifida group alone, since the primary disease (spina bifida) and atopy were shown to be independent risk factors in the multiple logistic regression analysis.

A genetic factor might be implicated. Latex allergy develops less frequently in adult patients with spinal cord injury and multiple surgical interventions than in children with a similar constellation.[15] HLA class II alleles DR4 and DQ8 were suggested as susceptibility factors in latex sensitized subjects reacting to hevein (which is not a major allergen in spina bifida).[16] However, analysis of HLA-D region genes DRB and DQB1 suggested no significant correlation with IgE responsiveness to the rubber elongation factor Hev b 1, one of the major antigens involved in latex allergic patients with spina bifida.[17]

Several studies have shown that latex sensitized patients with spina bifida recognize different latex proteins than other groups, for example health care workers.[18] This finding may suggest the existence of distinct pathogenetic subgroups within the complex of latex allergy. Moreover, children with latex allergy who had never undergone surgical interventions show a different latex antigen profile than those with a history of multiple operations.[19] It is not known whether these 2 groups differ in their IgE binding patterns.

Some have discussed the potential influence of the presence of a cerebrospinal shunt system on latex allergy. Indeed, although shunts are free of latex, a contamination by latex gloves during placement is unavoidable. These small amounts of latex may be sufficient to induce sensitization. However, most studies explained the higher prevalence of latex sensitization in patients with shunts by the higher number of operations. Moreover, it was concluded that the ventricular shunt does not seem to be an independent risk factor.[12] As the patients in our study population did all have shunted hydrocephalus, at least a study specific effect can be ruled out.

The entity of spina bifida cannot be explained by a simple deficiency of folic acid. Besides controversially discussed gene polymorphisms,[20] abnormal cell cycle properties in peripheral blood lymphocytes of children with myelomeningocele have also been demonstrated.[21] These cells are also involved in the Th1/Th2 immune response system. To date it remains pure speculation that this response system could represent a missing link between spina bifida, atopy and latex allergy.

In conclusion, our results corroborate previous studies indicating a disease associated propensity for latex allergy in patients with spina bifida. Further studies are needed to elucidate a possible genetic background, differences in antigen recognition or metabolic changes. The main clinical impact of our findings is the necessity of primary prevention measurements from the first day of life.

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EDITORIAL COMMENT

The prevalence of allergic diseases has increased substantially in industrialized countries during the last few years. The reasons are not well known, although they seem to be related to the western way of life, that is changes in food and feeding patterns, pollution from combustion motors and engines and home microclimates due to thermal and acoustic isolation. Recently, much attention has been given to the hygienic theory. According to this, the increase in allergic diseases is due to the hypersanitized way of life, which removes from the newborn environment the antigenic stimuli that adequately regulate the immune response.[1]

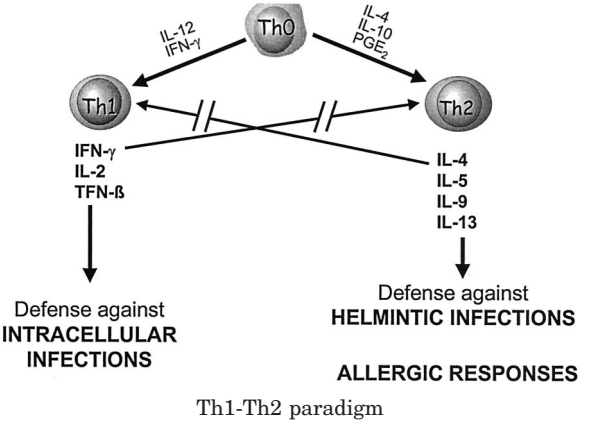
In the past decade 2 groups of cells have been identified inside the CD4+ T-helper lymphocyte population, namely Th1 and Th2. These lymphocytes are recognized through their cytokine secretion pattern: Th1—interferon-γ, interleukin (IL) 2, and so forth, and Th2—IL-4, IL-5, and so forth. These 2 different subsets are mutually antagonists. Thus, an environment with IL-4 prevents the development of Th1 mediated responses, and conversely, the predominance of interferon-γ inhibits Th2 lymphocyte responses (see figure). The function of these 2 types of cells are also different. Th1 lymphocytes have a defense role against intracellular infections (bacterial and viral), while Th2 lymphocytes are involved in extracellular infections, for example parasitic infestations, and in allergic responses.

During intrauterine life there is a predominance of Th2 responses in the fetus, thus protected against maternal predominant Th1 responses (which are particularly toxic to the placental-fetal interface). Hence, the fetus and newborn are physiologically Th2 responders, and prone to allergic responses. Under normal circumstances this neonatal allergic status is transient and, due to an adequate bacterial stimulus during an undefined period of days to weeks of extrauterine life, there is a switch towards Th1 responses. In some children such a switch does not occur and Th2 responses become long-lasting or permanent. Reasons for this occurrence are mainly of 2 types. The atopic nature includes genetic factors precluding the Th2 to Th1 switch, and environmental factors include the effect of repeated antigenic load, potent allergens or in early life may consolidate the Th2 responses.

The phenotypic expression of allergy is the result of the interaction between genetic and environmental factors. A strong association exists between allergy to latex and spina bifida. A disease associated propensity for latex sensitization has been described (reference 7 in article). As in these children sensitization to latex is significantly more frequent than in other patients who have undergone multiple operations. This propensity might be due to genetic factors, such as spina bifida or causes giving rise to spina bifida which may predispose to allergic responses or environmental factors particularly affecting children with spina bifida but not others who have undergone multiple operations.

The authors report further evidence of the higher association of sensitization to latex and spina bifida compared to other children with a ventricular-peritoneal shunt for hydrocephalus of other origin but the reasons for this association remain unclear. If genetic factors were responsible, we would expect to find a high rate of atopic children among those with spina bifida compared to the general population and to others who had undergone multiple operations. In fact, atopy was more frequent in children within this spina bifida study (39.6%) but not in that by Szépfalusi et al in which it ranged from 20% to 18% for spina bifida and the control group (reference 7 in article). In other studies the frequency of atopy in spina bifida is less than 20%, which is not so high and not far from the prevalence in the pediatric general population, especially when patients are specifically studied regarding this possibility.

Yet, even when a higher prevalence of atopy is confirmed in spina bifida, some environmental factors that specifically affect these children may be involved. The first operation usually takes place in the first day of life. Not many other malformations require such an early intervention. The contact with latex in the crucial first days of life might drive the cytokine pattern towards the Th2 allergic prone responses. If this response had an allergen specific effect, sensitization would imply just latex but not other inhaled or food antigens. If this response had a more general unspecific effect, sensitization would imply other allergens, and atopic diseases would be more frequent, just as in the case that genetic factors were responsible. Unfortunately, the effect of age at first operation, usually the first day in spina bifida cases, and several weeks in others with hydro-



Th1-Th2 paradigm

cephalus, has not been analyzed in these studies. In another study by Konz et al children were compared to patients who underwent their first operations as adults.[2] A large enough control group for epidemiological studies, comparable to spina bifida in this regard, remains to be found.

Another different environmental factor is the level of antigenic burden. Besides placement of the ventricular-peritoneal device and operations to adjust it because of growth or malfunction, children with spina bifida undergo a high number of orthopedic and urological operations and the closure of the neural defect. Orthopedic and urological surgeries are longer and more aggressive, and the contact with blood vessels and open mucosas expose these children to an overload of latex not present in hydrocephalus of other origin. As the authors recognize, the importance of this issue has not been addressed and poses another question on this association.

What remains clear and what concerns urologists is that children with spina bifida are at the highest risk for latex sensitization. As recommended by the American Academy of Allergy, Asthma and Immunology, all medical procedures on these patients must be performed in a latex-free environment to prevent allergic reactions in sensitized children and to prevent sensitization in those who are nonsensitized.[3] There has been a decrease in the prevalence of latex allergy in younger children with spina bifida born after latex avoiding measures were implemented[4,5] and a decrease in latex specific IgE has been demonstrated in some sensitized patients after removing latex,[6,7] so we all hope this occurrence will soon become a problem of the past. The solution lies on our hands.

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