Risk factors for latex sensitization in children with spina bifida


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SUMMARY

Background: Children with spina bifida represent the major risk group for latex sensitization.

Purpose: To determine the prevalence of latex sensitization in these children and to identify risk factors.

Material and methods: We studied 57 patients with spina bifida. The mean age was 5.6 years and the male/female ratio was 0.8/1. In all patients a questionnaire, skin prick test (SPT) with latex (UCB-Stallergènes, Lofarma and ALK-Abelló), common aeroallergens and fruits (UCB-Stallergènes) and serum determination of total IgE (AlaSTAT) were performed.

Results: The prevalence of latex sensitization was 30%; only two sensitized children (12 %) had symptoms after exposure. Risk factors for latex sensitization were age ≥ 5 years (p = 0.008; OR = 6.0; 95% CI = 1.7-22.1), having at least four previous surgical interventions (p < 0.0001; OR = 18.5; 95% CI = 3.6-94.8), having undergone surgery in the first 3 months of life (p = 0.008; OR = 5.4; 95% CI = 0.7-29.2) and total serum IgE ≥ 44 IU/ml (p = 0.03; OR = 3.8; 95% CI = 1.1-13.1). Multiple logistic regression analysis showed that only a history of four or more surgical interventions (p < 0.0001; OR = 26.3; 95% CI = 2.9-234.2) and total serum IgE ≥ 44 IU/ml (p = 0.02; OR = 8.6; 95% CI = 1.4-53.4) were independently associated with latex sensitization. Sex, family and personal allergic history, hydrocephalus with ventriculoperitoneal shunt, cys tourethrogram, intermittent bladder catheterization and atopy were not related to latex sensitization.

Conclusions: In children with spina bifida, significant and independent risk factors identified for latex sensitization were multiple interventions and higher levels of total serum IgE. A prospective study will clarify the clinical evolution of assymptomatic children sensitized to latex.

Key words: Latex. Spina bifida. Sensitization. Children. Risk factors.


INTRODUCTION

The first case of latex allergy was described in 1979 by Nutter (1). Since then, particularly in the last years, this clinical entity has been more frequently referred as a cause of urticaria and angioedema, rhinoconjuntivitis, asthma and anaphylaxis. Most reactions are mild, but more serious and potentially lethal situations can occur, with systemic involvement, namely during surgical and diagnostic procedures with mucosal exposure to latex products (2-4). In spite of the diversity of symptoms, in some studies most sensitized individuals are assymptomatic (5-8).

The prevalence of latex sensitization in the general population is unknown, but it seems to be lower than 1% (8-12). Higher prevalences, determined by some authors (13, 14), seems to be related with the diagnostic method used (SPT and/or serum specific
IgE determination) and the existence of occupational exposure in the studied populations.

In selected groups, higher prevalences are found. Hospital workers, through frequent contact with latex products, have rates of sensitization ranged between 2.9% and 16.9% (9, 15-20). Rubber industry workers also have high sensitization prevalence (21). Atopy also seems to be another risk factor of latex sensitization, mainly if associated with frequent contact to latex products (22-27).

Children with spina bifida are considered the major risk group. Several published studies found prevalences between 4.3% and 73.3% (table I) (5-7, 28-42). The variability of results can be related with differences in the methodology, namely variables related with the population in study (dimension and age group) or the diagnostic method (SPT and/or serum IgE determination, absence of allergenic extract standardization and different methodology of SPT).

Several authors tried to identify risk factors for latex sensitization in children with spina bifida. The high prevalence of sensitization seems to be a result, mainly, of early (33, 34, 39-41) and frequent contact with latex products (7, 29, 30, 37, 39-43). The exposure begins, frequently, in the first day of life, with myelomeningocele surgical closure, and continues during several surgical procedures to correct neurologic, urologic and orthopedic congenital malformations. Mucosal contact occurring during surgical and diagnostic procedures (catheterizations and cystourethrograms) promotes sensitization (28, 41).

The predisposition to produce high levels of specific IgE in response to allergenic exposure, related to a high atopic risk, has been a factor frequently associated to latex sensitization in this population (7, 29, 30, 37, 40, 41).

The aim of this study was to determine the prevalence of latex sensitization and to evaluate the relevance of clinical data (age, gender, personal and/or family history of atopy and ventriculoperitoneal shunt), exposure to latex products (precociousness and number of surgeries, performance of cystourethrograms and bladder catheterization), allergenic sensitization and serum levels of total IgE, as risk factors for latex sensitization in a population of spina bifida children.

**MATERIAL AND METHODS**

**Population**

From August to November of 1997, we studied 57 children with spina bifida of the Spina Bifida Nucleus of Dona Estefânia Hospital, with a mean age (± SD) of 5.6 (± 4.1) years (aged between 6 months and 18 years); most of them less than 5 years old.
A predominance of female gender was found (54%), corresponding to a ratio male/female of 0.8/1.

All the children underwent a questionnaire, SPT and serum total IgE determination. Parents or tutors consent was obtained for children’s participation. The study was approved by the Dona Estefânia Hospital Ethics Committee.

**Questionnaire**

A trained doctor performed a questionnaire for allergic diseases in children, evaluating the following parameters:

- Demographic data.
- Personal and family history of allergic diseases.
- History of latex exposure (number and type of surgical interventions, bladder catheterization and cystourethograms).
- Symptoms upon contact with latex products.

**SPT**

SPT were performed under medical supervision, always using the same methodology and respecting avoidance periods recommended for relevant drugs. SPT were performed on the anterior face of the forearm, respecting a minimum distance of 2 cm between each allergenic extract and using metallic lancets of perpendicular application on the skin, with 1 mm penetration (Dome Hollister Stier Prick Lancetter) (44). The following allergenic extracts were used:

- Latex (three extracts): UCB-Stallergènes, Lofarma and ALK-Abelló.
- Common aeroallergens (UCB-Stallergènes): Dermatophagoides pteronyssimus (Dpt), Dermatophagoides farinae (Df), mixture of grass and tree pollen, ragweed, cat and dog.
- Fruits and vegetables (UCB-Stallergènes): banana, avocado, pineapple, kiwi, apricot, peach, grape, chestnut and potato.

As a positive reference, we used histamine extract at 10 mg/ml concentration (45) and as a negative reference, a phenol solution at 0.5%, with no positivity with this reference. SPT response were interpreted 15 minutes after application, evaluating wheal area (45) and considering 7 mm² as positive cut off. The reading method used consisted of a digitalized graphics table, connected to a microcomputer with computer assisted design (CAD) software, a method previously validated by our group (46).

**Total IgE**

Serum total IgE determination was performed by a method of radioimmunoassay in micro-plates-AlaSTAT® (Amerlab/Diagnostic Products Corporation). The results were expressed in IU/ml.

**Statistical analysis**

Fisher’s exact test was used to evaluate the differences regarding the studied characteristics among latex sensitized and non-sensitized children; \( p < 0.05 \) was considered significant. Student’s t test was used to compare values of total IgE among latex sensitized and non-sensitized children; \( p < 0.05 \) was considered significant. The relative importance of the studied characteristics as risk factors for latex sensitization was obtained through the determination of the odds ratio, with a confidence interval of 95%. A model of multiple logistic regression was performed, including the characteristics considered significant in the univariate analysis method, to identify independent risk factors for latex sensitization. Statistical analysis was done with SPSS version 6.0

**RESULTS**

**Latex sensitization**

Seventeen of the 57 children studied were sensitized to latex, corresponding to a sensitization prevalence of 30%. The prevalence of sensitization was 26% with ALK-Abelló extract, 25% with UCB-Stallergènes extract and 25% with Lofarma extract. The prevalence of latex sensitization with all latex extracts was 23%.

There was no adverse reactions to latex SPT.

Only two of the latex sensitized children (12%) had symptoms of latex allergy. A female child 4 years old, with rhinitis after inflating balloons and history of 6 surgical interventions. A male child 5 years old, with urticaria and angioedema after inflating balloons and contacting with gloves, with a history of 10 surgical interventions.
Demographic data

The mean age of the latex sensitized children was higher than that of non-sensitized children, respectively 7.6 (± 4.5) years and 4.8 (± 3.6) years (p = 0.03). In children with 5 or more years, the prevalence of latex sensitization was significantly higher than in the younger group, 48 % to 13 %, (p = 0.008, OR = 6.0, 95 %CI = 1.7-22.1).

Personal and family history of allergic diseases

Family history of allergic diseases (bronchial asthma, rhinitis, allergic conjunctivitis or atopic eczema), was present in 49 % of the population. Personal history of allergic pathology was verified in 23 % of the children (18 % with rhinitis, 11 % with asthma and 2 % with atopic eczema).

Family history (p = 0.78; OR = 1.2; 95 %CI = 0.4-3.9) or personal history of allergic diseases (p = 0.98; OR = 1.1; 95 %CI = 0.3-4.0) was not identified as risk factors for latex sensitization.

Hydrocephalus with ventriculoperitoneal shunt

Most children (68 %) had hydrocephalus with ventriculoperitoneal shunt. These children presented higher prevalence of latex sensitization, 36 % vs 17 % in children with no ventriculoperitoneal shunt, without statistical significance (p = 0.21; OR = 2.8; 95 %CI = 0.7-11.4).

Surgical interventions

The average number (± SD) of surgical interventions was 3.7 (± 2.5), ranged 1 to 12 surgeries. The prevalence of latex sensitization increased with the number of surgical interventions (fig. 1). The average number of surgeries was significantly higher (p = 0.0001) in sensitized children, 6.3 (± 2.7) vs 2.7 (± 1.5) in non-sensitized children.

The existence of at least 4 surgeries was identified as a risk factor for latex sensitization: p < 0.0001; OR = 18.5; 95 %CI = 3.6-94.8. The prevalence of sensitization was 56 % in children submitted to 4 or more surgical interventions, compared to 6 % in children with less than 4 surgeries.

Almost all of the children were precociously submitted to surgical interventions, 55 % in the first day of their lives, 80 % in the first week and 97 % before 3 months old. The average number of surgeries in the first 3 months was 1.9 (± 1.3), ranged 1 to 8. Latex sensitized children had a higher average number of interventions in the first 3 months of life, 2.6 (± 1.9) vs 1.6 (± 0.9) in non-sensitized children (p = 0.008; OR = 5.4; 95 %CI = 0.7-29.2).

Cystourethrograms and intermittent bladder catheterization

Intermittent bladder catheterization, occurring in the majority of children in study (56 %), was not identified as a risk factor for latex sensitization (p = 0.55; OR = 0.8; 95 %CI = 0.2-1.9). Cystourethrograms, performed in almost half of the population (49 %), were also not identified as a risk factor for sensitization (p = 0.89; OR = 1.0; 95 %CI = 0.3-3.2).

Prevalence of atopy

The prevalence of atopy was 21 % (12 children). Eleven of the atopic children (19 %) were sensitized to house dust mites (Dpt and/or Df). Three children (5 %) were sensitized to grass and ragweed pollen. Four children (7 %) were sensitized to fruits and vegetables (banana, pineapple, apricot and potato), without symptoms.

There were more latex sensitized children among the atopic group (50 %), in comparison with non-atopic children (24 %), however without statistical significance (p = 0.15; OR = 3.1; 95 %CI = 0.8-11.6).
Total IgE

The average value (± SD) of total IgE was 98.9 (± 196.0) IU/ml, corresponding to a geometric average of 32.0 IU/ml and a median value of 44 IU/ml. The geometric average for total IgE was significantly higher in the latex sensitized children, 71.2 vs 22.6 IU/ml in non-sensitized (p = 0.004). High serum levels of total IgE was identified as a risk factor for latex sensitization, 46 % of children with total IgE ≥ 44 IU/ml were sensitized, vs 14 % of children with total IgE < 44 IU/ml (p = 0.03; OR = 3.8; 95 %CI = 1.1-13.1).

Multiple logistic regression analysis

We performed a multivariate logistic analysis of significant risk factors (table II), namely age ≥ 5 years, 4 or more surgeries, higher average number of surgeries in the first 3 months of life and serum total IgE ≥ 44 IU/ml. It was identified as independent risk factors for latex sensitization (table III): existence of at least 4 interventions (p < 0.0001; OR = 26.3; 95 %CI = 2.9-234.2) and total IgE ≥ 44 IU/ml (p = 0.02; OR = 8.6; 95 %CI = 1.4-53.4).

DISCUSSION

In a population of 57 children with spina bifida the prevalence of latex sensitization was 30 %, a value lower than those found in other published studies (5, 6, 29-34, 38, 40, 41). The age of these children (most of them younger than 5 years old) can justify the prevalence of sensitization in our study, as well as the small number of symptomatic children (12 %). In the studies involving children older than 7.5 years (5, 6, 28, 29, 32, 33, 38, 41), the prevalence of latex allergy was higher, varied between 24 % and 63 %. In the available studies, none of the works included children with an average age under that observed in our study. The low prevalence of sensitization found by Capriles-Hulett et al (35), is probably related to socioeconomic factors, namely the re-utilisation of gloves (washing and sterilisation).

The use of different methodology in the diagnosis of latex sensitization, including serum specific IgE determination or SPT, in most studies with non-standardized extracts, prepared from natural latex or surgical gloves, could justify the disparity of results.

In our study, the prevalence of sensitization was determined by SPT, the most sensitive diagnostic method (30, 31, 40, 47, 48), using three commercial latex extracts. SPT were performed with no adverse reaction, contrary to Kelly et al (31), who found a prevalence of 8 % of systemic reactions.

Several studies tried to identify risk factors for latex sensitization in children with spina bifida. Demographic data, such as age (37, 40) and gender (6), contact with latex products, including number of surgical interventions (7, 29, 30, 33, 37, 39-43) performing cystourethrograms and bladder catheterization (37), existence of hydrocephalus with ventriculoperitoneal shunt (37, 41, 49), atopy (7, 29, 30, 37, 40, 41), fruit sensitization (7) and high levels of total IgE (7, 37) have been identified as risk factors. Some of these characteristics are related to each other. Exposure to latex, during surgical interventions and other diagnostic and therapeutic procedures, increases with age. Serum levels of
total IgE depend on age and atopy. There are few studies performing logistic regression analysis, allowing the identification of significant and independent risk factors (7, 37, 40).

The importance of a high number of surgeries in latex sensitization was documented in most studies (7, 29, 30, 33, 37, 39-43), although the value from which there is a risk is not usually mentioned. Bernardini et al (7), in a population of 59 patients with spina bifida, identified 5 or more surgical interventions as a risk factor. Niggemann et al (41), in 159 patients, identified 8 or more surgeries as a risk factor for sensitization and 9 or more interventions as a risk for symptoms related to latex exposure. In only one study (35) the number of surgeries was not identified as a risk factor, presenting however a low prevalence of latex sensitization.

In our study, we verified that the prevalence of latex sensitization increased with the number of surgeries, we identified 4 or more interventions as a risk factor for sensitization, with an adjusted relative risk of 26.3 (95 %CI from 2.9 to 234.2).

Almost all children studied had been precociously submitted to surgical interventions, as other authors had referred (7, 41, 50). There are few studies identifying early exposure as a risk factor for latex sensitization, although this has been suggested by several authors (33, 34, 39-41). Niggemann et al (41), identified the existence of 3 or more surgeries in the first year of life as a risk factor for sensitization.

In our study, the precociousness of interventions, namely in the first three months of life, proved to be dependant on the number of surgeries, after performing multiple logistic regression analysis, although it had been identified as a risk factor for sensitization (univariate analysis).

Other forms of latex exposure, including cystourethromgrams and intermittent bladder catheterization, were not identified as risk factors as expected, because these procedures in our Hospital are performed with latex free material. On the opposite, Nieto et al (37), studying 100 patients with spina bifida identified both, cystourethromgrams and intermittent bladder catheterization, as risk factors for sensitization, although with no mention to the type of material used.

Some authors have documented the existence of hydrocephalus with ventriculoperitoneal shunt as an important factor related to latex sensitization in spina bifida children (37, 41, 49). Early intratectal exposure and the higher number of surgeries related to shunt, are possible mechanisms. The hypothesis that meningeal contact with latex gloves justifies this higher sensitization was supported by a publication of a clinical case of a child with ventriculoperitoneal shunt where latex specific IgE appears to be locally synthetized in cerebrospinal fluid (51). On the opposite, in our study, ventriculoperitoneal shunt was not identified as a risk factor, in spite of a higher prevalence of sensitization in these patients.

Besides latex exposure during surgical interventions, atopy is considered by the majority of authors as the most important risk factor for latex sensitization in patients with spina bifida (7, 29, 30, 37, 40, 41), as well as for latex allergy (5, 32, 37, 41, 52). Moneret-Vautrin et al (30), suggest the possibility of a synergetic effect resulting from the combination of these two factors towards promoting sensitization.

In our study, the existence of atopy was not a risk factor for latex sensitization. In this population, although the atopic children present a sensitization prevalence of 50 %, vs 24 % in non-atopics, this difference had no statistical significance. Also Cremer et al (6), in a study with 148 patients, with a similar prevalence of atopy (18.4 %), concluded that this was not a risk factor for latex sensitization. Capriles-Hulett et al (35), also did not find a relationship between latex sensitization and atopy.

Some authors suggest that atopy is not a risk factor for latex sensitization, but inversely the existence of latex sensitization is a predisposing factor for the development of atopy (40, 53). Children who are sensitized to latex and continue to be exposed to this potent allergen, would present continuous production of Th2 cytokines pattern, such as IL-4 and IL-13, favouring sensitization to common aeroallergens. In our study, the high number of younger children, mostly under 5, rises the hypothesis that sensitization to other aeroallergens has not yet developed. Prospective study could clarify this supposition.

Some authors suggest that children with spina bifida are predisposed to be sensitized to latex, independently of atopic status and level of latex exposure. The significantly higher prevalence of latex sensitization in children with spina bifida compared with patients with other pathologies, with similar number of surgeries (33, 34, 36, 54) and similar prevalence of atopy, (33) supports the existence of a genetic predisposition. This hypothesis was not confirmed in a study performed by Porri et al (38), in which the prevalence of latex sensitization was equivalent in patients with and without spina bifida, submitted to a similar number of surgeries.

There are few studies regarding the importance of serum total IgE as a risk factor for latex sensitization (7, 37). Nieto et al (37), and Bernardini et al, (7) studying samples of 100 and 59 patients with spina
bifida, verified that high levels of total IgE, adjusted to age, was correlated to latex sensitization. Swert et al (52), studying patients with and without latex allergy, diagnosed by challenge test (surgical glove band in the arm) matched by age, gender and number of surgeries, found that the geometric average of total IgE was significantly higher in allergic patients. Kelly et al (32), in a population of 60 children, identified total IgE > 84 IU/ml as a risk factor for anaphylactic reaction during surgical intervention.

In our study, the existence of serum total IgE ≥ 44 IU/ml was identified as an independent risk factor for latex sensitization, with an adjusted relative risk of 8.6 (95 %CI from 1.4 to 53.4).

Allergy to latex represents an important health problem for children with spina bifida, enhancing the need to implement more aggressive diagnostic and preventive measures. Direct contact with latex products in hospital environment, particularly during surgery, must be avoided in all latex sensitized children, and ideally in all spina bifida children since birth. We must stress the need of a detailed description of the components of all medical products, which frequently contain small amounts of hidden allergens.

Cremer et al (55), in a pioneer study, recently, demonstrated that primary prevention could avoid the appearance of latex sensitization in children with spina bifida. The authors performed a prospective study with 2 years of duration, involving 12 newborns with spina bifida, which underwent surgery in a latex-free environment since the first day of their lives, verifying that none of these children were sensitized. In comparison, in a sample of 8 children with spina bifida, submitted to equivalent number of surgeries with no avoidance measures, 38 % were sensitized to latex before they were 2 years old. However, these results need confirmation by studies with longer duration and involving more patients.

The natural history of assymptomatic sensitized children, as well as children not yet sensitized, with sustained latex exposure, remains to be clarified.

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RESUMEN

**Introducción:** Los niños con espina bífida son el principal grupo de riesgo para sensibilización al latex.

**Objetivo:** Se pretendió con este estudio determinar la prevalencia e identificar factores de riesgo para sensibilización al latex en niños con espina bífida.

**Método:** Se estudiaron 57 niños con espina bífida, con una edad media de 5,6 años y una relación sexo masculino/femenino de 0,8/1. A todos los niños les realizamos cuestionario, pruebas cutáneas en prick incluyendo latex (extractos UCB-Stallergènes, Lofarma y ALK-Abelló), aeroalergenos comunes y frutos (UCB-Stallergènes) y determinación sérica de IgE total (AlaSTAT).

**Resultados:** La prevalencia de sensibilización al latex fue del 30 %; sólo dos niños sensibilizados (12 %) presentaban sintomatología relacionada con la exposición. Fueron identificados como factores de riesgo para sensibilización al latex: edad ≥ 5 años (p = 0,008; OR = 6,0; IC95 % = 1,7-22,1); existencia de 4 o más intervenciones quirúrgicas (p < 0,0001; OR = 18,5; IC95 % = 3,6-94,8); cirugías en los primeros tres meses de vida (p = 0,008; OR = 5,4; IC95 % = 0,7-29,2); niveles séricos de IgE total ≥ 44 UI/ml (p = 0,03; OR = 3,8; IC95 % = 1,1-13,1). Mediante la realización de un análisis de regresión logística múltiple se identificaron como factores de riesgo independientes, historia de 4 o más intervenciones quirúrgicas (p < 0,0001; OR = 26,3; IC95 % = 2,9-234,2) y niveles séricos de IgE total ≥ 44 UI/ml (p = 0,02; OR = 8,6; IC95 % = 1,4-53,). No se identificaron como factores de riesgo, el sexo, antecedentes familiares y personales de enfermedad alérgica, hidrosefalia con derivación ventriculoperitoneal, cirotografías, cateterismo vesical intermitente ni atopía.

**Conclusiones:** Identificamos como factores de riesgo significativo e independientes para sensibilización al latex en niños con espina bífida la existencia de un número elevado de intervenciones...
quirúrgicas y niveles séricos más elevados de IgE total. Un estudio prospectivo esclarecerá la evolución clínica de los niños sensibilizados asintomáticos.

**Palabras clave:** Latex. Espina bífida. Sensibilización. Niño. Factor de riesgo.

### REFERENCES