

Prenatal latex sensitization in patients with spina bifida: a pilot study

Clinical article

MICHAEL BOETTCHER, M.D.,¹ SUSANNE GOETTLER, M.D.,² GEORG ESCHENBURG, PH.D.,¹
THORBEN KRACHT, M.D.,³ PHILIP KUNKEL, M.D.,⁴ AXEL VON DER WENSE, M.D.,³
AND KONRAD REINSHAGEN, M.D., PH.D.¹

¹Department of Pediatric Surgery, University Medical Center Hamburg-Eppendorf and Children's Hospital Altona; Departments of ³Neonatology and ⁴Pediatric Neurosurgery, Children's Hospital Altona, Hamburg; and ²Department of Neonatology, University Hospital Heidelberg, Germany

Object. Patients with spina bifida are particularly vulnerable to developing immunoglobulin E (IgE)-mediated latex sensitization. Even though many risk factors leading to latex allergy in these patients have been described, it is still unclear whether the increased prevalence of latex sensitization is disease associated or due to the procedures used to treat spina bifida. The aim of this study was to assess prenatal latex sensitization in patients with spina bifida by examining IgE levels in umbilical cord blood.

Methods. Patients with spina bifida and matched healthy infants were recruited from the University Medical Center Hamburg-Eppendorf and Children's Hospital Altona. Latex-specific and total IgE were assessed in umbilical cord blood using ImmunoCAP testing to evaluate the degree of prenatal latex sensitization.

Results. Twenty-two subjects, 10 with spina bifida and 12 healthy individuals, were included. Subjects were selected after matching for sex, gestational age, weight, parental allergy profile, number of prenatal examinations, and utilization of latex tools during pregnancy (propensity score estimates, $p = 0.36$). In patients with spina bifida, latex-specific and total IgE levels were significantly higher than those in healthy individuals ($p = 0.001$). After normalization to total IgE, latex-specific IgE levels were higher, yet not significantly increased ($p = 0.085$).

Conclusions. Perinatally, there is a significant augmentation of total and latex-specific IgE in patients with spina bifida. After correcting for total IgE, latex-specific IgE was increased, yet not significantly higher than in matched, healthy controls. This pilot study gives novel insights in the immunological reactions related to spina bifida. The increased latex-specific IgE levels could possibly be associated with the occurrence of a latex allergy in the future. (<http://thejns.org/doi/abs/10.3171/2013.12.PEDS13402>)

KEY WORDS • spina bifida • latex • sensitization • allergy • congenital

ALLERGY to latex represents a serious health problem in several distinct populations. Individuals with spina bifida are at particular risk of immunoglobulin E (IgE)-mediated latex sensitization and hypersensitivity reactions.¹¹ The prevalence among these patients ranges from 25%–65% in different studies, compared with only 0.7% in healthy children.¹ A family history of atopy and repeated exposure to latex allergens through multiple surgical procedures have been identified as major risk factors.² Moreover, it is well established that the earlier the first exposure to these allergens, the more likely a latex sensitization occurs.⁴ The presence of a ventriculoperitoneal shunt, however, has not proved to be an independent risk factor.⁹

The fetus is able to produce IgE starting in the 11th week of gestation and as IgE may not cross the placental

barrier, levels measured in umbilical cord blood reflect fetal production.⁶ Several reports have demonstrated the association of total IgE levels, allergen-specific IgE, and allergen-specific T-cell memory in cord blood and the development of atopic disease in childhood.^{5,13} Intrauterine allergen exposure has been documented in cord blood and amniotic fluid, indicating the possibility of intrauterine sensitization.¹³ It has been reported that contact of latex allergens with cerebrospinal fluid or the meningeal layer induces localized allergic reactions.¹² Therefore, one might presume that exposure of meningeal layers to allergens in the amniotic fluid leads to prenatal latex sensitization in children with spina bifida.

The aim of this pilot study was to answer this question by comparing spina bifida patients with matched subjects who, other than the presence of the neurodysraphia, are at comparable risk for latex sensitization.

Abbreviation used in this paper: IgE = immunoglobulin E.

Methods

Patient Samples

The ethics review committee at the medical council Hamburg approved the study (PV3896). The participants were recruited from the University Medical Center Hamburg-Eppendorf and Children's Hospital Altona. From April 2011 until June 2013, patients with spina bifida and a similar number of matched controls were included. The control group consisted of healthy individuals who were selected to match the spina bifida patients regarding their sex, gestational age, birth weight, allergy profile of the parents and their close relatives, and number of prenatal examinations and utilization of latex tools (such as preservatives) during pregnancy. All subjects were delivered via cesarean section.

Measurements

Umbilical cord blood that had been obtained immediately after delivery by the nursing staff from each participant whose parents had given written informed consent was used. Measurements of total and latex-specific IgE in umbilical cord blood were performed using ImmunoCAP (Phadia/Thermo Fisher Scientific) according to the instructions of the manufacturer. The WHO International Reference Preparation for human IgE 75/502 was used for total IgE and specific IgE; values are expressed in kUA/L.

Questionnaire

To reduce confounding factors, a family history of allergic disorders (asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, and urticaria) and other environmental factors that might influence the immune response and the onset of atopy was obtained.

Statistical Analysis

Statistical analysis was performed using SAS (version 9.3, SAS Institute, Inc.) and SPSS (version 21.0, IBM). Data are presented as means $\pm$ SD. The subjects in the control group had features similar to the neonates with spina bifida with regard to sex, gestational age, birth weight, allergy profile of the parents, and number of prenatal examinations and exposure to latex tools during pregnancy. The selection was controlled using nearest neighbor propensity score matching. Differences between groups and predictive values were calculated using the Mann-Whitney U-test and chi-square analysis. The level of significance was set at $p \leq 0.05$.

Results

Umbilical cord blood (2–3 ml) from 22 matched subjects who were either healthy ($n = 12$) or presented with spina bifida ($n = 10$) was used for ImmunoCAP testing to measure total and latex-specific IgE (Table 1). Fifty-five percent of all subjects were female with an average gestational age of 35.6 weeks and a body weight of 2775 g. On average the subjects underwent 3.6 prenatal examinations. Nine percent of the mothers reported that they had

regular contact with latex products during gestation. All subjects' parents completed the questionnaire, and 3 of 22 mothers (1 with bronchial asthma and 3 with hay fever) and 2 of the 22 fathers (1 with bronchial asthma and 1 with hay fever) reported that they had known allergies. The patients with spina bifida and controls had similar sex distribution ($p = 0.71$), gestational age ($p = 0.95$), birth weight ($p = 1$), and allergy profile of the parents (maternal $p = 0.66$ and paternal $p = 0.90$) as well as number of prenatal examinations ($p = 0.55$) and utilization of latex tools (such as preservatives) during pregnancy ($p = 0.90$). Propensity score estimates (considering the factors mentioned above) were similar in both groups ($p = 0.36$). Subjects with spina bifida had significantly higher levels of total IgE than healthy fetuses (3.534 ± 0.910 vs 2.179 ± 0.425 kUA/L, $p = 0.001$) and latex-specific IgE (0.123 ± 0.031 vs 0.058 ± 0.026 kUA/L, $p = 0.001$). However, after correcting for total IgE, fetuses with spina bifida (0.033 ± 0.010) had a higher, yet not significantly higher, ratio of specific and total IgE than the control group (0.026 ± 0.001 , $p = 0.085$). The latex-specific levels were slightly lower and total IgE levels were slightly higher in females than in males (Table 2).

Discussion

A latex allergy in patients with spina bifida has serious health-related and socioeconomic implications. Thus, exploration of effective measures to prevent latex sensitization is of great interest. Many protocols, such as hospital-wide latex-free policies and procedures, have been established and have resulted in a reduction of primary sensitization in newborns with spina bifida from 26.7% to 4.5%.¹⁰ Latex-free gestational care to reduce prenatal latex sensitization in high-risk patients could be another option. However, these measures are costly, and the establishment of a relatively simple immunological test based on possible spina bifida-related changes in total and latex-specific IgE levels in umbilical cord blood to reduce the risk of developing a latex allergy would be a serious improvement.

Analyzing the data in this current study, we found significantly higher latex-specific and total IgE levels in patients with spina bifida than in controls. In line with previous reports, slightly higher total IgE levels were found in females.¹⁶ After correcting for total IgE levels, patients with spina bifida had higher latex-specific IgE levels than the matched, healthy controls. The difference was not significant because of the small sample size. However, it is still possible that the augmentation of latex-specific IgE is due to a nonspecific reaction rather than allergen-specific priming.

Nevertheless, there is increasing evidence suggesting that prenatal exposure to allergens plays an important role in the development of allergy. For instance, the presence of allergen-specific T cells at the time of birth signify that specific immune responses can develop in utero.¹³ It has been reported that contact of latex allergens with cerebrospinal fluid or the meningeal layer induces localized allergic reactions.¹² One might hypothesize that the strong association of relative latex-specific IgE with spina bifida, as

Prenatal latex sensitization in spina bifida

TABLE 1: Features of patients with spina bifida and matched controls*

Parameter	Group		p Value
	Spina Bifida (n = 10)	Control (n = 12)	
female	6	6	0.71
gestational age (wks)	35.7 ± 2.5	35.5 ± 1.7	0.95
gestational weight (kg)	2.8 ± 0.7	2.8 ± 0.6	1
no. of prenatal examinations	3.6 ± 0.5	3.5 ± 0.7	0.55
regular latex contact	1	1	0.90
history of maternal allergies	1	2	0.66
history of paternal allergies	1	1	0.90
propensity score estimation	0.470 ± 0.053	0.442 ± 1.069	0.36
latex-specific IgE (kUA/L)	0.123 ± 0.031	0.058 ± 0.026	0.001
total IgE (kUA/L)	3.534 ± 0.910	2.179 ± 0.425	0.001
latex-specific IgE/total IgE	0.033 ± 0.010	0.026 ± 0.001	0.085

* Groups were comparable (propensity score estimation, $p = 0.36$), but subjects with spina bifida had significantly higher total and specific IgE. Even after correction for total IgE, there was a strong, yet not significant, trend. Significant values are in boldface.

found in this current study, is due to the prenatal exposure to atypical allergens, as can happen when the CNS tissue alters the immune response and leads to latex sensitization.

Unfortunately, data about prenatal latex sensitization are scarce. However, several studies have concentrated on sensitization to food and environmental antigens. For instance, the neonatal T-cell response to environmental allergens is not associated with prenatal antigen exposure, indicating that T-cell memory to specific allergens develops postnatally rather than in utero.^{14,17} Moreover, Sybilski et al. assessed correlations of total IgE as well as food and environmental antigen-specific cord blood IgE with allergic symptoms in the 1st year of life.¹⁶ They found no association between high total IgE and specific IgE levels in umbilical cord blood with a family history of atopy and the outcome of atopic diseases. It seems that total and specific IgE levels combined with atopic family history could not be used as an indicator to single out high-risk infants. Lopez et al. examined the relationship between asthma and serum IgE levels in early life.⁸ They

found that neither isolated total IgE concentration nor its combination with a positive maternal allergy history are suitable to sufficiently predict the future development of atopic diseases within the first 12 months of life.

There are several factors that may influence IgE levels in the fetus. Among others, it has been proposed that atopy in parents and close relatives presages a significant increase in the IgE levels, which could be followed by an increased incidence of atopic diseases during infancy.¹⁵ Most authors point to the presence of atopic diseases, particularly in the mother, as a key factor contributing to elevated levels of IgE in umbilical cord blood. However, the influence of maternal allergen exposure resulting in pre- or postnatal allergen transfer and the impact on developing immune responses of the fetus remains controversial.^{3,7} The fact that allergic symptoms usually appear early in life implies that the neonate is subjected to these factors, perhaps even at the fetal stage. Fusaro et al. showed in a rat model that maternal mucosal allergen exposure during the pre- or postnatal period led to

TABLE 2: Differences between males and females regarding total and relative latex-specific IgE*

Sex†	Group		p Value
	Spina Bifida	Control	
female			
latex-specific IgE (kUA/L)	0.100 ± 0.023	0.057 ± 0.018	0.012
total IgE (kUA/L)	3.495 ± 1.178	2.208 ± 0.510	0.013
latex-specific IgE/total IgE	0.031 ± 0.009	0.025 ± 0.008	0.30
male			
latex-specific IgE (kUA/L)	0.115 ± 0.013	0.060 ± 0.030	0.041
total IgE (kUA/L)	3.308 ± 0.925	2.150 ± 0.367	0.041
latex-specific IgE/total IgE	0.037 ± 0.012	0.027 ± 0.008	0.14

* Females had slightly higher total IgE and lower latex-specific IgE values. However, the differences between spina bifida patients and controls remain similar. Significant values are in boldface.

† There were 6 females in the spina bifida group and 6 in the control group. There were 4 males in the spina bifida group and 6 in the control group.

the occurrence of allergen-specific IgE depending on the timing and amount of allergen administration.⁷ It seems that although gestation is a time for developing immunological tolerance in the fetus, high antigen exposure to the mother's mucosa might result in induction of fetal IgE antibody production. Thus, regular mucosal exposure to latex during pregnancy could result in latex sensitization and should be avoided in high-risk patients.

The main limitation for reliable findings of this pilot study is the small number of available samples. Even though statistical significance was reached for most aspects, this could result in over- or underestimation of the effects described. To confirm the results of the current study, further research with a larger cohort is therefore urgently needed. Furthermore, the strong maternal influence is not well accounted for due to the current study design. Thus the acquisition of maternal IgE levels to reduce this factor as a confounder in subsequent studies is advisable.

Conclusions

The present study shows a significant increase in latex-specific IgE and total IgE in patients with spina bifida, which may indicate that latex sensitization occurs prenatally. In turn, this could mean that latex products ought to be avoided during pregnancy, especially in high-risk fetuses. Unfortunately, because of the small sample size, the study failed to reach significance for relative latex-specific IgE. The increase in latex-specific IgE and total IgE in spina bifida patients could also be from a nonspecific reaction rather than allergen-specific priming. Nevertheless, this pilot study revealed novel insights in the immunological reactions related to spina bifida and a strong tendency for increased latex-specific IgE levels that could be associated with the occurrence of a latex allergy in the future, possibly due to the early exposure of the CNS to allergens in the amniotic fluid. The examination of cord blood from spina bifida patients will be continued with several improvements, particularly to better account for maternal influences.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Boettcher, Goettler. Acquisition of data: Boettcher, Kracht, Von der Wense. Analysis and interpretation of data: Boettcher, Eschenburg. Drafting the article: Boettcher, Reinshagen. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Boettcher. Statistical analysis: Boettcher. Administrative/technical/material support: Eschenburg, Kunkel, Von der Wense, Reinshagen. Study supervision: Reinshagen.

References

- Bernardini R, Novembre E, Lombardi E, Mezzetti P, Cianferoni A, Danti AD, et al: Prevalence of and risk factors for latex sensitization in patients with spina bifida. **J Urol** **160**:1775–1778, 1998
- Bernardini R, Novembre E, Lombardi E, Mezzetti P, Cianferoni A, Danti DA, et al: Risk factors for latex allergy in patients with spina bifida and latex sensitization. **Clin Exp Allergy** **29**:681–686, 1999
- Bønnelykke K, Phipps CB, Bisgaard H: Sensitization does not develop in utero. **J Allergy Clin Immunol** **121**:646–651, 2008
- Degenhardt P, Golla S, Wahn F, Niggemann B: Latex allergy in pediatric surgery is dependent on repeated operations in the first year of life. **J Pediatr Surg** **36**:1535–1539, 2001
- Edenharter G, Bergmann RL, Bergmann KE, Wahn V, Forster J, Zepp F, et al: Cord blood-IgE as risk factor and predictor for atopic diseases. **Clin Exp Allergy** **28**:671–678, 1998
- Furuhashi M, Sugiura K, Katsumata Y, Oda H, Murase Y, Imai N: Cord blood IgE against milk and egg antigens. **Biol Neonate** **72**:210–215, 1997
- Fusaro AE, de Brito CA, Taniguchi EF, Muniz BP, Victor JR, Orii NM, et al: Balance between early life tolerance and sensitization in allergy: dependence on the timing and intensity of prenatal and postnatal allergen exposure of the mother. **Immunology** **128** (1 Suppl):e541–e550, 2009
- Lopez N, de Barros-Mazon S, Vilela MM, Condino Neto A, Ribeiro JD: Are immunoglobulin E levels associated with early wheezing? A prospective study in Brazilian infants. **Eur Respir J** **20**:640–645, 2002
- Mazon A, Nieto A, Pamies R, Felix R, Linana JJ, Lanuza A, et al: Influence of the type of operations on the development of latex sensitization in children with myelomeningocele. **J Pediatr Surg** **40**:688–692, 2005
- Nieto A, Mazón A, Pamies R, Lanuza A, Muñoz A, Estornell F, et al: Efficacy of latex avoidance for primary prevention of latex sensitization in children with spina bifida. **J Pediatr** **140**:370–372, 2002
- Niggemann B: Atopy and latex allergy in spina bifida: what's chicken, what's egg? **Pediatr Allergy Immunol** **8**:51, 1997 (Letter)
- Niggemann B, Bauer A, Jendroska K, Wahn U: Latex allergy as a cause of eosinophilia in cerebrospinal fluid in a child with a ventricular shunt. **J Allergy Clin Immunol** **100**:849–850, 1997
- Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG: Development of allergen-specific T-cell memory in atopic and normal children. **Lancet** **353**:196–200, 1999
- Rowe J, Kusel M, Holt BJ, Suriyaarachchi D, Serralha M, Hollams E, et al: Prenatal versus postnatal sensitization to environmental allergens in a high-risk birth cohort. **J Allergy Clin Immunol** **119**:1164–1173, 2007
- Scirica CV, Gold DR, Ryan L, Abulkerim H, Celedón JC, Platts-Mills TA, et al: Predictors of cord blood IgE levels in children at risk for asthma and atopy. **J Allergy Clin Immunol** **119**:81–88, 2007
- Sybilski AJ, Doboszynska A, Samolinski B: Prediction of atopy in the first year of life using cord blood IgE levels and family history. **Eur J Med Res** **14** (Suppl 4):227–232, 2009
- Thornton CA, Upham JW, Wikström ME, Holt BJ, White GP, Sharp MJ, et al: Functional maturation of CD4+CD25+ CTLA4+CD45RA+ T regulatory cells in human neonatal T cell responses to environmental antigens/allergens. **J Immunol** **173**:3084–3092, 2004

Manuscript submitted August 6, 2013.

Accepted December 5, 2013.

Please include this information when citing this paper: published online January 3, 2014; DOI: 10.3171/2013.12.PEDS13402.

Address correspondence to: Michael Boettcher, M.D., Department of Pediatric Surgery, University Medical Center Hamburg-Eppendorf and Children's Hospital Altona, Martinistr. 52, 20246 Hamburg, Germany. email: michboettcher@gmail.com.