

Cytokine Detection in Three Children with Spina Bifida and Health Care Workers with Latex Allergy

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ABSTRACT

Children with spina bifida are known to have a greater incidence of latex allergic reactions including generalized urticaria and anaphylaxis. We present three cases along with data using a sensitive radioimmunosorbent assay (RIA) to three latex proteins and serum interleukin (IL)-4 levels, a cytokine known to regulate IgE production which stimulates mast cell proliferation.

A 13-year-old boy with a history of spina bifida and multiple surgeries was diagnosed with latex allergy after a facial rash developed while playing with a rubber ball. Subsequently, the patient was evaluated for a burn injury and developed diffuse urticaria with wheezing after contact with latex gloves during examination. A specific RIA to several latex proteins revealed very high levels of specific IgE to ammoniated latex extract (818 U/ml) and buffered latex and glove extract (>1,000 U/ml). A 7-year-old boy with a history of spina bifida and multiple surgeries with daily urinary catheterizations was evaluated for a diffuse rash, which occurred 15 times in the past two years. A specific RIA to several latex proteins showed a highly positive reaction to ammoniated, buffered, and glove extract (>1,000 U/ml). A 14-year-old boy with a history of spina bifida, multiple surgeries, and asthma was evaluated for a local rash on his hands after contact with latex gloves. Latex specific RIA tests were negative. The highest serum IL-4 levels of 40 to 69 pg/ml by a sensitive enzyme-linked immunosorbent assay were noted in these three patients when compared with 16 health care controls. Undetectable levels of serum IL-4 were noted in the first case two months after latex avoidance and decreased serum IL-4 levels were noted in all other health care workers after barrier protection or avoidance.

INTRODUCTION

LATEX ALLERGY IS AN important medical problem for an increasing number of patients. Children with spina bifida and urogenital abnormalities are at high risk for latex allergy. Circulating mast-cell-related cytokines, stimulated by latex-activated T cells, may play a role in the allergy in these patients.

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History and routes of exposure

Type I reaction to latex was first reported in Germany in 1927.^(1,2) The next report appeared 52 years later, and American reports followed 10 years later.⁽³⁻⁵⁾ Type I, or immediate, latex hypersensitivity is mediated by IgE. The antigen in the IgE-mediated response is latex protein or polypeptide. Type IV hypersensitivity to latex products is associated with chemicals added to latex during this process.⁽⁶⁾

The protein content of natural rubber varies with different lots. The antigen is readily eluted from latex gloves, condoms, and catheters under mild physiologic conditions such as normal saline buffer at 37°C for 1 to 2 hours.^(7,8)

Latex exposure can occur via cutaneous, mucosal, or parenteral routes. Aerosol transmission of latex antigen has been documented in case reports.^(9,10) Direct mucosal and parenteral exposure pose the greatest risk for anaphylaxis, though systemic reactions have been reported following cutaneous and respiratory exposure.^(5,11,12) Patients with previously mild cutaneous and respiratory reactions may experience more severe reactions with mucosal or parenteral exposure.⁽¹³⁻¹⁵⁾

Risk groups for latex allergy

The groups at risk for developing latex allergy are well defined. They are health care workers, rubber industry workers, and children with spina bifida and urogenital abnormalities, all of whom share a common risk: a high degree of exposure to latex.

Prevalence of type I latex allergy in the general population is not known, although the risk appears to be higher in atopic than nonatopic individuals.⁽¹⁶⁾ Health care workers have a 5% to 10% risk of latex allergy. Recent reports have indicated a greater percentage. According to a study from Finland,⁽¹⁷⁾ risk was 2.8% in chemical units and laboratories and 7.4% among operating room physicians. The incidence of type I latex allergy in children with spina bifida is much higher. Several studies have reported an incidence up to 28%.^(18,19) In one study, 15% of children with spina bifida had experienced intraoperative anaphylaxis. A serologic survey of children with spina bifida revealed that 37% (35 of 93 patients) had latex specific IgE by radioallergosorbent test (RAST); 8 of the 35 patients had clinical history suggesting latex allergy while 1 of 58 RAST negative patients had a history of latex allergy.⁽²⁰⁾ In addition, children with other conditions requiring frequent surgery, such as bladder exstrophy, cerebral palsy, and Pandy-Walker cysts, may be at risk.

The risk of pediatric patients with spina bifida developing latex-related operating room anaphylaxis is 500 times greater than that of the general population.⁽²¹⁾ Between 28% and 67% of patients with spina bifida have latex-specific IgE antibody, but not all have clinical manifestations of latex hypersensitivity. Unfortunately, the first recognized reaction to latex may be the development of anaphylaxis during medical procedures in the operating room or elsewhere in the hospital. A history of atopic disease such as asthma or food allergy, prior anaphylaxis, and symptoms of urticaria related to latex contact (e.g., symptoms after blowing up toy balloons or contact with rubber toys) help to identify patients with spina bifida at highest risk of anaphylaxis.⁽²²⁾

The spina bifida population frequently requires multiple surgical procedures and often requires clean intermittent catheterization. Since latex allergy correlates with the number of surgical procedures and has been thought to develop as a result of long-standing exposure, it would appear that the risk of latex allergy could be decreased by performing all surgical procedures, starting from birth, in a latex-free environment.⁽²³⁾ All spina bifida patients who previously have not been evaluated for latex allergy should undergo a thorough history and testing, including testing before any subsequent invasive procedures. In individuals with a positive history, positive skin test and/or positive radioallergosorbent or radioimmunosorbent assay (RIA) test, appropriate therapy should be available in the procedure suite.⁽²³⁾

Several studies have reported clinical and immunochemical crossreactivity between latex, banana, chestnut, and avocado.⁽²⁴⁻²⁶⁾ In health care workers, the natural history of the disease seems to progress from cutaneous reactions to rhinoconjunctivitis to bronchospasm to anaphylaxis.⁽²⁶⁾ There are no prospective studies regarding the natural history of latex allergy.

Diagnosis of latex allergy

Patients in a high risk group—children with spina bifida or congenital urologic abnormalities, health care workers, and workers in rubber industry—should be identified. Specifically, a history of latex associated

reactions and allergic reactions of unknown causes should be evaluated, although this may not identify the patients who will subsequently develop latex-induced anaphylaxis.

Skin testing using two or more testing materials (i.e., latex gloves, ammoniated latex, nonammoniated latex, and Hevea leaves) has shown to be quite sensitive. In the study of Moneret-Vautrin and Laxenaire, which is the largest published series, epicutaneous testing was 100% sensitive and 99% specific.⁽²⁷⁾ Though at this time skin testing with latex extract or latex glove extract may be the best and most rapid diagnostic test available, it is not without danger of anaphylaxis,^(5,11,13,28) and it has not been approved by the Food and Drug Administration.⁽²⁶⁾

Sensitivity and specificity of in vitro tests for latex-specific IgE are dependent on the population being tested. Spina bifida patients have very high specific IgE titers, as noted in our two patients, and most in vitro tests are highly sensitive.^(20,28,29) In contrast, not until recently the in vitro test for latex allergy in health care workers was less sensitive.⁽²⁹⁻³¹⁾ Hamilton et al.⁽³²⁾ have reported that 82% of health care workers with respiratory symptoms due to latex had latex-specific IgE when the antigen was derived from Baxter-Triflex gloves. The sensitivity of the assay used in these patients was 91% to 100%. The specificity was 63% when glove extract, ammoniated latex extract, and nonammoniated latex extract were used as antigens.⁽³³⁾ Avoidance of latex products is the only measure that can avert a serious allergic reaction. Both the American College of Allergy, Asthma and Immunology and American Academy of Allergy, Asthma and Immunology have issued recommendations for latex testing and latex avoidance.^(34,35)

Possible role of cytokines in latex allergy

Systemic reactions to latex appear to be an IgE-mediated phenomena. In this case, latex proteins are first taken up by a suitable antigen-presenting cell and presented to antigen-specific T lymphocytes in context with a major histocompatibility complex (MHC) II receptor. Subsequently, these T-cells elaborate appropriate cytokines, including interleukin-4 (IL-4), which influence the selection of IgE class antibody production from B cells. IL-10 can also synergize with IL-4. The cause for preferential induction of IgE antibody as opposed to other classes of antibody is still unknown, but innate properties of the host immune system and the sensitizing antigen play a major role in this process. The exact nature of the allergens and specific epitopes in natural latex that stimulate allergic antibody production by B cells and are capable of triggering mast cell degranulation and the events of anaphylaxis are the subject of several ongoing studies.⁽³⁶⁾

In preliminary studies in our division, 17 patients (14 males, 3 females; age range 8 to 60 years) were evaluated, including health care workers and spina bifida patients.⁽³⁷⁾ Contact urticaria syndrome was present in 10 patients, contact dermatitis in 4 patients, and systemic anaphylaxis in 3 patients, which included two of the spina bifida patients. Latex-specific IgE by RIA was elevated to one or more latex antigens in 2 of 3 of our spina bifida patients, especially in those with systemic reactions (Fig. 1). Serum IL-4 levels increased in 80% of the subjects with systemic reactions and were greatly elevated in the three patients with spina bifida (Fig. 2). The mean IL-4 levels in the 3 patients with spina bifida were elevated compared with 16 other health care workers and nonatopic controls (Fig. 3). Interestingly, the level of IL-4 was undetectable in Patient 1 after 2 months of latex avoidance. Patient 2 also had an elevated IL-10 level of 37.5 pg/ml.⁽³⁷⁾ The highest IgE, IL-4, IL-10, and latex-specific IgE levels were found in the spina bifida patients. Symptoms improved clinically in all patients using latex-free gloves and latex avoidance in patients with spina bifida.⁽³⁷⁾

CASE REPORTS

Case 1

A thirteen-year-old boy was seen in the emergency room for a burn on his left foot. Medical history was significant for spina bifida, paraparesis, neurogenic bladder, scoliosis, multiple surgeries, ventriculoperitoneal, and latex allergy.

Physical examination revealed no distress; blood pressure (BP) was 112/80 mmHg, respiratory rate was 20 beats per minute (bpm), temperature was 99.2°F, and pulse was 100/min. The physician examining the

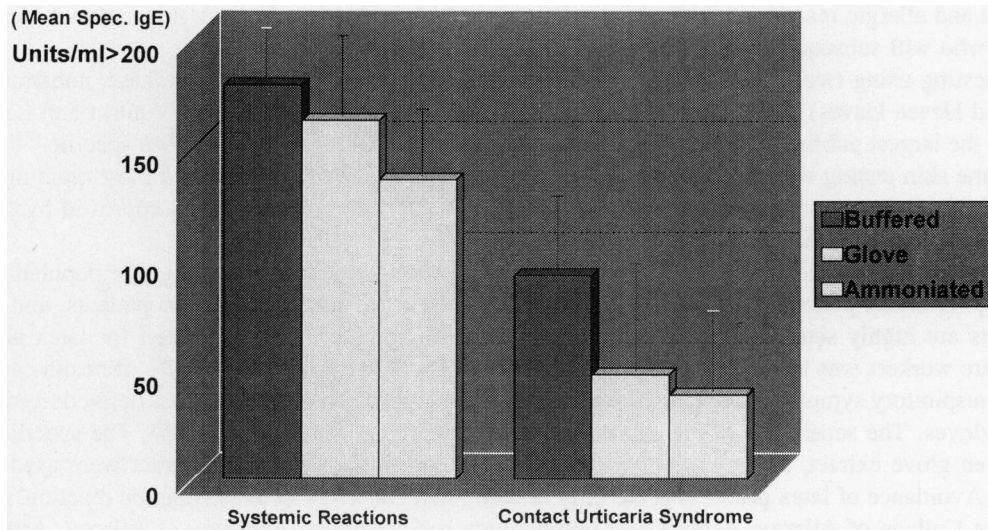


FIG. 1. Mean specific IgE latex hypersensitive systemic and contact urticarial reactions by radioimmunosorbent assay in U/ml in all patients (N = 17) to buffered, glove, and ammoniated latex proteins.

patient wore latex gloves. A few minutes after the left foot was touched with latex gloves the patient developed a diffuse erythematous rash over his entire body and complained of difficulty breathing. His upper lip also became edematous. Examination revealed bilateral wheezing, and the patient was given appropriate doses of subcutaneous epinephrine, nebulized albuterol, and intramuscular diphenhydramine. Over the next 20 minutes, he improved with subsidence of wheezing, lip swelling, and rash. Within the next 10 minutes, he was comfortable and was discharged on an appropriate dose of diphenhydramine syrup every 8 hours.

This patient had been evaluated 8 months earlier for rash over the face and arms, which developed while playing with a rubber ball. The rash had subsided after two days. Latex-specific RIA had been performed and was found to be highly positive (ammoniated latex extract = 818 U/ml, buffered latex extract = 1,000 U/ml, latex glove extract = 1,000 U/ml). Serum IL-4 was 40 pg/ml. Total IgE was 128 U/ml. The patient

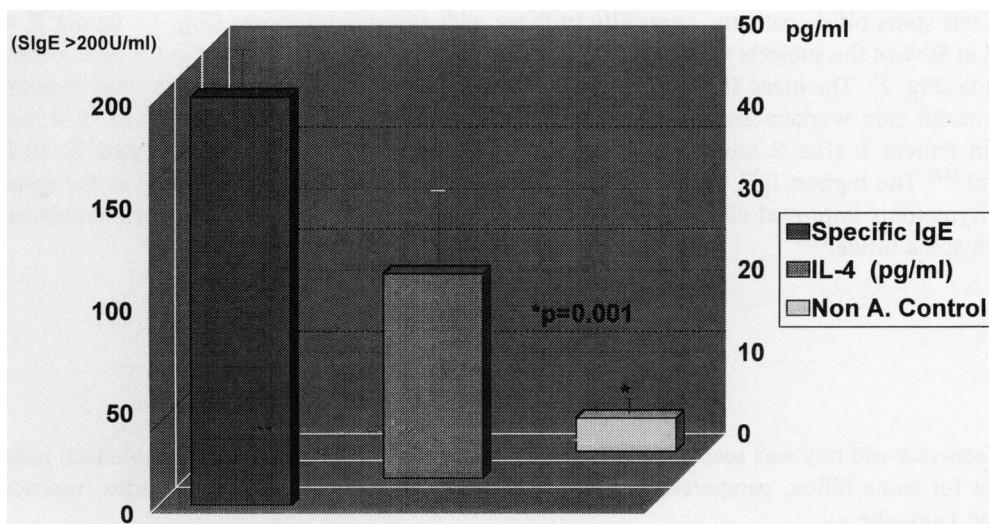


FIG. 2. Mean specific IgE and IL-4 levels in pg/ml in systemic reactions in all patients (N = 17). Non A = nonatopic controls.

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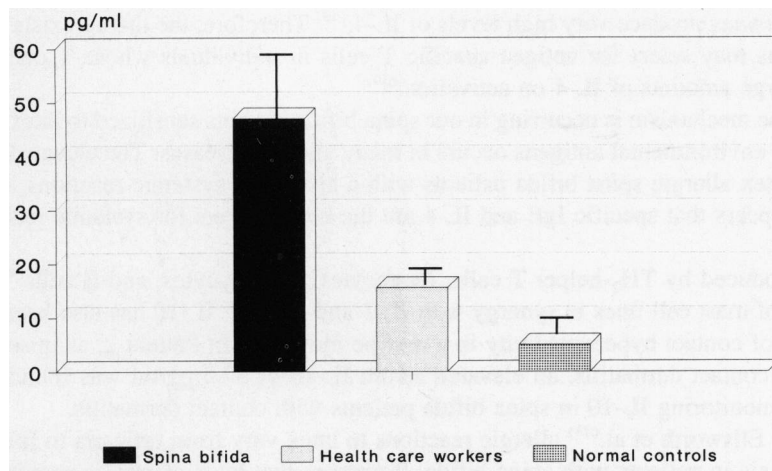


FIG. 3. Mean IL-4 levels in pg/ml in 3 patients with spina bifida and 16 health care workers and nonatopic controls.

had been advised to avoid latex products, and the family had been educated about common sources of latex. They were also provided with epinephrine injection for emergency use.

Case 2

A seven-year-old boy was evaluated for 12 to 15 episodes of a rash in the last two years. The patient had a medical history of spina bifida, multiple surgeries, mild mental retardation, and urinary retention. The patient also needed regular urinary catheterization. The rash usually began as maculopapular and would rapidly spread to his face and other parts of the body, accompanied by pruritus. A recent emergency room visit for the rash revealed that he had no wheezing, although he complained of difficulty breathing. He was treated with epinephrine and diphenhydramine injections. The patient was evaluated with a battery of RAST. He was found to be mildly allergic to egg yolk, egg white, wheat, and corn. A latex-specific RIA was performed and revealed IgE levels of >1,000 U/ml to ammoniated latex extract, buffered latex extract, and latex glove extract. Serum IL-4 was 69 pg/ml and serum IL-10 was 37.5 pg/ml. Total IgE was >300 U/ml.

The patient's family was advised to avoid egg, wheat, and corn in patient's diet and they were educated about latex avoidance. Latex-free catheters were recommended for regular use.

Case 3

A 14-year-old boy with a medical history of spina bifida, multiple surgeries, and asthma was evaluated for a history of developing a rash within minutes of touching latex gloves. The rash was located on his hands and was described as a wheal and flare, which later became vesicular and resolved in a few hours. There were no symptoms to suggest any systemic reaction. The patient had been advised to use vinyl catheters for self-urinary catheterization and powderless latex gloves.

Latex-specific IgE against all three fractions of latex antigen (ammoniated, buffered, and latex glove extract) were negative at <50 U/ml and serum IL-4 was 31 pg/ml. Total IgE was 9 U/ml.

The patient was advised to avoid latex products and foods likely to crossreact with latex antigen.

DISCUSSION

In this report, we clinically evaluated three children with spina bifida, along with in vitro analysis for latex specific IgE and IL-4, a mast-cell-related cytokine.

IL-4 is a T-cell cytokine that regulates IgE production and the immune response to allergens in atopic subjects. CD4⁺ T cells secrete IL-4, which is antagonized by interferon.⁽³⁸⁾ IL-4 is secreted by TH₂ T cells, and T-cell clones resembling TH₂ type T cells isolated from atopic patients and specific for *Dermato-*

phagoides pteronyssinus produce very high levels of IL-4.⁽³⁹⁾ Therefore, the theory exists that chronic stimulation by allergens may select for antigen specific T cells in individuals whose T cells are intrinsically prone to secrete large amounts of IL-4 on activation.⁽³⁹⁾

Perhaps this same mechanism is occurring in our spina bifida patients sensitized to latex antigen. Elevated synthesis of IgE to environmental antigens occurs in many allergic diseases. The elevated specific and total IgE, IL-4 in our latex allergic spina bifida patients with a history of systemic reactions, supports this relationship. It also appears that specific IgE and IL-4 are the best markers for systemic reactions in our population.

IL-10 is also produced by TH₂-helper T cells, monocytes, keratinocytes, and B cells⁽⁴⁰⁾ and supports in vitro the viability of mast cell lines in synergy with IL-3 and IL-4.⁽⁴¹⁾ IL-10 has also been shown to inhibit the effector phase of contact hypersensitivity in a murine model.⁽⁴²⁾ In Patient 2, as in several other health care workers with contact dermatitis, an elevated serum IL-10 of 37.5 pg/ml was found. Therefore, there may be a role for monitoring IL-10 in spina bifida patients with contact dermatitis.

As described by Ellsworth et al.⁽²³⁾ allergic reactions to latex vary from urticaria to life-threatening IgE-mediated anaphylaxis in patients with spina bifida. It appears that latex allergy is acquired through multiple exposures due to breakdown of blood tissue barriers. Any surgical procedure on patients with spina bifida should be performed in a latex-free environment.⁽²³⁾

By identifying patients with latex allergy, it may be possible to characterize those patients at risk for latex-induced anaphylaxis. Circulating levels of IL-4 were the highest noted in this small population compared with other groups at risk. As we previously reported, perhaps monitoring these circulating levels along with latex-specific cytokine levels in mononuclear cell cultures may provide another immunologic marker in this high risk group.⁽⁴³⁾

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