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Latex Anaphylaxis in a Child with a History of Multiple Anesthetic Drug Allergies

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Life-threatening anaphylactic reactions to anesthetic agents are rare in adults and even rarer in children.[1–3] The unpredictable and rapid onset of the potentially serious circulatory and ventilatory consequences of anaphylaxis demands prompt identification of the causative agent(s) to avoid future reexposure. Recently, latex hypersensitivity has become a recognized etiology for immunoglobulin E (IgE)-mediated anaphylaxis during operative procedures.[4] Presented below is the case of a child with myelodysplasia with repeated episodes of intraoperative anaphylaxis who presented a diagnostic dilemma prior to her diagnosis of latex hypersensitivity.

CASE REPORT

A 7-yr-old girl was admitted for an elective pelvic osteotomy to correct a congenitally dislocated left hip. She was born with a lumbosacral myelomeningocele and Arnold Chiari Type II malformation. Physical examination at birth revealed an incomplete sensory and motor deficit below the fourth lumbar spinal segment, congenitally dislocated hips, club feet, and urinary and anal sphincter incontinence. She was able to void spontaneously and did not require bladder catheterization. During the first 2.5 yr of life she had undergone nine surgical procedures uneventfully under general anesthesia. Anesthetic agents and medications administered during these procedures were halothane, nitrous oxide, succinylcholine, pancuronium, methohexital, morphine, fentanyl, atropine, neostigmine, oxacillin, gentamycin, vancomycin, and cephapirin sodium (Cefadyl). Chronic medications included co-trimoxazole (Bactrim®) and oxybutynin chloride (Ditropan®) for long-term urinary tract prophylaxis.

The patient did not have any history of atopic disease, asthma, food, medication, or insect-sting hypersensitivity. The family history was positive for atopic disease. Her father reported a history of childhood asthma, atopic dermatitis, and food hypersensitivity. Her sister had a possible history of asthma, and her mother reported a possible history of Hymenoptera hypersensitivity. An aunt had a history of eczema, and her grandfather experienced allergic rhinoconjunctivitis.

At age 2.5 yr, she underwent a lower extremity osteotomy. She was premedicated with rectal methohexital (30 mg/kg), and anesthesia was induced with nitrous oxide, oxygen, halothane, and pancuronium. Five minutes after the administration of fentanyl and shortly after urethral catheterization, she developed urticaria over the face, trunk, and extremities. The lungs were difficult to ventilate, requiring increased inspiratory pressures from 12 to 35 cmH_2O. Chest auscultation revealed diminished breath sounds bilaterally and wheezing. The systolic blood pressure decreased from 80 to 60 mmHg. Intravenous epinephrine (1 $\mu g/kg$) was followed by decreased wheezing and an increase in blood pressure. Aminophylline (5.7 mg/kg followed by 0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ intravenously) was required to resolve the persistent inspiratory and expiratory bronchial wheezing. The urticaria remained throughout the procedure despite the administration of diphenhydramine (1.6 mg/kg). The trachea was extubated at the end of surgery; no evidence of laryngeal edema was noted. The remainder of the postoperative and hospital course was uneventful.

At age 3 yr, with a presumed history of hypersensitivity to fentanyl, this child underwent revision of a ventriculoperitoneal shunt. She was premedicated with rectal methohexital and anesthetized with intravenous sodium thiopental, isoflurane, nitrous oxide, and pancuronium. Within 2 min of the administration of pancuronium, generalized urticaria were observed, without evidence of wheezing or hemodynamic instability. Diphenhydramine (1.5 mg/kg) was administered intravenously, and the urticaria diminished in severity but persisted without other sequelae. Hypersensitivity to pancuronium was now suspected, and she was referred to an allergist/immunologist for appropriate testing. The parents declined the skin test evaluation because the child had a significant fear of needles.

At age 4 yr, she underwent pelvic osteotomy with uneventful general anesthesia. With a history of possible pancuronium and fentanyl hypersensitivities, she received rectal methohexital, halothane, nitrous oxide, atropine, atracurium, and morphine. She also received repeated doses of cefazolin sodium during the procedure without adverse sequelae.

At age 5 yr, she was seen by an allergist/immunologist for skin testing with various intravenous anesthetic drugs. Amide local anesthetic testing was also considered after it was revealed that the patient had developed perioral and periorbital edema, a papular pruritic facial rash, and ocular pruritus during a recent dental visit. She had received lidocaine 1.0% (0.6 ml) with epinephrine (1:50,000) for the local anesthetic.

Skin prick and intradermal testing were performed for succinylcholine, pancuronium, methohexital, sodium thiopental, and *d*-tubocurarine.[5,6] The skin testing, using appropriate positive (histamine phosphate) and negative (normal saline without preservatives) controls re-

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vealed a 2+ positive skin prick reaction to succinylcholine, consistent with an IgE-mediated sensitivity. Subsequent intradermal testing revealed trace positive reactions to methohexital and pancuronium. Radioallergosorbent (RAST) testing performed for the intravenous muscle relaxants was indeterminate, showing nonspecific reactivity. RAST binding activity was present at three to four times greater than background for succinylcholine and thiopental, but RAST inhibition assays were negative, suggesting that the binding was nonspecific.[7] Local anesthetic hypersensitivity could not be definitively assessed, with nonspecific skin reactivity present at all concentrations.

At age 7 yr, the patient underwent her 13th surgical procedure, a pelvic osteotomy. She was anesthetized with halothane, nitrous oxide, and oxygen. A lumbar epidural catheter was placed uneventfully at the L2–L3 interspace (above the myelomeningocele) as an adjunct to general anesthesia to avoid the use of intravenous anesthetic drugs and to enhance postoperative pain management. Atracurium was administered intravenously to facilitate adequate surgical relaxation. Lidocaine 1.5% with epinephrine 1:200,000 (2 ml) as a test dose was followed by 3 ml plain lidocaine 2%. One hour later, a supplemental dose of bupivacaine 0.5% was given *via* the epidural catheter.

Five minutes after the administration of bupivacaine and 40 min after the start of the surgery, a generalized rash occurred, followed by urticaria. Expiratory wheezing, increased inspiratory pressure, and decreased ventilatory compliance followed. The systolic blood pressure decreased from 100 to 65 mmHg, and the heart rate increased from 80 to 110 beats/min. Oxygen saturation by pulse oximetry decreased from 100% to 80%. Repeated doses of intravenous epinephrine (1 μg/kg) were promptly administered and resulted in resolution of the bronchospasm, improvement in ventilation, and restoration of blood pressure and oxygenation status. This episode occurred 1.5 h after the initial dose and 0.5 h after the repeat dose of atracurium. Halothane was discontinued, and small doses of intravenous morphine were administered for the maintenance of the anesthesia and completion of the procedure. Intermittent doses of epinephrine (0.2 μg/kg) were necessary to maintain the systolic blood pressure greater than 80 mmHg. Diphenhydramine (1 mg/kg) also was administered later in the course of the procedure. The rash persisted throughout surgery, with the development of marked periorbital and facial edema. The trachea was extubated at the end of the procedure without evidence of laryngeal edema.

The patient's postoperative course was unremarkable. Pain was managed with a continuous epidural infusion of bupivacaine for 48 h and parenteral morphine subsequently, without any allergic reactions.

Additional history obtained from the parents revealed that the patient had developed lip edema while blowing up a balloon prior to this admission. Further detailed history specific to latex products revealed that she had developed significant periorbital edema, ocular pruritus, and a papular pruritic rash near the affected eye within 0.5 h of departure from her dentist. This had occurred over the previous 4 or 5 yr, when the dentist wore gloves, but was temporally related to blowing up the latex balloons she would receive at the completion of the dental procedure. Despite the avoidance of latex gloves during subsequent dental procedures, the reactions continued to occur until exposure to the balloons was also discontinued. The parents attempted premedication with diphenhydramine (Benadryl®) prior to dental visits; this resulted in diminution but not prevention of these symptoms. At no point did she experience any other systemic signs or symptoms.

Given this new history and the recent appreciation that latex products may precipitate IgE-mediated anaphylactic reactions, the patients was skin-tested with a latex extract (provided courtesy of J. Dolovich, M.D., Canada). Skin prick testing revealed a 4+ positive reaction to liquid latex suspension at a 1:100 dilution. Histamine phosphate was used as the positive control, and normal saline without preservatives was used as the negative control. Four normal subjects were tested with this latex extract and were nonreactive to similar and higher concentrations of the latex extract. Subsequent RAST testing for latex was performed in two separate laboratories. In one, specific IgE binding was 18.3% (mean control of 2.5%; Johns Hopkins University, Reference Laboratory for Dermatology, Allergy, and Clinical Immunology). In the other, binding was 15.3% (mean control 0.4%; 95% confidence interval 0.17–0.95%). Although RAST inhibition was not performed with this patient's serum, the latter laboratory has verified antigen-specific inhibition with soluble latex antigen.[8]

β-Lactam antibiotic skin testing was also performed to assess all potential drug hypersensitivity. The β-lactam penicillin skin-testing was performed using native penicillin G, the major determinant benzylpenicilloyl poly-L-lysine, and a minor determinant mixture (minor determinant mixture was specially prepared in the Massachusetts General Hospital pharmacy) and contained the following: penicillin G, benzylpenicillin G, benzyl penicilloate, and benzylpenilloate. It was stored at −70° C, transported on dry ice, and diluted at the time of use. Skin tests were considered positive if the wheal diameter of the agent was 50% larger than the wheal of the negative control and associated with significant surrounding erythema.[9] The β-lactam antibiotic skin testing revealed positive intradermal reactions to all three of the reagents tested, with appropriately reactive controls. The patient's IgE serum level was 1,830 IU/ml (normal 0–200), and separate testing for airborne seasonal and perennial allergens revealed no antibodies. There was no evidence of dermatographism during the skin-testing.

A bladder neck fascial sling for urinary incontinence was performed in May, 1991. Preoperative medications included only co-trimoxazole (Bactrim®), oxybutynin chloride (Ditropan®), and pseudoephedrine. With parental informed consent obtained, no preoperative medication prophylaxis was used. The duration of the procedure was approximately 5 h and 15 min. Anesthetic management included nitrous oxide, halothane, sodium thiopental (repeated doses), vecuronium (repeated doses), morphine (multiple doses), gentamicin, and vancomycin. The trachea was extubated at the end of the procedure. Meticulous attention was directed to avoid all pre-, intra-, and postoperative exposure to latex products and to any hospital material that may have contained latex components. This included all rubber products used in the anesthetic machine, circuit, mask, blood-pressure cuffs, gloves, syringes (glass syringes were required), and intravenous infusion tubing, as well as multidose medication vials.

Postoperatively, the patients received bupivacaine (Marcaine®) local anesthetic infusion for 24 h *via* a subcutaneous catheter placed around the surgical wound. She received a single intravenous dose of morphine, multiple doses of intravenous methadone, and then oral methadone for successful postoperative pain control. Postoperatively, she continued to receive gentamicin and vancomycin; all β-lactam antibiotics were avoided. The procedure was conducted without any adverse sequelae or reactions. No evidence for any IgE-mediated reactions was noted during this procedure.

Discussion

In a previous report, two patients with repeated episodes of intraoperative anaphylaxis were eventually found to be allergic to latex.[10] Our patient was tested and indeed found to be allergic to multiple substances in common use during her serial anesthetics. The first anaphylactic event, if latex-related, may have occurred after bladder catheterization and as a result of sensitization developed during the nine prior uncomplicated surgical procedures. This episode developed prior to the surgical incision and administration of the cefazolin sodium but immediately after administration of fentanyl. The second, milder ana-

phylactic reaction was suspected to be due to pancuronium. A positive response to skin-testing to succinylcholine (administered twice previously) suggested the possibility of an IgE-mediated hypersensitivity to the intravenous muscle relaxants. If pancuronium was the responsible agent, the hypersensitivity must have resulted from cross-reactivity between these agents, perhaps because of the quaternary ammonium moieties in the muscle relaxant group.[2,11,12]

At ages 4 and 7 yr, the patient underwent similar surgical procedures, was exposed to latex gloves, and received identical anesthetic management and antibiotics, but anaphylaxis occurred only as part of the latter operation. It is conceivable that prior to age 4, allergic reactions during general anesthesia were due to a hypersensitivity other than latex. After age 4, the allergic reactions may have been due to latex, as suggested from the history of cutaneous hypersensitivity to latex objects at age 5. Allergy skin-testing at age 7 confirmed the presence of latex-specific IgE and all determinants of the β-lactam antibiotic moiety.

Hypersensitivity to β-lactam antibiotics was considered but not initially tested for because these antibiotics, both cephalosporins and semisynthetic penicillins, were given multiple times previously without adverse sequelae. In addition, the urticaria and flushing during the procedure at age 3 were not associated with the administration of β-lactam antibiotics.

The most recent surgical procedure was conducted without prophylaxis against anaphylaxis and without exposure to latex allergens or to β-lactam antibiotics. The procedure lasted 5.5 h without any evidence of an IgE-mediated reaction. Of note, sodium thiopental, vecuronium, morphine, and local anesthetics were used in this last, uneventful procedure eliminating these drugs as suspected causative agents in the prior procedures. The patient's clinical history suggests that latex is the more likely causative agent than cefazolin because it was used during previous procedures without sequelae, and other cephalosporins and penicillins had been used with impunity.

As the use of latex rubber products proliferates with the adoption of universal precautions, the incidence of latex hypersensitivity is likely to increase. Contact dermatitis representing a type IV delayed-type hypersensitivity to rubber-based chemical additives and stabilizers has long been identified, and recently IgE-mediated anaphylaxis to latex has been recognized.[4,13–20] There is little information on the incidence of IgE-mediated immediate hypersensitivity to latex, but the overall incidence of hypersensitivity to surgical latex gloves among physicians is reported to be 7.5%, among nurses 5.6%, among hospital employees 1.3% and among nonmedical occupation controls 0.8%.[18] A recent preliminary prospective study suggested that approximately 34% of patients with spina bifida have IgE antibodies specific for rubber proteins.[21] In patients with myelodysplasia the incidence has been estimated from 18–28% by informal questionnaire.[22] A retrospective review suggested a high frequency of intraoperative anaphylaxis in children with myelodysplasia, probably as a result of latex hypersensitivity.[23] Histories of these children revealed contact urticaria to balloons, shortness of breath upon contact with a rubber dam used during a dental procedure, and tinnitus, pruritus, and dyspnea during urethral catheterization, possibly due to latex glove contact. Preliminary prick or scratch skin testing to latex is positive in most of these patients, with RAST testing corroborating the presence of latex-specific antibodies.

Although one clinical study reported the presence of immediate and delayed hypersensitivity in three atopic children, atopy is not consistently associated with latex allergy in children.[13,19] A recent report identified hypersensitivity to ethylene oxide and latex in three children with spina bifida. Repeated exposure to gloves and medical materials sterilized with ethylene oxide was suggested as the etiology of the sensitization.[24] Patients who have had repeated exposures to latex products for medical reasons (*e.g.*, catheterization in spina bifida patients) and who have undergone multiple surgical procedures may develop hypersensitivity to latex products.

Avoidance of exposure to latex in the perioperative period, including the use of nonlatex surgical gloves for medical personnel, is feasible. There may be certain patient populations, including those with a history of prior allergic reactions under general anesthesia, multiple surgical procedures, chronic latex exposure through repeat catheterization, or clinical outpatient reactions upon latex contact who are at higher risk for IgE-mediated hypersensitivity. Consideration should be given to pharmaceuticals and nonpharmaceuticals as potentially causative agents, including the now well-recognized latex allergen. Alternatives to standard instruments and medical products include silicone urinary catheters, nonlatex surgical gloves (Neolon® Becton Dickinson AcuteCare Division, Franklin Lakes, NJ, or Elastyren® Allerdem Labs., Mill Valley, CA), avoidance of multidose medication vials, avoidance of contact with latex-containing drains, and the use of non–rubber-based (polyvinylchloride) blood pressure cuffs. All patients proven to have true IgE-mediated hypersensitivity to latex should wear a proper allergy identification bracelet. These patients should also carry autoinjectable epinephrine should a severe systemic or anaphylactic event develop as a result of accidental latex exposure.

Intraoperative latex anaphylaxis, with its potential for life-threatening consequences, merits more attention by anesthesiologists and surgeons, particularly in patients with chronic disease.

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Pulmonary Hypertension Associated with Liver Disease Is Not Reversible after Liver Transplantation

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Pulmonary hypertension is an unusual but well-known complication of liver disease.[1] Patients with pulmonary hypertension are usually considered unacceptable candidates for liver transplantation because intraoperative morbidity and mortality is assumed to be high. The role of liver transplantation in reversing this form of pulmonary vascular disease is not known. We present a patient with severe pulmonary hypertension who underwent orthotopic liver transplantation.

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Case Report

A 23-yr-old woman with chronic active hepatitis was admitted for pre–liver transplant evaluation. The diagnosis of chronic active hepatitis was established by biopsy 12 yr prior to admission. Symptoms related