

Type I hypersensitivity to rubber

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Seven patients with type I hypersensitivity reactions to rubber are reported. Radioallergosorbent testing with crude latex antigen was positive in 6/7 patients. Five patients had coexisting spina bifida, and all had undergone surgery before the development of rubber allergy. Rubber allergy is a new phenomenon that should be in the differential diagnosis of idiopathic anaphylaxis and urticaria.

INTRODUCTION

Allergy to natural rubber has been associated, in the past, with type IV reactions to additives and stabilizers or, in one report, to corn starch powder on surgical gloves.¹ Since 1979, at least 55 cases of purported type I hypersensitivity to natural rubber have appeared in the English language medical literature.²⁻²² In 1989, one of us reported two children with spina bifida who experienced perioperative anaphylaxis, apparently by an IgE-mediated mechanism.²³ We report here seven more cases of type I rubber hypersensitivity, five in patients with spina bifida.

CASE REPORTS

DD is an 8-year-old female with spina bifida. She has had eight surgical procedures and has had several episodes of postoperative puffiness, congestion, and stridor. These symptoms had been treated with diphenhydramine. Because of these reactions together with a history of facial edema during a dental procedure, her last two procedures were performed with neoprene gloves.

During the first of these (that is, the seventh procedure) she developed some mild facial erythema and was given diphenhydramine and a glucocorticoid intravenously; the reaction abated. The last procedure, an osteotomy for which she was premedicated with diphenhydramine, ranitidine and a glucocorticoid, was uneventful. However, hives appeared 1-day postoperatively and continued until 1 day after the cast was removed. Between the seventh and eighth procedures, DD developed pruritic erythema of the face, hands, and arms a few minutes after playing with a rubber novelty toy ("Koosh ball"). DD has no history of atopic disease but has had urticarial reactions associated with the administration of amoxicillin and cotrimoxazole. Skin testing with benzylpenicilloyl polylysine (6×10^{-5} mol/L) and penicillin G (10^{-2} mol/L) was negative.²⁴

EG is an 18-year-old female with spina bifida and a history of multiple orthopedic and urologic procedures. While working as a hospital volunteer, she developed eye swelling, sneezing, and ear itching when exposed to rubber gloves. She experienced similar reactions when exposed to balloons. Handling of kitchen gloves or a rubber toy led to local urticaria. One dental procedure, in which the dentist and dental assistant wore rubber gloves, was associated with itchy eyes.

RG is a 7-year-old male with spina bifida, multicystic kidney, and juvenile rheumatoid arthritis. He is allergic to codeine, methadone, and grass pollen. His rubber allergy was

first noted 4 years ago. He has had generalized urticaria and angioedema after placement of a rubber catheter and use of a rubber prophylactic cup in the dentist's office.

BF is an 11-year-old male with spina bifida. He has had five surgical procedures and has a history of allergic reactions to rubber products. He develops urticaria when exposed to balloons and latex gloves. He has experienced severe facial angioedema and sneezing when an open wound was touched with a rubber glove. His only other intraoperative reaction was a contact urticarial reaction to an anesthesia mask that was used at the time of his last back surgery 2 years ago. BF has seasonal rhinitis and asthma, and is sensitive to juniper pollen and cat.

MF is a 31-year-old female, and is the mother of BF. She does not have spina bifida; her prior surgery includes laparoscopy, hysterectomy, and wrist surgery. Since age 5, she has noted circumoral urticaria whenever she blows up balloons. She has allergic rhinitis, asthma, cat and pollen sensitivity, and sulfite sensitivity.

JO is a 3-year-old male with a 15-month history of hives associated with rubber exposure. These have occurred approximately 15 times with exposure to balloons, surgical gloves, and a rubber novelty toy ("Koosh ball"). Episodes begin with ocular itching and progress to facial urticaria and angioedema. There has been no history of respiratory compromise or hypotension. Two episodes of urticaria have occurred without obvious rubber contact.

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The first was associated with egg ingestion at age 1 and the second occurred during a dental visit in which no obvious source of natural rubber was used. JO has asthma and is sensitive to dust mite, some molds, and grass, weed, and tree pollens. He has been hospitalized three times, once at age 15 months for hydrocele surgery and tympanostomy.

BT is a 16-year-old male with spina bifida, asthma, and allergic rhinitis. He has had several surgical procedures and has wheezed twice during surgery; one episode was associated with facial angioedema. Since the age of 2 years he has experienced facial angioedema about ten times; some of these have been associated with balloon exposure.

METHODS

Serum specimens were collected from each patient and stored frozen until use. Control serum specimens from 20 patients were obtained from random outpatient laboratory samples in the Children's Hospital Department of Laboratory Medicine. No demographic or medical information was available on the control patients.

RAST Testing

Latex extract was prepared from ammoniated latex concentrate by dialysis, centrifugation, and filtration as previously described.²³ It was then desalted and lyophilized for long-term storage. Polystyrene microtiter plates were coated with lyophilized latex extract (1 µg/well) dissolved in a sodium carbonate-bicarbonate buffer (0.1 mol/L, pH 9.6). Wells were washed with 0.9% NaCl containing 0.05% Tween 20 and serum was added, diluted 1:3 (vol/vol) in phosphate buffered saline (pH 7.4) containing 3% bovine serum albumin, 0.05% Tween 20, and 0.01% sodium azide. After overnight incubation at 4 °C, the wells were washed and ¹²⁵I-labelled rabbit anti-human IgE (Pharmacia Diagnostics, Fairfield, NJ), 20 µL containing 6,000 to 12,000 cpm,

was added along with 50 µL of buffered saline-albumin-Tween-azide. After overnight incubation at 4 °C, the wells were washed, cut, and counted in an LKB Ultragamma counter. Data are presented as bound cpm/total cpm.

RESULTS

When outpatient control sera were incubated with the latex extract-coated plates, 0.4% ± 0.3 (mean ± SD) of added rabbit anti-human IgE bound to the plates after overnight incubation; only 1/20 of these control sera had binding greater than 2 SD above the mean (1.0%). When sera from the seven patients described here were used, binding was greater than 2 SD above the mean of the controls for six out of seven of the patients. Serum from 1 patient (MF), however, yielded only 0.4% ± 0.04 binding (Table 1).

DISCUSSION

Natural rubber is a highly processed plant product derived from the sap (or latex) of the commercial rubber tree *Hevea brasiliensis*. Patients with type I rubber hypersensitivity appear to have IgE specific for *H. brasiliensis* proteins that persist in the final product, perhaps in amounts as much as 2% by weight.²⁵ There is some disagreement regarding the molecular weight of the important antigens,^{9,19,22,26} probably due to the different source materials used as well as the heterogeneity of the human immune response to these proteins.

As demonstrated in these seven cases, significant reactions may occur following relatively trivial exposures by cutaneous, mucosal, or parenteral routes. This exquisite clinical sensitivity is more typical of food and drug allergy than of aeroallergen reactions, and may suggest the systemic absorption of relatively large amounts of antigen. These histories also suggest that allergy to natural rubber should be seriously considered in all patients with idiopathic anaphylaxis, especially recurrent idiopathic anaphylaxis.

Recent studies of patients with rubber allergy, including the present one, have included a disproportionate number of patients with spina bifida; among the 62 rubber allergy cases reported in detail so far, eight have coexisting spina bifida. Although such case reporting may be subject to selection bias, one prospective study suggests that as many as 41% (5/12) of spina bifida patients have IgE antibody specific for rubber proteins.²⁷ All surviving patients with spina bifida have had early parenteral exposure to rubber proteins, from latex surgeon's gloves during primary closure of the meningomyelocele. Most undergo many subsequent operative procedures as well. This early initial exposure and frequent reexposures may predispose this group of patients to rubber allergy. It is of interest that both of our patients without spina bifida had prior histories of surgery (Table 1).

Table 1. Characteristics of Patients and Results of RASTs

Patient	Age, yr	Symptoms	Prior Surgery	Spina Bifida	RAST B/T (mean ± SD)
DD	8	Urticaria, upper and lower airways	Yes	Yes	11.2% ± 0.25%
BF	11	Urticaria, upper airway	Yes	Yes	13.5% ± 0.03%
MF	31	Urticaria	Yes	No	0.4% ± 0.04%
EG	18	Urticaria, upper airway, ocular symptoms	Yes	Yes	21.4% ± 0.8%
RG	7	Urticaria, angioedema	Yes	Yes	6.5% ± 0.05%
JO	3	Urticaria, ocular symptoms	Yes	No	6.7% ± 0.20%
BT	16	Angioedema, bronchospasm	Yes	Yes	3.3% ± 0.20%

The diagnosis of rubber allergy remains, for the most part, clinical. No single diagnostic technique has been shown to be of sufficient predictive value in large scale studies. The commercially available RAST disks were found to be only 53% sensitive to Turjanmaa's study.²⁸ In our hands, radioallergosorbent testing was negative in one patient (MF) with a clearly positive history. Passive sensitization leukocyte histamine release²³ was positive in two out of three of the patients tested (DD and BT were positive, JO negative; data not shown), but this laborious method remains of research value only. Skin testing has been useful to most investigators, but the source materials and methods of extraction have not yet been standardized. Although the latex extract used in the RAST has been used for skin testing in other patients,²³ skin testing was not done in this study because of patient reluctance and, in some cases, distance from the investigators.

For patients with a history of rubber-induced allergic reactions, as with all life-threatening allergy, avoidance is the main form of treatment. This may be difficult, considering the ubiquity of natural rubber products as well as synthetic (non-allergenic) elastomers with remarkable similarity to natural rubber. Patients with a clinical history consistent with rubber allergy should be counselled to avoid common natural rubber products and to purchase a Medic-Alert bracelet. Health care personnel should use nonrubber gloves when treating these patients. Patients should be counselled to purchase a supply of such nonrubber gloves for use by emergency medical personnel who may not have their own supply. (Some nonrubber gloves are listed in references 17 and 20.) Allergists treating such patients should provide them with a letter explaining the condition, with appropriate references, for other health care workers. When in doubt about the rubber content of a prod-

uct, the manufacturer should be contacted for assistance.

Precautions notwithstanding, accidental exposures will certainly occur. Some of the patients reported here have suggested that direct contact with the rubber is not necessary for the initiation of a reaction, indicating that at least some of the antigen may be aerosolized. In addition, Silverman²⁹ has raised the intriguing possibility that antigen may be carried on syringe needles from the rubber stoppers of multi-use vials. In our series, DD experienced prolonged urticaria following orthopedic surgery. Her symptoms resolved only after the cast was removed, suggesting the presence of antigen in the cast material.

Physicians should prescribe autinjectable epinephrine for these patients and carefully instruct them in its proper use. Presurgical patients should be premedicated, probably according to one of the protocols suggested for the prevention of anaphylactoid reactions to radiocontrast media.³⁰⁻³² Patients undergoing routine dental examination may not need premedication, if the dentist and staff will be using nonrubber gloves. More involved procedures, however, increase the risk of accidental exposure with rubber-containing implements, and premedication should be considered.

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