

IgE-mediated anaphylactoid reactions to rubber

J. G. K. AXELSSON,¹ S. G. O. JOHANSSON² and K. WRANGSJÖ³

¹Departments of Thoracic Medicine, ²Clinical Immunology and ³Occupational Dermatology, Karolinska Hospital, Stockholm, Sweden

Delayed hypersensitivity to rubber chemicals is well known, but there are only a limited number of case reports on an immediate type of hypersensitivity inducing contact urticaria. We have recently seen several patients with rubber glove-induced contact urticaria who have had both positive skin prick tests and positive RAST tests to natural latex from the rubber tree (*Hevea brasiliensis*). We now report on five patients who also developed systemic reactions. It is clear that sensitized subjects are at risk of developing anaphylaxis during medical examination or surgery when rubber gloves are used. The occurrence of IgE-mediated allergy to rubber is probably underestimated.

Key words: anaphylaxis; contact urticaria; *Hevea brasiliensis*; IgE-mediated; rubber.

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Rubber gloves are used in various occupations and household work to protect the hands from noxious agents. Most rubber gloves are made of latex from the rubber tree (*Hevea brasiliensis*). Among patients with eczema, 5-10% are sensitized to rubber additives (3). These are low molecular weight substances which are added to the latex in the manufacturing process to act as accelerators, antioxidants, stabilizers and vulcanizers. In the sensitization process some of these additives act as haptens and cause allergic reactions of the delayed type.

Only a limited number of cases with contact urticaria of the immediate type attributed to the latex in rubber gloves have been reported (5-7, 10-14, 17). Turjanmaa et al. (17) and Frosch et al. (5) have detected specific IgE antibodies to rubber latex using radioimmunoassays. We have seen several patients with contact urticaria caused by rubber gloves and with positive skin prick tests (SPT) and RAST to natural latex from the rubber tree. We now report five such patients who also developed systemic reactions. One patient suffered anaphylactic shock and four patients anaphylactoid reactions.

PATIENTS AND METHODS

Case 1

A 27-year-old woman had had atopic eczema, allergic rhinoconjunctivitis and bronchial asthma since childhood. She began working as a cleaner in 1977 and occasionally used rubber gloves at work. In 1978 she developed hand eczema and started to use rubber gloves more frequently to protect her hands. After about 1 year she noticed that the skin of her hands started itching about 1 h after she had put on rubber gloves and she therefore stopped using them so often. One year later her hands started itching after 15 min and she immediately removed the gloves. The hands and wrists were swollen and wheals were present. Her eyelids were also oedematous. In 1983 she again used rubber gloves in household work. After about 5 min she developed a severe reaction with itching and urticaria on the hands, periorbital Quincke's oedema and dyspnoea, and she almost fainted. She took an antihistamine tablet and the symptoms diminished and disappeared within 1 h.

Routine SPTs and RAST showed sensitization to animal dander, grass, birch and mug-

wort pollens, and house-dust mite allergen. A standard patch test was positive for balsam of Peru and fragrance mix. One finger of the patient's own rubber glove, which was made of latex from *Hevea brasiliensis*, was cut off and slid on to the patient's index finger. This elicited itching, redness, swelling and urticaria on the finger within 15 min.

Case 2

A 43-year-old woman, who worked in a market garden, had a 26-year history of psoriasis and had had hand eczema for 20 years. When working with chrysanthemums she had experienced slight symptoms of rhinoconjunctivitis. For the past 15 years she had used rubber gloves occasionally both at work and at home. In July 1984, 2–3 min after putting on rubber gloves, she experienced itching, swelling and urticaria on the hands and swelling of the face. The patient also felt faint and had a sensation of pressure in the ears, together with palpitations, sweating and tiredness. She took two tablets of antihistamine and went to an emergency clinic where she was kept under observation. The symptoms disappeared within 1–2 h without further therapy.

Routine SPTs and RAST were positive for mugwort. Standard patch tests were positive for nickel and cobalt. A provocation test with a piece (1 cm²) of the patient's rubber glove (made of latex from *Hevea brasiliensis*) moistened with physiological saline and laid open on the volar aspect of the forearm, produced a wheal and flare reaction within 15 min.

Case 3

A 33-year-old woman had had atopic dermatitis from the age of 6 months to early teenage, the eczema being located on the end phalanges of both hands. At the age of 13 she developed rhinoconjunctivitis and mild bronchial asthma as reactions to birch pollen and animal dander. Because of her hand eczema she often used rubber gloves during household work.

In 1980, after wearing rubber gloves for about 5 min, her hands began to itch and she

immediately removed the gloves. Both hands were swollen, especially the fingers. One year later she wore rubber gloves again and after only a few minutes she felt strong itching and took off the gloves at once. Her hands were swollen and she felt dizzy and tired, and had dyspnoea and palpitations. She rested in bed and the symptoms disappeared in about half an hour.

In 1984 she became pregnant and the hand eczema healed and she experienced no allergic airway symptoms. A Caesarian section was performed in December 1984, because of a breech presentation, and even though the gynaecologist wore rubber gloves, no complications or symptoms of allergy occurred.

Routine SPTs and RAST revealed sensitization to birch and timothy pollens, and dog and horse epithelia. A scratch test with the patient's own rubber gloves (made of latex from *Hevea brasiliensis*) was positive. Challenge with one glove finger, as in case 1, elicited itching, swelling and urticae within 5 min.

Case 4

A 44-year-old female clerk had suffered from atopic eczema since early childhood, mainly on the body and arms and to a lesser degree on the wrists and hands. In 1971 she began to suffer from rhinitis during the birch pollen season and after exposure to cats. Wheezing in the chest in cold weather and after exercise started in 1976. In 1977 she had a probably food-related anaphylactic reaction. For many years she had often used rubber gloves in household work, but they started to cause itching and after some time small urticae and swollen fingers developed after 10–15 min. During the last 10 years she had tried a few times to use rubber gloves, but with the same results, i.e. itching and urticae on the hands after 10–15 min. She had also noticed itching and swelling of the lips when blowing up balloons for her children.

In 1984 she received a root filling. A cofferdam made of latex from *Hevea brasiliensis* was applied. After 20 min, itching and swelling of the cheek occurred and the patient became dyspnoeic and felt faint. She was immediately transferred to a

general practitioner, who treated her with antihistamine and hydrocortisone intravenously and she recovered within an hour.

Routine SPTs and RAST showed sensitization to timothy, birch and mugwort pollens, and to cat dander. A standard patch test was negative. A provocation test was performed in the same manner as in case 2, with a piece of the offending cofferdam, which elicited a wheal and flare reaction within 15 min.

Case 5

A 39-year-old dentist had had atopic eczema and hay fever since early childhood. At the age of 7 years she was hyposensitized to pollens of deciduous trees and grass and to animal dander. The treatment was repeated at the age of 24 years with good results. The eczema was mainly located on the trunk, but was also present on the hands. In the early 1970s she began to use rubber gloves in household work and after about 1 year she developed small itching urticae after 2–3 min. When she used rubber gloves at work, she wore plastic or cotton gloves under them and had no discomfort.

When the patient's skin came into contact with cofferdam, she experienced contact urticaria. In 1977 she underwent uterine curettage without any complications. In 1979 an abortion was performed because of intrauterine fetal death and shortly afterwards she felt itching in the vulva, hands and pharynx. She also became dyspnoeic. The symptoms disappeared without treatment in half an hour. In 1980 the patient underwent a routine gynaecological examination 6 weeks after a normal delivery. The gynaecologist used rubber gloves when palpating per vaginam. After 2–3 min the patient felt itching in the fingertips and exhibited dyspnoea with rhonchi. Periorbital oedema and generalized urticaria developed, her pulse was not palpable and she became unconscious. Conventional shock treatment was immediately administered and after about 5 min the patient awoke; about 1 h later her blood pressure was stable at 100/60. She was fully recovered in 2–3 h.

Skin tests were not performed. RAST showed sensitization to deciduous trees, grass and

mugwort pollen, animal dander, and house-dust mite.

Control group

Two control groups comprising 10 non-atopic, healthy persons and 10 atopic patients sensitized to common inhalant allergens were tested with the latex extract. All 10 atopic patients reported skin irritation from rubber gloves, seven had atopic eczema and four eczema of the hands.

Allergen extracts

Latex from *Hevea brasiliensis* was collected directly from a cut in the trunk into a test tube (Sandofire Works and Rubber Estate, Katiyala, Demanhandiya, Sri Lanka). One gram of latex was extracted in 9 ml of physiological saline with 0.3% phenol. After centrifugation the allergen extract used for SPT was sterilized through a Millipore filter® (0.22µm) and diluted to 1:100 w/v with an unbuffered saline solution containing 0.03% human serum albumin (Albumin diluent®, Pharmacia Diagnostics).

Skin tests

SPTs with extract from *Hevea brasiliensis* and a standard panel consisting of 14 common inhalant allergens were performed according to the method of Pepys (15), using a disposable blood lancet. Test reactions were scored in accordance with the Nordic guidelines, with histamine chloride 1 mg/ml corresponding to 3+ (16).

A standard patch test, including 11 different rubber additives, was performed as described by the International Contact Dermatitis Research Group (4).

RAST test

One hundred microlitres of the allergen extract from *Hevea brasiliensis*, 1:10 w/v, was coupled to 100 CNBr-activated paper discs (9, 18). The discs were negative (< 0.35 PRU/ml) in RAST with non-atopic serum samples with IgE-con-

centrations of 10 to 4000 kU/l. Commercially available discs with latex (Latex, K82, Pharmacia Diagnostics AB, Uppsala) were also used. RAST was performed according to the manufacturer's instructions (Pharmacia Diagnostics AB, Uppsala) using the commercially available ¹²⁵I-labelled anti-IgE (Phadebas anti-IgE) and expressing the results in PRU/ml as derived from the Phadebas RAST Reference System (Pharmacia Diagnostics AB, Uppsala).

RESULTS

IgE antibodies to *Hevea brasiliensis* were detected in the serum of all five patients. The results of SPT and RAST and total IgE concentrations are presented in Table 1. SPT and RAST were negative in the two control groups.

DISCUSSION

The natural latex from *Hevea brasiliensis* contains several different proteins (1), and most allergens giving IgE response are proteins or glucoproteins. That the RAST tests in these sensitized patients were positive supports the hypothesis that the allergen is a protein, since CNBr-activated paper discs only bind proteins. In the process of manufacturing rubber gloves, several low molecular weight chemical substances, such as ammonia, sulphur, zinc oxide, zinc diethyl dithiocarbamate (ZDC), mercaptobenzothiazole, 2-2 methylene-bis (4-methyl-6-tert) butylphenol, and sodium naphthalin sul-

phoxide (Opett®, Semperit, Austria) are added and the rubber gloves are then heated to about 100°C for 5 min for vulcanization. It therefore seems likely that the allergen(s) is fairly stable to chemical and heat denaturation. It is also possible that some of the rubber additives might give rise to an immediate type of hypersensitivity. There is one case report on contact urticaria attributed to ZDC (8).

All five patients had a history of long-standing atopic dermatitis of the hands and had used rubber gloves fairly frequently for many years preceding the development of IgE-mediated contact urticaria. In addition, they all had an atopic status and were sensitized to common airborne allergens. That all are women is probably because women use rubber gloves more often. We have also seen several male patients sensitized to rubber, but without systemic reactions.

It is obvious that the allergen(s) are able to cross the skin barrier. All five patients had impairment of the skin barrier due to eczema, and the allergen(s) could thereby reach immunocompetent cells and induce sensitization. It is also probable that the presence of skin inflammation might have had an adjuvant effect on the sensitization process. In Cases 1-3 anaphylactoid reactions occurred when the allergen(s) passed through the skin barrier and reached the blood stream. In Cases 4 and 5 the allergen(s) crossed the buccal mucosa and the vaginal mucosa, respectively, and caused more severe reactions.

The sensitization was induced by rubber gloves in all five patients and the offending agent was easily recognized. However, unintended exposure to natural rubber may occur, e.g. during surgical operations, medical examinations and in dentistry. In such situations sensitized subjects are apparently at risk of developing anaphylaxis, as illustrated by Cases 4 and 5. Furthermore, there is a preliminary report on two patients who suffered anaphylactic reactions to surgeons' gloves during operation (17). Patient No.3, however, underwent a Caesarian section without any allergic symptoms. There are at least two possible explanations for this. During pregnancy the cortisone

Table 1

Results of skin prick tests and RAST to natural latex from the rubber tree (*Hevea brasiliensis*) in five sensitized female patients

Case	Age (years)	Atopic status	Skin prick test	RAST (PRU/ml)	Total IgE (kU)
1	27	yes	4 +	4.6	1500
2	27	yes	3 +	0.8	160
3	33	yes	4 +	9.4	300
4	44	yes	4 +	5.1	300
5	39	yes	n.d.	0.6	140

Skin prick test with histamine chloride 1 mg/ml = 3 + ;
n.d. = not done

concentration in the blood is doubled or trebled and this might have protected the patient (2). It is also well known that the specific IgE concentration decreases as time passes without exposure and the operation was performed 2½ years after the patient's last exposure to rubber gloves. The exposure to rubber during the operation could have acted as a booster, as the specific IgE concentration to natural latex was rather high (9.4 PRU/ml).

Patient No. 4 had an anaphylactoid reaction after contact between the oral mucosa and a cofferdam made of natural latex. We have seen several patients who have had a local reaction either to cofferdam or to rubber gloves used by the dentist. Dentists use gloves more often nowadays because of the risk of infection from agents such as hepatitis virus and HIV. Local anaesthetics of the caine type are frequently used in dentistry and when local or general allergic symptoms occur the local anaesthetic is often incriminated as the offending agent. The symptoms are similar to those of rubber allergy and some of these cases might have been caused by the latter.

The occurrence of IgE-mediated allergy to natural rubber is probably underestimated and is yet to be elucidated.

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Address:

Göran Axelsson, M.D.

Department of Thoracic Medicine

Karolinska Hospital

S-104 01 Stockholm

Sweden

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