

IgE-mediated allergy to natural rubber in 30 patients with contact urticaria

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30 patients who had experienced contact urticaria after exposure to gloves, contraceptives, balloons or dental cofferdams went through a detailed examination including interviews on: exposure to rubber; local and distant symptoms; provocation tests; skin prick tests with (among other substances) latex extracts from the rubber tree *Hevea brasiliensis*; patch testing, IgE and RAST analyses. 23 patients (77%) reported additional symptoms from distant organs. 13 belonged to medical occupations; 25 were classified as atopics based on history; 21 had raised IgE-values; 25 were RAST-positive to the extracts from *Hevea brasiliensis*. 13 had a pre-existing hand dermatitis, of whom 6 were patch test positive to standard allergens. Skin prick tests with extracts from *Hevea brasiliensis* were the most sensitive diagnostic tool, while the RAST analysis was positive in 25/30 cases. These tests and analyses including RAST were negative in 40 control subjects. Provocation tests are of great value, but difficult to standardize. Several patients reported severe reactions at medical and dental examination/treatment situations (surgical gloves, dental cofferdams), and the risk of life-threatening anaphylactic reactions is emphasized.

Key words: anaphylaxis; contact urticaria; contraceptives; dental cofferdams; gloves; *Hevea brasiliensis*; latex; prick test; provocation test; RAST; respiratory effect; rubber.

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IgE-mediated latex rubber allergy is a fairly recently described entity in view of the widespread use of latex rubber products during the last century. Natural rubber made from latex from the rubber tree (*Hevea brasiliensis*) is found in many products used in close contact with skin or mucous membranes, such as household or surgical latex gloves, cofferdams used by dentists, balloons and rubber contraceptives. Also baby pacifiers, anaesthetic tubes and envelope adhesives are among the many articles often manufactured of latex rubber.

Since 1979, when Nutter (1) first described contact urticaria (CU) from rubber gloves, some 60 cases have been reported (2-17). A high frequency (2.9%) of rubber-induced CU among medical personnel is reported from Finland (16). Allergic reactions elicited by glove powder are also reported in 3 cases

(18-20) and in 1 case of angioedema due to a dental cofferdam (21). Specific IgE antibodies to latex rubber have been demonstrated in several reports (10-15, 17). Most allergens giving an IgE response and proteins or glycoproteins, and the latex from *Hevea brasiliensis* contains several proteins (22) which may act as allergens.

Of 25 patients described in sufficient detail in the reports (1-11, 15, 17), 7 showed merely local contact urticaria, while the remaining 18 also had symptoms such as facial oedema and rhinoconjunctivitis. 9/25 patients also developed symptoms of anaphylaxis: dyspnoea, tachycardia, general urticaria and compromised general condition.

Since 1982, 36 patients with rubber-induced CU have been studied in the Department of Occupational Dermatology, and 13 of these

have been described in separate reports (12, 15, 17). The aim of the present study was to survey the history of their CU, regarding pattern, distribution and intensity of symptoms; relationship to atopy; products inducing and eliciting; and also what exposure conditions could imply a risk of anaphylaxis. We also wished to evaluate the different clinical test methods and blood analyses (IgE, RAST) we had used during the period.

Material and Methods

Patients

During 1982–1987, 36 patients with CU provoked by rubber products were studied. 30 of these have been amenable to detailed examination, blood analyses, interviews following a questionnaire, and testing. 6 patients were not accessible for these interviews and for this reason were excluded from the study.

17/30 of the patients were recruited from the outpatient group referred to the Department of Occupational Dermatology, 7 were referred from the Department of Allergology at Karolinska Hospital, 4 from other dermatological clinics in Sweden and 2 children came from the Paediatric Clinic at St. Göran's Hospital, Stockholm.

To be included in the study, the patients had to demonstrate convincing anamnestic reports of rubber-provoked CU and a positive skin prick test (SPT) to an extract from *Hevea brasiliensis* or, if not accessible to SPT, a positive RAST to *Hevea brasiliensis*. The patients were also required to be available for clinical examination including a questionnaire. 2 patients were examined at other dermatological departments and included after telephone interviews, review of their records and the results of the RAST investigations.

Control groups

4 control groups were investigated, 3 of them with RAST and SPT with *Hevea brasiliensis* extract, the 4th with RAST only.

(i) 10 non-atopic adults.

(ii) 10 atopic adults.

(iii) 10 non-atopic theatre nurses with at least 3 years in the profession (mean 14 years), and who had used rubber gloves without any skin problems.

(iv) 10 consecutive new outpatients at the Department of Occupational Dermatology.

Questionnaire and interview

Age, sex, current and previous occupations and rubber exposure were recorded. Heredity for atopy in parents and siblings, previous and current symptoms of personal atopic dermatitis, allergic rhinoconjunctivitis, asthma and food intolerance were asked about. As a definition, the criteria for atopic dermatitis given by Hanifin and Rajka were used (23). The presence of atopic dermatitis or rhinoconjunctivitis or asthma, combined with the presence of IgE antibodies to common inhalant allergens, was also counted as a sign of atopy. Previous skin disease, especially hand dermatitis and contact allergy, was asked about. Questions about exposure to, and symptoms from, household gloves, surgical latex gloves, dental cofferdams, balloons and rubber contraceptives were included, and symptoms from dental cofferdams or surgical latex gloves during dental or medical examination or treatment were recorded. The subjects were also asked about other symptom-provoking rubber products.

Test Methods

Provocation tests

Provocation tests were performed in different ways according to the history. 14/30 patients were provoked with their own symptom-giving product, and when this was not possible, surgical latex glove material manufactured by Semperit (Austria) was used. Patients with no former generalised symptoms wore whole gloves on one hand for 20 min or until wheals were noted. Patients with a history of generalised symptoms were tested with 1 cm² pieces of

rubber material moistened with saline on intact skin of the volar aspect of the forearm for 20 min, or tested by wearing one glove finger. Redness of the skin and itch were recorded, but only palpable wheals were accepted as indicating a positive provocation test result. Clearly-time-related distant symptoms, such as signs of rhinoconjunctivitis or facial redness and itching, were also recorded. All positive reactions were photographed. In 2 cases with an initially negative provocation test, a modified skin prick test (SPT) was performed with a moistened piece of rubber applied to the test site.

Skin prick tests (SPT)

Skin prick tests using an extract from *Hevea brasiliensis* and a standard panel of 5 common inhalant allergens, birch, timothy, mugwort, cat, *D. pteronyssinus* (Pharmalgen Pharmacia, Uppsala), were performed according to Pepys (24), using a disposable blood lancet. Test reactions were scored in accordance with the Nordic guidelines, with histamine chloride 1 mg/ml corresponding to 3+ (25).

Allergen extracts

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

Patch test

The patch test procedure recommended by the International Contact Dermatitis Research Group (ICDRG) was used with Finn Chambers[®] on Scanpor[®] tape.

Allergens

A standard patch test series including 11 different rubber chemicals was used. Patch testing was also performed with 1 cm² pieces of glove or dental cofferdam material brought by the patients. The readings took place 72 h after application.

Total IgE

The total IgE in the patients' sera was determined using the Phadebas PRIST (Pharmacia Diagnostics) according to the manufacturer's instructions.

RAST

100 µl of the allergen extract from *Hevea brasiliensis* 1:10 w/v was coupled to 100 CNBr-activated paper discs (25, 26). The discs were negative (<0.35 PRU/ml) in RAST with non-atopic serum samples, with IgE-concentrations of 10 to 4000 kU/l. Commercially available discs with latex (Latex K 82) were also used. RAST was performed according to the manufacturer's instructions (Pharmacia Diagnostics), using the commercially available 125 I-labelled anti-IgE (Phadebas anti IgE), and the results were expressed in PRU/ml, as derived from the Phadebas RAST Reference System (Pharmacia Diagnostics). RAST was also performed using the commercially available RAST-discs with cornstarch allergen (Pharmacia Diagnostics).

Results

The results are shown in Tables 1–6.

Contact urticaria

In 23 of the 30 patients (77%), the localised CU was combined with various symptoms from distant organs, while 7 patients (23%) reported only localised CU (Tables 1, 2). 9/23 had experienced an initial period (range 0.5–20 years) of merely localised CU. The intensity of symptoms varied considerably at different periods and exposure conditions. 10 patients reported development of dermatitis following

their CU, while 11 were uncertain and 9 had no such experience.

Atopy

In Table 3, age, sex, occupation and family and personal atopy are listed. The female/male ratio is 24/6. A family history of atopy was reported by 16 patients, and 25 were classified as being atopic. 25 patients had experienced food intolerance (mainly of fruits, vegetables and fish) and 23 of these were atopic. 13 patients had a pre-existing hand dermatitis; 6 of these were patch - test - positive to one or more allergens in the standard tray.

Exposure to rubber

In Table 4, the frequency of CU reported from exposure to various rubber products is given. 27 patients had used gloves; 24 in occupations involving wet work. 13 patients belonged to medical occupations (3 nurses, 2 auxiliary nurses, 2 physicians, 2 technicians, 4 dentists). 2 patients stated that hand dermatitis was the only reason, and 10 a contributing reason, for wearing gloves.

Table 1. Distribution of symptoms in 30 patients

	No.	(%)
localised CU only	7	23
localised CU with mild distant symptoms	12	40
localised CU with distant symptoms and compromised general condition	11	36

Table 2. Reported distant symptoms in 12 patients without, and 11 patients with, compromised general condition in connection with CU

Symptoms	No. 12	No. 11
facial oedema	8	10
rhinitis	3	5
conjunctivitis	7	4
dyspnoea	-	10
tachycardia	-	9
generalised urticaria	-	6
shock	-	3

16/27 reported daily use of 0.5-12 years before the onset of their CU, while in 9/27 using gloves 2-3 times/week, the corresponding figures were 1-15 years. The rubber products that caused the first signs of CU are shown in Tables 3, 4. Other CU-provoking products mentioned by patients were: envelope adhesive (positive provocation test in case 26); cycle tyre inner tube; cosmetic facial mask; soft rubber plugs; special soft elastic band; elastic bandage. The 2 children had both had contact with pacifiers and bottles for only a short period and then refused further use.

7/20 patients with reported rubber glove exposure during medical treatment had noted reactions in examination/treatment situations. Case no. 20 had developed localised and generalised urticaria after a gynaecological procedure. Case nos. 24, 29 (15) developed documented anaphylactic shock, both after a post-partum examination. In these 2 cases, other explanations of the reactions were excluded by testing. 6/8 patients with reported glove or cofferdam contact during dental treatment had noted swelling of lips and cheeks; case no. 25 had severe angioedema which compromised her general condition. Case no. 23 developed anaphylactic shock after exposure to a dental cofferdam (15).

In Table 5, the elicitation time for CU and its duration are shown.

Tests

In Table 6, the results of the provocation test, SPT, and of IgE and RAST (to *Hevea brasiliensis*) analyses are given.

21/26 patients reacted to the provocation test, 3 of these with remote symptoms only (conjunctivitis, rhinitis, dyspnoea, facial redness). 2/26 were negative to the first provocation test but positive to the SPT with rubber materials. The SPT was positive in all cases tested.

12/22 patients were patch - test - positive to 1 or more of the standard allergens. Patient no. 13 was the only one who reacted to the rubber chemicals (thiuram-mix, carba-mix)

and she was the only one (1/10) who also reacted to glove materials during a 48 h patch test with rubber materials.

IgE and RAST analyses

21/30 patients had elevated IgE values (> 122 kU/l) (Table 6).

Table 3. 30 patients with rubber-induced CU grouped according to severity

Case no.	Sex/age (years)	Occupation	Family atopy	Personal atopy*	Original rubber product
<i>et(I) 7 patients with localised urticaria</i>					
1	♀/27	cleaner	+	RC	surgical latex glove
2	♀/50	dentist	+	AD RC	surgical latex glove
3	♀/25	gardener	+	AD RC	household glove
4	♀/23	student	—	RC A	household glove
5	♂/13	student	+	AD	household glove
6	♀/23	bath attendant	—	RC A	contraceptive
7	♀/31	cold buffet manageress	+	—	household glove
<i>(II) 12 patients with localised CU combined with mild distant symptoms</i>					
8	♀/38	dentist	unknown	AD RC	dental cofferdam
9	♀/30	nurse	+	AD	surgical latex glove
10	♀/26	physician	+	AD RC	contraceptive
11	♂/44	dental technician	—	—	household glove
12	♀/29	mental nurse	+	AD RC	surgical latex glove
13	♀/63	cleaner	unknown	—	household glove
14	♂/23	painter	—	—	household glove
15	♂/30	clerk	unknown	AD RC A	household glove
16	♂/33	surgeon	—	—	surgical latex glove
17	♀/69	clerk	+	RC	household glove
18	♀/41	cold buffet manageress	unknown	AD	household glove
19	♀/28	nurse	+	AD RC	surgical latex glove
<i>(III) 11 patients with CU combined with systemic reactions</i>					
20	♀/28	clerk	—	AD RC	surgical latex glove
21	♀/44	gardener	—	RC	household glove
22	♀/27	cleaner	+	AD RC A	household glove
23	♀/45	clerk	+	AD RC A	household glove
24	♀/36	nurse	—	RC A	surgical latex glove
25	♀/48	dentist	—	AD RC A	surgical latex glove
26	♀/32	child nurse	+	AD RC A	household glove
27	♂/ 4	—	+	AD RC A	balloon
28	♀/34	clerk	+	AD RC	contraceptive
29	♀/40	dentist	+	AD RC	surgical latex glove
30	♀/30	lab technician	—	RC	surgical latex glove

* AD: atopic dermatitis. RC: rhinoconjunctivitis. A: asthma.

Table 4. Exposure to, and reported CU from, rubber products in 30 patients

Product	Exposed no.	Reported CU no.	First reported symptoms by no.
household glove	26	25	14
surgical latex glove	17	14	11
balloon	22	14	1
dental cofferdam	4	4	1
rubber contraceptives	9	5	3

Based on their history, 18 of these patients were classified as atopics. The remaining 9

patients had normal IgE values, but based on their history, 7 were judged atopic.

Table 5. Contact time to elicit CU and its duration as reported by the patients ($n=30$)

Elicitation time (min)	No.	Duration time (h)	No.
<5	18	0.5-2	16
5-15	10	2-4	7
>15	2	>4	7

25/30 patients showed positive RAST reactions (>0.35 PRU) to the extract from *Hevea brasiliensis*. However, the 5 patients with a negative RAST all showed positive SPT to the *Hevea brasiliensis* extract. Only 1 of the 5 RAST-negative patients had a raised IgE-value. 2/11 patients showed weak positive RAST reactions (normal range <0.35 PRU) to cornstarch (0.4 and 0.5 PRU). These 2 pa-

Table 6. Tests and laboratory findings in 30 patients with CU

Case no.	Provocation test	SPT extract <i>Hevea bras</i>	RAST <i>Hevea bras</i> norm range <0.35 PRU	IgE norm range <122 kU/l
<i>(I) 7 patients with localised CU</i>				
1	pos	+++	1.0	200
2	NT	+++	0.9	460
3	neg	++++	5.4	2000
4	neg	+++	47	260
5	neg	+++	0	110
6	pos	+++	0	190
7	pos	++++	0	120
<i>(II) 12 patients with localised CU and mild distant symptoms</i>				
8	pos	+++	0.9	8
9	pos	+++	1.1	74
10	neg	+++	160	1500
11	pos	+++	1.8	16
12	pos	++++	14	140
13	pos*	+++	1.1	33
14	pos**	++++	6.9	160
15	NT	+++	8.0	340
16	pos	++	0	51
17	NT	+++	0.8	2900
18	pos	+++	19	3500
19	pos	++++	1.4	370
<i>(III) 11 patients with localised CU and systemic reactions</i>				
20	pos*	++++	12	740
21	pos	+++	0.8	160
22	pos	++++	4.6	1500
23	pos**	++++	5.1	300
24	pos*	NT	7.8	69
25	pos	++++	9.2	670
26	pos	++++	12	1300
27	neg	+++	11	970
28	pos	++++	9.4	300
29	NT	NT	0.6	140
30	pos	+++	0	53

* Only distant symptoms during test.

** positive with modified STP.

tients were also RAST positive to *Hevea brasiliensis*.

Control groups

The 40 control subjects were RAST negative to *Hevea brasiliensis* extract. The 30 exposed to SPT were all negative to extracts from *Hevea brasiliensis*.

Discussion

The findings from this study indicate that symptoms from IgE-mediated allergy are not restricted only to situations in which a sensitized person uses his/her own rubber gloves. Allergic symptoms of varying severity also arise during exposure to gloves and other rubber materials during medical and dental examination and treatment, with special risks of anaphylactic reactions when the contact with rubber involves mucous membranes – as exemplified by severe allergic reactions in relation to gynaecological and dental treatment (15, 17).

Rubber contraceptives were reported by our patients to provoke immediate intolerance symptoms in both men and women. The possibility of IgE-mediated latex allergy would be worth considering when contraceptive allergies are investigated, besides the well-documented rubber allergy of the delayed type.

A growing consciousness of the possibility of such reactions among dentists and physicians, especially gynaecologists, paediatricians and surgeons, may lead to detection and clarification of causes of intolerance reactions to gloves, dental cofferdams, contraceptives and balloons. Pacifiers and anaesthetic tubes contain latex, but no reactions to such products were reported by our patients.

Since IgE-mediated allergy implies the risk of systemic allergic reactions, it is important to make a correct diagnosis and recommend safe alternatives. To know whether the concentration of specific latex IgE antibodies in atopic children correlates to their exposure to rubber pacifiers and balloons would be of special

interest, since alarming angioedema developed in our patient no. 27 after blowing up a balloon (17).

Among our patients, persons in wet work and medical work, and atopics with food intolerance symptoms and hand dermatitis, predominated. The non-atopic individuals belonged to the groups with merely local CU and local CU combined with mild distant symptoms. However, there seems to be no clear relationship between the severity of symptoms and the observed IgE and RAST values (Table 6).

SPT with extracts from *Hevea brasiliensis* seems to be specific, judging by the absence of reactions among control subjects, and appears to be the most sensitive diagnostic tool for revealing rubber latex allergy. On the other hand, with the RAST technique, there is a slight risk of missing the diagnosis, especially in persons with low total IgE values. This is exemplified in this study where 4/5 patients with positive STP and negative RAST had normal IgE values. In some of the 5 cases, the absence of RAST reactions could be due to the time-lag between the actual symptom period and the examination time, which in 3 cases was more than 1 year.

The different provocation tests are also a useful tool, if the risk of eliciting systemic reactions is taken into account. However, it is difficult to standardize the provocation test due to different reports from patients and unknown allergen content in rubber materials, as well as penetration of the allergen into the skin. Since there are reports of suspected cornstarch allergy from glove powder (18–20), and also the possibility of allergens other than latex components in rubber products (4), provocation tests remain important. The possibility of latex allergens absorbed by the glove powder should be considered in cases with glove-powder reactions.

In our experience, we have only seen positive SPT reactions to powder taken from gloves, not to cornstarch powder as is (12). 2/11 positive RAST reactions to cornstarch in

this patient group indicate the need for further studies.

Investigations of the nature of the latex allergens should indicate how to modify the manufacturing process to obtain latex-allergen-free rubber products.

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