

Follow-up Study of Latex-allergic Health Care Workers in Japan

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ABSTRACT

Background: While many cases of latex allergy have been reported in Japanese health care workers (HCWs) since 1992, there have been no follow-up studies after removing latex from the workplace. We had previously replaced all working environment latex gloves and latex products with low-allergen or non-latex products. The purpose of the investigation was to evaluate the benefits of the latex allergy countermeasures that were taken in our hospital, and the effects of life guidance education.

Methods: We investigated 16 latex-allergic HCWs in our hospital. We gave them a detailed questionnaire and tested them by a skin prick test (SPT) with latex extract and specific IgE antibodies against latex using the Pharmacia CAP RAST system, RAST FEIA. We compared these results with earlier results from the time of diagnosis.

Results: According to the questionnaire, none of the HCWs had changed their work habits, though all were avoiding the use of latex products as much as possible. Of the 16 patients, 81.2% were eating foods for which cross reactivity with latex has been reported. However, the foods had not induced severe allergic symptoms. In the SPT, 62.5% of scores decreased and 81.2% of patients had decreases in specific IgE antibody levels.

Conclusions: After avoiding latex products and following our educational suggestions, the patients' allergy symptoms had generally improved. This indicates that our countermeasures against latex allergy were largely successful.

KEY WORDS

follow-up study, health care workers, latex allergy, latex gloves, skin prick test

INTRODUCTION

Immediate allergy to natural rubber latex (NRL) in health care workers (HCWs) is a well-known problem. Between 3% and 17% of HCWs have become sensitized to NRL.¹⁻³

Shono reported the first case of contact urticaria in Japan, from NRL gloves, in 1992.⁴ In the following years, reports of latex allergy increased rapidly.^{5,6} To improve natural rubber products, medical institutions and rubber producing companies cooperated, and the Japanese Society of Latex Allergy and the Latex Allergy Forum were established in Japan. These groups began educating the public about latex allergy, and due to the success of their activities, there have been no latex allergy-related deaths in Japan. Even when compared with Europe and the United States, the results in Japan suggest that the response was prompt

and effective. We first encountered a case with latex allergy in our hospital in 1995, after which such cases increased in frequency. In light of this, we began educational activities regarding latex allergy and replaced the hospital's powdered gloves with low-allergenic latex or non-latex gloves. As a result, no new latex allergy patients have appeared among the HCWs in our hospital since June 2001. Thus, we consider our educational activities successful. The aim of this follow-up study was to evaluate the outcome of our activities using a questionnaire and by performing a skin prick test to measure latex-specific IgE antibodies.

DIAGNOSIS OF NRL SENSITIZATION

Diagnosis of NRL sensitization was based on compatible symptoms, a history of exposure to NRL products, and a positive SPT using latex extract. The clini-

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Table 1 List of 16 cases with latex allergy

case	sex	age	occupation	history of allergic disease	time interval (years)	severity (Stage ⁹)	clinical symptoms from latex product	food allergy	the results of SPT in food allergy	IgE RIST (U/MI)
1	M	24	Ns of general ward	(-)	7	4	anaphylaxis from latex allergy	negative	NT	78
2	M	33	Ns of general ward	AR	2	4	anaphylaxis from latex allergy	negative	NT	139
3	F	26	Ns of ICU	AD, AR, asthma	7	3	dyspnea and systemic urticaria	anaphylaxis from chestnut	positive	900
4	F	25	Ns of ICU	AD, AR, AC, asthma	7	3	dyspnea and systemic urticaria	anaphylaxis from chestnut	positive	320
5	F	24	Ns of general ward	AD, AR, AC, asthma	6	3	dyspnea and systemic urticaria	negative	NT	13500
6	F	23	Ns of general ward	AD, AR	5	3	dyspnea and systemic urticaria	negative	NT	3400
7	F	26	Ns of general ward	(-)	5	2	contact urticaria	systemic urticaria and dyspnea from buckwheat	positive	21
8	F	27	Ns of operating room	(-)	5	2	contact urticaria	systemic urticaria from kiwi	positive	93
9	F	26	dermatologist	AD	4	2	contact urticaria	OAS from kiwi	NT	469
10	F	26	medical laboratory technician	AD, AR, AC	6	1	contact urticaria	negative	NT	4089
11	F	23	Ns of general ward	AD	2	1	contact urticaria	negative	NT	1020
12	M	23	physician	AD, AR	5	1	contact urticaria	OAS from bamboo shoot, apple, melon, water melon	positive	2000
13	F	23	Ns of general ward	AR	2	1	contact urticaria	negative	NT	87.8
14	F	25	Ns of general ward	(-)	3	1	contact urticaria	negative	NT	50
15	F	38	helper	AR, AC	2	1	contact urticaria	negative	NT	135
16	F	47	dermatologist	urticaria	7	1	contact urticaria	OAS from kiwi	NT	27.3

Ns: nurse, AD: atopic dermatitis, AR: allergic rhinitis, AC: allergic conjunctivitis, OAS: oral allergy symptoms, NT: not tested.

cal symptoms of latex allergy range from more minor indications such as contact urticaria, eye symptoms, facial edema and generalized urticaria, rhinitis, and asthma, to severe symptoms like anaphylactic shock.^{7,8} We classified the degrees of symptoms in four groups, Stages 1–4, according to the classification of contact urticaria syndrome described by Krough and Maibach.⁹ The stage descriptions were as follows: Stage 1, localized urticaria, dermatitis, nonspecific symptoms, itching, tingling, burning, etc.; Stage 2, general urticaria and extracutaneous reactions; Stage 3, bronchial asthma, rhinoconjunctivitis, orolaryngeal symptoms, and gastrointestinal symptoms; and Stage 4, anaphylactic reactions. An SPT was considered positive when the wheal diameter was at least 3 mm and the negative control was zero. All patients were informed of the hazards of latex allergy and instructed on preventative measures. We gave patients a list of latex-containing products used in the hospital and in daily life, and possible latex-free replacements. Finally, we instructed them to avoid

foods that are cross-reactive with latex, as reported by Blanco.¹⁰

SUBJECTS AND TEST PERIOD (Table 1)

We studied 16 latex-allergic HCWs from our university hospital. They were given diagnoses of latex allergy between 1998 and 2001, and we conducted all parts of the follow-up study (questionnaire, SPT, and blood test) in July 2003.

METHODS

INVESTIGATION QUESTIONNAIRE

The questionnaire included questions regarding the patients' workplaces and hand eczema. Other questions asked about current allergic disease complications, latex products they had touched, and the symptoms that appeared after contacting the latex products. Patients were asked about their intake of the fruits involved in latex fruit syndrome and whether they had experienced reactions. In addition, patients responded about the clinical symptoms that ap-

Table 2 Follow-up questionnaire results among 16 health care workers in comparison with diagnosis time

case	allergic symptoms at diagnosis	getting allergic symptoms at follow-up	hand eczema at diagnosis	hand eczema at follow-up	change of work place	contact of latex products	present symptoms from latex products	existence of intake in fruits	existence of allergic symptoms
1	negative	AR, AC	negative	slight HE (untreated)	NC	latex glove, rubber band	contact urticaria	intook almost fruits	negative
2	AR	AR	severe HE	negative	NC	rubber band, dice bag	negative	intook almost fruits	negative
3	AD, AR, asthma	AD, AR, asthma	severe HE	severe HE (untreated)	NC	condom	contact urticaria	tomato	negative
4	AD, AR, AC, asthma	AD, AR, AC, asthma	severe HE	negative	NC	rubber band, dice bag	negative	kiwi, tomato, peach, grapefruit	negative
5	AD, AR, AC, asthma	AD, AR, AC, asthma	severe HE	slight HE (treated)	NC	rubber band	negative	negative	negative
6	AD, AR	AD, AR	severe HE	negative	NC	rubber band	negative	banana, kiwi, chestnut, tomato, peach, grapefruit	negative
7	negative	negative	severe HE	negative	NC	rubber band	negative	banana, kiwi, chestnut, tomato, peach	negative
8	negative	negative	slight HE	slight HE (untreated)	NC	rubber band	negative	negative	negative
9	AD	AD	slight HE	negative	NC	latex gloves, rubber band	contact urticaria	banana, chestnut, tomato, peach, grapefruit	negative
10	AD, AR, AC	AD, AR, AC	slight HE	slight HE (untreated)	NC	rubber band, dice bag	negative	tomato, peach	negative
11	AD	AD	slight HE	negative	NC	rubber band	negative	banana, tomato, peach, grapefruit	OAS from tomato and grapefruit
12	AD, AR	AD, AR	slight HE	negative	NC	rubber band	negative	negative	negative
13	AR	AR	negative	negative	NC	rubber band	negative	banana, chestnut, tomato, grapefruit	OAS from grapefruit
14	negative	negative	negative	negative	NC	negative	negative	intook almost fruits	negative
15	AR, AC	AR, AC, contact dermatitis	slight HE	negative	NC	rubber band	negative	tomato	mouth edema from tomato
16	urticaria	urticaria	negative	negative	NC	negative	negative	banana, chestnut, tomato, peach, grapefruit, avocado	negative

AD: atopic dermatitis, AR: allergic rhinitis, AC: allergic conjunctivitis, HE: hand eczema, NC: not change, OAS: oral allergy symptoms.

peared, their concerns regarding latex allergy, and the most difficult parts of coping with daily life.

SKIN PRICK TEST

An extract from the sap of *Hevea brasiliensis*, clone RRIM 600, obtained from the Rubber Research Institute of Malaysia, Kuala Lumpur, Malaysia, was provided by the Japanese Latex Allergy Forum. The primary extract solution was 6.5 mg/ml, and it was diluted 1 : 10, 1 : 100, or 1 : 1000 into sterile physiologic saline (PS). One drop of the diluted solution was applied to the skin of the forearm, which was then

pierced with a lancet (Prick-Lancetter, Ewo Care AB, Sweden). The drops were wiped off with a paper towel, and the test was evaluated 15 minutes later. A wheal half the size of or larger than that caused by histamine dihydrochloride (10 mg/ml) was considered a positive reaction. PS was used as a negative control, and the scores were assigned as follows: 2+, between half to the same size (as that caused by histamine); 3+, the same size; and 4+, a larger size. Scores of 2+ or greater were considered positive.

Table 3-1 Changes of SPT scores from 1998 (–2001) to 2003

		2003				
	(n)	score 0	score 1	score 2	score 3	score 4
1998 – 2001	score 0	1				
	score 1					
	score 2		2	3		
	score 3			4		1
	score 4			1	2	2

Lower-left half shows patients with a decrease of SPT score, Upper-right half shows those with an increase of at least one SPT score.
n = number of patients.

Table 3-2 Changes of latex specific IgE-classes (Pharmacia CAP FEIA) from 1998 (–2001) to 2003

		2003						
	(n)	class 0	class 1	class 2	class 3	class 4	class 5	class 6
1998 – 2001	class 0	1						
	class 1			1				
	class 2	3	1	4				
	class 3			2	1			
	class 4				2			
	class 5			1				
	class 6							

Lower-left half shows patients with a decrease of specific IgE-class, Upper-right half shows those with an increase of at least one specific IgE-class.

n = number of patients. Specific IgE-classes: 0–0.35kU/L = class 0, 0.36–0.70 = class 1, 0.71–3.5 = class 2, 3.6–17.5 = class 3, 17.6–50 = class 4, 50.1– = class 5, > 100 = class 6.

SERUM SPECIFIC IgE

Laboratory tests included measurements of serum IgE specific for latex or certain foods (CAP FEIA) under standardized conditions, according to the manufacturer's instructions. The obtained values ranged from classes 1 to 6.¹¹ IgE levels ≥ 0.70 IU/mL (Class 2) were considered positive.

STATISTICS

Changes of latex-specific IgE and SPT score in correlation to the extent of latex-avoidance were analyzed using contingency tables and Wilcoxon rank sum-test was used (SPSS II for Windows). A *P*-value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS

SUBJECTS' CHARACTERISTICS AND QUESTIONNAIRE RESULTS (Table 2)

The study group consisted of 3 men and 13 women (mean age, 27.4; range, 23–52), with a mean follow-up time of 4.68 years. None of the subjects had changed departments or job titles. At the time of follow-up, 11 subjects worked as nurses in the general administration unit, one was a dialysis laboratory technician, and one was a nursing assistant in the general ward.

Two were dermatologists, and one was an internist. None of the subjects had resigned or retired from work, though 68.7% (11/16) had hand eczema at the time of diagnosis. The severe cases (with eczema across the entirety of both hands) had made up 54.5% (6/11) of the subjects, but only five subjects had slight hand eczema at the time of follow-up. Only one patient had complications of other allergic symptoms after the diagnosis; he was in stage 4, as classified by the degree of his symptoms, and showed no other allergic symptoms at the time of diagnosis. After diagnosis, he developed allergic rhinitis and allergic conjunctivitis.

After diagnosis, all the subjects tried to stop using latex products in their workplaces and homes. Fourteen subjects, however, used latex products in the workplace, and of these, four were experiencing clinical symptoms. These subjects had used latex gloves and/or condoms, and their symptoms were localized contact urticaria. These symptoms appeared before March 2000, which was when we changed the gloves in the hospital. Although thirteen patients had used rubber bands, they did not cause allergic symptoms. Thirteen of the 16 (81.2%) patients had eaten fruits related to latex-fruit syndrome; oral symptoms appeared in three patients after they ate tomatoes or

grapefruits, and they were classified as Stage 1. Ten of the sixteen (62.5%) patients ate bananas, kiwis, avocados, or chestnuts; these fruits are thought to have frequent and significant associations with latex fruit syndrome.¹⁰ In these cases, however, no allergic symptoms appeared.

RESULTS OF THE SPT (Table 3-1)

At follow-up, the SPT scores of 10 patients had decreased (patients from Stage 4, 1; Stage 3, 2; Stage 2, 2; and Stage 1, 5; according to the classification of contact urticaria syndrome).⁹ The scores from five patients did not change (Stage 4, 1; Stage 3, 2; Stage 1, 2), while the score of one patient (the doctor with atopic dermatitis) rose. SPT scores were significantly decreased in the follow up study compared to those of the first study ($P < 0.05$).

RESULTS OF LATEX-SPECIFIC IgE ANTIBODY DETECTION (Table 3-2)

The antibody values for 81.2% (13/16) of the subjects decreased, and that of one subject was below the limit of detection. Two subjects' antibody values increased (Stage 4, 1; Stage 1, 1). The classes of latex-specific IgE were significantly decreased in the follow up study compared to those of the first study ($P < 0.05$).

DISCUSSION

Our hospital's first case of latex allergy occurred in 1995, and 89 cases were seen from 1995 to the present. Sixty of these subjects were hospital HCWs. Beginning in 1997, we attempted to prevent new allergy occurrences and latex-related medical accidents by the following methods:

- 1) We examined the prevalence of latex allergy in nurses deemed at "high-risk" in our hospital (1997).¹²
- 2) We changed the hospital-issued powdered surgical and examination latex gloves to powder-free latex gloves (2000).
- 3) We held informational seminars about latex allergy for HCWs in the dental center and in the emergency and operating rooms, which have also been deemed high-risk groups (2001).
- 4) We conducted a survey of awareness and the current state of latex allergy in all HCWs at our hospital (2001).¹³

As a result, we diagnosed no new latex allergy cases in our hospital after June 2001. In addition, as mentioned above, we provided lifestyle guidance and other suggestions to the diagnosed patients. We have handed the explanation card about latex allergy to all patients and taught them to always carry it. In the card, it shows that 1) on what symptom the diagnosis of latex allergy was based, 2) the typical clinical symptoms and the danger of anaphylaxis of latex allergy, 3) steps to take when symptoms appeared, 4) information about natural rubber products causing la-

tex allergy, 5) substitute product information, 6) information about the latex-fruit syndrome and the food which they should be careful about, 7) the homepage addresses about latex allergy, 8) methods to communicate with us. Subsequently, severe allergic symptoms have not been seen in these patients.

The current study was intended to evaluate the efficacy of the above studies and lifestyle guidance.¹⁴⁻²⁰ We conducted a follow-up survey of the latex-allergic HCWs; previously, no follow-up studies of latex allergy patients had ever been published in Japan.

According to the results of the questionnaire, all the patients had continued their work. All had attempted to avoid latex products, and in doing so were free of severe, immediate allergy symptoms. Ten patients had used rubber bands and ice bags but did not experience any allergy symptoms. Because these products are relatively hydrophobic, we speculated that they do not release the latex antigen. In another case, Turjanmaa *et al.* replaced powdered gloves with powder-free gloves, which reduced the rate of latex-related hand eczema in HCWs from 54% to 38%.¹⁹ Similarly, 90.9% of our patients reported an improvement or cure of hand eczema. How could the HCWs with latex allergy continue working in the same medical units?

Turjanmaa *et al.* did a follow-up survey of 71 HCWs with latex allergy and reported that no patients had retired or otherwise stopped working due to latex allergy.¹⁹ They suggested, therefore, that the use of low-allergen or non-latex gloves throughout the health care industry seemed an adequate step to protect HCWs with natural rubber latex allergy. In addition, Levy *et al.* reported that the use of these gloves also prevented latex allergy in dental students.²¹ In 1997, the surgical gloves used in our hospital contained 758 µg/g latex protein, which is a relatively high latex content. We surmised that the number of latex allergy patients had increased because HCWs used these gloves frequently. Up to 17% of HCWs had become sensitized to NRL, and most had an occupational allergy to NRL.^{1,2} Akita *et al.* examined the conditions of 88 nurses working in the emergency and operating rooms in 1999, and diagnosed latex allergy in 6.8% (6/88) of the nurses.¹² Their incidence rate was similar to those described in the previous reports.¹⁻³

In 2000, our hospital began issuing low-allergen and powder-free gloves instead of powdered gloves. Hamilton *et al.* reported that in situations where powdered latex gloves are used in close proximity to other medical staff, personal avoidance might be insufficient to prevent latex sensitization.¹⁵ In 2001, we found that latex was also present in medical tools, though the majority of medical tools were latex-free. After this finding, HCWs were instructed on how to select latex-free medical tools, which also decreased the latex exposure of patients. After trials of these

new guidelines and tools, the number of HCWs sensitized to latex was reduced; indeed, we have not diagnosed an HCW with latex allergy since June 2001. In April 2001, Kano *et al.* investigated latex allergy in all HCWs ($n = 1512$) in our hospital.¹³ Using questionnaires and SPTs, they concluded that 44 people (3.3%) were affected by latex allergy. This rate was lower than those described in other reports, so we concluded that our countermeasures had been effective.

We performed both the skin prick test and CAP FEIA measurements to evaluate the levels of latex-specific IgE antibodies in our patients. The sensitivity of CAP FEIA is reportedly 23–83%,²² thus we consider the SPT more useful. The total SPT scores of 62.5% (10/16) of patients had decreased. Hamilton *et al.* also reported a decrease in skin sensitivity, as evaluated by the lowest concentration of latex allergen applied in the SPT that produced a positive wheal and erythema, in 30% of sensitized subjects originally given a diagnosis of latex allergy.¹⁵ Nettis *et al.* reported that 93.3% of patients showed at least a 10-fold reduction in SPT reactions with glove elute,⁶ and a decrease of the mean SPT diameter when using commercial extract, in comparison to tests during the original latex allergy diagnosis.²⁰ In our study, however, 1 of the 16 patients showed an increased response to the SPT. This case had sometimes used latex gloves, so we hypothesized that the increase was due to continued contact with latex products. We also measured latex-specific IgE antibody levels; latex-specific IgE antibody levels have decreased in 81.2% (13/16) of patients thus far. Similarly, after Hamilton *et al.* changed the gloves in medical workplaces to gloves made of plastic and nitrile, the quantity of latex-specific IgE antibodies declined in 14 of 16 doctors over a period of 10–15 months.¹

Based on these results, we concluded that SPT reactions and latex-specific IgE antibody levels had declined after the reduction of exposure to latex in the workplace and daily life.

Latex-fruit syndrome is induced due to the cross reactivity of latex and food antigens.¹⁰ Most of the major antigens related to the cross reactivity are members of a group of defense-related proteins.²³ At the time of diagnosis in our investigation, 43.7% (7/16) of patients had complained that certain foods caused a feeling of urticaria in the mouth. Of these patients, 57% (4/7) had positive reactions to the original SPTs. As part of our study, we provided patients with a list of fruits for which cross reactivity had been reported.¹⁰ Likewise, we suggested that they stop eating bananas, chestnuts, avocados, and kiwis, which tend to induce severe symptoms of cross-reactivity. In our current questionnaire, however, 81.2% (13/16) of patients stated that they had since eaten these fruits. Ten of the subjects had eaten bananas and kiwis without immediate allergy symptoms. For obvious rea-

sons, it is difficult to restrict patients' food intake. However, we concluded that the cross-reactivity with foods decreases along with the overall decrease in latex antigen exposure.

This study, a follow-up survey of latex allergy patients after education and the reduction of workplace latex exposure, is apparently the first of its kind in Japan. The patients' allergy symptoms decreased from their pre-diagnosis levels, and the results of the SPTs and latex-specific IgE antibody evaluations were also encouraging. We therefore conclude that our countermeasures have been successful thus far, and recommend that such educational activities continue in the future.

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