*Allergology International. 2009;58:***-***
DOI: 10.2332/allergolint.08-OA-0046

ORIGINAL ARTICLE

Hev b 6.02 Is the Most Important Allergen in Health Care Workers Sensitized Occupationally by Natural Rubber Latex Gloves

Akiko Yagami[1,2], Kayoko Suzuki[2], Hirohisa Saito[1] and Kayoko Matsunaga[2]

ABSTRACT

Background: Natural rubber latex (NRL) allergy is a common occupational disease in health care workers (HCW). However, few reports have compared the major allergen of HCWs to those in gloves that are routinely used in the hospital. The aim of this study was to evaluate the major NRL allergens in gloves used by HCWs.

Methods: We studied 20 HCWs who were suspected to have latex allergy (LA). We performed a skin prick test (SPT) using NRL allergens. Serological testing was performed using the ImmunoCAP™. The total amount of protein and the antigenic protein concentrations extracted from NRL gloves were measured. Four different types of FITkit™ were used to measure the concentrations of Hev b 1, 3, 5, and 6.02 in the gloves.

Results: A SPT using NRL extract identified 14 cases with positive reactions. The sensitivity and specificity of the SPT scores to the NRL glove extract were 100%. The sensitivity of latex specific IgE was 100% but the specificity was 14.2%. The sensitivity and specificity of rHev b 6.02 specific IgE were 100% in the LA group. The total amounts of protein from the medical gloves for surgery and examination were 265 μg/g and 95 μg/g, respectively. The antigenic protein concentrations in the gloves were 24.9 μg/g and 1.0 μg/g, respectively. The total amounts of the specific four allergens in the NRL gloves were 2.18 μg/g and 0.45 μg/g, respectively.

Conclusions: We concluded that the main allergen of HCWs who have been sensitized occupationally by NRL gloves was Hev b 6.02.

KEY WORDS

allergen, health care workers, latex allergy, latex gloves, skin prick test

INTRODUCTION

Type I 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] In February 2006, the WHO/IUIS Allergen Nomenclature Committee (www.allergens.org) listed 13 NRL Hev b allergens as molecularly characterized proteins.[4-13] Among children with latex allergy (LA), who is often associated with spina bifida (SB), hydrophobic proteins bound to rubber particles, such as Hev b 1 (rubber elongation factor) and Hev b 3 (small rubber particle protein), have been reported to be very important allergens.[4,14] On the other hand, in HCWs with LA, hydrophilic proteins, such as Hev b 5 (acidic latex protein) and Hev b 6.02 (hevein), have been reported to be important allergens.[7,15] Such differences are attributed to different routes of allergen exposure and different amounts of major allergic proteins eluted from the causable products in these patient groups. In most children with LA, sensitization and induction of LA may occur by direct contact of the internal mucosa with NRL products during surgery to treat SB or congenital disorders, which is repeated many times after birth, or catheterization for the maintenance of excretion routes.[14,15] On the

[1]Department of Allergy and Immunology, National Research Institute for Child Health & Development, Tokyo and [2]Department of Dermatology, Fujita Health University School of Medicine, Aichi, Japan.
Correspondence: Akiko Yagami, Department of Allergy and Immunology, National Research Institute for Child Health & Development, 2–10–1 Okura, Setagaya-ku, Tokyo 157–8535, Japan.
Email: ayagami@nch.go.jp
Received 16 September 2008. Accepted for publication 8 January 2009.
©2009 Japanese Society of Allergology

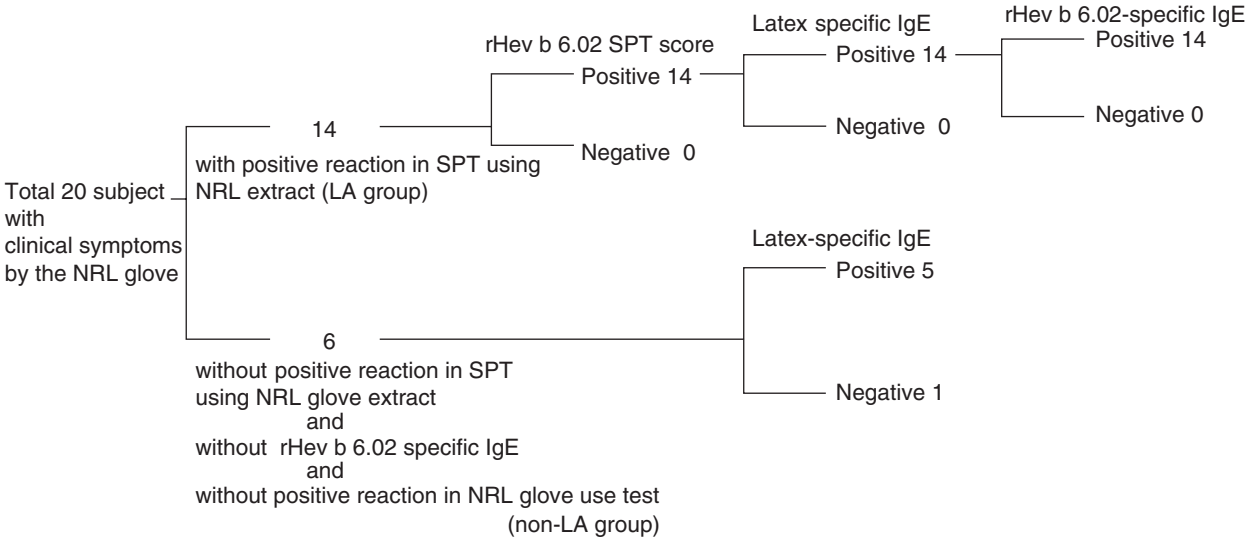

Fig. 1 Subjects.

other hand, in HCWs with LA, sensitization and induction of LA may mainly occur by skin contact, such as wearing NRL gloves or by inhaling latex aeroallergens, such as allergic protein-adsorbed powder.[16-18] No studies have examined the amount of allergic proteins eluted from commercially available NRL products in Japan. The aims of this study were to characterize the major allergens in HCWs occupationally sensitized to latex in and to clarify the difference with the LA observed in children often complicated by SB.

METHODS

SUBJECTS

We studied 20 HCWs at the Fujita Health University Hospital (Aichi, Japan) in the 1990s who were suspected to have LA. These workers had used the same types of surgical and examination NRL gloves. We performed the skin prick test (SPT) using NRL glove extract, and used these test results to divide the HCWs into allergen-positive and -negative groups (LA group and non-LA group, respectively). The study group consisted of three males and 17 females (mean age, 29.3 years; range, 23–46 years). With regard to the clinical symptoms of LA, three patients had anaphylaxis, three had respiratory symptoms and urticaria, three had generalized urticaria and five had contact urticaria. The LA clinical symptoms ranged from minor indications such as contact urticaria, eye symptoms, facial edema, generalized urticaria, rhinitis, and asthma, to more severe symptoms such as anaphylactic shock. We classified the degree of symptoms into four groups, Stages 1–4, according to the classification of the contact urticaria syndrome described by Krough and Maibach.[19] 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, rhino conjunctivitis, pharyngeal larynx symptoms, and gastrointestinal symptoms; and Stage 4, anaphylactic shock. In the LA group, three patients were Stage 4, three were Stage 3, three were Stage 2, and five were Stage 1 (Fig. 1, Table 1, 2). At the time of diagnosis, five subjects worked as nurses in the intensive care unit or the operating room, nine worked as nurses in the general ward, two were medical technicians, two were nursing assistants in the general ward, and two were doctors. Twelve out of the 20 subjects (60.0%) had complications from other allergic diseases such as atopic dermatitis (AD), allergic rhinitis (AR), allergic conjunctivitis (AC), and bronchial asthma (BA). Three subjects had AD, AR, and BA, two had AD and AR, four had only AD, three had only AR, and one had BA. HCWs were diagnosed with NRL sensitization based on positive SPT results with NRL glove extract or a positive NRL glove use test and clinical symptoms compatible with NRL glove use.

SKIN TEST

SPT

We made extracts from NRL gloves that HCWs had used in the 1990s following the method of Turjanmaa *et al.*[20] and purchased recombinant (r) allergens (rHev b 1, 3, 5, 6.02, 8, 9, and 11) from BIOMAY, Vienna, Austria. The allergens were diluted to 100 μg/ml in distilled water. As for quality control, all materials were stored at −20℃ to avoid repeat freezing/thawing.

One drop of the diluted solution was applied to the skin on the forearm, which was then pierced with a lancet (PRICK-LANCETTER, Ewo Care AB, Sweden).[20,21] The drops were removed with a paper towel, and the test was evaluated 15 minutes later. A wheal at least half the size of that caused by hista-

Table 1 List of 14 cases with latex allergy

Case No	Sex	Age	Occupation	Clinical symptoms by LA	Severity stage of contact urticaria syndrome by LA	Personal allergic history	IgE RIST (IU/ml)	Latex SPT score	rHev b6.02 SPT score	Latex specific IgE (UA/ml)	rHev b6.02 specific IgE (UA/ml)
1	M	24	Ns of operating room	anaphylaxis	4	AR	78	4	4	1.28	7.32
2	F	23	Ns of ICU	anaphylaxis	4	(−)	203	4	4	11.4	5.96
3	F	45	Ns of operating room	anaphylaxis	4	(−)	130	4	4	1.3	10.40
4	F	25	Ns of ICU	respiratory symptoms and urticaria	3	AD, AR, asthma	320	4	4	13.1	13.90
5	F	26	Ns of ICU	respiratory symptoms and urticaria	3	AD, AR, asthma	900	4	4	53.7	42.50
6	F	23	Ns of general ward	respiratory symptoms and urticaria	3	AD	240	3	3	7.23	5.38
7	F	26	Ns of general ward	generalized urticaria	2	(−)	21	4	4	2.17	8.85
8	F	26	Dermatologist	generalized urticaria	2	AD	469	2	3	3.25	3.53
9	F	27	Ns of general ward	generalized urticaria	2	(−)	93	2	2	3.03	4.48
10	F	30	Medical laboratory technician	contact urticaria	1	AD, AR, asthma	712	3	3	21.3	14.90
11	F	26	Medical laboratory technician	contact urticaria	1	AD	4089	3	4	25.4	20.50
12	F	37	Medical assistant	contact urticaria	1	AD	3880	1	3	14.3	24.60
13	F	41	Ns of general ward	contact urticaria	1	Asthma, SB	39.2	1	3	3.66	1.19
14	F	25	Ns of general ward	contact urticaria	1	(−)	1620	4	2	38.9	3.25

ICU, intensive care unit; Ns, nurse; AD, atopic dermatitis; AR, allergic rhinitis; SB, spina bifida.

Table 2 List of 6 cases without latex allergy

Case No	Sex	Age	Occupation	Personal allergic history	IgE RIST (IU/ml)	Latex skin prick test score	rHev b6.02 skin prick test score	NRL glove use test	Latex specific IgE (UA/ml)	rHev b6.02 specific IgE (UA/ml)
1	F	23	Ns of general ward	AD, AR	1020	negative	ND	negative	0.77	< 0.35
2	F	23	Ns of general ward	AR	87.8	negative	ND	negative	0	< 0.35
3	M	23	Ns of general ward	AD, AR	250	negative	ND	negative	3.01	< 0.35
4	F	38	Medical assistant	AR	135	negative	ND	negative	2.01	< 0.35
5	F	32	Ns of general ward	(−)	78	negative	ND	negative	1.51	< 0.35
6	M	43	Radiologist	(−)	1100	negative	ND	negative	4.22	< 0.35

ND, Not done.

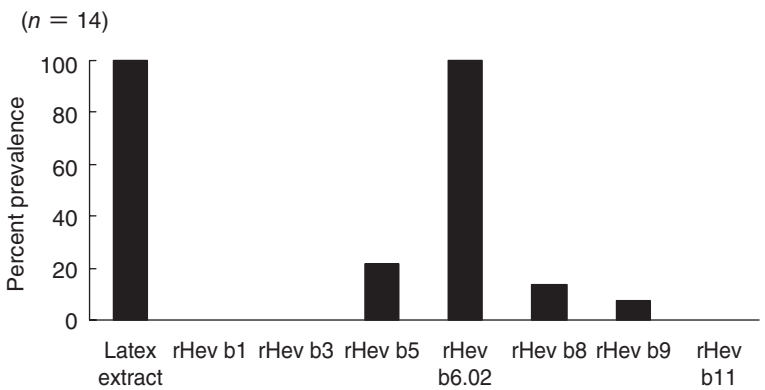

Fig. 2 Prevalence percent of LA group exhibiting positive SPT responses to *Hevea brasiliensis* proteins.

mine 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.

NRL Glove Use Test

The subject who showed a negative reaction in SPTs wore a NRL glove on one finger, which was wetted with water, and a control chloroprene glove on the opposite finger for 15 minutes.[20,21] If subjects showed no symptoms, they wore the NRL glove on the whole hand and the chloroprene glove on the opposite hand.

IMMUNOGLOBULIN E ANTIBODY ANALYSES

Serological testing was performed using the ImmunoCAP™ system (Phadia, Uppsala, Sweden). All sera were analyzed for latex specific IgE. The LA group was analyzed with rHev b 1, 3, 5, 6.01, 6.02, 8, 9, and 11.

The values obtained ranged from Classes 1 to 6. IgE levels more than 0.70 IU/ml (Class 2) were considered positive.

GLOVE ANALYSIS

Glove Collection

The Fujita Health University provided two brands of medical gloves for surgery and examinations used in the 1990s. The surgical glove was a powdered one (Micro-Touch Surgical Gloves, Johnson & Johnson, NJ, USA), and the examination glove was a non powdered one (Glovex Eco Latex Exam Gloves, Termo Beiersdorf, Tokyo, Japan).

Extraction of Latex Allergens

The NRL gloves were cut into small pieces which were mixed carefully. Subsequently, 1 g of the mixture was weighed and extracted in 5 ml of phosphate-buffered saline, pH 7.2.

Measurements of Total Amounts of Proteins and Allergens

The total amount of protein in each extract was measured by the ASTM D5712-95 method (modified Lowry method), and the antigenic protein concentra-

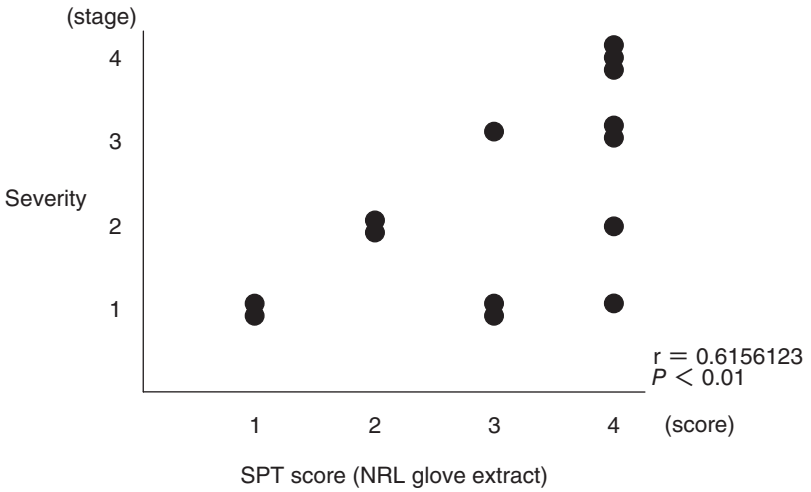

Fig. 3 The correlation of the severity and SPT scores of NRL glove extract in LA group.

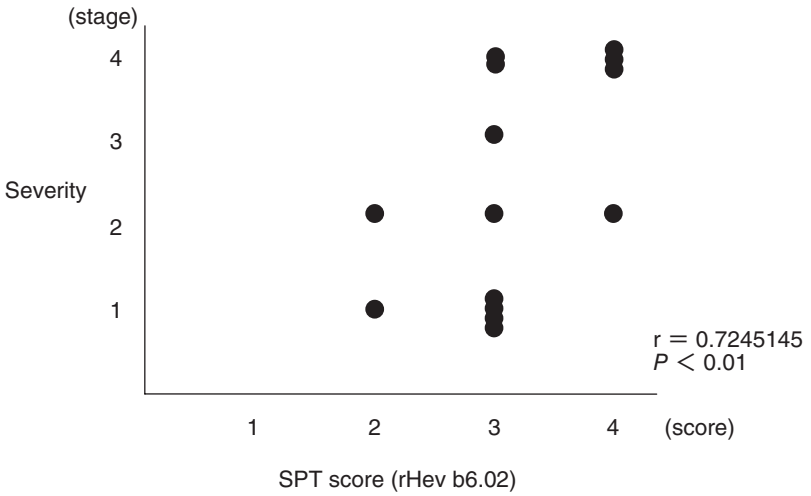

Fig. 4 The correlation of the severity and SPT scores of rHev b 6.02 in LA group.

tion was measured by the ASTM D6499-00 method (ELISA inhibition assay).[22]

Quantification of Individual Allergens

Four different allergens with FITkit™ (FIT Biotech Ltd, Tampere, Finland) were used to measure the concentrations of Hev b 1, Hev b 3, Hev b 5 and Hev b 6.02 in the NRL glove extracts.[23] The detection limits of FITkit™ for allergens are as follows: Hev b 1, 50 ng/g; Hev b 3, 50 ng/g; Hev b 5, 25 ng/g; Hev b 6.02, 25 ng/g. Values below these detection limits were denoted as zero. The sum of the four allergens in the NRL glove extracts was denoted as the allergen sum (μg/g).

STATISTICS

Fisher's exact test was performed to examine the sensitivity and specificity of the SPT score and serum specific IgE analysis.

The correlation between individual SPT scores or the serum IgE antibody levels and the severities of the LA group was assessed by a non-parametric Spearman's r-test.

ETHICAL CONSIDERATION

We obtained informed consent from each subject to perform the examination and to publish the final results.

RESULTS

First, we performed a SPT on 20 subjects using NRL extract and identified 14 cases with positive reactions and six cases with negative reactions. Then, we performed a SPT using recombinant allergens in the 14 cases that reacted positively to the NRL extract.

Table 3 Allergen levels of different brands of NRL gloves

	Type of glove	Manu-facturing time	Powderd or Non powdered	Total amount of proteins (μg/g)	Antigenic protein concentration (μg/g)	Hev b 1 (μg/g)	Hev b 3 (μg/g)	Hev b 5 (μg/g)	Hev b 6.02 (μg/g)
Johnson & Johnson	Micro-Touch Surgical Gloves	1996	Powderd	265	24.9	ND	ND	0.03	2.15
Termo Beiersdorf	Glovex Eco Latex Exam Gloves	1998	Non powdered	95	1.0	ND	ND	0.22	0.23

ND, not detected.

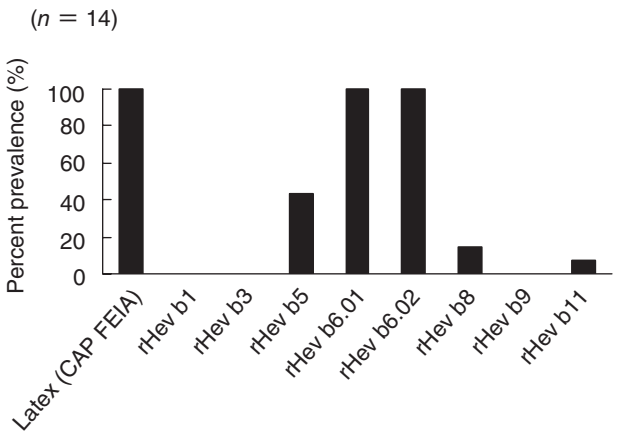

Fig. 5 Prevalence percent of LA group exhibiting positive specific IgE responses to *Hevea brasiliensis* proteins.

In the SPT-negative subjects, we performed the glove use test.

SKIN TEST RESULTS

SPT Results

The sensitivity and specificity of the SPT scores to the NRL glove extract were 100%. The positive ratios of SPT for latex extract and rHev b 6.02 in the LA group were 100%, while those for rHev b 5, rHev b 8, and rHev b 9 were 21.4 %, 13.3 %, and 7.1 %, respectively. rHev b 1, 3, and 11 were all negative in the LA group (Fig. 2). There were significant correlations between the severity stage and the SPT scores for the NRL glove extract or rHev b 6.02 in the LA group (Spearman's rank correlation coefficient; r = 0.615; $P < 0.01$ and r = 0.724; $P < 0.01$, respectively) (Fig. 3, 4).

Glove Use Test Results

We performed a glove use test in the six cases with a negative SPT reaction to NRL gloves. All of them reacted negatively in the use test (Fig. 1, Table 2).

SERUM SPECIFIC IgE RESULTS

The sensitivity of latex specific IgE was 100%, whereas the specificity was 14.2%. The latex specific IgEs were not significantly different in the LA group compared to the non-LA group (Table 1, 2). The positive ratios of serum specific IgE for latex, rHev b 6.01, and 6.02 in the LA group were 100%, while those for rHev b 5, rHev b 8, and rHev b 11 were 42.8%, 14.2%, and 7.1%, respectively (Fig. 5). rHev b 6.02 specific IgE had the highest frequency of positive reaction in comparison with the other allergen proteins in HCWs.

There were no significant correlations between the severity stages and serum specific IgEs against latex or rHev b 6.02 in the LA group.

GLOVE ANALYSIS RESULTS

The results of the total protein, antigenic protein concentration, and each specific NRL glove allergen are summarized in Table 3.

1. The total amounts of protein of the surgery and examination NRL gloves were 265 μg/g and 95 μg/g, respectively.

2. The antigenic protein concentrations of the surgery and examination NRL gloves were 24.9 μg/g and 1.0 μg/g, respectively.

3. The total amounts of the four specific allergens in the surgery and examination NRL gloves were 2.18 μg/g and 0.45 μg/g, respectively.

DISCUSSION

As in other western countries, in Japan the number of LA patients increased rapidly from 1990 to 2000.[24-29] In Japan, various preventative procedures were quickly implemented, such as low-protein processing of NRL products, developing NRL free products, and creating LA guidelines, and as a result, the prevalence of LA has been decreasing.[29] However preventative procedures for HCWs with LA have not been well-established.

We believe that it is important to identify the source allergens by serologic and skin tests and to examine the amount of protein allergens in NRL

products. The results will provide a better understanding of the features of LA in Japan and find the most efficient diagnostic procedures for diagnosis of LA in HCWs. It was previously reported that HCWs with LA were sensitized to LA by contact with NRL products, such as NRL gloves, or inhalation of air borne NRL allergens.[16-18] Although it was reported that HCWs with LA were mainly sensitized by NRL gloves, no report has examined whether Japanese HCWs are sensitized to the main extracted allergens in NRL gloves. In this study, we examined 20 HCWs who had worked at the Fujita Health University Hospital in the 1990s and used the same NRL glove brands. Although they worked in different hospital settings, they used the same brands of NRL gloves in the hospital. Therefore, we considered that these HCWs had been sensitized to the same allergens in NRL gloves.

The purpose of this study was to investigate the sensitized allergens of these patients. First, we performed a SPT with NRL glove extract in 20 HCWs who had clinical symptoms, such as itchiness and erythema, due to wearing NRL gloves at the Fujita Health University Hospital in the 1990s. From the results, we identified 14 cases as the LA group and six cases as the non-LA group. We considered that the symptoms associated with NRL gloves in the non-LA group were irritations and dank.

Both the sensitivity and specificity of the SPT with NRL extract in the LA group were 100%. These results were similar to previously published results.[30] We also performed SPTs with recombinant allergens in the LA group. The positive ratios of SPT scores to NRL glove extract, rHev b 6.01, and rHev b 6.02 in the LA group were 100%. There were significant correlations between the severity stages and SPT scores to NRL glove extract or rHev b 6.02 in the LA group (Spearman's rank correlation coefficient; r = 0.615; $P < 0.01$ and r = 0.724; $P < 0.01$, respectively) (Fig. 2, 3). These results suggested that the SPT reflected the clinical symptoms of LA and was a useful tool to diagnose LA. These results also suggested that among the LA allergens, rHev b 6.02 reflected LA clinical symptoms better than NRL extract in the SPT. Bernstein *et al*. performed a SPT with 7 native proteins purified from nonammoniated latex (Hev b 1, 2, 3, 4, 6.01, 7.01, and 13) and rHev b 5 in HCWs.[31] They reported positive ratios of Hev b 2, 5, 6.01, and 13 greater than 60%. Our positive ratio of rHev b 6.01 was consistent with their results. Sussman *et al*. also reported that using a combination of recombinant latex allergens Hev b 5, 6, and 7 could identify LA with 93% sensitivity and 100% specificity.[32] They reported that the results of SPTs using recombinant allergens were comparable to the results of SPTs using NRL extract.

It has been reported that the diagnostic sensitivity of latex specific IgE is 23–83%.[32] ImmunoCAP™, the EIA with fluorescent substrate (FEIA) from Pharmacia Diagnostics, uses a non-ammoniated latex allergen preparation with at least 10 different protein components. Because of the possibility of mistakes in identifying the most responsible antigen, use of recombinant allergens may therefore be of great value. Rihs H-P *et al*. reported the IgE-binding prevalence of the allergens as follows, the prevalence of rHev b 1 for SB was 81%, while HCWs was 52%. The prevalence of rHev b 3 for SB was 76–78%, while HCWs was 13–20%. The prevalence of rHev b 6.02 for HCWs was 75%, while SB was 27%.[33] Based on the these results, we considered that it was useful to measure recombinant allergens of LA in the specific IgE rather than crude LA allergen.

We measured the serum specific IgE for latex and recombinant latex allergens in the LA group ($n = 14$). The positive ratios of serum specific IgE for latex, rHev b 6.01, and 6.02 in the LA group were 100%, while those of rHev b 5, rHev b 8, and rHev b 11 were 42.8%, 14.2%, and 7.1%, respectively. We considered that Hev b 6.02 mainly contributed to LA sensitization. Although five of the six cases in the non-LA group showed positive reactions for latex specific IgE, all cases showed negative reactions for rHev b 6.02 specific IgE. This suggested that false positive reactions occurred with latex specific IgE when using latex extract. In this study, the sensitivity of latex specific IgE was high but the specificity was low, while both the sensitivity and the specificity of rHev b 6.02 specific IgE were high. Therefore, we concluded that rHev b 6.02 specific IgE was more useful than latex specific IgE for diagnosing LA.

When SPT was compared with specific IgE for diagnosis, we considered that SPT with latex allergen was most relevant for diagnosis of LA in HCWs compared to measurement in specific IgE. We have further shown that the accuracy of the examinations would increase by using the recombinant allergen, especially rHev b 6.02, for HCWs with LA. Hamilton *et al*. also reported that in vitro assays possess suboptimal diagnostic sensitivity compared to SPTs in identifying HCWs with LA.[34]

We measured the total amount of proteins and allergens in each NRL glove that had been used in our hospital. The total amounts of proteins were 265 μg/g in the surgery glove and 95 μg/g in the examination glove. The antigenic protein concentrations were 24.9 μg/g and 1.0 μg/g in each respective glove. Our results of allergen levels with the gloves were low compared with the NRL gloves used in Europe and the US.[23]

Children with neural tube defects such as SB have a particularly high prevalence of LA. Latex-sensitive persons with SB reacted preferentially to Hev b 1 and Hev b 3 proteins, whereas latex-sensitive HCWs are more apt to be sensitized to Hev b 5 and Hev b 6. Such differences are considered due to the different

amounts of major allergic proteins eluted from causable products in patient groups. In our research, the allergens of the NRL gloves were only Hev b 5 and Hev b 6.02. We consider that those results have reflected the clinical conditions of HCWs. Yip *et al*. have reported that the allergenicity of NRL products can be estimated only by measuring the levels of four allergens: Hev b 1, Hev b 3, Hev b 5, and Hev b 6.02.[35] Koh *et al*. performed similar examinations in Singapore HCWs and reported that NRL allergen levels (Hev b 1, Hev b 3, Hev b 5, and Hev b 6.02) are present in the majority of examination gloves at sufficiently high levels to cause LA among sensitized persons.[36] They concluded that their research provides evidence that could require manufacturers to produce gloves with low NRL allergen levels and to report allergen levels in the glove product information. Therefore, in this study we analyzed these four allergens in NRL gloves. Yeang *et al*. suggested that Hev b 5 and Hev b 13 played important roles in determining the allergenicity of NRL gloves.[37] In this study, we did not estimate the amount of Hev b 13 because it was difficult to prepare native Hev b 13 with sufficient purity. On the other hand, Palosuo *et al*. quantified four NRL allergens (Hev b 1, 3, 5, and 6.02) in all medical glove brands marketed in Finland in 1999, 2001, and 2003 by a capture enzyme immunoassay.[23] They concluded that when the sum of these four allergens was 0.15 μg/g, these gloves could be distinguished as 'low allergenic'. In our examinations, the sum of four allergens was 2.18 μg/g in the surgery glove and 0.45 μg/g in the examination glove, suggesting that these gloves had high allergenicity. Hev b 5 and Hev b 6.02 were detected in the surgery glove, and Hev b 6.02 was detected in the examination glove. The allergenicity results in the NRL gloves were the same as the SPT results and specific IgE analysis using recombinant latex allergens in HCWs. Although, the ideal method for measuring the allergenicity of NRL products is to perform SPTs in LA patient volunteers, this test method is ethically impossible. Therefore, when purchasing NRL gloves, this allergen measuring method will be useful. We described the actual procedures for preventing sensitization in the HCWs previously.[29] We have considered that the most effective procedure was using powder-free latex gloves in medical settings. Because powder free gloves usually undergo low-proteinized procedures in the manufacturing process, the risk of sensitization to latex would be much smaller. Although recent change from latex to latex free tools are often found in many of the medical institutions, there are still many that select latex-powdered gloves. If latex-free gloves are employed exclusively in all medical settings, there will be no chance of latex sensitization a priori and further more, no symptoms will be induced even in HCWs with LA, although this poses as an economical burden for the hospital administration. In order to address these points, HCWs with LA should use latex-free gloves while others without LA should use the powder free gloves. In Japan, the guideline for LA was made in 2006.[38] The guideline includes many educational suggestions. It is very useful for HCWs and hospital managers. However, because of the limitation due to data derived from only retrospective studies, Bousquet *et al*. reported that the effect of these interventions could not be assessed with powder-free NRL gloves.[39] The effect of powder-free gloves was examined only in one prospective cohort study, which failed to show a protective effect of powder-free NRL gloves for LA. Further studies are needed to investigate this point. In this study, we characterized the most important allergen in HCWs sensitized occupationally by NRL gloves. We concluded that the main allergen in HCWs sensitized occupationally by NRL gloves was Hev b 6.02. More measurements for LA are needed in hospital settings. In addition, hospitals will have to continue to be cautious about latex exposure and be particularly mindful of the amounts of Hev b 5 or Hev b 6.02 in latex gloves.

ACKNOWLEDGEMENTS

This study was funded by the Grant-in-Aid for Scientific Research in Japan (C) (1) 16591123, 2004–2006.

REFERENCES

1. Kelly KJ, Kurup V, Zacharisen M, Resnick A, Fink JN. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol* 1993;**91**:1140-5.
2. Garabrant DH, Schweitzer S. Epidemiology of latex sensitization and allergies in health care workers. *J Allergy Clin Immunol* 2002;**110**:S82-95.
3. Turjanmaa K, Kanto M, Kautiainen H, Reunala T, Palosuo T. Long-term outcome of 160 adult patients with natural rubber latex allergy. *J Allergy Clin Immunol* 2002;**110**: S70-4.
4. Yeang HY, Cheong KF, Sunderasan E *et al*. The 14.6 kd rubber elongation factor (Hev b 1) and 24 kd (Hev b 3) rubber particle proteins are recognized by IgE from patients with spina bifida and latex allergy. *J Allergy Clin Immunol* 1996;**98**:628-39.
5. Sunderasan E, Hamzah S, Hamid S, Ward MA, Yeang HY, Cardosa MJ. Latex B-serum beta-1,3-glucanase (*Hev b* II) and a component of the microhelix (*Hev b* IV) are major latex allergens. *J Nat Rubb Res* 1995;**10**:82-99.
6. Akasawa A, Hsieh L-S, Martin BM, Liu T, Lin Y. A novel acidic allergen, Hev b 5, in latex. *J Biol Chem* 1996;**271**: 25389-93.
7. Alenius H, Kalkkinen N, Lukka M *et al*. Prohevein from the rubber tree (*Hevea brasiliensis*) is a major latex allergen. *Clin Exp Allergy* 1995;**25**:659-65.
8. Kostyal DA, Hickey VL, Noti JD, Sussman GL, Beezhold DH. Cloning and characterization of a latex allergen (*Hev b 7*): homology to patatin, a plant PLA2. *Clin Exp Immunol* 1998;**112**:355-62.
9. Vallier P, Balland S, Harf R, Valenta R, Deviller P. Identification of profilin as an IgE-binding component in latex from *Hevea brasiliensis*: clinical implications. *Clin Exp Al-*

lergy 1995;**25**:332-9.
10. Wagner S, Breiteneder H, Simon-Nobbe B *et al*. Hev b 9, an enolase and a new cross-reactive allergen from hevea latex and molds. Purification, characterization, cloning and expression. *Eur J Biochem* 2000;**267**:7006-14.
11. Wagner S, Sowka S, Mayer C *et al*. Identification of a *Hevea brasiliensis* latex manganese superoxide dismutase (Hev b 10) as a cross-reactive allergen. *Int Arch Allergy Immunol* 2001;**125**:120-7.
12. O'Riordain G, Radauer C, Hoffmann-Sommergruber K *et al*. Cloning and molecular characterization of the *Hevea brasiliensis* allergen Hev b 11, a class I chitinase. *Clin Exp Allergy* 2002;**32**:455-62.
13. Beezhold DH, Hickey VL, Kostyal DA *et al*. Lipid transfer protein from *Hevea brasiliensis* (Hev b 12), a cross-reactive latex protein. *Ann Allergy Asthma Immunol* 2003;**90**:439-45.
14. Lu LJ, Kurup VP, Hoffman DR, Kelly KJ, Murali PS, Fink JN. Characterization of a major latex allergen associated with hypersensitivity in spina bifida patients. *J Allergy Clin Immunol* 1995;**155**:2721-8.
15. Wagner S, Breiteneder H. *Hevea brasiliensis* latex allergens: current panel and clinical relevance. *Int Arch Allergy Immunol* 2005;**136**:90-7.
16. Yeang HY, Hamilton RG, Bernstein DI *et al*. Allergen concentration in natural rubber latex. *Clinical Exp Allergy* 2006;**36**:1078-86.
17. Liss GM, Sussman GL, Deal K *et al*. Latex allergy: epidemiological study of 1351 hospital workers. *Occup Environ Med* 1997;**54**:335-42.
18. Jaeger D, Kleinhans D, Czuppon AB, Baur X. Latex specific proteins causing immediate type cutaneous, nasal, bronchial, and systemic reactions. *J Allergy Clin Immunol* 1992;**89**:759-68.
19. Krogh VG, Maibach HI. The contact urticaria syndrome. *Semin Dermatol* 1982;**1**:59-66.
20. Turjanmaa K, Makinen S, Reunala T *et al*. Natural rubber latex allergy. In: Fink JN (ed). *Immunology and Allergy Clinics North America*. Philadelphia: WB Saunders, 1995; 71-88.
21. Turjanmaa K, Reunala T, Rasanen L. Comparison of diagnostic methods in latex surgical glove contact urticaria. *Contact Dermatitis* 1988;**19**:241-7.
22. Palosuo T, Mäkinen-Kiljunen S, Alenius H, Reunala T, Yip E, Turjanmaa K. Measurement of natural rubber latex allergen levels in medical gloves by allergenspecific IgE-ELISA inhibition, RAST inhibition, and skin prick test. *Allergy* 1998;**53**:59-67.
23. Palosuo T, Reinikka-Railo H, Kautiainen H *et al*. Latex allergy: the sum quantity of four major allergens shows the allergenic potential of medical gloves. *Allergy* 2007;**62**: 781-6.
24. Akita H, Matsunaga K, Tomitaka A *et al*. Actual conditions of latex allergy in high-risk nurses at Japanese general hospital. *Environ Dermatol* 1999;**6**:26-34.
25. Tomitaka A, Matsunaga K, Akita H *et al*. [Relevance of latex specific IgE and skin test (skin prick test or use test) to severity of clinical symptoms in thirty cases with latex allergy]. *Nihon hifu arerugi- gakkai zasshi [Jpn J Dermatoallergol]* 1999;**7**:28-35 (in Japanese).
26. Tomitaka A, Matsunaga K, Akita H, Suzuki K, Ueda H. [Four cases with latex allergy followed by anaphylaxis to chestnut]. *Arerugi [Jpn J Allergol]* 2000;**49**:327-34 (in Japanese).
27. Fujie S, Yagami A, Suzuki K *et al*. [A case of the latex-induced anaphylaxis by contact with barium enema catheter]. *Arerugi [Jpn J Allergol]* 2004;**53**:38-42 (in Japanese).
28. Kano H, Yagami A, Suzuki K *et al*. [Survey of awareness and current state of latex allergy among all health care workers at a university hospital]. *Arerugi [Jpn J Allergol]* 2004;**53**:659-68 (in Japanese).
29. Yagami A, Suzuki K, Kano H, Matsunaga K. Follow-up study of latex-allergic health care workers in Japan. *Allergol Int* 2006;**55**:321-7.
30. Smith AM, Amin HS, Biagini RE *et al*. Pericutaneous reactivity to natural rubber latex proteins persists in health care workers following avoidance of natural rubber latex. *Clin Exp Allergy* 2007;**37**:1349-56.
31. Bernstein DI, Biagini RE, Karnani R *et al*. In vivo sensitization to purified *Hevea brasiliensis* proteins in health care workers sensitized to natural rubber latex. *J Allergy Clin Immunol* 2003;**111**:610-6.
32. Sussman GL, Beezhold DH, Kurup VP. Allergens and natural rubber proteins. *J Allergy Clin Immunol* 2002;**110**: S33-9.
33. Rihs H-P, Raulf-Heimsoth M. Natural rubber latex allergens: Characterization and evaluation of their allergenic capacity. *New Horizons, Pharmacia Diagnostics AB* 2003; No3.
34. Hamilton RG, Biagini RE, Kreig EF. Diagnostic performance of Food and Drug administration-cleared serologic assays for natural rubber latex-specific IgE antibody: The Multi-Center Latex Skin Testing Study Task Force. *J Allergy Clin Immunol* 1999;**103**:925-30.
35. Yip L, Hickey V, Wagner B *et al*. Skin prick test reactivity to recombinant latex allergens. *Int Arch Allergy Immunol* 2000;**121**:292-9.
36. Koh D, Ng V, Leow YH, Goh CL. A study of natural rubber latex allergens in gloves used by health care workers in Singapore. *Br J Dermatol* 2005;**153**:954-9.
37. Yeang HY, Arif SAM, Raulf-Heimsoth M *et al*. Hev b 5 and Hev b 13 as allergen markers to estimate the allergenic potency of latex gloves. *J Allergy Clin Immunol* 2004;**114**: 593-8.
38. Akasawa A, Matsunaga K, Yagami T. *[Guideline of Safety Practice of Latex Allergy 2006]*. Tokyo: Japanese Society of Latex Allergy, 2006 (in Japanese).
39. Bousquet J, Flahault A, Vandenplas O *et al*. Natural ruuber latex allergy among health care workers: A systematic review of the evidence. *J Allergy Clin Immunol* 2006;**118**:447-54.