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ORIGINAL ARTICLE

Patterns and risk factors of causative contact allergens in Thai adult patients with contact dermatitis

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Abstract

Background: Surveillance on common allergens identified by patch testing plays an important role in emerging allergen detection, which leads to both individual and societal level prevention.

Objective: To study the changes in the pattern of contact sensitization and to identify risk factors associated with allergens.

Method: The data of 206 patients who underwent patch testing at King Chulalongkorn Memorial Hospital during 2012 to 2015 were assessed. The associations between patient risk factors and positive reactions to each allergen were evaluated. The results were compared with data from 2003-2004.

Results: The top five most common allergens during 2012-2015 were nickel sulfate (19.4%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (13.6%), fragrance mix I (FM I) (10.7%), carba mix (9.2%) and cobalt chloride (6.3%) whereas, during 2003-2004, these were nickel sulfate, cobalt chloride, FM I, potassium dichromate and Myroxylon pereirae. A positive patch test to nickel was strongly associated with a history of metal and seafood allergy ($p<0.001$; OR, 4.94; 95% CI = 2.33-10.47 and $p=0.028$; OR, 2.55; 95% CI, 1.11-5.85, respectively). MCI/MI was correlated with a history of personal care products allergy, and fragrance was correlated with a history of urticaria ($p=0.005$; OR, 4.05; 95% CI = 1.54-10.66 and $p=0.031$; OR, 2.71; 95% CI, 1.10-6.68, respectively).

Conclusions: There was an alteration in the pattern of contact sensitization detected by our standard series. MCI/MI has become the most common preservative causing contact allergy.

Keywords: Patch test, allergic contact dermatitis, contact allergen, standard series, patient risk factor

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Introduction

Allergic contact dermatitis (ACD) is one of the most common skin diseases diagnosed at dermatology clinics throughout the world. The prevalence of contact allergy to at least one allergen varies from 12.5 to 40.6% in Europe and North America.[1] Several reports have demonstrated that age, gender, race, occupation and atopic status are the basic risk factors associated with contact allergy.[2-10] Moreover, the pattern of the causative allergen seems to differ among populations and alters over a period of time. Over the past decade, there have been several studies on the prevalence of contact allergy in Thailand. The common causative allergens from those studies were varied.[11-14]

Patch testing is an important tool for the diagnosis and detection of the causative allergens in patients with ACD. In addition, it helps to identify emerging allergens in contact allergen surveillance, which may eventually lead to the regulation of components used in personal care and industrial products. Therefore, patch testing is beneficial in terms of the management and prevention of ACD.[15]

The aim of this study was to determine the common

causative allergens and risk factors in patients with contact dermatitis seen at King Chulalongkorn Memorial Hospital from November 2012 to January 2015 and to compare the results with a previous report containing data from 2003-2004.[16] The results of this study provides information on the emergence of new allergens and may lead to regional and global prevention of contact sensitization.

Methods

Patients

Two hundred and six patients suspected of having contact dermatitis and who underwent standard patch testing at King Chulalongkorn Memorial Hospital from November 1, 2012, through January 31, 2015 were enrolled into the study. All patients were free from topical medication, direct sunlight exposure on the testing sites, phototherapy, immunosuppressive therapy and systemic corticosteroids for at least two weeks prior to the test. Patch testing was performed with 39 allergens (allergEAZE, SmartPractice, Phoenix, AZ, USA) applied to an unaffected area of the upper back, using 8 mm Finn Chambers® on Scanpor® tape (SmartPractice, Phoenix AZ, USA). The allergen series used in this study was adjusted from series used in 2003-2004: three allergens (quinoline, GST, parthenolide) were removed due to low prevalence, while eleven allergens were added due to increasing prevalence, as shown in **Table 3**. After 48 and 72 hours, patch test results were interpreted by an experienced dermatologist, following the criteria of the International Contact Dermatitis Research Group (ICDRG).[15] An additional delayed reading (7 days after application) was done in cases suspected of having contact allergy to slow-reacting allergens, i.e., neomycin sulfate, 4-phenylenediamine base, potassium dichromate and corticosteroids.[17] This retrospective study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Statistical analysis

The demographic data were analyzed by descriptive statistics. In order to evaluate the influence of patient risk factors on a positive reaction for each allergen, binary logistic regression (forward Wald method) was applied using SPSS version 22.0 (IBM Corp, Armonk, NY, USA). A p-value <0.05 was considered to be statistically significant. Odds ratios with a 95% confidence interval were also reported. Allergens with positive results from fewer than 10 patients were excluded from the statistical analysis due to poor reliability and validity in the logistic regression model.

Results

Patient characteristics

One hundred and forty-six females (70.9%) and 60 males (29.1%) were enrolled. The average age of the patients was 43.2±15 years (range from 14 to 84 years). The average age of females and males was 42.4±13.9 years and 45.1±17.5 years, respectively. The median duration of dermatitis was 12 months. The most common occupations of the patients were office/sales worker (37.8%), student/educator (16.3%) and health care worker (10%) (**Table 1**). Hand dermatitis was the most common clinical manifestation, followed by facial dermatitis and leg dermatitis (39.4%, 32.4% and 21.2%, respectively). The most frequent pattern of localization of dermatitis was multiple sites (30.9%), followed by hands and feet (26%) and face and neck (20.6%) (**Table 2**). Concerning the history of atopic diathesis, there were 31 patients (15.4%) with atopic dermatitis, 87 patients (43.3%) with a personal history of atopy (atopic dermatitis, asthma, or allergic rhinitis), 57 patients (31.3%) with a family history of atopy and 106 patients (51.5%) with a personal or family history of atopy.

Table 1. Patients' Occupation

Occupation	n (%)
Office / sales	79(38.3)
Student / educator	34(16.5)
Health care worker	21(10.2)
Retired / unemployed	20(9.7)
Housewife	16(7.8)
Food related	9(4.4)
Metal related	7(3.4)
Construction / maintenance workers	4(1.9)
Spa / cosmetologist	4(1.9)
Other	12(5.8)

Table 2. Body Sites of Dermatitis

Dermatitis site	All patients n (%)	Female n (%)	Male n (%)
Multiple*	63(30.9)	44(30.6)	19(31.7)
Hands and feet	53(26.0)	36(25.0)	17(28.3)
Face and Neck	42(20.6)	32(22.2)	10(16.7)
Extremities	17(8.3)	11(7.6)	6(10.0)
Generalized†	17(8.3)	14(9.7)	3(5.0)
Trunk	12(5.9)	7(4.9)	5(8.3)

* Dermatitis involved more than 1 site.
† Dermatitis involved more than 2 sites.

Results of the patch testing

There were 152 patients (73.8%), 81 patients (39.3%) and 38 patients (18.4%) who had a positive reaction to at least one, two and three allergens, respectively. The top five positive allergens were nickel sulfate (19.4%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (13.6%), fragrance mix I (FM 1) (10.7%), carba mix (9.2%) and cobalt chloride (6.3%). Nickel sulfate (22.6%), MCI/MI (16.4%) and FM I (12.3%) were the most common allergens in females, whereas carba mix (16.7%), nickel sulfate (11.7%), and cobalt chloride, propylene glycol and 4-pheylenediamine base (8.3%) were the most common allergens in males. When compared to our previous

Table 3. Number and Percentage of Positive Patch Test Reactions from This Study and Our Previous Report

Allergen and Concentration	n (%) of patients with positive reaction			
	This Study			Previous Report
	Females (N=146)	Male (N=60)	Total (N=206)	Total (N=129)
Nickel sulfate hexahydrate, 2.5%	33(22.6)	7(11.7)	40(19.4)	24(18.6)
MCI/MI, 0.01%	24(16.4)	4(6.7)	28(13.6)	0
Fragrance mix I, 8%	18(12.3)	4(6.7)	22(10.7)	19(14.7)
Carba mix*	9(6.2)	10(16.7)	19(9.2)	-
Cobalt (II) chloride hexahydrate, 1%	8(5.5)	5(8.3)	13(6.3)	22(17.1)
Propylene glycol, 30%	7(4.8)	5(8.3)	12(6)	0
4-phenylenediamine base, 1%	7(4.8)	5(8.3)	12(6)	2(1.6)
M. pereirae resin, 25%	8(5.5)	2(3.3)	10(4.9)	14(10.9)
Lanolin alcohol, 30%	8(5.5)	1(1.7)	9(4.4)	4(3.1)
Bacitracin, 20%*	7(4.8)	0	7(3.4)	-
Colophony, 20%	7(4.8)	0	7(3.4)	5(3.9)
Formaldehyde, 1%	6(4.1)	1(1.7)	7(3.4)	4(3.1)
Thiuram mix [A], 1%	7(4.8)	0	7(3.4)	4(3.1)
Potassium dichromate, 0.25%	3(2.1)	3(5)	6(2.9)	15(11.6)
4-tert-butylphenol formaldehyde resin, 1%	5(3.4)	1(1.7)	6(2.9)	1(0.8)
Ethylenediaminedihydrochloride, 1%	3(2.1)	2(3.3)	5(2.4)	2(1.6)
Paraben mix [B], 12%	3(2.1)	1(1.7)	4(1.9)	7(5.4)
Benzocaine, 5%	3(2.1)	0	3(1.6)	3(2.4)
Neomycin sulphate, 20%	2(1.4)	1(1.7)	3(1.5)	6(4.7)
Quaternium 15, 2%	2(1.4)	1(1.7)	3(1.5)	0
2-mercaptobenzothiazole, 1%	3(2.1)	0	3(1.5)	4(3.1)
Tixocortol-21-pivalate, 1%	1(0.7)	2(3.3)	3(1.5)	0
Black rubber mix – PPD, 0.6%*	1(0.7)	1(1.7)	2(1)	-
Mercapto mix [A], 1%	1(0.7)	1(1.7)	2(1)	5(3.9)
Disperse blue mix (124/106)*	1(0.7)	1(1.7)	2(1)	-
2-bromo-2-nitropropane-1,3-diol (broponol), 0.5%*	2(1.4)	0	2(1)	-
Lidocaine-HCl, 15%*	0	1(1.7)	1(0.5)	-
Diazolidinyl urea, 2%	0	1(1.7)	1(0.5)	1(0.8)
Imidazolidinyl urea (Germall ®115), 2%	0	1(1.7)	1(0.5)	2(1.6)
Budesonide, 0.1%	1(0.7)	0	1(0.5)	1(0.8)
Hydrocortisone-17-butyrate, 1%	0	1(1.7)	1(0.5)	0
Sesquiterpenelactone mix, 0.1%	1(0.7)	0	1(0.5)	2(1.6)
Methyl methacrylate, 2%*	1(0.7)	0	1(0.5)	-
4-chloro-3,5-xylenol (PCMX), 1%*	0	1(1.7)	1(0.5)	-
Bisphenol A epoxy resin, 1%	0	0	0	2(1.6)
Al alpha tocopherol, 100%*	0	0	0	-
Triclosan, 2%*	0	0	0	-
Tosylamide/formaldehyde resin, 10%*	0	0	0	-
DMDM hydantoin*	0	0	0	-

*allergens used only in standard series during 2012-2015.

Table 4. Significant relation of patients' risk factors to each allergen, in form of odds ratio (95% confidence interval).

Risk Factor	Odds ratio (95% confidence interval)				
	Nickel sulfate	MCI/MI	Fragrance mix I	Carba mix	*M. pereirae*
Age group [a]	-	-	-	6.78 (1.52-30.20)*	-
Sex [b]	-	-	-	3.04 (1.17-7.93)*	-
Housework [c]	-	-	-	-	-
Location [d]	-	5.24 (1.09-25.12)*	-	-	-
Location [e]	-	8.33 (1.43-48.54)*	-	-	-
Atopic dermatitis [c]	-	-	-	-	-
Atopy diathesis [c]	-	-	-	-	-
Urticaria [c]	-	-	2.71 (1.10-6.68)*	-	-
Metal allergy [c]	4.94 (2.33-10.47)***	-	-	-	-
Seafood allergy [c]	2.55 (1.11-5.85)*	-	-	-	-
Topical medication allergy [c]	-	-	-	-	-
Personal care products allergy [c]†	-	4.05 (1.54-10.66)**	-	-	5.87 (1.53-22.56)*

All tests were carried out by binary logistic regression: *p<0.05, **p<0.01, ***p<0.001.
†History of eczematous skin lesion after using any leave-on or wash-off products use on face or body (for example, moisturizer, cosmetic, soap)
a Age ≥40 vs. <40 years.; b Male vs. Female.; c Presence vs. Absence.; d Hands and feet vs. Face and neck.; e Generalized vs. Face and neck.

data, the positive rates for MCI/MI, propylene glycol, 4-phenylenediamine, 4-tert-butylphenol formaldehyde resin, quaternium-15 and tixocortal-21-pivalate were remarkably increased, whereas the positive rates for cobalt chloride, *Myroxylon pereirae*, potassium dichromate, paraben mix, neomycin sulfate, mercapto mix and 2-mercaptobenzothizole decreased (**Table 3**).

Regarding the positive rate of each allergen in our standard series, the eight most common allergens (nickel sulfate, MCI/MI, FM I, carba mix, cobalt chloride, propylene glycol, 4-phenylenediamine base and *Myroxylon pereirae*) were selected to analyze the correlation between the positivity of each allergen and the patients' risk factors. Only five of eight allergens showed statistically significant results (**Table 4**). Nickel sulfate was associated with patient history of metal allergy and seafood allergy (p<0.001; OR, 4.94; 95% CI = 2.33 -10.47 and p=0.028; OR, 2.55; 95% CI, 1.11-5.85, respectively). MCI/MI was associated with a history of personal care product allergy, generalized dermatitis, and dermatitis on the hands and feet (p=0.005; OR, 4.05; 95% CI, 1.54-10.66 and p=0.018; OR, 8.33; 95%CI,1.43-48.54, p=0.038; OR, 5.24; 95%CI,1.09-25.12, respectively). Interestingly, patients with a history of urticaria had a high positive rate for FM I (p=0.031; OR, 2.71; 95% CI,1.10-6.68). Carba mix was associated with age ≥40 and male gender (p=0.012; OR, 6.78; 95% CI, 1.52-30.20 and p=0.023; OR, 3.04; 95% CI, 1.17-7.93, respectively). *Myroxylon pereirae* was associated with a history of personal care product allergy (p=0.01; OR, 5.87; 95% CI, 1.53-22.56). To clarify whether each patient risk factor was independent from each other, the association between each patient risk factor was analyzed. It was found that only two patient risk factors (urticaria and atopy) were associated with each other (p=0.002).

Discussion

The overall rate of positive standard patch test at King Chulalongkorn Memorial Hospital during 2012-2015 rose to 73.8%, compared to 59.7% in our previous report on data collected in 2003-2004.[16] Our recent data demonstrate that nickel, MCI/MI, FM I, cobalt and carba mix are the five most common allergens. Several recent studies have reported that nickel, FM I and cobalt are common contact allergens. This study revealed that nickel is still the most common contact allergen, compared to our previous study. This may reflect a lack of awareness regarding nickel exposure in daily life from items such as jewelry, apparel, household items, coins and diet. A positive patch test for nickel is strongly associated with a patient history of metal allergy and seafood allergy. Shellfish and some species of fish are sources of nickel in the diet, as they contain considerable levels of nickel. In addition, a modified meta-analysis study concluded that oral nickel exposure could contribute to systemic contact dermatitis in 1% of patients with nickel allergy.[18] Another study demonstrated that seafood oral exposure is a significant risk factor for nickel contact allergy in Thai patients.[19] Therefore, it could be possible that

some of our patients had systemic contact dermatitis caused by exposure to nickel in seafood. The chance of developing this problem depends on the nickel level in the diet, which can vary in different areas of the world, the process of food preparation and the individual physiology of nickel absorption.[18]

Our recent data revealed that the most common preservative allergens were MCI/MI (13.6%) and formaldehyde (3.4%), while paraben (5.43%), formaldehyde (3.1%) and 1,2-dibromo-2,4-dicyanobutane (3.1%) were most common in 2003-2004. The prevalence of formaldehyde allergy did not show a significant change. MCI/MI is an outstanding emerging causative allergen in our contact clinic, as the positive rate for MCI/MI has increased from 0% to 13.6%. However, the prevalence of MCI/MI and MI allergy might be underestimated in this study due to the use of a low concentration (100 ppm, instead of 200 ppm) of MCI/MI and the absence of MI in our standard patch test series.[20,21] MCI/MI is a preservative frequently used in personal care and industrial products. An increased rate of MCI/MI allergy has been reported in many countries.[22-24] Thus, it is not surprising that MCI/MI has become the most common cause of preservative allergy in our clinic, and is related to a history of personal care product allergy. In contrast, the positive patch test rate for paraben decreased from 5.4% to 1%. As some cosmetic industries have reduced the concentration of or removed paraben from personal care products due to its potential estrogen toxicity, the decline in the positive rate of paraben in our population might therefore be attributed to a decrease in exposure to paraben.[22,25]

Fragrance has long been known as a common causative allergen reported around the world.[22,26-29] The positive rates of FM I varied from 3.7% to 28.3%.[28] To date, fragrance exposure and sensitization can occur not only by perfume use but also by exposure through many personal care products and foods. Thus, our study revealed that the positive rate of FM I was still rather high, the same as in our previous report (14.7% and 10.7%, respectively). The positive rate was not statistically different between males and females. Excitingly, FM I positivity was significantly correlated with a patient history of urticaria. Since fragrance can cause both immediate and delayed type hypersensitivity[30-32], it is possible that fragrance might be the concealed cause of urticaria in these patients.

Carba mix is a common rubber additive that causes ACD. The worldwide prevalence of carba mix allergy is diverse.[33] Its positive rate in our study was 9.2%. We found that both age and sex were factors influencing the rate of positivity. A previous report by the North American Contact Dermatitis Group (NACDG) disclosed that the incidence of carba mix allergy increases with age.[2] This finding might be explained by prolonged duration of exposure in the older population compared with the younger population. In addition, vinyl gloves have replaced rubber gloves in many occupations due to a latex allergy epidemic in the past, so younger workers have much less rubber glove exposure. Occupational dermatitis might explain the higher rate of carba mix allergy in males compared with females.[33] Heavy industry, as opposed to health care or food service, are occupations in which rubber gloves are still widely used. This is probably why most of our carba mix allergic patients were male.

The prevalence of propylene glycol allergy has increased remarkably from 0 to 6%. Eleven of twelve patients had a positive patch test to propylene glycol, with a reading of at least 1+ on both the first and final readings. The increase in the positive rate of propylene glycol allergy might be due to increased use in personal care products or an increase in the number of products containing propylene glycol.

In conclusion, this study demonstrated an alteration in the pattern of contact sensitization, detected by our standard series at King Chulalongkorn Memorial Hospital. MCI/MI has now become the most common cause of preservative allergy in our clinic. Interestingly, the association between a positive patch test to some allergens and patient risk factors were identified. The information may be beneficial for disease prevention by the regulation of the chemicals used in personal care products and a revision of the appropriate allergens used in standard screening series.

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