Risk factors for common contact allergens and patch test results using a modified European baseline series in patients tested during between 2000 and 2009 at Siriraj Hospital

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Summary

***Background*: Surveillance of contact allergy using patch testing has demonstrated its value in detecting time trends. This study demonstrates the results of patch testing performed between 2000 and 2009 at the contact dermatitis clinic, Siriraj Hospital, Bangkok and risk factors for the top 5 common allergens.**

***Methods*: A retrospective review of medical records was conducted from January 2000 to December 2009. All Patients who were patch tested using a modified European baseline series were studied.**

***Results*: There were 852 cases (206 males and 646 females; mean age 39.14 years). The top 5 most frequent allergens were gold sodium thiosulfate (30.7%), nickel sulfate (27.6%), potassium dichromate (20.8%), fragrance mix (18.3%) and cobalt chloride (16.0%), respectively. There was no statistically significant difference in the trends of positive patch test reactions for individual allergens during the 2000s. Gold sensitivity was found more common in females and in the head and neck regions. Nickel sensitivity was more common in females. Chromate sensitivity was more common in males and subjects aged ≥ 40 years. Fragrance sensitivity was more common in females and subjects aged ≥ 40 years. Among the patients with metal (chromate, nickel, cobalt and gold) allergy, the patient's recollection of a history of an allergic reaction to metal was significantly associated with a positive patch test reaction to either one of these metals, ($P < 0.001$; OR, 2.56; 95%CI, 1.87-3.50).**

Conclusions*: The prevalence of contact sensitization appears to have not changed much during the decade. Further study, involving patients from all institutions in Bangkok, would provide a more comprehensive view of contact allergens in the region and lead to the creation of a local standard series. *(Asian Pac J Allergy Immunol 2014;32:60-5)

Key words: *allergic contact dermatitis, epidemiology in Thais, patch testing, allergy trend, baseline series*

Introduction

Patch testing is the most important diagnostic tool used to discover allergens causing allergic contact dermatitis (ACD).[1] Most clinicians use a standard (baseline) series of allergens to identify common offending allergens in patients with ACD. The standard series is the main set of allergens used to patch test every suspected-ACD patient and represents the allergens that most commonly cause ACD in each population.[2] The number and details of allergens in the series vary from country to country, to suit each population.[3] Surveillance of prevalence of contact allergy of patch-tested patients has proven valuable for detecting trends in each population[4] over time, which may lead to revision of the standard series to suit populations in each geographical region. Some of the allergens used for patch testing in the basic series have altered over the years and this corresponds to the changes of environmental exposure.

Contact sensitization is also influenced by individual risk factors, genetic factors, age, gender, and atopy.[5] The objective of this study was to investigate results of allergenicity rates among our

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contact dermatitis patients between 2000 and 2009 and to analyze the influence of individual factors on the sensitization risk for the top 5 allergens. The value of this study is updating patch test results during the last decade and addressed the standard series to suit our patients.

Methods

Study population

The Siriraj Institutional Review Board approved this retrospective study of the use of clinical data from patients patch tested by the Contact Dermatitis Clinic, Siriraj Hospital during January 2000 to December 2009. Our clinic is in a tertiary academic hospital in an urban area of Bangkok, the capital of Thailand. All patients suspected of having allergic contact dermatitis who were referred to our clinic during this 10-year period were patch tested with the "Siriraj standard series" (SiSS), mainly based on the European baseline and International standard series (Table 1). The allergens (Chemotechnique Diagnostics AB, Vellinge Sweden) in aluminium Finn Chambers® (SmartPractice, Phoenix, Arizona, USA), were placed on unaffected skin on the upper back for 2 days and the reactions were read on D2, D3, and D7, according to the guidelines of the International Contact Dermatitis Research Group (ICDRG).[6] The clinical relevance of patch test results were determined according to criteria recommended by *Fisher's Contact Dermatitis.*[6] Patch test results and patient data were collected by chart review.

Statistical analysis

The data were analysed with descriptive statistics. The patch test results for each period of time were compared by using the χ^2 test with Yates' continuity correction or Fisher's exact test where appropriate. The *p*-value was adjusted by the Bonferroni method for the correction of 30 factors; therefore, a *p*-value < 0.002 was considered statistically significant. Multiple logistic regression (Stepwise backward wald) was performed to evaluate the influence of individual risk factors on the outcome of patch testing. All statistical analyses were carried out with SPSS™ v.18 (SPSS Inc., Chicago, IL).

Results

Over a period of 10 years (2000–2009), a total of 852 patients, 646 female (75.8%) and 206 male (24.2%) (F: M ratio, 3.1:1) were patch tested with our SiSS of 30 allergens. The average age of the patients was 39.14 ± 14.1 years (mean ±SD, range: 10-85 years). The duration of presenting skin lesions was 3.1 ± 4.1 years (mean ±SD, range: 0.1-40 years).

Among positive patch test patients, 281 (39.2%) had a personal history of atopic diathesis and 148 (20.2%) had a family history of atopy. However, there were no association with either personal or familial history of atopic diathesis and the results of the patch test, $p > 0.05$, 2-sided.

The patch test results of SiSS allergens are summarized in Table 1. A total of 852 patients were analyzed, yielding one or more positive reactions in 692 (81.2%) patients with 56.5% of clinical relevance. There was no statistically significant difference in the trends of positive patch test reactions for individual allergens during the study period.

The top 5 most frequent allergens were gold sodium thiosulfate (30.7%), followed by nickel sulfate (27.6%), potassium dichromate (20.8%), fragrance mix I (18.3%) and cobalt chloride (16.0%) with clinical relevance of 14.6%, 88.1%, 61.7%, 53.4% and 37.8%, respectively. Among the multiple allergen categories, metals were the most frequently identified allergens. Comparing males and females, potassium dichromate was predominant in males, whereas gold sodium thiosulfate dihydrate, nickel sulfate, fragrance mix I and cobalt were leading allergens in females, but only nickel sulfate was of statistical significance, *p*-value < 0.001.

Using the logistic regression model to analyze factors concerning the pattern of sensitivity of the top-5 most common allergens, we found five significant risk factors including age, gender, familial history of atopy, history of metal allergy and rash locations (Table 2).

Gold sodium thiosulfate dihydrate sensitivity was more common in female patients ($P < 0.05$; OR, 1.44; 95%CI, 1.01-2.06) and was found to be more common in the head and neck region ($P < 0.05$; OR, 2.18; 95%CI, 1.09-4.37). Nickel sulfate sensitivity was more common in female patients ($P < 0.05$; OR, 1.82; 95%CI, 1.16-2.87) and also statistically associated with a history of metal allergy ($P < 0.001$; OR, 4.83; 95%CI, 3.46-6.75). Potassium dichromate sensitivity was the only allergy that was found to be more common in male patients ($P < 0.05$; OR, 0.68; 95%CI, 0.47-0.99) and was also more common in those aged 40 years or above than those aged below 40 years ($P < 0.05$; OR, 1.49;

Table 1. SiSS patch test positive reactions during the study period, ranking from highest prevalence to lowest prevalence

Allergens	Tested concentration (%)	Total (n=852)	2000-1	2002-3	2004-5	2006-7	2008-9	*p*-value	Male (n=206)	Female (n=646)	*p*-value
		%positive							%positive		
Gold sodium thiosulfate dihydrate	0.5 pet	30.7	29.6	27.6	38.9	28.4	29.7	0.929	25.2	32.4	0.055
Nickel sulfate [E,I]	5 pet	27.6	25.9	25.5	26.2	29.6	29.1	0.323	14.1	31.9	<0.001[π]
Potassium dichromate [E,I]	0.5 pet	20.8	11.9	16.1	28.9	24.2	21.1	0.020	26.2	19.0	0.027
Fragrance mix I [E,I]	8 pet	18.3	21.0	16.1	26.2	17.7	13.5	0.082	11.2	20.6	0.002
Cobalt chloride [E]	1 pet	16.0	12.6	12.4	16.1	16.8	19.4	0.037	15.5	16.1	0.841
p-Phenylenediamine [E,I]	1 pet	7.5	7.0	3.6	9.4	9.1	7.6	0.359	12.6	5.9	0.001[π]
Thiuram mix [E,I]	1 pet	5.9	6.7	5.8	4.7	7.0	5.5	0.840	3.9	6.6	0.159
Neomycin sulfate [E,I]	1 pet	8.9	6.3	7.3	12.8	10.8	7.6	0.565	4.4	10.4	0.008
Benzocaine [E]	5 pet	2.6	3.5	2.2	3.4	1.6	2.5	0.540	3.9	2.2	0.177
Quinoline mix [E]	5 pet	1.3	1.4	.0	2.7	.5	1.7	0.682	2.4	.9	0.147*
Colophonium [E,I]	20 pet	7.4	9.8	5.1	7.4	9.1	5.9	0.490	5.4	8.0	0.201
Parabens [E]	16 pet	10.8	9.8	9.5	10.1	13.4	10.5	0.522	18.0	8.5	<0.001[π]
N-isopropyl-N-phenyl-4-phenylenediamine [E]	0.1 pet	1.6	.7	2.2	1.3	1.1	2.5	0.340	1.9	1.6	0.753*
Wool alcohols [E,I]	30 pet	4.0	4.9	2.9	2.7	4.8	4.2	0.852	3.9	4.0	0.928
Mercapto mix [E,I]	2 pet	3.1	4.2	3.6	4.0	2.7	1.7	0.122	4.4	2.6	0.207
Epoxy resin [E,I]	1 pet	2.4	2.1	.7	2.0	2.2	3.8	0.139	3.9	1.9	0.112*
Myroxylon pereirae resin [E,I]	25 pet	8.5	8.4	7.4	12.1	10.2	5.5	0.431	6.8	9.0	0.333
4-tert-Butylphenolformaldehyde resin [E,I]	1 pet	3.2	.7	1.5	5.4	3.8	3.8	0.068	3.4	3.1	0.829
Mercaptobenzothiazole [E,I]	2 pet	3.2	4.9	5.1	3.4	1.6	2.1	0.036	2.4	3.4	0.485
Formaldehyde [E,I]	1 aq	3.2	4.9	2.2	5.4	2.7	1.7	0.119	1.9	3.6	0.248
Sesquiterpene lactone mix [E]	0.1 pet	3.3	2.2	2.9	4.7	2.7	3.8	0.529	1.9	3.8	0.205
Quaternium-15 [E,I]	1 pet	1.5	2.8	.7	3.4	1.1	.4	0.096	1.9	1.4	0.572*
Methylchloroisothiazolinone /methylisothiazolinone [E,I]	0.01 aq	4.6	4.9	2.9	6.0	2.7	5.9	0.638	1.0	5.7	0.004
Ethylenediamine dihydrochloride	1 pet	2.1	1.5	.7	2.7	2.7	2.5	0.282	3.0	1.9	0.403*
Tetramethyl thiuram monosulfide	1 pet	4.8	6.5	4.4	3.8			0.332	.0	6.4	0.009*
Carba mix	3 pet	8.2	.0	2.9	13.5	12.0	7.2	0.059	10.3	7.6	0.239
Imidazolidinyl urea [I]	2 aq	2.0	2.6	1.5	1.3	2.7	2.1	0.786	1.6	2.2	0.773*
Budesonide [E,I]	0.01 pet	3.2	.0	.7	5.4	4.3	3.4	0.098	7.9	1.7	<0.001[π]
Tixocortol-21-pivalate [E,I]	0.1 pet	1.3	.0	.0	1.3	2.7	1.3	0.143	1.6	1.2	0.714*
Methyldibromo glutaronitrile [E,I]	0.5 pet	6.1	4.5	3.6	6.7	2.7	10.2	0.033	9.5	5.0	0.024

[E] European standard series, [I] International standard series
*Fisher's exact test and others; Chi-squared test
[π]Statistical significance by Bonferroni adjustment, p <0.002

Table 2. Odd ratios of risk factors for the top-5 allergens with positive patch test results

Factor	Odds ratio (95% confidence interval)																			
	Gold sodium thiosulfate				Nickel sulfate				Potassium dichromate				Fragrance mix I				Cobalt chloride			
	OR	95%CI		*p*-value	OR	95%CI		*p*-value	OR	95%CI		*p*-value	OR	95%CI		*p*-value	OR	95%CI		*p*-value
Age (≥ 40 years vs. < 40 years)					0.73	0.53	1.02	0.065	1.49	1.06	2.09	0.021	1.76	1.23	2.51	0.002	0.66	0.46	0.97	0.032
Sex (Female vs. Male)	1.44	1.01	2.06	0.047	1.82	1.16	2.87	0.010	0.68	0.47	0.99	0.046	2.37	1.46	3.84	<0.001				
Familial atopic history (presence vs. absence)									1.46	0.98	2.17	0.065	0.64	0.40	1.03	0.066				
Metal allergic history (presence vs. absence)					4.83	3.46	6.75	<0.001												
Rash site																				
Trunk	1																			
Head&neck	2.18	1.09	4.37	0.028																
Extermities	1.24	0.72	2.16	0.435																
Generalized	1.34	0.57	3.18	0.505																

95%CI, 1.06-2.09). Among those in the metal allergy group (chromate, nickel, cobalt and gold), the patient's recollection of a history of an allergic reaction to metal was significantly associated with the positive patch test reaction to either one of these metals, ($P < 0.001$; OR, 2.56; 95%CI, 1.87-3.50).

Discussion

This study focused on changing trends of standard patch test results during 2000s at our contact dermatitis clinic in Bangkok, Thailand. The "Siriraj Standard series" is the main screening set of allergens used in patients suspected to have allergic contact dermatitis in our clinic. The SiSS is a modified European baseline and international standard series, except that primin and lyral which were added to European baseline series in 2008[7] and four allergens: gold sodium thiosulfate dehydrate, ethylenediamine dihydrochloride, tetramethyl thiuram monosulfide (TMTM) and carba mix, were added. The frequency of sensitization to all 30 allergens in the SiSS was analyzed.

Fragrance mix I sensitivity was more common in female patients ($P < 0.001$; OR (female/male), 2.37; 95%CI, 1.46-3.84) and more common in those aged 40 years or above than those aged below 40 years ($P < 0.05$; OR, 1.76; 95%CI, 1.23-2.51). Furthermore, balsum of peru and fragrance mix II also showed the same tendency: sensitivity was found more commonly in female patients aged 40 years or above.

Except for gold, the frequencies of sensitization of our top 10 allergens were similar to those in other countries. [8-15] Gold was the most common allergen in our series. Prevalence of gold allergy during 1994-2000 were 2.1 – 13%.[16] Gold was allergen of the year 2001.[16] From our study, gold had the highest positive reaction (30.7%); however, its CR was low, 14.6%. Thais have usually experienced gold exposure since childhood. Thai babies have traditionally worn gold bangles to console the child's spirit. In Thailand, gold jewelry is mainly made from 96.5-99.9% gold. Thais also have a religious practice of using gold leaf to cover Buddha statues. Gold leaf, which is a very thin gold plate, can absorb through skin which might explain why we have such a high rate of sensitization. However, gold salt patch test positive patients apparently tolerate most gold metal contact because metallic gold is inert and difficult to dissolve, [16] which may lead to our low CR. The clinical relevance of gold allergy remains largely unclear. Currently, gold threads, gold-containing cosmetics and gold-containing dental restoration materials have acquired increased popularity, therefore we need to keep an eye on gold allergy.

Nickel was the second most common allergen (27.6%) in our series, following gold, which is comparable with most Asian studies. [14, 17] Nickel sulfate has the highest clinical relevance (81.2%). Logistic regression of nickel data showed that nickel sensitization was more common in female patients and in patients presenting with a previous history of metal allergy but not in atopic patients. The effect of atopy on nickel allergy is not conclusive. [18-19] The frequency of nickel and cobalt allergy was rather high compared to other studies, [9-10, 12, 15, 17] which may be explained by the lack of regulations limiting the release of nickel from any metal items in close contact with skin in Thailand. Among European countries, the rate of nickel allergy significantly decreased [20] because they have had a regulation controlling nickel release to < 0.5 $\mu g/cm^2$/week since 1991.[21]

Using logistic regression, the risks of chromate sensitization were increased for males ≥ 40 years of age, which is similar to previous reports. [22] It indicates that the rate of chromate allergy tends to increase with increasing age, mainly above 40 years, which is accounted for by leather and cement exposure. Cobalt was the last allergen in our top 5. This may be caused by a metal co-reactivity (e.g., nickel and cobalt) that is well recognized among dermatitis patients. [21]

Four of our top 5 allergens were metals (gold, nickel, chromate and cobalt). The prevalence of metal allergy is high among dermatitis patients. Metal allergy is mainly an environmental problem where exposures include jewelry, buttons, dental restorations, mobile phones, and leather.

Fragrance mix was the only non-metal allergen in our top 5 allergens. Its sensitization was more likely if the patients were aged ≥ 40 and female, comparable to the Lam et al. report from Hong Kong.[17] Balsum of Peru and fragrance mix II, markers of perfume allergy, also had similar risk factors. This may be explained by females having more and longer fragrance exposure from fragrance-containing cosmetics. Our previous report [23] found that fragrance substances are among the most common allergens in allergic contact dermatitis caused by cosmetics, which are main source of fragrance exposure.

In conclusion, even with rapid industrialization, Westernization of society and inadequate regulations in Thailand, the prevalence of contact sensitization appears to have not much changed during the decade 2000 to 2009. The SiSS, taking our epidemiologic study into account, seems to be suitable for our population.

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