

Standard patch test results in patients with contact dermatitis in Israel: age and sex differences

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Previous studies have shown that the prevalence of specific allergens varies by geographic area, population, age and sex. The objective of the present study was to determine the relative frequency of positive reactions to different sensitizers in Israeli patients with clinically suspected contact dermatitis (CD) and to identify possible sex and age differences. A total of 943 consecutive patients were tested for CD using the European standard patch test series. The most frequent allergen was nickel sulfate followed by potassium dichromate and fragrance mix. Positive reactions to nickel sulfate were more common among women, especially those in the younger age group (younger than 40 years). Positive reactions to balsam of Peru were more common among men, especially those in the older age group (40 years or older). This study presents the result of the standard patch test in Israel with stratification according to age and sex. The findings of the present study, combined with reports on geographic/population differences in the prevalence of specific allergens in CD, indicate the need for further investigations to identify prominent local allergens for better adaptation of the standard patch test to local needs.

Key words: allergic contact dermatitis; standard patch test. © Blackwell Munksgaard 2007.

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Contact dermatitis (CD) is a worldwide disease. Causative allergens are identified by patch test, considered the 'gold standard' diagnostic tool. In Israel, we use the European standard patch test series. Previous studies have shown that the prevalence of specific allergens varies by geographic area, population, age and sex. The purpose of the present study was to determine the relative frequency of positive reactions to different sensitizers in Israeli patients with clinically suspected CD and to identify possible sex and age differences. We also compared the results with published findings in populations in other areas to identify geographic differences in the prevalence of CD allergens.

Methods

The study sample included all patients with clinically suspected CD who were referred to the Contact Dermatitis Clinic of Rabin Medical Center between January 1999 and December 2000. All were tested with the European standard patch test series (Chemotechnique Diagnostics AB, Malmö, Sweden) using Finn Chambers on Scanpor tape (Hermal, Reinbeck, Germany). The series consists of 23 allergens. The allergens were placed on unaf-

fected skin of the upper back for 2 days, and the skin reactions were determined on day 2 and day 3 according to the guidelines of the International Contact Dermatitis Research Group (1). Patients with irritant reactions were excluded from the study, as were patients who had recently applied topical corticosteroids to test sites or took oral corticosteroids within the 2 weeks prior to the study.

Data on the patch test results and on patient age and sex were collected by chart review.

Statistical analysis

The statistical analysis was performed using SAS software. Continuous variables are shown as means $\pm$ standard deviations. To analyse statistically significant relationships between categorical variables, chi-square test or Fisher's exact test was used, as appropriate. Mean continuous parameters (i.e. age) were compared between 2 groups of patients (i.e. by allergens) using Student's *t*-test. A *P* value of ≤ 0.05 was considered statistically significant.

Results

Our chart review yielded 943 patients (59% women and 41% men) aged 1–87 years (mean $\pm$

Table 1. Results of European patch test series by frequency of positive reactions and sex ($n = 943$)

Allergen	Patients with positive reactions n (%)	Women ($n = 557$) n (%)	Men ($n = 386$) n (%)	P Value
Nickel sulfate	164 (17.4)	142 (25.5)	22 (5.7)	0.001
Potassium dichromate	100 (10.6)	66 (11.8)	34 (8.8)	NS
Fragrance mix (parfum)	80 (8.5)	47 (8.4)	33 (8.6)	NS
Cobalt chloride	71 (7.5)	56 (10.1)	15 (3.9)	0.001
Balsam of Peru (<i>Myroxylon Pereirae</i>)	62 (6.6)	29 (5.2)	33 (8.6)	0.042
Cl+Me-isothiazolinone (methylchloroisothiazolinone and methylisothiazolinone)	42 (4.5)	29 (5.2)	13 (3.4)	NS
4-Phenylenediamine base (p-phenylenediamine)	24 (2.5)	17 (3.1)	7 (1.8)	NS
Colophony (Colophonium)	21 (2.2)	11 (2.0)	10 (2.6)	NS
Formaldehyde	18 (1.9)	8 (1.4)	10 (2.6)	NS
4- <i>tert</i> Butylphenol formaldehyde	16 (1.7)	14 (2.5)	2 (0.5)	0.020
Wool alcohols (lanolin)	14 (1.5)	5 (0.9)	9 (2.3)	NS
Benzocaine	13 (1.4)	9 (1.6)	4 (1.0)	NS
Epoxy resin	12 (1.3)	8 (1.4)	4 (1.0)	NS
Mercaptobenzothiazole	11 (1.2)	5 (0.9)	6 (1.6)	NS
Neomycin sulfate	11 (1.2)	5 (0.9)	6 (1.6)	NS
Thiuram mix	11 (1.2)	6 (1.1)	5 (1.3)	NS
Mercapto mix	9 (1.0)	4 (0.7)	5 (1.3)	NS
Paraben mix (benzylparaben, butylparaben, ethylparaben, methylparaben, propylparaben)	8 (0.8)	5 (0.9)	3 (0.8)	NS
Quaternium 15	6 (0.6)	4 (0.7)	2 (0.5)	NS
Sesquiterpene lactone mix	6 (0.6)	5 (0.9)	1 (0.3)	NS
<i>N</i> -isopropyl- <i>N</i> -phenyl-4-phenylene-diamine	5 (0.5)	4 (0.7)	1 (0.3)	NS
Clioquinol	5 (0.5)	3 (0.5)	2 (0.5)	NS
Primin	1 (0.1)	1 (0.2)	—	NS

NS, not significant.

P values of <0.05 were considered statistically significant.

The International Nomenclature Cosmetic Ingredient is presented in parenthesis.

SD 42 ± 20 years) who were tested for CD with the European standard patch test series during the study period. At least 1 positive skin reaction was observed in 415 patients (44%). Table 1 summarizes the patch test results for individual allergens in order of frequency. The most frequent allergen was nickel sulfate (17.4%), followed by potassium dichromate (10.6%), fragrance mix (8.5%), cobalt chloride (7.5%), balsam of Peru (6.6%) and Cl+Me-isothiazolinone (4.5%). Only 1 patient showed a positive reaction to primin.

2 or more reactions were noted in 180 (43%) of the 415 patients with positive reactions. Statistically significant associations ($P < 0.01$) were found between 12 pairs of allergens: potassium dichromate/nickel sulfate, potassium dichromate/balsam of Peru, 4-phenylenediamine base/benzocaine, 4-phenylenediamine base/*N*-isopropyl-*N*-phenyl-4-phenylene-diamine, 4-Phenylenediamine base/epoxy resin, thiuram mix/cobalt chloride, thiuram mix/mercapto mix, cobalt chloride/fragrance mix, colophony/Cl+Me-isothiazolinone, balsam of Peru/sesquiterpene lactone mix, fragrance mix/quaternium 15, fragrance mix/Cl+Me-isothiazolinone. Highly statistically significant associations

($P < 0.0001$) were found in 9 pairs: potassium dichromate/cobalt chloride, thiuram mix/mercaptobenzothiazole, cobalt chloride/nickel sulfate, clioquinol/colophony, *N*-isopropyl-*N*-phenyl-4-phenylene-diamine/epoxy resin, wool alcohols/fragrance mix, epoxy resin/mercaptobenzothiazole, balsam of Peru/fragrance mix, formaldehyde/Cl+Me-isothiazolinone.

Positive skin reactions to 1 or more metal allergens were observed in 252 patients (61% of all positive patch test results). 40 patients reacted to both cobalt chloride and nickel sulfate (10% of all positive patch test results), 28 to potassium dichromate and nickel sulfate (7%) and 24 to potassium dichromate and cobalt chloride (6%); 9 patients showed positive reactions to all the 3 metals (2%).

Table 1 also illustrates the distribution of the patch test results for individual allergens by sex. Overall, female patients had a significantly higher rate of positive skin reactions (1 or more) than male patients (50% versus 36%, $P = 0.0002$). The most common allergen in women was nickel sulfate (25.5%), followed by potassium dichromate (11.8%), cobalt chloride (10.1%) and fragrance mix (8.4%). In men, the most common

allergen was potassium dichromate (8.8%), followed by fragrance mix (8.6%), balsam of Peru (8.6%) and nickel sulfate (5.7%). Comparison between the sexes showed that female patients had a significantly higher rate of allergic reaction than male patients to nickel sulfate (25.5% versus 5.7%, $P = 0.001$), cobalt chloride (10.1% versus 3.9%, $P = 0.001$), and 4-*tert* butylphenol formaldehyde (2.5% versus 0.5%, $P = 0.02$), whereas male patients had a significantly higher rate of allergic reaction to balsam of Peru (8.6% versus 5.2%, $P = 0.042$).

Analysis by mean age of the patients who reacted to specific allergens compared with the patients with clinically suspected CD who did not show two main findings. The patients who reacted to nickel sulfate were significantly younger than the other patients ($P = 0.0004$), and the patients who reacted to potassium dichromate, fragrance mix, balsam of Peru, benzocaine and *N*-isopropyl-*N*-phenyl-4-phenylene-diamine were significantly older.

Stratification of sex and age together was made by dividing the patients according to age younger and equal to or older than 40 years. Positive reactions to nickel sulfate were more common among women, especially those in the younger age group (younger than 40 years). Positive reactions to balsam of Peru were more common among men, especially those in the older age group (40 years or older). All the differences were statistically significant ($P < 0.05$).

To investigate geographic differences in the prevalence of allergens causing CD in Israel, we

compared our results with published ones from other areas (2–7) (Table 2). A prominent finding was the considerable variability in the prevalence of sensitivity to potassium dichromate. Standardization by age and sex was impossible, however, because of a lack of data in some of the studies.

Discussion

Previous studies have shown that early patch-test diagnosis of CD is associated with improved quality of life, increased response to treatment and decreased prediagnostic cost of treatment (8, 9). Moreover, identification of the causative allergen makes it possible for patients to avoid exposure, thereby preventing the development of the chronic phase of the disease (9).

Our study presents the European standard patch test results of 943 Israeli patients with clinically suspected CD. Like in most previous studies (Table 2), we found nickel sulfate to be the most common agent causing allergic CD, with a rate of 17.4% of cases, comparable with the worldwide incidence (2–5, 7). Also in agreement with previous studies, a positive reaction to nickel sulfate was significantly more prevalent among women (4, 6, 7), especially young women (7). Researchers explain this finding by the higher tendency of this population subset to wear pierced earrings and other jewellery.

Several studies have emphasized the occupational, social, cultural and environmental variability in the prevalence of specific sensitizers among different countries (4–7) and even between different

Table 2. Common allergens in different geographic areas (2–7)

Allergen (%)	Israel (<i>n</i> = 943)	North America (<i>n</i> = 3429–4095)	Turkey (<i>n</i> = 542)	UK (<i>n</i> = 4721)	India (<i>n</i> = 200)	Hong-Kong (<i>n</i> = 244)	Saudi Arabia* (<i>n</i> = 271)
Nickel sulfate (5)	17.4	14.2 (2.5%)	19.1	18.5	16.5	16.4	22.1
Potassium dichromate (0.5)	10.6	2.8 (0.25%)	11.8	3.4	20.5	1.6	18.5
Fragrance mix (8)	8.5	11.7	5.5	7.9	7.5	19.5	8.1
Cobalt chloride (1)	7.5	9.0	8.5	5.7	8.0	11.3	17.3
Balsam of Peru (25)	6.6	11.8	2.0	3.1	1.5	8.6	5.2
Cl+Me-isothiazolinone (0.01)	4.5	NT	0.2	0.9	1.0 (0.67%)	NT	NT
4-Phenylenediamine base (1)	2.5	6.0	3.7	2.3	11.5	NT	5.2
Colophony (5)	2.2	2.0 (20%)	1.3 (20%)	6.3	5.5 (20%)	5.1 (20%)	3.7
Formaldehyde (1)	1.9	9.3	0.6	3.0	6.5	5.9	5.9
4- <i>tert</i> Butylphenol formaldehyde (1)	1.7	1.8	0.2	0.7	1.0	0.4	4.4
Wool alcohols (30)	1.5	NT	NT	3.0	4.0	1.2	2.6
Benzocaine (5)	1.4	2.0	0.2	NT	2.5	1.6	0.4
Epoxy resin (1)	1.3	1.9	0.9	1.0	1.5	1.2	1.8
Mercaptobenzothiazole (2)	1.2	1.8 (1%)	1.7	1.6	NT	NT	0.7
Neomycin sulfate (20)	1.2	13.1	2.6	6.0	5.0	7.0	6.3
Sesquiterpene lactone mix (0.1)	0.6	0.7	0.6	NT	14.0	NT	NT

NT, not tested.

Allergen concentrations (%) are given in parentheses. If not otherwise noted, concentrations are as used for this study.

There was no standardization by age and sex because of lack of data in some of the studies. *In the original article, results were presented as percentage of positive reactions. To compare the findings with ours, the results are shown as percentage of all tested patients.

regions within the same country (10). In our series, the 2nd most common allergen was potassium dichromate, with a 10.6% rate of reaction. In a previous study in Israel (11), potassium dichromate was found to be the main allergen causing CD in housewives (91.6% of 250 patients). Geographically, the sensitivity to potassium dichromate varies from 1.6% in Hong Kong (5) to 20.5% in India (4) (Table 2). These differences may be due to differences in occupational exposure (especially in the construction industry) and in chromium levels in detergents and bleaches, which were found to be higher in products in Israel (12, 13). It is also possible that ethnic origin plays a role in the tendency to develop chromate sensitivity (12). In this regard, it is important to note that researchers use different concentrations of potassium dichromate in the patch test: 0.25% in USA (2, 10) versus 0.5% in other countries.

Like other studies on the effect of age on patch test results (4, 6, 7, 14–16), we found a higher rate of positive reactions to fragrance mix and balsam of Peru among older patients (7, 14–16) and a higher rate of sensitivity to nickel sulfate in younger ones (7, 16), especially in women. Other prevalent allergens in older patients in our study were potassium dichromate, fragrance mix, balsam of Peru, benzocaine and *N*-isopropyl-*N*-phenyl-4-phenylene-diamine (Table 1).

In this study, female patients had a significantly higher rate of positive allergic reaction to nickel sulfate, supporting many earlier studies (4, 6, 7, 15), and also to cobalt chloride and 4-*tert* butyl-phenol formaldehyde. By contrast, male patients had a significantly higher rate of allergic reaction to balsam of Peru. Previous studies showed a higher rate of positive reaction to fragrance mix among women (14, 17, 18), which was not observed in the present study.

Multiple positive reactions to metals, a well-documented phenomenon (19, 20), were noted in our series for cobalt chloride and nickel sulfate in 40 patients, potassium dichromate and nickel sulfate in 28 patients, and potassium dichromate and cobalt chloride in 24 patients. 9 patients showed a positive reaction to all the 3 metals. This association may be attributed to the use of mixtures of several metals in different instruments. Concomitant reactions to nickel sulfate and cobalt chloride were also shown in previous studies (19, 20) and were attributed to cosensitization. This may explain the significantly higher rate of positive reaction to cobalt chloride among women in our sample.

Among the pairs of allergens that showed highly statistically significant associations, several were chemically related or used for the same purpose; for example, thiuram mix/mercaptobenzo-

thiazole, balsam of Peru/fragrance mix and formaldehyde/CI+Me-isothiazolinone. The relationship between other pairs is unclear; for example, clioquinol/colophony, *N*-isopropyl-*N*-phenyl-4-phenylene-diamine/epoxy resin, wool alcohols/fragrance mix, epoxy resin/mercaptobenzothiazole and formaldehyde/CI+Me-isothiazolinone. Further studies are needed to clarify these findings.

The findings of the present study, combined with the reports on geographic/population differences in the prevalence of specific allergens in CD, indicate the need for further investigations to identify prominent local allergens for better adaptation of the standard patch test to local needs. In Israel, exclusion of the 6 allergens that yielded positive reactions in less than 1% of the patients might be considered.

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