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Patch Test Reactions to Metal Salts in Patients with Different Types of Dermatitis

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SUMMARY Metal allergies can be a clinical problem, especially in atopic individuals. This study is unique and contributes with new knowledge in everyday life skin care of irritant and atopic dermatitis patients. The aim of the study was to determine the frequency of positive patch test reactions to metal contact allergens (potassium dichromate, cobalt chloride, nickel sulfate, white mercury precipitate) in patients diagnosed with allergic contact dermatitis, irritant contact dermatitis, and atopic dermatitis. Between 2007 and 2011, patch testing was performed in 2185 patients according to the International Contact Dermatitis Research Group technique. Study results showed statistically significant differences in patch test responses to 2 allergens, nickel sulfate (χ^2=24.22; p<0.001) and cobalt chloride (χ^2=22.72; p<0.001). Nickel sulfate was the most common allergen in allergic contact dermatitis and atopic dermatitis, while for irritant contact dermatitis the most common allergen was cobalt chloride. Among the 4 tested metal allergens, the most common and relevant was nickel sulfate (χ^2=17.25; p<0.004), found in almost all study subjects. In conclusion, the increased awareness of allergens and their potential sources may help limit the use of these chemicals in consumer product manufacturing.

KEY WORDS: contact dermatitis, patch testing, potassium dichromate, cobalt chloride, nickel sulfate, white mercury precipitate

INTRODUCTION

Metal contact allergies can be a serious clinical problem, especially in atopic individuals because of the ubiquity of metals in consumer products (1). Metals are found in jewelry, alloys, stainless steel, fasteners, coins, soap, detergents, cosmetics, and hair dyes. Alloys containing Ni^{2+}, Co^{2+}, and Cr^{3+} are components of the implants used in reconstructive surgery, dentistry, orthodontic wires, and components of various others aids that cause deleterious metal ion reactions and pose serious problems in medical practice such as incompatible reactions to metal-containing biomaterials (2,3). Testing for metal allergies should precede endoluminal surgical procedures (4). A positive patch test for nickel sulfate and cobalt chloride is used when installing a self-expanding metal stent that contains roughly 55% of nickel (5). Often, metallic salts are responsible for the development of local skin reactions. Reactions are usually highly specific to a particular metal, but cross-sensitivity to other metals is also common because of simultaneous

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exposure to 2 or more metals. For example, metallic watches may be flashed with bright chromium after nickel plating. This is particularly the case with cobalt, nickel, and chromium (2). Ten to fifteen percent of the human population are affected by contact dermatitis due to metal ions (6,7). Patients may be sensitized to one or more chemical substances and reactions can be acute, subacute, subchronic, or chronic. Contact allergens with high sensitization indices frequently cause acute reactions. Metal ions such as Ni^{2+}, Co^{2+}, Cr^{6+}, and Hg^{2+} are haptens with a high immunogenic potential. Allergic contact dermatitis reactions to metal generally occur only if the metal salts are in the solution, as occurs with perspiration or exposure to body fluids. Irritative contact dermatitis is common in workers exposed to metal salts, dust, and fumes. Patch testing remains the gold standard to identify one or more substances that may contribute to the etiology of contact allergies. Patch testing with metals is usually included in standard series, at least with common metal allergens. All metal allergens may give false positive pustular reactions, especially when tested in atopic patients or on dermatitis-affected skin. Cobalt usually produces a non-allergic "poral" reaction due to toxicity to the acrosyringium (2). This study sought to establish the most common metallic allergens such as Ni^{2+}, Co^{2+}, Cr^{6+}, and Hg^{2+} associated with clinical diseases such as allergic contact dermatitis, irritant contact dermatitis, and atopic dermatitis. For the first time, this study contributes new knowledge important in the prevention of metallic allergens in patients with risk dermatoses.

PATIENTS AND METHODS

Patients

During a 5-year period (2007-2011), we reviewed the files of 2321 patients (age range 3-80, mean age 38 years) with different clinical diagnoses who were submitted to patch testing. Our investigation included patients with clinical diagnoses of allergic contact dermatitis (n=1684, 72.6%), irritative contact dermatitis (n=215, 9.3%), and atopic dermatitis (n=422, 18.2%). Patients receiving topical or systemic steroids or immunosuppressive therapy, and those suffering from chronic illnesses were excluded from the study. The enrolled population included 2185 patients, 1520 (69.5%) females and 665 (28.6%) males.

Test materials

The tested metal salts were potassium dichromate (0.5% petrolatum), cobalt chloride (1% petrolatum), nickel sulfate (5% petrolatum), and white mercury precipitate (10% petrolatum), obtained from the Zagreb Immunology Institute, Zagreb, Croatia.

METHODS

Data for 5 consecutive years (2007-2011) were collected at the Allergy Clinic, Department of Dermatology and Venereology, University Hospital Center Zagreb, Zagreb, Croatia. All patients were from the Zagreb area. All patch tests were applied on the upper back with 2 days of occlusion. According to the International Contact Dermatitis Research Group (ICDRG), we used a standard technique with Beiersdorf Scanpor tape. Test results were read on days 2 and 3 (D2 and D3) (8,9). Test results were interpreted using the following scale: negative reaction (0); macular erythema (+/-); erythema/infiltration and possibly papules (1+); erythematous papules and/or vesicles (2+); spreading blisters and/or crust with ulceration (3+); and irritant reaction (IR), whereby 1+, 2+, and 3+ were considered a positive allergic reaction (5,7). For statistical analyses, we used STATISTICA, Version 7.1. (StatSoft, Inc.). The χ^2-test was used to estimate differences between categories of variables and odds ratios with relative risks were used to calculate the probability of predictors. All statistical values were considered significant at $p \leq 0.005$.

RESULTS

The results of our study showed a correlation between allergens and clinical diagnoses or age. During the 5-year period (2007-2011), out of 2185 (1520 [69.5%] female and 665 [28.6%] male) patients, 1684 (72.6%) patients were diagnosed with contact allergic dermatitis, 215 (9.3%) with irritative contact dermati-

Table 1. Positive patch test reactions to metal salt allergens in 2185 patients according diagnosis

	ACD		74.3%	CD		19.9%	AD		14.3%	Total
Metal allergen	n	%	RR	n	%	RR	n	%	RR	
Potassium dichromate	445	17.8	**0.156**	13	20.6	**0.004**	94	19.6	**0.029**	552
Cobalt chloride	744	29.8	**0.292**	25	39.7	**0.008**	161	33.5	**0.051**	930
Nickel sulfate	1029	41.3	**0.455**	18	28.6	**0.005**	173	36.0	**0.055**	1220
White mercury precipitate	275	11.0	0.091	7	11.1	0.002	52	10.8	0.016	334

ACD = allergic contact dermatitis; ICD = irritative contact dermatitis; AD = atopic dermatitis; n-number of patients; RR = relative risk

Table 2. Distribution of 2185 subjects according to age (2002-2009)

Metal allergen	Age (yrs) 3-20		Age (yrs) 21-60		Age (yrs) 61-80		χ	*p*
	n	%	n	%	n	%		
Potassium dichromate	117	6.6	149	2.8	59	8.8	4.87	0.080
Cobalt chloride	251	14.1	541	10.3	60	8.9	15.10	**<0.001**
Nickel sulfate	244	13.7	613	11.7	67	9.9	23.55	**<0.001**
White mercury precipitate	67	3.8	114	2.2	27	4.0	0.06	0.970

χ^2-test; n = number of patients

tis, and 422 (18.2%) with atopic dermatitis. The analysis of the correlation between clinical diagnoses and patch test reactions revealed a prevalence of positive reactions in all clinical diagnoses, particularly in allergic contact dermatitis. We observed statistically significant differences in patch test response according to clinical diagnosis for 2 allergens, nickel sulfate (χ^2=24.22; p<0.001) and cobalt chloride (χ^2=22.72; p<0.001). Nickel sulfate and cobalt chloride were found to be the most relevant allergens. Nickel sulfate was the most common allergen in allergic contact dermatitis and atopic dermatitis; in irritative contact dermatitis, the most common allergen was cobalt chloride (Table 1). Among all 4 metal allergens, the most common and relevant allergen was nickel sulfate (χ^2=17.25; p<0.004), found in almost all subjects. If we look at the concordance between allergens and age, we see statistically significant differences in patch test responses to 2 allergens according to age (nickel sulfate (χ^2=23.55; p<0.001) and cobalt chloride (χ^2=15.10; p<0.001) (Table 2). Female patients were more allergic to nickel sulphate (n=1146; 75.4%) in all age groups and to cobalt chloride (n=783; 51.5%) in 21-60 age groups. Male patients aged 3-20 were mostly allergic to nickel sulfate (n=207; 31.1%) and those aged 61-80 were largely allergic to cobalt chloride (n=257; 38.6%); those age 21-60 were largely allergic to potassium dichromate (n=229; 34.4%) (Tables 3 and 4).

Our study was not randomized, so the results could not be extrapolated to explain contact sensitivity in the general population.

DISCUSSION

Traditionally, nickel, cobalt, and chromium are the most important contact allergens. Nickel sulfate is the leading allergen, followed by cobalt chloride, whereas allergies to white mercury precipitate are least common; our results also reflected these trends. Our study confirmed that diagnosing the four metal salt allergies is important because of exposure in everyday life skin care as well as professional allergens in patients with irritative contact dermatitis. Similar results have been reported by Jenerowicz *et al.* (6). Women were sensitized to all metals significantly more often than men (69.5% *vs.* 28.6%). A similar population were included in the study by Dou and Veien (10,11). Thyssen *et al.* estimated that up to 17% of women and 3% of men were allergic to nickel and that 1%-3% were allergic to cobalt and chromium (12). Nickel and cobalt allergies are more frequent in females, according to reports by Veien *et al.* and Schefer *et al.*; however, nickel sensitivity in women decreased with age, which could be explained by a reduced exposure to nickel (jewelry) and increasing public awareness (11,13). The prevalence of nickel allergy is decreasing among young women, whereas the prevalence of cobalt allergy remains stable. The prevalence of chromium allergy is currently increasing significantly in both sexes, mainly because of exposure (14). Female sex is the strongest risk factor for nickel allergy (prevalence ratio 3.74; 95% CI 3.51-3.98), according to a study by Uter *et al.* (15). In all 3 clinical diagnoses, positive reactions were predominantly found in females, mostly in those with allergic con-

Table 3. Distribution of positive patch test reactions in 1520 females according to age

Metal allergen	Age (yrs) 3-20		Age (yrs) 21-60		Age (yrs) 61-80		All	
	n	%	n	%	n	%	n	%
Potassium dichromate	63	11.8	282	15.0	24	21.8	396	24.2
Cobalt chloride	183	34.3	569	30.3	31	28.2	783	51.5
Nickel sulfate	245	45.9	857	45.6	44	40.0	1146	75.4
White mercury precipitate	43	8.1	170	9.1	11	10.0	224	14.7

n = number of patients

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Table 4. Distribution of positive patch test reactions in 665 males according to age

Metal allergen	Age (yrs) 3-20		Age (yrs) 21-60		Age (yrs) 61-80		All	
	n	%	n	%	n	%	n	%
Potassium dichromate	54	23.6	147	29.6	28	26.9	229	34.4
Cobalt chloride	66	28.8	164	33.0	27	26.0	257	38.6
Nickel sulfate	70	30.6	108	21.7	29	27.9	207	31.1
White mercury precipitate	39	17.0	78	15.7	20	19.2	137	20.6

n = number of patients

tact dermatitis. In adolescents (age 10 to 19), Duarte *et al*. (2003) found allergic contact dermatitis more frequently in fair-faced girls and on the faces of nickel-sensitive patients (31%) (16). In our study, the rate of nickel sulfate sensitivity was lower (13.7%) in this age group and in young females. In our study, patch test positive reactions to potassium dichromate did not differ significantly among different age groups (3-20 years, 6.6% and 61-80 years, 8.8%). This study yielded no major difference or reduction in the prevalence of dichromate sensitivity, unlike the study by Olsavszky *et al*. (17). It is important to consider the possibility of allergic contact dermatitis due to chromate exposure from handling cellular phones (which often contain hexavalent chromium plating) (18). Hegewald *et al*. (2005) found 11.05% of patients tested positive for nickel allergy, 2.10% for potassium dichromate, and 2.32% for cobalt chloride (19). The results of our study showed concordance between allergens and clinical diagnoses. The relationship between atopic dermatitis and allergic contact dermatitis has long been a discussed issue. Recent studies have revealed that atopic dermatitis patients are more or equally likely to develop allergic contact dermatitis (20). Allergic contact dermatitis is a T-cell mediated skin inflammation caused by repeated skin exposure to contact allergens, in our case to metals. In atopic dermatitis, a mixture of both Th2 and Th1 occurs and the interactions between them account for the clinical characteristics of the disease. Quantitative balance between Th1 and Th2 reactions along a time axis is very important to predict whether the cytokine pattern of atopic dermatitis patients favors or inhibits the development of allergic contact dermatitis (21). Nickel sulfate was the most common allergen for allergic contact dermatitis and atopic dermatitis; for irritative contact dermatitis, the most common allergen was cobalt chloride. Among dermatitis patients, the prevalence of metal allergy is even higher. Metal allergy may result in allergic contact dermatitis and systemic allergic (contact) dermatitis. Systemic contact dermatitis due to nickel caused by continual local skin contact could elicit a systemic reaction (Baboon syndrome) (10,22). In our study, the relative risk of allergic contact dermatitis to nickel was 0.455, increasing steadily and significantly with decreasing age for nickel and cobalt chloride. Recently, an alarming increase in the prevalence of nickel-induced allergic contact dermatitis has been noted worldwide, with the majority of cases occurring in women and children. A known risk factor for the development of nickel sensitization is early and prolonged exposure to the allergen. Children frequently encounter nickel in many everyday objects, and it has become apparent that cell phones may constitute a substantial source of nickel exposure (23). Machovcova reports the frequency of contact allergy to nickel and potassium dichromate in children and adolescents (24). Danish investigators conclude that at least 1% of nickel-allergic persons will develop systemic allergic contact dermatitis from daily exposure to "normal" amounts of dietary nickel (0.22-0.35 mg) (25). Treatment with disulfiram (250 mg/day) reduces the reaction to nickel by chelating the metal and increasing its excretion (26).

CONCLUSION

Three of the four frequent contact allergens in our study were metal salts. Nickel allergy is the most common skin allergy, with approximately 15% of women and 1% of men affected in the European Union (EU). Exposure occurs most often through nickel-releasing earrings or other jewelry. The EU Nickel Directive has resulted in a reduction of consumer exposure to nickel by setting a maximum limit of 0.5 μg/cm^2/week in items expected to be in prolonged contact with the skin. Standardized patch tests in which suspected allergens are applied to the skin are required for the investigation of suspected allergic contact dermatitis. To the best of our knowledge, no allergic reaction to these four metal salts have been described in epidemiological studies previously, particularly not in irritant and atopic dermatitis patients. For prevention of clinical exacerbation, avoidance of identified allergens is the mainstay of treatment, but occasionally, despite avoidance, other treatments such as

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corticosteroid creams, dietary regimens that avoid consumption of nickel-containing vegetables, phototherapy with ultraviolet light, or regimens that are even more aggressive may be required.

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