

ORIGINAL ARTICLE

Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population

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Abstract

Background Positive patch test results to transition metals (nickel sulphate, palladium chloride, cobalt chloride and potassium dichromate) alone and in combinations with one another are well known. Numerous factors may play a role in isolated and concurrent sensitization to these allergens.

Objective This study aims to describe the isolated and concurrent prevalence of sensitization to transition metals in a Spanish Dermatology Department, between 2000 and 2005, and to determine the prevalence of concomitant positive patch test reactions to different transitional metals.

Patients/methods Patients ($N = 1092$) were tested with the standard series of our Allergic Contact Unity, using a standardized technique. Data from these patients were recorded on a computer entry form and analysed. Statistical analyses to evaluated associations of metal contact allergy were performed, and we evaluated the concordance among these associations of transition metals.

Results Three hundred twenty (29.3%) patients reacted positively to nickel, 128 (11.7%) to palladium, 118 (10.8%) to cobalt and 82 (7.5%) to chromium. The prevalence of positive reactions to metals was 32.4%. The association of palladium–nickel was the most frequent, with an acceptable concordance ($k = 0.46$).

Conclusion This study illustrates that concomitant positive patch test reactions to different transitional metals are frequently seen in patients with allergic contact dermatitis. Our results reflect the high prevalence of sensitization to nickel in Spain.

Introduction

Positive patch test results to transition metals [nickel sulphate (Ni), palladium chloride (Pd), cobalt chloride (Co) and potassium dichromate (Cr)] alone and in combinations with one another are well known. At present, Ni and Cr have been acknowledged as very important contact allergens.

To our knowledge, Ni sensitization is more frequent in women mostly because of cheap jewellery and Cr sensitization affects men more often, generally in construction workers due to the contact with the cement. In contrast, most of the sensitization to Co, potent contact sensitizer in the human, although frequent in patients of both sexes, is

considered of unclear relevance. Equally, the sensitization to the Pd is still considered a puzzle, and its relevance is difficult to assess.

Ni, Cr and Co allergens are present in almost all standard patch test series worldwide; nevertheless, Pd is not included. Concomitant positive patch test reactions to different transition metals are frequently seen in patients with allergic contact dermatitis (ACD). The purpose of our study was to determine the isolated frequency of contact sensitization to transitions metals in our Allergic Contact Unity and to realize a description of present situation of ACD in our area. In addition, we evaluated the prevalence of the associations between them.

Materials and methods

A retrospective study was performed. We reviewed the history of all patients that were studied in our Allergic Contact Unity from 1 January 2000, to 31 December 2005. During this period, a total number of 1092 patients were studied in our unity.

Patch tests were performed on all patients using the standard series of our unity that included all allergens of standard series of Spanish Research Group in Contact Dermatitis and Cutaneous Allergy (GEIDAC) and other different allergens. Patch testing was performed on the upper back using approved allergens given by *Trolab® Hermal* (Reinbek, Germany) and *Chemotechnique Diagnostics®* (Malmö, Sweden). The metals allergens that we studied were nickel sulphate 5% in petrolatum (pet.), cobalt chloride 1% pet., potassium dichromate 0.5% pet. and palladium chloride 1% pet. These allergens were applied in adhesive strips of epicutaneous test (*Curatest®-Lohmann-Rauscher*) fixed with adhesive tape (*Omnifix®-Hartmann*). Additional patch test being applied depending on the patient's history and personal or occupational exposure. Readings were made after 2 and 4 days according to International Contact Dermatitis Research Group (ICDRG) criteria. A positive allergic patch test result was generally interpreted as homogeneous redness, and infiltration in the entire test area was scored as a 1+ reaction. Homogeneous redness, infiltration, papules and vesicles in the test area were scored as a 2+ reaction, and homogeneous redness, infiltration, and coalescing vesicles in the test area as a 3+ reaction.

In the present study, only allergic reactions were accepted as positive and those clinical reactions suggestive of an irritative reaction were excluded from the analysis (they were not considered negatives). Clinical relevance of positive reactions was established in relation to the clinical history of the patient. Atopic dermatitis was diagnosed according to the criteria of *Hanifin and Rajka*.¹

We calculated the overall prevalence of metal sensitizations in study population and prevalence of cosensitization to transition metals. Data were encoded and processed on an compatible computer. The data analysis was done using the statistical software programme SPSS (*Statistical Package for Social Sciences*, version 11.5, Chicago, IL, USA, with licence of University of Valladolid). Statistical analysis was performed with the Pearson's chi-squared test for the table of contingency 2×2 and with, as necessary, Fisher's exact test. Statistical significance level was taken as $P < 0.05$, with the odds ratio (OR) and its corresponding confidence interval (CI) at 95%. Logistic regression was used to examine the relationships between the variables and patch test results to the metal. We calculated

the concordance between the sensitization to different transition metals with table of contingency using kappa coefficient (k). A refined interpretative scale has been proposed with k -values of 0–0.2 suggesting slight, 0.2–0.4 suggesting fair, 0.4–0.6 suggesting moderate, 0.6–0.8 suggesting substantial and 0.8–1.0 suggesting perfect agreement.²

Results

During the years 2000–2005, we studied 1092 patients: 673 (61.6%) women and 419 (38.4%) men. The mean age of the patients was 41.4 ± 16.5 years. Of the patients tested, 29.3% ($N = 320$) had positive reaction to Ni. Individuals sensitized to Ni were more likely to be female (OR, 9.39; 95% CI, 6.2–14; $P < 0.000$) and have not occupational dermatitis (OR, 0.59; 95% CI, 0.4–0.8; $P < 0.007$); 11.7% of the patients ($N = 128$) had positive reaction to Pd, which also were more likely to be female (OR, 6.74; 95% CI, 3.7–12.2; $P < 0.000$); just like the sensitization of Co (10.8%; $N = 118$), which was more likely to be a woman (OR, 2.56; 95% CI, 1.6–4.0; $P < 0.000$). However, those who reacted to Cr (7.5%; $N = 82$) were more likely to be male, but these did not reach statistically significant. The association between the sensitization to Cr and occupational exposure were statistically significant (OR, 0.37; 95% CI, 0.2–0.6; $P < 0.000$; Table 1). The overall prevalence of metal sensitizations in study population is 32.4%.

Tables 2–5 summarize the results of prevalence of cosensitization between the transition metals, where ' n ' represents the absolute number of patients who presented both sensitizations. The concordance between the sensitization to different transition metals was calculated by the value of ' k ', with its corresponding CI at 95% (e.g., in Table 2 of all the 320 patients sensitized to Ni, a whole of 124 patients also was sensitized to Pd, with an acceptable concordance: $k = 0.46$; 95% CI, 0.40–0.52). The cosensitizations among Ni, Pd, Co and Cr are represented in fig. 1.

Table 1 Isolated prevalence of sensitization to transition metals

Metal	<i>n</i>	%	Sex		OD
			Women, <i>n</i> (%)	Men, <i>n</i> (%)	
Nickel	320	29.3	286 (89.4)*	34 (10.6)	Non OD*
Palladium	128	11.7	115 (89.8)*	13 (10.2)	NS
Cobalt	118	10.8	91 (77.1)*	27 (22.9)	NS
Chromate	82	7.5	45 (54.9)	37 (45.1)	OD*

*Statistically significant ($P < 0.05$).

NS, not significant.; OD, occupational dermatitis.

fig. 1 Cosensitization between transition metals (Ni, Co, Cr and Pd) in our study. Percentages in rectangle represent overall prevalence of metal sensitization in our population. Percentages on arrows represented the prevalence of patients cosensitized (i.e. 76.3% of those who reacted to Co also reacted to Ni). Continuous line: statistically significant association; discontinuous line: association to the limit of the statistical significance and discontinuous line (with points): not significant association.

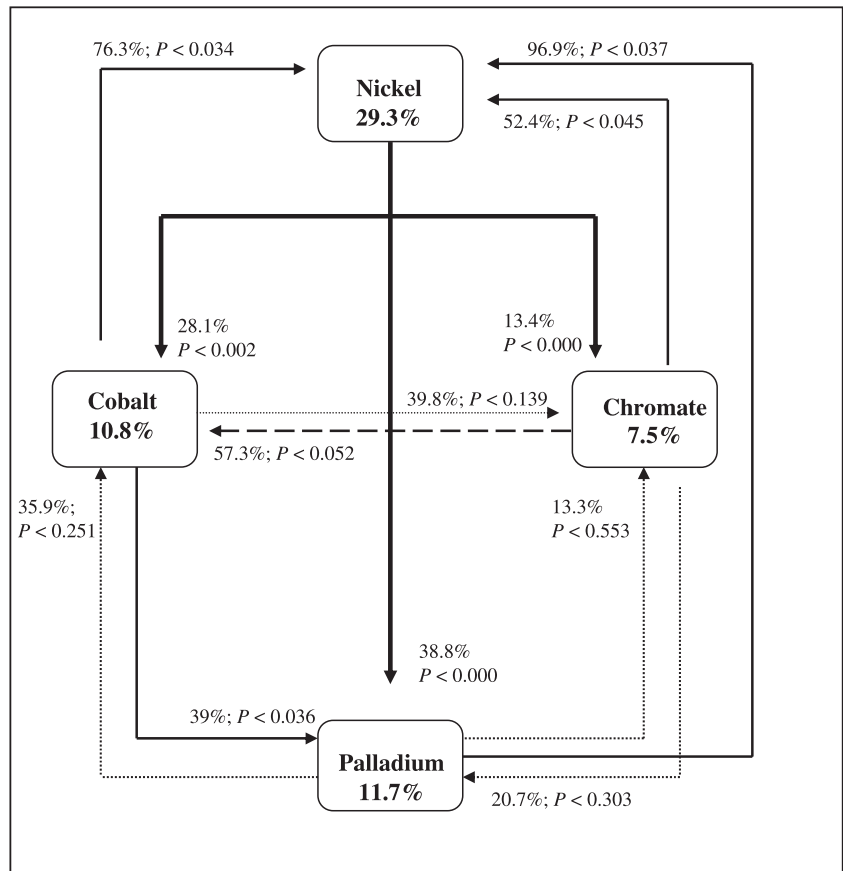


Table 2 Patients sensitized to Ni. Cosensitization and concordance with others transition metals (Pd, Co and Cr)

	<i>n</i>	%	<i>k</i> (95% CI)
Pd	124	38.8	0.46 (0.40–0.52)
Co	90	28.1	0.30 (0.24–0.35)
Cr	43	13.4	0.10 (0.05–0.15)

Table 3 Patients sensitized to Pd. Cosensitization and concordance with others transition metals (Ni, Co and Cr)

	<i>n</i>	%	<i>k</i> (95% CI)
Ni	124	96.9	0.46 (0.40–0.52)
Co	46	35.9	0.29 (0.21–0.37)
Cr	17	13.3	0.07 (0.00–0.14)

Table 4 Patients sensitized to Co. Cosensitization and concordance with others transition metals (Ni, Pd and Cr)

	<i>n</i>	%	<i>k</i> (95% CI)
Ni	90	76.3	0.30 (0.24–0.35)
Pd	46	39	0.29 (0.21–0.37)
Cr	47	39.8	0.42 (0.32–0.50)

Table 5 Patients sensitized to Cr. Cosensitization and concordance with others transition metals (Ni, Pd and Co)

	<i>n</i>	%	<i>k</i> (95% CI)
Ni	43	52.4	0.10 (0.05–0.15)
Pd	17	20.7	0.07 (0.00–0.14)
Co	47	55.3	0.42 (0.32–0.50)

Discussion

Metals are the most common cause of ACD in many countries.³ Ni, Cr and Co allergens are present in almost all standard patch test series worldwide, and these allergens are common causes of ACD;^{4–15} nevertheless, Pd

is not included in standard series. Positive patch test results to Ni, Co and Cr alone and in combinations with one another are well known and have been a source of much investigation.^{16–20}

Ni continues to be the major allergen, as shown by the patch test reactions of different studies⁴⁻¹⁵ largely due to a high prevalence in young women sensitized by jewellery. Women with ear piercing were more likely to be Ni allergic than women without piercing, and the frequency of Ni allergy increased with the number of piercing, but these associations were not observed in men.⁶

In our study, Ni allergic is through non-occupational exposure to costume jewellery and metallic accessories with a prevalence of sensitization of 29.3%. As in most previous studies, a positive reaction to Ni was significantly more prevalent among women. This high frequency of allergy to Ni previously reported by other Spanish authors^{14,21} reflects the local customs of frequent use of blue jeans with metal buttons, zippers and growing popularity of ear piercing and the use of several items of jewellery. A recent Spanish study has reported an increase in the frequency of positive reactions to Ni during the last decades (from 18.8% in 1977 to 26.6% in 2001),¹⁴ and at present, it is considered an important problem of public health. Recently, *Goon* and *Gohn*³ also observed in a study an increasing frequency in metal allergy in Singapore, between them an increase of sensitization to Ni. According to these authors, this increase is due to absence of legislative measures to limit Ni release in Ni-containing products. The recent legislation applied in some European cities,²² with the aim to reduce the quantity of Ni contained in products, has contributed to an important decrease of this sensitization in their younger population since in Germany²³ and Denmark,²⁴ but no such measures have yet been undertaken in Spain. In conclusion, the effects of this regulation has so far been demonstrated in clinical patients as well as population general.⁶ In Spain, we believe necessary the quick application of the European legislation, with the aim to diminish the sensitization to Ni. It will probably require decades before the decreasing load of Ni allergy can be demonstrated.

Pd is a known sensitizer in humans that use has increased in the past 10 years, and this increase in the utilization of this metal seems to go parallel to increase of sensitization.²⁵ It is used in dental appliances, jewellery, electrical appliances and as an automotive emission-control catalyst.²⁶ The frequency of Pd allergy in patch tests was reported to be 8% in Austria,²⁷ 9% in Turkey,²⁸ and 13% in Israel.²⁹ No data on Pd allergy were available from the previous studies in Spain; it has not been included in standard series of GEIDAC. In our study, this frequency is in accordance with values found others authors (11.7%). Since we have observed, the isolated allergy to the Pd is rare and, in most cases, it is observed together with positivity to other metals, especially with the Ni and or Co, appearing as concomitant sensitivities in patients with history of allergy to jewellery. Only two patients, electronics

industry workers, showed a positive reaction to Pd, without other concomitant reaction to transition metals; both positive results were considered relevant, reflecting of multiple uses in the world of electronics. Pd has emerged as a suitable substitute in Ni products, and there, female population is most at risk. In our study, female subjects were significantly more sensitized to Pd. We considered the need to follow this sensitization in future years, and for that reason, we propose to add the palladium chloride 1% in pet. to standard series.

Co is a common sensitizer that is associated to other allergens. Most positive patch tests to Co were associated with positive patch tests to Ni and Cr because pure Co allergy is uncommon.³ In this study, the prevalence of sensitization to Co was 10.8%. As the sensitization to Ni and to Pd, a positive reaction to Co was significantly more prevalent among women. Allergy to jewelry is a common cause of ACD to Co in women. Given the high frequency with which this allergen can be associated with hand eczema in those responsible for domestic work, in occasions, it has been suggested that contamination of household products may be of importance.³⁰

Cr is one of the most frequent causes of occupational diseases and the main cause of ACD due to cement in the construction industry. Of the four metals examined, only Cr was shown to have an association with an occupational exposure, and this allergen is seen more commonly in men, without significant difference. Cr sensitivity was found in 7.5% of our patients. In the last years, high Cr sensitization was explained by the expansion in the construction industry in parallel with an inadequacy of protective methods among workers. Nevertheless, at present, we observed a decrease of this sensitization that it has been attributed to successful preventive works measures practised by construction workers,¹⁴ and the European normative that restricts the marketing and use of cement containing more than 2 ppm hexavalent chromium came into effect on January 2005.³¹ In conclusion, our results are agreement with previously published reports, excluding the high sensitivity rates to Ni, with a rate of 29.3% of cases, non-comparable with the worldwide incidence.^{4,9-11,25}

Concomitant positive patch test reactions to different transition metals are frequently seen in subjects with ACD. These positive reactions, in fact, occur more frequently with salts of metals such as Ni, Pd, Co and Cr. Ni, Co and Cr have, for many years, been recognized as relatively common causes of ACD, but recently, we also must consider the Pd. *Hegewald et al.*¹⁸ reported a multifactorial analysis of the occurrence of metal cosensitization in a population in Germany and Austria, and *Ruff and Belsito*²⁰ recently reported a study of impact of various patient factors on contact allergy to Ni, Co and Cr. These authors

Table 6 Prevalence of isolated and concurrent transition metal allergy in different studies

Metals	Ruff and Belsito ¹⁹	Hegewald <i>et al.</i> ¹⁷	Kränke <i>et al.</i> ²⁴	Our study
Ni	13.1*	11.05	23	29.3
Co	6.8	1.3	6.8	10.8
Cr	3.8	2.1	3.2	7.5
Pd	–	–	8	11.7
Ni–Co	32.7	2.32	23.4	28.1
Co–Ni	63	–	78.9	76.3
Ni–Cr	10.9	0.65	5.5	13.4
Cr–Ni	37.8	–	39.6	52.4
Ni–Pd	–	–	33	38.8
Pd–Ni	–	–	94.6	96.9
Co–Cr	13.6	0.71	14.7	39.8
Cr–Co	24.4	–	31.3	57.3
Co–Pd	–	–	42.5	39
Pd–Co	–	–	36.2	35.9
Cr–Pd	–	–	–	20.7
Pd–Cr	–	–	–	13.3
Prevalence of sensitization metals	17.5	18.7	–	32.4
N	1.187	57.341	11.516	1.092

*Nickel 2.5% in pet.

– : Not provided.

demonstrate that cosensitization to transition metals occurs more frequently than would be expected by chance alone.

All our patients were tested to Ni, Co, Cr and Pd, and the prevalence of sensitization and cosensitization to transition metals was calculated. The results obtained were similar to that of previous studies as shown in Table 6. When we analyse this table, we observed only small differences to refer to high isolated prevalence of sensitization to Ni, Co and Pd in our patients. These discrepancies may be due to the fact that some studies¹⁶ are previous in the time (minor sensitization to metals than in present) and may be due to the high prevalence of women in our study (principally housewives). The most frequent association metal allergy was found between Pd and Ni, and these simultaneous hypersensitivities occur more frequently than others.^{32,33} The extended series of patch tests illustrates that Pd is a major coallergen with Ni in patients with a history of jewelry reactions.³³ In our patients, Pd allergy was found in 124 (38.8%) of 320 Ni-sensitive patients, and the 96.9% of patients sensitized to Pd were positive reactions to Ni, with a moderate concordance ($k = 0.46$). Isolated Pd allergy is rare; a minority of patients does react to Pd and not to Ni, to Co or to Cr: only 2 (1.6%) patients in our study. It has been reported that the coexistence of Pd and Ni sensitivities is not due to Ni contamination.³³ It might be due to immunologic cross-reactivity between the two metals. Co–Ni positive reactions were also frequent, Co allergy was found in 90

(28.1%) of 320 Ni-sensitive patients, with a regular concordance ($k = 0.30$). Concomitant allergy occurs mainly in female patients with history of intolerance to cheap jewellery. Ni–Cr, Cr–Ni, Co–Cr and Cr–Co positive reactions presented a slightly top percentage to other studies. These results can explain for the high isolated prevalence of Ni and Co in our area.

In conclusion, our study presents the isolated prevalence of sensitization to Ni, Pd, Co and Cr in a dermatology department and the prevalence of cosensitization to transition metals. Limitations of the study include its retrospective and exploratory nature, along with its availability of relatively small numbers of patients with particular metal allergy.

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