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The Significance of Previous Contact Dermatitis for Elicitation of Contact Allergy to Nickel

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In 2 earlier studies, we found increased nickel re-test reactivity at earlier experimentally induced nickel eczema sites. The aim of this study was to investigate if earlier contact dermatitis caused by another allergen or earlier irritant contact dermatitis also influenced the reactivity when nickel was applied topically on earlier but healed dermatitis sites. Twenty-three females with contact allergy to both nickel and cobalt were involved in the study. Experimental contact dermatitis from nickel, cobalt and SLS was induced on the lower back. One month later, challenge patch testing with a serial dilution of nickel on the previous but healed dermatitis sites, and on a control area, was done. The tests were read blindly. Significantly higher test reactivity was found at the site with previous allergic contact dermatitis from nickel, and significantly lower test reactivity was observed at the previous SLS dermatitis site. ***Key words: nickel allergy; cobalt dermatitis; SLS dermatitis; re-challenge; memory function; hyporeactivity; hyperreactivity.***

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Recently we have investigated the significance of previous allergic contact dermatitis from nickel for the provocation of nickel dermatitis upon topical re-exposure of the allergen. We found significantly higher test reactivity in areas where there had been nickel contact dermatitis previously, compared with areas where there had never been nickel eczema before. We also found that the shorter the time interval between previous eczema and topical re-exposure, the stronger the reaction (1). Whether this increased re-test reactivity is allergen-specific or also exists after allergic contact dermatitis from other sensitizers is unclear. In contrast to the increased nickel reactivity on re-exposure on skin with previous nickel dermatitis, similar testing with sodium lauryl sulfate (SLS) on skin with previous SLS dermatitis resulted in decreased reactivity (2). The aim of this study was therefore to investigate and compare the degrees of nickel reactivity on skin where there had previously been allergic contact dermatitis from nickel and cobalt, or irritant contact dermatitis from SLS. The combination of nickel allergy and hand eczema is common. Often there is a multifactorial background of exposure to irritants and sensitizers other than nickel. Better knowledge of the interaction of these different factors is necessary for our understanding of the development of hand eczema, and treatment, rehabilitation and prevention of allergic contact dermatitis from nickel.

MATERIAL AND METHODS

Subjects

Twenty-three female patients with contact allergies to both nickel and cobalt, as demonstrated by patch testing with the European Standard Series, were involved in the study after its approval by the Ethics Committee of Lund University Medical Faculty. Informed consent was obtained from each patient. The mean age of the nickel/cobalt-hypersensitive females was 39.4 years (range 21 – 57 years).

Experimental allergic and irritant contact dermatitis

Before provocation of experimental allergic and irritant contact dermatitis, the patients were tested with a serial dilution of nickel, cobalt and SLS to determine the present degree of reactivity. An aqueous stock solution with nickel (nickel sulfate $\times 6$ H_2O, Merck, Germany) at 12.5% w/v was prepared and further diluted by a factor of 2.5 down to 0.0032% w/v. An aqueous stock solution of cobalt (cobalt chloride $\times 6$ H_2O, Janssen Chimica, Belgium) at 7.8% w/v was prepared and further diluted by a factor of 2.5 down to 0.2% w/v. An aqueous stock solution with SLS (Sigma Chemical, USA, 95% purity) at 2.0% w/v was prepared and further diluted by a factor of 2.0 down to 0.25% w/v.

Each patient was tested with 10 consecutive dilutions of nickel within the range of 12.5 – 0.0032% w/v, 5 consecutive dilutions with cobalt within the range of 7.8 – 0.2%, and 4 consecutive dilutions with SLS within the range of 2.0 – 0.25%. Fifteen µl of the test solutions was micropipetted onto filter paper discs of small Finn Chambers (Epitest Ltd., Oy, Finland) on Scanpor (Norgesplaster A/S, Norge). The tests were applied on the upper part of the back. The nickel and cobalt tests remained for 2 days, while the SLS tests remained for only 1 day. The reading for all tests was performed on day 3. After reading of the serial dilutions, 3 areas on the lower back were provoked with nickel, cobalt and SLS, respectively, to induce contact dermatitis. On this occasion, 1.0 ml of the solutions with the lowest concentration resulting in a ++ reaction (according to ICDRG criteria) was micropipetted onto 6.0×7.0-cm filter paper and attached onto an 8.0×9.0-cm hydrocolloid dressing (Duoderm, Convatec, Denmark).

Four patients (numbers 4, 8, 12 and 13) were excluded because they tested negatively to all nickel solutions. Before this provocation, the lowest part of the back, an area where the patients had not been tested before, and an area unusual for nickel, cobalt and irritant contact dermatitis, was divided in 4 symmetrical parts. For each patient, randomization according to a Latin square table determined the test area to be used for the different test solutions: nickel, cobalt, SLS, and one blank.

The hydrocolloid dressing test was applied under an adhesive tape (Mefix, Mölnlycke, Sweden) on the back for 2 days for the nickel and cobalt solutions and 1 day for the SLS solution.

On day 6, the areas were inspected to assure that the experimentally provoked dermatitis was, as expected (Fig. 1), at least a homogeneous infiltrated erythema. To enable exact localization of the experimentally induced dermatitis areas even after healing, the distances from the most proximal and distal part of the 6.0×7.0-cm dermatitis areas from the spine were measured. We also measured the shortest distance to the lowest part of the scapula, to the most prominent vertebra of the neck and to the hip. With a skin marker, the corners of all experimentally induced dermatitis sites were indicated. During the following weeks we also instructed the patients to keep these corners visible with a skin marker.

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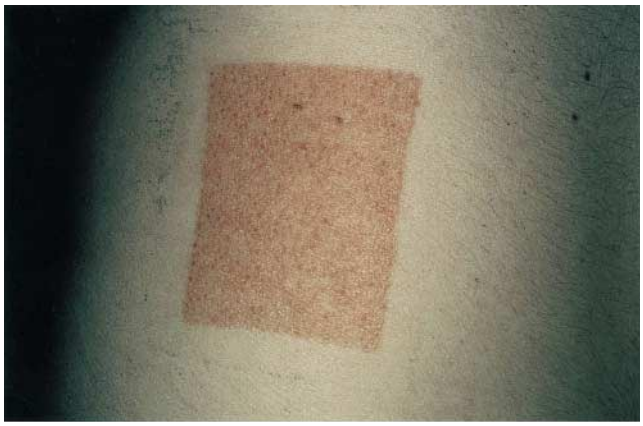

Fig. 1. Experimental contact dermatitis from nickel on the lower back, day 3.

Challenge patch-testing

One month after the provocation, when the dermatitis was completely healed, the patients were patch-tested with a serial dilution of nickel sulfate on the 4 symmetrical parts of the lower back, in 3 of which there had been dermatitis one month before, and in the remaining area where there had never been dermatitis (control area).

Each individual was tested with 6 consecutive test preparations within the range of 12.5–0.0013% w/v (12.5, 2.0, 0.32, 0.051, 0.0082 and 0.00013% w/v). Fifteen μl of the nickel solutions was micropipetted onto filter paper discs of small Finn Chambers on Scanpor and applied for 2 days. Reading was performed one day later by a reader who did not know the localities of the various provocation areas. The patients were told not to communicate with the reader. The reactions were scored according to ICDRG criteria, with 2 classifications added between the 3 usual positive gradings: strong + and ++ reactions were graded as + (+) and ++ (+), respectively (3). The different steps, including the intermediate steps, are defined as follows: + =erythema, infiltration; + (+)=erythema, infiltration and a few papules; ++=erythema, infiltration and papules; ++(+)=erythema, infiltration, papules and a few vesicles; +++=intensive erythema, infiltration and vesicles.

Statistical calculations

The scores were transformed into numerical values to enable statistical calculations as follows: −=0, (+)=0.5, +=1, + (+)=1.5, ++=2, ++(+)=2.5 and +++=3. Based on these numerical scores, the challenge patch test reactivity was calculated in 2 ways: (i) the scores for all reactions representing one area were summed (summarized test scores=STS) (1) and for the same area; (ii) the minimal eliciting concentration (MEC) (4), which was defined as the lowest concentration eliciting at least a + reaction, was registered.

The positive test reactions were not always continuous. When negative and/or doubtful reactions were followed by the same number or more of positive reactions, the lowest positive concentration was registered as the MEC. In all other situations, the concentration above the first negative or doubtful reaction was registered as the MEC. For example, a patient could have positive reactions of 12.5, 2.0 and then 0.051%, meaning that 0.32% was negative or doubtful. In this case, 0.051% would be registered as the MEC.

Non-parametric statistical methods were applied (5, 6). To compare the reactions in the 4 test sites, Friedman's test was used. In addition, pairwise comparisons (blank vs. SLS, blank vs. nickel, blank vs. cobalt, nickel vs. cobalt and nickel vs. SLS) were performed using the two-sided Wilcoxon signed-rank test.

RESULTS

In Table I, STS and MEC data are given for each of the 4 challenge sites. Table II gives the results of the statistical calculations.

Hence, a systematic difference in reactivity for both STS and MEC was observed when considering the 4 test areas altogether ($p<0.001$, Table II). The highest reactivity for both STS and MEC was noted for the nickel area, followed by cobalt, the blank, and finally the SLS area, which had the lowest reactivity. The pairwise comparisons revealed no significant difference in reactivity between blank and Co. When compar-

Table I. *Individual summarized test scores (STS) and minimal eliciting concentrations (MEC) are given for all patients for the 4 challenge sites*

Patient no.	Never eczema		Nickel		Cobalt		SLS	
	STS	MEC	STS	MEC	STS	MEC	STS	MEC
1	2.5	12.5	9	0.008	1.5	12.5	4	2.0
2	5.5	0.32	11.5	0.008	6.5	0.32	5.5	0.32
3	7	0.32	6.5	0.05	6.5	0.32	4	2.0
4	5	2.0	3	12.5	6	2.0	3	12.5
5	7	0.32	7	0.05	8	0.05	6	0.32
6	4.5	2.0	2.5	12.5	1.5	12.5	2.5	12.5
7	6	0.32	4.5	0.05	3.5	12.5	2	12.5
8	7.5	0.32	7.5	0.32	7.5	0.32	6.5	0.32
9	6	0.32	6	0.05	5.5	0.32	5	0.32
10	7	0.32	7	0.32	7	0.32	5	2.0
11	2	12.5	3	0.32	2	12.5	2	12.5
12	8	0.32	16	0.0013	10	0.008	9	0.05
13	4.5	2.0	10.5	0.05	4.5	0.32	8	0.32
14	9.5	0.0013	11.5	0.0013	7.5	0.32	6	0.05
15	14	0.0013	9	0.008	12	0.05	6	0.32
16	8.5	0.32	7.5	0.32	9.5	0.05	6	2.0
17	5	2.0	7.5	0.32	12	0.008	4.5	2.0
18	5.5	0.05	11.5	0.0013	4.5	2.0	7	0.05
19	6	0.32	11	0.008	6.5	0.32	6.5	0.32

Table II. *The results of the statistical calculations*

STS	$P_F < 0.001$
Blank vs. SLS	$P_W = 0.05$
Blank vs. Co	$P_W = 0.8$
Blank vs. Ni	$P_W = 0.08$
Ni vs. Co	$P_W = 0.09$
Ni vs. SLS	$P_W < 0.001$
MEC	$P_F = < 0.001$
Blank vs. SLS	$P_W = 0.15$
Blank vs. Co	$P_W = 0.7$
Blank vs. Ni	$P_W = 0.05$
Ni vs. Co	$P_W = 0.04$
Ni vs. SLS	$P_W < 0.001$

$P_F = p$ value obtained from Friedman's test; $P_W = p$ value obtained from Wilcoxon's rank test.

ing blank with SLS, a significant difference was observed for STS; there was only a tendency towards difference for MEC ($p = 0.15$). When comparing blank with Ni and Ni with Co, significant differences were observed for MEC, while there were only tendencies towards difference for STS ($p = 0.08$ and $p = 0.09$, respectively). Ni vs. SLS revealed significant differences for STS and MEC.

DISCUSSION

On the design

In this study, we chose cobalt as the other allergen because cobalt allergy is very common in nickel-allergic individuals (7). To induce irritant contact dermatitis, SLS was used. This substance has frequently been used in experimental studies on irritant contact dermatitis (8). With regard to SLS, the test occlusion time used was 24 h, the time most frequently used in studies of irritant skin reactions (8).

The same test system was used as in a previous study (1) to produce an experimental eczema as homogeneous as possible. In order to provoke the same degree of epidermal inflammation from the experimentally induced allergic and irritant contact dermatitis, the patients were patch tested with a serial dilution of nickel sulfate, cobalt chloride, and SLS immediately before the provocation. This procedure also allowed us to assess the present degrees of reactivity, because we have earlier shown large intra-individual variation in patch test reactivity from one test occasion to another. The lower back was chosen as the test area for the experimentally induced dermatitis because it is an area where this kind of dermatitis seldom appears. The lower back was divided into 4 symmetrical parts and the 3 types of contact dermatitis were induced randomly. Thus, any undesired influence of the anatomical sites on the test results could be avoided (9). Furthermore, the design included a blind reading.

A time interval of one month between the experimentally induced contact dermatitis and the topical challenge with nickel was chosen because of previous findings of strongest re-test reactivity at that time, and the expectation of macroscopically completely healed skin (1). In support of our choice of this time interval, a recent study on SLS irritation showed normalized skin after 4 weeks (10).

On the results

In 2 earlier studies (1, 11), we have found increased re-test reactivity at earlier nickel eczema sites when re-exposing the test area with topical application of nickel. In the first study (1), we found increased reactivity after both 3 and 6 weeks at earlier nickel dermatitis sites. In the second study, we found increased reactivity even after 8 months. The increased reactivity was also found to be time-related: the shorter the time since previous eczema, the stronger the reaction (1). These results were confirmed in the present study, where the highest nickel reactivity was found at the previous nickel dermatitis site (Tables I and II). However, no increased nickel reactivity was found on skin with previous allergic contact dermatitis from cobalt as compared with control skin. These results speak in favour of an allergen-specific memory function in the skin. Other studies also point in that direction. Oral challenge with nickel may cause flare-up of previous nickel patch test sites (12, 13), but no flare-up reactions at previous irritant patch test sites or tuberculine test sites (14). Furthermore, in patients hypersensitive to gold and other sensitizers in the standard series, systemic administration of gold induced flare-up of previous positive gold patch tests, but not positive tests from other sensitizers (15).

The lowest test reactivity after topical challenge with nickel was seen in the area where there had been experimental irritant contact dermatitis before. This test reactivity was even lower than that of the control skin. Hyporeactivity caused by SLS has earlier been observed in skin where SLS has been applied once daily for 3 weeks, followed by topical SLS challenge 3, 6 and 9 weeks later. Hyporeactivity was only demonstrated at SLS challenge after 6 and 9 weeks (2). The mechanism of this hyporeactivity is unclear (2). SLS-induced hyporeactivity from skin applications of SLS has also been reported in skin distant from the SLS exposure sites (16). It is possible that such hyporeactivity may also exist in this study, but if so, this influence ought to be the same for all test areas. Although there was individual variation in nickel test reactivity, this variation included both increased and decreased reactivity between the 2 test occasions with nickel dilutions, and thus no general tendency of up- or downgrading was shown. This degree of variation was similar to that reported in an earlier study. Like irritants, UV radiation also induces a state of hyporeactivity in the skin (2).

We have recently investigated the significance of previous irritant contact dermatitis for the elicitation of nickel dermatitis (11). Irritant contact dermatitis was induced by SLS and dithranol. However, no decreased nickel reactivity was observed when topical challenge was carried out 3 and 6 weeks after the induction of the experimentally induced contact dermatitis (11). The reason for this discrepancy in nickel reactivity between our 2 studies is unclear. In a previous study, the intensity of the experimentally induced contact dermatitis was significant for the subsequent flare-up reactions after oral nickel provocation (in manuscript). Because of this finding, efforts were made in this study to make the intensity of the epidermal inflammation from the experimentally induced contact dermatitis from nickel, cobalt and SLS as equivalent as possible. In our previous study (11), there was no testing with serial dilutions of SLS and dithranol prior to the provocation, i.e. the same degree of attention was not paid to the intensity of the experimental contact dermatitis. Stronger reactions were therefore seen in some patients.

On the disease

Nickel allergy is very common (17) and often found in adults with hand eczema (18). Occasionally, a single nickel exposure may cause hand eczema, and when such an exposure is repeated, the nickel hyperreactivity may be significant for the elicitation. However, most often, hand eczema has a multifactorial background. Clinically, the combination of wet work and nickel allergy in particular has been considered to constitute a high risk for the development of hand eczema (19). This opinion is also supported by experimental data. An enhanced reactivity to nickel was observed some hours after damage of the skin barrier by SLS (4). Patch testing with SLS and nickel in combination has also resulted in increased nickel reactivity (20). However, most hand eczemas are chronic, which means that both previous and present factors of possible significance for the hand eczema have to be considered. In a nickel-hypersensitive patient, previous nickel dermatitis (1, 11) and present irritant exposure (4, 20) may enhance the hand eczema, while previous irritant dermatitis may impair. The interaction of these factors is unclear, and further investigations are needed.

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REFERENCES

1. Hindsén M, Bruze M, Christensen OB. The significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel. Contact Dermatitis 1997; 37: 101 – 106.
2. Widmer J, Elsner P, Burg G. Skin irritant reactivity following experimental cumulative irritant contact dermatitis. Contact Dermatitis 1994; 30: 35 – 39.
3. Fregert S. Patch testing. In: Fregert S, ed. Manual of contact dermatitis. Copenhagen: Munksgaard, 1981: 71 – 81.
4. Allenby CF, Basketter DA. An arm immersion model of compromised skin. II. Influence on minimal eliciting patch test concentrations of nickel. Contact Dermatitis 1993; 28: 129 – 133.
5. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.
6. StatXact 3 for Windows. User's Manual. Cambridge MA: CYTEL Software Corporation, 1995.
7. Andersen KE, Burrows D, White IR. Allergens from the standard series. In: Rycroft RJG, Menné T, Frosch PJ, Benezra C, eds. Textbook of contact dermatitis. Berlin: Springer-Verlag, 1992: 413 – 456.
8. Agner T. Non-invasive measuring methods for the investigation of irritant patch test reactions. Acta Derm Venereol (Stockh) 1992; Suppl 173: 7 – 10.
9. Lindelöf B. Regional variations of patch test response in nickel-sensitive patients. Contact Dermatitis 1992; 26: 202 – 203.
10. Young Lee J, Effendy I, Maibach HI. Acute irritant contact dermatitis: recovery time in man. Contact Dermatitis 1997; 36: 285 – 290.
11. Hindsén M, Christensen OB. Delayed hypersensitivity reactions following allergic and irritant inflammation. Acta Derm Venereol (Stockh) 1992; 72: 220 – 221.
12. Christensen OB, Möller H. External and internal exposure to the antigen in hand eczema of nickel allergy. Contact Dermatitis 1975; 1: 136 – 141.
13. Cronin E, Di Michiel AD, Brown SS. Oral challenge in nickel-sensitive women with hand eczema. In: Brown SS, Sunderman FW, eds. Nickel toxicology. London: Academic Press, 1980: 149 – 152.
14. Christensen OB, Lindström C, Löfberg H, Möller H. Micromorphology and specificity of orally induced flare-up reactions in nickel-sensitive patients. Acta Derm Venereol (Stockh) 1981; 61: 505 – 510.
15. Möller H, Björkner B, Bruze M. Clinical reactions to systemic provocation with gold sodium thiomalate in patients with contact allergy to gold. Br J Dermatol 1996; 135: 423 – 427.
16. Lammintausta K, Maibach HI, Wilson D. Human cutaneous irritation: induced hyporeactivity. Contact Dermatitis 1987; 17: 193 – 198.
17. Nielsen NH, Menné T. Nickel sensitization and ear piercing in an unselected Danish population. Contact Dermatitis 1993; 29: 16 – 21.
18. Lantinga H, Nater JP, Coenraads PJ. Prevalence, incidence and course of eczema on the hands and forearms in a sample of the general population. Contact Dermatitis 1984; 10: 135 – 139.
19. Fregert S. Occupational dermatitis in 10-year material. Contact Dermatitis 1975; 1: 96 – 107.
20. Grandolfo M, Pipoli M, Foti C, Bonamonte D, Rigano L, Vena GA, et al. Influence of vehicle on patch test response to nickel sulfate. Contact Dermatitis 1996; 35: 173 – 174.