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Irritant Reactivity Is a Better Risk Marker for Nickel Sensitization than Atopy[1]

PETER ELSNER and GÜNTER BURG

Department of Dermatology, University of Zurich, Switzerland

In order to optimize patch test strategies and counselling in occupational dermatology, it is important to identify risk markers of contact sensitization. Since nickel is the most frequent contact allergen in European countries, we studied the potential of the irritant response to sodium lauryl sulfate (SLS) to predict nickel sensitization. In 100 patients subsequently tested in our patch test clinic with the standard patch test series of the German Contact Dermatitis Group (DKG), the atopy score as described by Diepgen et al. was determined and an SLS patch test was performed. Relative transepidermal water loss (TEWL), expressed as the ratio between the TEWL of the SLS-irritated and the control site, atopy score, age and sex were tested by logistic regression analysis for their association with patch test-proven nickel sensitization. Age, sex and relative TEWL were found to be significant predictors of nickel sensitization, whereas the atopy score was not. Patients with nickel sensitization were significantly younger (mean age 35.0 ± 4.1 versus 46.2 ± 2.1 years), more frequently of female gender (28.6% versus 3.9%) and had a significantly higher relative TEWL following SLS exposure (471.0 ± 40.8% versus 344.0 ± 16.2%). The mean atopy score of nickel-sensitized patients was slightly higher than that of patients not sensitized (6.0 ± 1.3 versus 5.3 ± 0.5), but the difference was not significant. In previous studies on larger patient samples, atopy was found to be a predictor of nickel allergy. This discrepancy may be explained by the smaller statistical power of our study. We conclude that although nickel sensitization may be frequently associated with atopy, TEWL response to SLS irritation seems to be more closely associated with nickel allergy. ***Key word: Contact dermatitis.***

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P. Elsner, Department of Dermatology, University of Zurich, Gloriastr. 31, CH 8091 Zurich, Switzerland.

Both in Europe and in the US, nickel is the most frequent allergen causing delayed-type hypersensitivity (1). Furthermore, it has been stated that the prevalence of nickel allergy is still increasing (2, 3). Certain risk factors for nickel sensitization have been identified. There is agreement that nickel allergy is more prevalent in patients of female sex and in younger persons (4, 5). Ear-piercing has been identified as another important risk factor, at least in women (6).

An association between nickel sensitization and atopy proposed by some studies (4, 7, 8) could not be confirmed by other investigators (5, 6). This may at least in part be due to the fact that there is no agreement how atopy should be defined in a reproducible manner and in a practical way for epidemiological studies. A solution to this problem has recently been suggested by Diepgen et al. (9), who published statistically evaluated clinical criteria for a quantitative assessment of atopic disposition by an "atopy score" which was used in the present study.

Irritant reactivity, i.e. an individual's inflammatory response to irritants applied to the skin, may be another risk factor for nickel sensitization that has not been studied in a systematic manner so far. Irritant reactivity has been shown to depend on the type of irritant, mode and time of exposure, age, race and atopic disposition. The anionic surfactant sodium lauryl sulfate (SLS) has been used as a model irritant in many studies (10, 11). We assessed irritant reactivity in this study by inducing subliminal irritant dermatitis with SLS and quantified the irritant reaction by evaporimetry, a non-invasive bioengineering technique.

PATIENTS AND METHODS

Study population

In a prospective study of 100 consecutive adult patients at our patch test clinic routinely tested for contact dermatitis of unknown origin with the standard patch test series of the German Contact Dermatitis Group (DKG), the atopic disposition was quantified by determining the Erlangen atopy score and irritant reactivity was evaluated by an SLS patch test. The sex distribution of the patient population was 51 males and 49 females. The patients were between 18 and 86 years of age (mean 44.4, standard error of the mean (SEM) 2.0 years).

Patch-testing

The patients were patch-tested with the DKG standard series in Finn chambers on Scanpore® (Hermal, Reinbek, Germany). The strips were applied to the subjects' upper backs, using adhesive tape, and left in place for 24 h, which is an application time accepted by both the DKG and the Swiss Contact Dermatitis Research Group (SCDRG). The patches were removed by clinic staff. The first reading took place 30 min after removal of the strips when the traumatic erythema had faded. A 2nd and a 3rd reading were made at 48 h and 72 h, respectively. Test reactions were scored as recommended by the ICDRG.

Erlangen atopy score

The Erlangen atopy score, as a quantitative marker of disposition to atopic dermatitis, was determined as described by Diepgen et al. (9). The patients are examined for 20 clinical criteria. If a feature is present, between 1 and 3 score points are given, depending on the statistical association of the feature with atopy. Based on this score system patients with more than 10 points are considered atopic; patients with 6–10 points are suspected to be atopics. None of our subjects suffered from chronic flexural dermatitis, which is used as the definition of atopic dermatitis in the Erlangen atopy assessment.

Determination of irritant reactivity

75 µl of a 1% aqueous solution of SLS (Sigma, St. Louis, MO) and of physiological saline (0.9% NaCl in distilled water) as a control were

[1] Results of this study were presented at the 74th Annual Meeting of the Swiss Society for Dermatology and Venereology, Bern, September 18–19, 1992.

Table I. *Logistic regression analysis of factors possibly influencing the occurrence of nickel sensitization*

Variable	B	Exp(B)	*p*
Age	−0.0366	0.9641	0.0397
Sex	−1.2180	0.2958	0.0039
Atopy score	0.0248	1.0251	0.7436
Irritant reactivity	0.0048	1.0048	0.0169
Constant	−2.6367		0.0355

applied to filter paper disks in large Finn chambers (inner diameter 1.2 cm, Epitest Ltd., Hyrlä, Finland). The Finn chambers were applied to the skin with adhesive dressing. Application site was the medial volar side of one forearm.

After 24 h, the chambers were removed. Irritant reactivity was assessed by measuring the transepidermal water loss (TEWL) at the test and the control site one day later (at 48 h). All measurements were performed after the subjects had been physically inactive for at least 15 min. TEWL was measured with an evaporimeter (Servo Med Ep 1, Servo Med, Stockholm, Sweden) under neutral environmental circumstances. The hand-held probe was fitted with a 1-cm tail cimmey extension to reduce air turbulence around the hydrosensors, and the metallic shield (supplied by Servo Med) minimized the possibility of sensor contamination.

Skin temperature was monitored by placing a thermistor (WTW Instruments, Waldkirch, Germany) on the skin surface. TEWL values were converted to values at a standard reference temperature of 30°C as previously described (12).

Statistical methods

Statistical computations were performed with a statistical package (SPSS for the Macintosh, SPSS, Chicago, IL) on an Apple Macintosh computer.

Relative TEWL was computed in percent of SLS-treated to water-treated control sites. Differences in frequency of variables between nickel-sensitive and non-sensitive patients were evaluated for significance by chi-square statistics (procedure CROSSTABS). Difference between means of variables for nickel-sensitive and non-sensitive patients were checked for significance using the Wilcoxon U-test for non-paired samples (procedure NPAR TESTS).

The association of several independent variables (age, sex, atopy score and irritant reactivity as expressed by relative TEWL) with a dependent variable (nickel sensitivity) was evaluated by logistic regression analysis (procedure LOGISTIC REGRESSION).

RESULTS

Of the 100 patients, 15 had an atopy score of >10 (high probability of atopy), 32 had an atopy score between 6 and 10 (possible atopy) and 58 had an atopy score of <6 (low probability of atopy).

Among the 100 patients tested, 16 showed positive reactions to nickel sulfate in the patch test. Patients with nickel sensitization were significantly ($p < 0.05$) younger (mean age 35.0 ± 4.1 versus 46.2 ± 2.1 years) and significantly ($p < 0.001$) more often of female sex (28.6% nickel-positives in females versus 3.9% in males) than non-sensitized patients.

Baseline TEWL did not differ significantly between nickel-negative and nickel-positive patients (5.2 ± 0.4 versus 5.3 ± 0.4 g/m^2*h). Baseline TEWL in patients with a low risk of atopy (atopy score <6) was 5.4 ± 0.5, in patients with possible atopy (atopy score between 6 and 10) it was 4.5 ± 0.3, and in patients with a high probability of atopy it was 6.1 ± 1.1 g/m^2*h. These differences were not significant.

Relative TEWL of the SLS-treated site as an indicator for irritant reactivity was significantly ($p < 0.01$) higher in nickel-sensitized patients ($471.0 \pm 40.8\%$ versus $344.0 \pm 16.2\%$ in non-sensitives). There was no significant difference in irritant reactivity for any other allergen in the standard series. Regarding atopy and nickel sensitivity, there was no significant difference in the atopy score between the two groups (mean score of 6.0 ± 1.3 in nickel sensitives compared to 5.3 ± 0.5 in non-sensitives).

The results of logistic regression analysis are shown in Table I.The Table shows that the factors age, sex and irritant reactivity were significantly associated with the occurrence of nickel positivity in the patch test, whereas this was not the case for atopic disposition as expressed by the atopy score. B is coefficient of the logistic regression equation estimated from the data; Exp(B) is e raised to the power B indicating the factor by which the odds change when the independent variable is increased by one unit; *p* is the likelihood of error. Although atopy was similarly associated with nickel sensitivity as irritant reactivity, this association did not reach significance. The closest significant association with nickel sensitivity was found for irritant reactivity, followed by age and, less closely, by sex. Using the logistic regression model, a correct classification into the groups of sensitized and not sensitized patients could be made in 89%.

DISCUSSION

Regarding baseline TEWL, no significant difference was noted between nickel-sensitive and non-sensitive subjects and between subjects with different probabilities of atopy. The finding of Werner & Lindberg, who showed a higher TEWL in clinically normal skin in patients with atopic dermatitis (13), is not in contrast to our results, since there were no patients with atopic dermatitis as defined by dermatitis of the flexures in our population, but only subjects with signs of atopic disposition.

Nethercott & Holness noted in a study of 1074 subjects with contact dermatitis that patients who had positive reactions to nickel reacted more frequently to marginal irritants such as formaldehyde and benzoyl peroxide (14). They speculated that the irritancy threshold might be reduced in nickel-sensitive subjects.

In the present study, we were able to show a significant association between nickel sensitivity and irritant reactivity. In a larger patient sample, this confirms the results of a study by van der Valk et al. who showed a higher TEWL increase following SLS treatment in nickel-allergic persons compared to a control group (15).

How the various risk factors or risk markers for nickel sensitivity are related to each other cannot be decided at this stage. Irritant reactivity may well play a key role in the development of nickel sensitization. Irritant reactivity is age-dependent with higher irritability in young persons (16). Furthermore, irritant reactivity is increased in atopic subjects. Increased irritant reactivity will result in a higher frequency of irritant dermatitis, which will enhance sensitization when the individual is exposed to the allergen (afferent phase of delayed-type allergy), and which will enhance allergic dermatitis

(efferent phase of delayed-type allergy) (17). However, nickel seems to be a special irritant-dependent allergen in this context, since we did not observe any association with irritant reactivity for any other allergen in the standard series.

Hand eczema is a frequent occupational disease in women doing "wet work". Nilsson & Back have hypothesized that while metal dermatitis and atopy seem to be related to the occurrence of hand eczema in this population, both variables may be just indicators of a "skin vulnerability factor", predisposing the individual to hand eczema (18). In the light of our findings, we suppose that irritant reactivity may be this common denominator.

We conclude from our study that irritant reactivity is more closely related to nickel sensitivity than atopic disposition. While this holds true for patients already sensitized to nickel, only prospective studies can tell if irritant reactivity can be used to predict the risk of developing nickel sensitization and, subsequently, hand dermatitis in unsensitized subjects. This would be an important information in the counselling of young workers entering high-risk professions such as hair-dressing and nursing.

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