Patch Test Results with Metals and Meteorological Conditions

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Key Words

Dermatitis, allergic contact · Epidemiology · Patch testing

Abstract

Background: Nickel, cobalt and chromium are some of the most common causes of type IV sensitizations and subsequent allergic contact dermatitis. Accurate diagnosis of contact sensitization to these metal salts is made possible through standardized patch testing; however, patch tests with metal allergens may be influenced by meteorological conditions at the time of testing. We aimed to investigate how patch test reactions to these metals relate to outdoor temperature and humidity at the time of testing. **Methods:** Clinical patch test results from 61,435 patients tested at Austrian and German dermatology departments participating in a contact sensitization surveillance network (www.ivdk.org) from 1993 through 2001 were evaluated with weather data measured near the testing location and at the time of testing. Test reactions and ambient temperature and humidity were examined with multinomial logistic regression models. **Results:** The odds of irritant and doubtful reactions to all 3 ionized metals increased during cold/arid conditions, and the odds of weak allergic (positive) reactions to nickel and cobalt also increased during cold/dry weather. Strong allergic reactions were essentially independent of weather conditions. **Conclusions:** The increase in irritant and doubt-

ful reactions coinciding with decreasing temperature and humidity may be the result of an overall increase in skin irritation brought about by these ambient conditions. The observed increases in erythematous and infiltrated ('weak allergic') reactions may be due to doubtful reactions increasing in intensity and being (falsely) classified as positive during colder and drier conditions.

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Introduction

Metals in their ionized form, in particular nickel, chromium and cobalt, rank high in the list of common contact allergens. Nickel is of special public health interest due to the historically high prevalence of nickel sensitization in the general population and the ensuing governmental intervention to prevent nickel allergies induced by consumer goods (European Union Directive 94/27/EEC). Cobalt, like nickel, is found both in industrial and consumer products, and concomitant allergies to cobalt and nickel are detected regularly [1]. In contrast, chromium is primarily an important occupational allergen.

Accurate diagnosis of contact sensitizations enables future allergen avoidance and promotes secondary prevention of the active allergic contact dermatitis. However,

the reproducibility of the patch test, the gold standard diagnostic procedure for type IV sensitizations, is regarded as satisfactory but far from perfect [2]. Unfortunately, patch test reactions are not always easy to categorize; particularly, the distinction between doubtful (equivocal) and weak positive (mildly allergic) reactions is difficult [3].

External environmental factors, such as meteorological conditions, can conceivably obscure patch test interpretation by making the skin irritable by perturbing the epidermal barrier function, thereby adding to the inherent inaccuracy of the patch test. Studies examining the seasonality of patch test reactions in very different climates report conflicting observations [4–11]. However, a number of studies identify dry/cold meteorological conditions to be a risk factor for (experimental) skin irritation [12–15]. In light of the fact that metal allergens are partly marginal irritants under patch test conditions, potentially yielding false-positive reactions [16], we undertook an examination of the impact of meteorological conditions on patch test reactions to a set of important metal allergens.

Materials and Methods

Clinical Data

The Information Network of Departments of Dermatology (www.ivdk.org) provided standardized clinical data and test results of 61,435 patients with suspected allergic contact dermatitis patch tested with the metal salts [17]. The patients were tested in 1 of 28 departments in 23 cities situated within a 30-km vicinity of an Austrian or German weather station from 1993 through 2001. The 3 metals were tested as part of the German Contact Dermatitis Research Group standard series, i.e. in the course of virtually every patient's consultation, as potassium dichromate (0.5% in petrolatum), cobalt chloride (1% in petrolatum) and nickel sulfate (5% in petrolatum). Patch test procedures followed international guidelines [18], with readings taken 3 days after application considered definitive for the purposes of the analysis. The categories considered here included (1) irritant/doubtful allergic, (2) weak positive allergic, (3) strong positive allergic, and (4) negative reactions.

Meteorological Data

Standardized weather data were obtained from the Austrian Central Institute for Meteorology and Geodynamics (Vienna, Austria) and the German Meteorological Service (Offenbach, Germany). The data collected by the 23 weather stations comprised daily average temperature (degrees Celsius) and relative humidity (percent). According to previous research, absolute humidity, a measure of the atmospheric water vapor concentration, is preferable for the analysis in terms of an observed association with irritant skin damage, while relative humidity, which describes the relative proportion of water vapor in the air compared

with the maximum amount possible at a given temperature, is unrelated to skin irritation [15, 19, 20]. Therefore, absolute humidity values, expressed as grams per cubic meter, were derived from the temperature and relative humidity values for the analysis with published formulas [21, 22].

Statistical Analysis

We averaged the values of temperature and absolute humidity on the day of patch test application and the 2 days preceding application and matched these with the corresponding dates and locations of patch test application. Although the patch test readings appear to follow an order from negative to strong positive, the basis of the reaction categorization is a collection of morphological skin alterations which does not strictly comply with the assumptions of ordinal variables. Therefore, multinomial logistic regression was used to examine the relation between temperature and absolute humidity, with the 4 nominal categories of patch test results serving as the dependent variable. We first examined temperature and absolute humidity, divided into 4 categories at their quartiles, in separate models. Subsequently, we combined the temperature and absolute humidity categories to create 16 (nominal) categories. However, the 6 categories representing extremely divergent (and physically unlikely) conditions, i.e. high temperature + low absolute humidity and low temperature + high absolute humidity combinations were excluded from the analysis because they were not or too infrequently observed. All models were controlled for the potential confounders of age, sex, atopic eczema/dermatitis syndrome (AEDS) and duration of patch test application (1 or 2 days). AEDS was considered a particularly important confounder, as (1) consultation peaks in winter according to previous analyses (data not shown), and (2) atopic dermatitis is positively associated with reactivity to metals [23]. The association between the ambient factors and the patch test outcome was quantified with the odds ratio (OR) and accompanying 95% confidence interval (CI). Data management and analysis was performed with the statistical software package SAS (version 9.1, SAS Institute, Cary, N.C., USA).

Results

The clinical population included predominantly female (63%, $n = 38,721$) patients, and past or present AEDS was found in 21% ($n = 12,666$) of the patients. Both the mean and median patient age was 46 years, with an interquartile range of 31–59 years. Patch test exposure time was 2 days among 62% ($n = 38,349$) and 1 day among the remaining patients. Mean values of temperature and absolute humidity stratified by patch test results reveal that conditions on the day of patch test application among patients diagnosed with irritant or doubtful reactions were colder and drier compared with other reaction categories (table 1). During the study period, the seasonal variation in meteorological variables typical for a temperate climate was observed. In the northern and southern parts of the study region, the me-

Table 1. Mean and 95% CIs of temperature and absolute humidity on the day of testing according to metal patch test results

	Patients		Temperature		Absolute humidity	
	n	%	mean	95% CI	mean	95% CI
Overall	61,435	100	9.79	9.7–9.9	7.43	7.4–7.5
Potassium dichromate						
Negative	57,457	94	9.82	9.8–9.9	7.44	7.4–7.5
Doubtful/irritant	1,250	2	8.57	8.2–9.0	6.97	6.8–7.1
Weak positive	1,612	3	9.28	8.9–9.6	7.34	7.2–7.5
Strong positive	852	1	10.45	10.0–10.9	7.70	7.5–7.9
Cobalt chloride						
Negative	56,648	93	9.86	9.8–9.9	7.46	7.4–7.5
Doubtful/irritant	1,464	2	8.31	8.0–8.7	6.92	6.8–7.1
Weak positive	1,960	3	9.00	8.7–9.3	7.15	7.0–7.3
Strong positive	1,037	2	9.71	9.3–10.2	7.44	7.3–7.6
Nickel sulfate						
Negative	50,169	83	9.87	9.8–9.9	7.46	7.4–7.5
Doubtful/irritant	1,426	2	8.50	8.1–8.9	7.00	6.9–7.2
Weak positive	4,412	7	9.46	9.2–9.7	7.31	7.2–7.4
Strong positive	4,704	8	9.58	9.4–9.8	7.36	7.3–7.5

dian summer (April to September) temperature was 15.0 and 15.9°C and the median winter (October to March) temperature was 4.6 and 4.5°C, respectively. Median relative humidity in the northern and southern parts was 73 and 71% in summer and 83 and 83% in winter, respectively, with overall variability largely similar between the North and South.

Table 2 depicts the results of the temperature and absolute humidity regression models. Adjusted OR estimates for irritant/doubtful and weak allergic reactions to all 3 metal salts tended to increase with decreasing temperature. Regarding weak positive reactions, only the cobalt model indicated a clearly significant increase in odds of reactions during cold weather. In contrast, the estimates indicate that the odds of weak positive reactions to nickel and chromium during low temperatures were only slightly increased and just short of statistical significance (95% CI included unity). Likewise, OR estimates for the metal salts decreased with increasing (allergic) reaction intensity, so that no clear association was observed for cobalt or nickel, and the OR for chromium during the coldest weather dropped significantly below 1. The results from the absolute humidity models closely mirrored those of the temperature model. However, the OR estimates of weak positive reactions to chromium diverged from the otherwise observed gradient and peaked for the second driest humidity category.

Combining the weather factors in 1 model resulted in comparable results. A closer examination of the ORs and 95% CIs representing the combinations of the temperature and humidity categories further substantiated the results of the marginal models. In other words, the estimates of the models considering the combined effects of temperature and humidity were analogous to the results of the separate analysis in magnitude and direction. Like the separate analyses, the estimates were greatest for irritant/doubtful reactions to the metals with the ORs ranging from 1.39 (95% CI 1.00–1.94) to 1.91 (95% CI 1.48–2.46) in the 4 winter weather categories. Associations between the combined meteorological conditions and weak positive reactions were weaker, in particular, with regard to chromium. Finally, as with the separate temperature and absolute humidity models, the estimated ORs were either near or below unity for strong positive reactions, with the odds of strong positive reactions to chromium and cobalt during the winter weather categories being lower than the odds of negative reactions. In the case of an interaction between temperature and humidity, the magnitude of the OR estimates should have been distinctly amplified, especially for the combination of the coldest and driest weather; however, the results of the combined models indicate that this was not the case.

Table 2. ORs and 95% CIs (in parentheses) of patch test reactions (vs. no reaction) from marginal models¹ with categories of 3-day averages of temperature or absolute humidity

	Temperature (reference >15°C)			Absolute humidity (reference >10 g/m ³)		
	≤4°C	5–10°C	11–15°C	≤5 g/m ³	6–7 g/m ³	8–10 g/m ³
Potassium dichromate						
Irritant/doubtful	1.59 (1.4–1.9)	1.44 (1.2–1.7)	1.27 (1.1–1.5)	1.68 (1.4–2.0)	1.43 (1.2–1.7)	1.32 (1.1–1.6)
Weak positive	1.18 (1.0–1.4)	1.18 (1.0–1.4)	1.17 (1.0–1.4)	1.09 (0.9–1.3)	1.13 (1.0–1.3)	1.04 (0.9–1.2)
Strong positive	0.75 (0.6–0.9)	0.93 (0.8–1.1)	1.07 (0.9–1.3)	0.74 (0.6–0.9)	0.84 (0.7–1.0)	0.97 (0.8–1.2)
Cobalt chloride						
Irritant/doubtful	1.71 (1.5–2.0)	1.54 (1.3–1.8)	1.30 (1.1–1.5)	1.66 (1.4–2.0)	1.62 (1.4–1.9)	1.31 (1.1–1.6)
Weak positive	1.34 (1.2–1.5)	1.25 (1.1–1.4)	1.20 (1.1–1.4)	1.29 (1.1–1.5)	1.24 (1.1–1.4)	1.02 (0.9–1.2)
Strong positive	1.01 (0.9–1.2)	0.96 (0.8–1.1)	1.01 (0.9–1.2)	0.94 (0.8–1.1)	0.98 (0.8–1.2)	0.90 (0.8–1.1)
Nickel sulfate						
Irritant/doubtful	1.64 (1.4–1.9)	1.38 (1.2–1.6)	1.31 (1.1–1.5)	1.59 (1.4–1.9)	1.38 (1.2–1.6)	1.26 (1.1–1.5)
Weak positive	1.14 (1.0–1.2)	1.1 (1.0–1.2)	1.02 (0.9–1.1)	1.13 (1.0–1.2)	1.04 (1.0–1.1)	0.95 (0.9–1.0)
Strong positive	1.10 (1.0–1.2)	1.13 (1.0–1.2)	1.04 (1.0–1.1)	1.05 (1.0–1.2)	1.11 (1.0–1.2)	1.00 (0.9–1.1)

¹ Models adjusted for sex, atopic dermatitis, duration of patch test application and age.

Discussion

Our analysis of the association of patch test reactions with environmental factors, namely temperature and absolute humidity, confirms the association between dry/cold ambient conditions and skin irritability identified by experimental research [24], observational studies [19, 20, 25] and systematic skin irritation testing [12–15], at least regarding the special situation of patch testing.

The fact that the results of each metal varied with regard to strong positive reactions corresponds to the results of previous examinations of seasonal patch test reactions, insofar as the contact allergens displayed distinctive seasonal patterns [7, 9–11]. Possible explanations for inconsistent weather-reaction associations may be the physical properties of the haptens. Differences in how each contact allergen penetrates the skin and produces irritant or allergic reactions could account for their unique relations with weather. For example, unlike other contact allergens, some metal ion haptens may not need to form covalent bonds with proteins in the epidermis before binding with the immunological cells responsible for beginning the delayed allergic reaction [3]. Which physical properties of the metal patch test allergens, if any, may be related to temperature and humidity conditions remains unclear. However, the results of this study and previous research indicate that irritant properties may play an important role.

Overall increased skin irritation observed during arid conditions could be a likely biological explanation for the increase observed in explicitly irritant and very weak erythematous (doubtful) reactions which were pooled for this analysis. Impairment of the skin barrier function due to overall irritation may also increase the susceptibility of the skin to the irritant properties of the metal salts. Skin irritation is known to increase in winter [20, 26] and in conjunction with low absolute humidity [19, 25]. Moreover, irritability, the susceptibility of the skin to irritants that damage the barrier function (such as sodium lauryl sulfate), also intensifies during winter-like conditions [12, 14, 15]. The occurrence of irritant reactions to allergens with marginal irritant qualities, such as the metal salts, may have resulted from generally increased skin irritation during winter conditions.

As Fischer and Rystedt [16] point out in their research, even morphologically ‘positive’ reactions to metal salts may be irritant rather than allergic. The slight increase observed in weak positive reactions under dry/cold or ‘irritating’ weather conditions, the magnitude of which is in between the clear-cut increase in irritant and doubtful reactions and the lack of increased risk in the case of stronger positive reactions, is well in line with this notion. In other words, during cold and dry weather, a certain proportion of reactions which may have only reached a doubtful level under non-irritating conditions may have been categorized as weak positive. Curiously, chromium, which is a notorious marginal irritant in the test concen-

tration used [18], displayed no significant weather association for weak positive reactions.

An alternative explanation for the slightly increased odds of weak positive reactions could be a decreased barrier function resulting from increased weather-related irritation allowing more allergen to penetrate the epidermis. Intensification of immunological reactions brought upon by arid conditions could also have yielded more allergic reactions. Experimental research demonstrates that low humidity amplifies the immunological activity of the skin, increases the amounts of allergen in the local lymph nodes and increases cytokine production in mice subjected to a dry environment under a constant temperature [27, 28]. However, the general, possibly systemic, alteration in the immune function that played a large role in these experiments was not perceptible in our clinical examination, as indisputably allergic patch test reactions (strong positive) were not enhanced by low humidity in our analysis. Hence, it appears that a portion of the weak positive reactions observed in winter are much more likely false positive (i.e. irritant) than the lower occurrence of reactions during warm/humid conditions, the result of false-negative (in terms of only doubtful) readings. Admittedly, without the application of verification tests, such as a 'Repeated Open Application Test' [18], neither hypothesis can be confirmed with absolute certainty.

Although the best available regional and time-specific weather data were utilized in the investigation, thereby improving upon past research regarding patch test results and meteorological conditions [10], the accuracy of weather exposure data remains a shortcoming of the present study design. While the summer weather conditions should be relatively accurate estimates of exposure due to the scarcity of air conditioning in homes and offices in Austria and Germany, winter temperature estimates are probably less accurate with people wearing warmer clothing and generally restricting the frequency and duration of outdoor activities. Encouragingly, unlike relative humidity, indoor absolute humidity values may correspond with outdoor values despite indoor heating in winter [29]. Moreover, the results of the marginal temperature and absolute humidity analyses were fairly similar. Therefore, low temperatures or humidity impact patch test results of the metals increased despite clothing and warmer indoor conditions. Furthermore, even body sites usually covered by clothing in winter are affected by seasonally increased irritability [12].

The gradient of increasing OR estimates observed in irritant/doubtful and weak reactions with decreasing temperature or humidity serves as ancillary evidence of

a connection between these reactions and weather. Interestingly, although strong positive reactions to nickel and cobalt, both strongly chemically related, displayed no obvious 'dose response', similar reactions to chromium exhibited a reversed gradient, i.e., the odds of stronger allergic reactions to chromium were lowest during the coldest or driest conditions.

One potentially influential weather condition that was not considered during the current study was ultraviolet (UV) exposure. Most previous seasonal patch test research focused on a potential inhibition of patch test reactions caused by UV exposure [4–9]. While UV exposure is known to protect the skin from contact dermatitis by suppressing the immune reaction and increasing the barrier function of the skin, 1 large study of UV exposure and patch test reactions found that patch test results were not associated with UV exposure [5]. This may be due to the fact that testing patients with recent or extreme UV exposure is not in line with current guidelines [18]. Therefore, it is unlikely that UV exposure greatly impacted the results of this study.

Conclusions

The odds of irritant/doubtful and weak positive patch test reactions to chromium, nickel and cobalt – all important, frequent allergens – increased with decreasing temperature and absolute humidity. Hence, a certain proportion of the weak positive reactions may be false positive. Examination of reactions with temperature and absolute humidity together revealed no definitive signs of additive or multiplicative interaction of the weather parameters. Consideration of either factor should be sufficient for increasing suspicion of – possibly false positive – weak allergic patch test reactions. In this case, repetition of the patch test under warmer conditions and/or verification tests such as the 'Repeated Open Application Test' are recommended, especially in case of grave (e.g., medicolegal) consequences of a diagnosis of metal contact sensitization.

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