

Original article

Strong allergic patch test reactions may indicate a general disposition for contact allergy

Background: Patch test patients have two or more positive reactions to unrelated allergens more often than to be expected by chance. This study evaluates synchronous patch test reactions to test the hypothesis that in such cases an allergen-independent disposition for contact sensitization may be involved.

Methods: Data of 87 834 patients tested with a standard patch test series in 42 centers of a Central European Network were retrospectively evaluated. Analyses were done for synchronous positive reactions of graded strength to nickel sulfate, fragrance mix, and to those five allergens that followed in frequency of positive results. All seven allergens selected were not related by chemical structure or exposure. Descriptive univariate and bivariate analyses as well as a polytomous logistic regression analysis were performed. Odds ratios with 95% confidence intervals were calculated.

Results: With an increasing strength of a positive reaction to nickel or to fragrance mix the likelihood of further positive reactions to unrelated contact allergens increased significantly, and the mean strength of such additional reactions raised steadily with an increasing strength of a nickel or fragrance reaction.

Conclusions: Our findings support the idea that patients who respond with a strong patch test reaction may have a particular general disposition to acquire contact sensitivity to additional unrelated allergens. They should therefore not only be advised to avoid their known allergen but in addition to minimize exposure other contact allergens.

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Patch testing is the established method to prove contact sensitization in patients suffering from eczema (1). Usually a standard series comprising 20–30 common contact allergens is applied for screening patch tests (2, 3), and quite often patients show positive allergic patch test reactions to more than one of these standard allergens. Many of such synchronous reactions occur to chemically unrelated allergens that are neither cross-reacting nor have common sources of exposure (2, 4). Therefore, one may speculate that some individuals have a marked disposition for contact allergy that is not restricted to allergens with a special chemical structure. Such a disposition – if identifiable – would be of considerable importance for the prevention of contact sensitization.

An above average disposition for contact allergy may have the following two clinically visible effects: first, positive patch test reactions may be stronger than in persons without such an enhanced readiness for contact allergy (5, 6); secondly, the occurrence of multiple sensitization may be more frequent than in normal persons (4, 5). This consideration led to our hypothesis

that if a strong allergic reaction to a contact allergen indicates not only a strong sensitization to this particular antigen but is also related to an outstanding disposition for contact allergy in general, patients with a strong patch test reaction to one allergen should be more likely to have reactions to additional allergens than patients with only a weak patch test reaction (6). Furthermore, their responses to additional allergens should also be stronger than those of individuals with a weak patch test reaction.

To test our hypothesis, we analyzed a large data pool of patients who had been patch tested with contact allergens comprising the standard test series in a Central European Network. In order to obtain large enough numbers of positive reactions for statistical analyses we have focused on those two contact allergens that elicit positive reactions most frequently: nickel sulfate and fragrance mix (7, 8). Both allergens are almost ubiquitous, they are chemically unrelated and they are not linked by coupled exposure. The high numbers of positive reactions to these two allergens rendered a separate analysis statistically powerful. In addition, the pooled

positive reactions to five other unrelated allergens of the German standard patch test series yielding positive reactions most frequently next to nickel and fragrance mix were analyzed.

Materials and methods

Data of the Information Network of Departments of Dermatology (IVDK) were retrospectively analyzed. The data had been collected over 11 years from 1993 to 2003 by 42 patch test centers* all over Germany and in Austria.

All patients tested with the German standard series of contact allergens in this period were included, provided their data was complete. In all centers, patch testing had been performed in accordance with common guidelines (9, 10), mostly by use of small Finn Chambers attached for 2 days or, in a minority of centers, for 1 day to the patients' back. Positive allergic reactions had been classified as weak (+), moderate (++) or strong (+++) (9, 11) and reaction indices and positivity ratios were calculated (11–13). For calculations of mean reaction strengths, a numerical strength of 1, 2, and 3 was attributed to a +, ++, and +++ reaction respectively.

For each patient the following clinical and demographic characteristics were analyzed in this study: gender, age, history of atopic dermatitis, and strength of patch test reactions on day 3 to nickel sulfate (5% in petrolatum) and fragrance mix (8% in petrolatum). In addition, the reactions on days 3–5 other allergens of the standard series (p-phenylenediamine 1.0%, lanolin alcohol 30.0%, methyldibromo glutaronitrile + phenoxyethanol 0.3%, thiuram mix 1.0%, neomycin sulfate 20.0%; all in petrolatum) were evaluated. These allergens were chosen because they are chemically unrelated to each other and to nickel sulfate and fragrance mix, do not cross-react with these two allergens, have no relevant irritant potential, and elicit positive reactions more often than other standard allergens meeting these criteria (7). The positive reactions to these five allergens were pooled for the purpose of this study.

Stratified for different strengths of positive reactions to nickel sulfate and fragrance mix, respectively, the percentages of positive reactions to the other allergen and the mean strength of the positive patch test reaction were determined. Similarly, for patients with graded positive reactions to nickel sulfate or fragrance mix the percentages of patients with additional reactions to one or more of the pooled five other standard contact allergens were calculated along with the mean reaction strengths to these other allergens.

Statistical analysis followed current guidelines (14). In addition to descriptive univariate and bivariate analyses as outlined above, a polytomous logistic regression analysis was performed. As outcome variable, graded positive reactions (+, ++ and +++ vs non-positive) to nickel (fragrance mix) were included in the model, while graded positive reactions (+, ++ and +++ with nonpositive as reference category) to the fragrance mix (nickel) – i.e. the respective other allergen – were modeled as explanatory factor, along with gender, age, atopic eczema, occupational causation and the anatomical site of dermatitis (10 categories) as potential confounders. The polytomous model was chosen after preliminary analyses had indicated that the proportional odds assumption underlying an ordinal logistic regression model was violated. In another polytomous logistic regression model, the number of additional positive reactions to the set of five allergens considered was employed as outcome, and graded positive reactions (+, ++ and +++ with

nonpositive as reference category) to the fragrance mix (nickel) as explanatory factor. As risk estimate, the odds ratio (OR), accompanied by 95% confidence intervals (CI), was calculated. For data management and analysis the software package SASTM (version 8.2; SAS Institute, Cary, NC, USA) was used.

Results

Complete files of 87 834 patients were available. Out of these, 15.2% had a positive reaction to nickel sulfate, 11.2% to fragrance mix, and 16.9% had at least one positive reaction to the five pooled allergens. The numbers of patients with weak (+), moderate (++) and strong (+++) positive reactions to nickel sulfate, fragrance mix, and to one or more of the five pooled standard allergens are shown in Table 1, accompanied by the reaction index and positivity ratio for nickel sulfate and fragrance mix.

The characteristics of the patients with different grades of positive reactions to nickel sulfate, fragrance mix, and to the five pooled standard allergens are shown in Table 2. For nickel-positive individuals, the percentage of females increased with an increasing reaction strength, while for fragrance mix-positive individuals the percentage of females declined with an increasing strength of the

Table 1. Numbers of patients with positive reactions to nickel sulfate, fragrance mix and to five pooled standard allergens. A total number of 87 834 patients was included

	Nickel sulfate	Fragrance mix	Pooled standard allergens*
Nonpositive	74 518	77 975	75 224
Reaction+	6440	6499	9749
Reaction++	5229	2692	3931
Reaction+++	1647	668	1129
Positivity Ratio	48.4	65.9	Not determined
Reaction index	0.73	0.47	Not determined

*Sum of reactions of the respective grade. Numbers add up to more than total number due to the fact that in 1731 cases two, in 203 cases three, in 17 cases four and in three cases five positive reactions to 'pooled allergens' were observed.

Table 2. Characteristics of patients with graded positive reactions to nickel sulfate (Ni), fragrance mix (FM) and to five pooled standard allergens (Pool)

	Female			Age <40 years			History of atopic dermatitis		
	Ni	FM	Pool	Ni	FM	Pool	Ni	FM	Pool
Nonpositive	58.6	62.2	62.4	35.5	40.4	40.9	16.7	17.4	17.6
Reaction +	84.6	69.6	67.6	54.2	29.6	27.0	21.1	17.7	16.4
Reaction ++	88.5	67.7	62.7	63.3	27.7	26.1	21.7	17.2	14.9
Reaction +++	90.0	65.7	59.3	64.2	25.9	35.6	19.8	18.0	15.9

The table shows the percentages of patients with a reaction of the strength indicated to nickel sulfate, fragrance mix, or the pooled allergens who were female, younger than 40 years, or had a history of atopic dermatitis. In case of more than 1 positive reaction to the pooled allergens in one patient, data shown in this table are based on the strongest reaction.

*The Patch test centers are given in the Appendix.

reaction. A stronger reaction to nickel was found in younger patients, whereas an obverse trend was seen for patients with positive reactions to fragrance mix. Analysing demographic data of the patients with positive reactions to the five pooled allergens it is evident that the subgroup with very strong reactions had the lowest percentage of women and the highest percentage of young patients as compared with the subgroups with a maximum reaction graded + or + +. Interestingly, however, for nickel sulfate, fragrance mix and the five pooled allergens, a history of atopic dermatitis was rather uniformly distributed among patients with different grades of reactions (Table 2).

For nickel sulfate and for the fragrance mix, an increase of reaction strength was accompanied by a rising percentage of positive reactions to the other allergen. Concurrently, the mean intensity of positive reactions increased slightly, but steadily. Out of the patients with a + reaction to nickel 12.6% had a positive reaction to fragrance mix with a mean strength of the reaction to fragrance mix of 1.3 (+ = 1, ++ = 2, +++ = 3, see Methods), whereas 12.9% of the patients with ++ reactions to nickel and 16.5% of patients with a +++ reaction to nickel had a positive reaction to fragrance mix (mean strength 1.5 and 1.6 respectively). Patients with +, ++, and +++ reactions to fragrance mix had positive reactions to nickel in 17.6%, 18.0%, and 19.3% with a mean strength of reaction of 1.6, 1.8, and 2.9. High ORs indicated that strong and moderate reactions to one allergen were significantly associated with additional positive reactions to the other allergen, and in particular with strong ones (Tables 3 and 4).

Furthermore, the percentage of patients with an additional positive reaction to one ore more of the five pooled standard allergens increased with an increasing strength of a positive reaction to nickel sulfate or to fragrance mix (Tables 5 and 6). In parallel, the mean strength of the positive reactions to the five pooled allergens increased with an increasing strength of a reaction to nickel sulfate or to fragrance mix as well

Table 3. Results of an adjusted polytomous logistic regression analysis (see Methods): odds ratios for the association of strong (+++), moderate (++), and weak (+) reactions to nickel sulfate (Ni) compared with nonpositive (negative, doubtful, irritant) reactions to nickel sulfate as explanatory factor, and strong, moderate, or weak positive reactions to fragrance mix (FM) as outcome

	Outcome: FM	Odds ratio	95% Confidence limits
Ni +++ vs Ni nonpositive	+++	4.38	3.14–6.13
	++	1.89	1.49–2.40
	+	1.56	1.32–1.85
Ni ++ vs Ni nonpositive	+++	1.77	1.32–2.36
	++	1.70	1.47–1.96
	+	1.19	1.07–1.32
Ni + vs Ni nonpositive	+++	0.86	0.61–1.22
	++	1.06	0.91–1.24
	+	1.37	1.25–1.50

Table 4. Results of an adjusted polytomous logistic regression analysis (see Methods): odds ratios for the association of strong (+++), moderate (++), and weak (+) reactions to fragrance mix (FM) compared with nonpositive (negative, doubtful, irritant) reactions to fragrance mix as explanatory factor, and strong, moderate, or weak positive reactions to nickel sulfate (Ni) as outcome

	Outcome: Ni	Odds ratio	95% Confidence limits
FM +++ vs FM nonpositive	+++	4.27	3.05–5.97
	++	1.73	1.30–2.32
	+	0.85	0.60–1.21
FM ++ vs FM nonpositive	+++	1.85	1.46–2.35
	++	1.66	1.43–1.92
	+	1.05	0.90–1.22
FM + vs FM nonpositive	+++	1.53	1.29–1.82
	++	1.16	1.04–1.30
	+	1.35	1.23–1.48

(Tables 5 and 6, last columns). However, the risk of having one, two, three or four further positive reactions to the set of ‘pooled allergens’ differed between nickel and the fragrance mix: while nickel exhibited a limited and partly inconsistent risk gradient with increasing strength of the patch test reaction (Table 5), the fragrance mix exhibited a clear and mostly consistent increase of risk of further positive reactions with increasing strength of its patch test reaction (Table 6). For both allergens, however, a continuous increase of risk to have four additional reactions to pooled allergens was associated with an increasing reaction strength.

Discussion

The percentages and characteristics of nickel- and fragrance-positive patients in our study population are well within the expected range (7). Also in accordance with previous findings, nickel sulfate and fragrance mix were characterized by a markedly positive reaction index and an acceptable positivity ratio. Both parameters therefore indicate that irritant and doubtful reactions were not a major problem in our study population (11, 13).

The group of patients with positive reactions to nickel sulfate was essentially different from the group of patients with positive reactions to fragrance mix. Compared with the latter, the nickel positive group was characterized by higher percentages of young and female patients, respectively. This is in accordance with earlier reports on nickel sensitive individuals (15). Interestingly, and as a new observation, these differences became progressively obvious with an increasing strength of the reactions (Table 2). The different characteristics of nickel-positive and fragrance-positive patients confirm the premise for our analysis that we had selected two allergens to which synchronous reactions do not mainly occur because of a coupled exposure or because of cross reactivity. A comparison of the nickel-positive or the fragrance-posit-

Table 5. Percentages of nickel-positive persons with additional positive reactions to five pooled standard allergens (Pool) and average strength of positive reactions to Pool

Nickel	% With further positive reactions to Pool	Mean strength of reactions to Pool*†	Risk of additional positive reactions to pooled allergens (OR/95% CI):					Association between graded positive reactions to nickel and mean intensity of pooled positive allergen reactions (increase by one unit†, e.g. from + to ++ or ++ to +++), irrespective of the number of reactions (OR/95% CI)
			No other reaction	One reaction	Two reactions	Three reactions	Four reactions	
Non-positive	13.8	1.2			Reference			Reference
+	17.2	1.3	1.0 (reference)	1.4 (1.3–1.5)	1.7 (1.4–2.0)	2.3 (1.5–3.6)	1.5 (0.2–11.6)	1.13 (1.08–1.18)
++	17.6	1.5	1.0 (reference)	1.6 (1.4–1.7)	1.9 (1.5–2.3)	2.1 (1.2–3.7)	2.4 (0.3–19.2)	1.23 (1.17–1.28)
+++	19.6	1.8	1.0 (reference)	1.8 (1.6–2.1)	1.8 (1.2–2.5)	1.6 (0.5–5.1)	15.5 (3.2–74.0)	1.48 (1.38–1.58)

*Significant trend, $P < 0.0001$. †+ = 1, ++ = 2, +++ = 3.

Table 6. Percentages of fragrance mix-positive persons with additional positive reactions to five pooled standard allergens (Pool) and average strength of positive reactions to Pool

Fragrance Mix	% with further positive reactions to Pool	Mean strength of reactions to Pool*†	Risk of additional positive reactions to pooled allergens (OR/95% CI):					Association between graded positive reactions to the FM and mean intensity of pooled positive allergen reactions (increase by one unit †, e.g. from + to ++ or ++ to +++), irrespective of the number of reactions (OR/95% CI)
			No other reaction	One reaction	Two reactions	Three reactions	Four reactions	
Non-positive	12.2	1.1			Reference			Reference
+	29.8	1.3	1.0 (reference)	2.5 (2.4–2.7)	4.2 (3.7–4.8)	5.9 (4.2–8.2)	17.9 (5.6–56.7)	1.77 (1.71–1.84)
++	33.3	1.6	1.0 (reference)	2.8 (2.5–3.0)	6.0 (5.2–7.1)	11.0 (7.5–16.0)	25.1 (6.7–93.9)	2.11 (2.01–2.21)
+++	34.9	1.7	1.0 (reference)	2.9 (2.4–3.5)	6.5 (4.9–8.7)	9.8 (4.7–20.4)	25.8 (3.0–222)	2.27 (2.08–2.47)

*Significant trend, $P < 0.0001$. †+ = 1, ++ = 2, +++ = 3.

ive patients to the patients with positive reactions to the other five allergens is not feasible because of the 'mixed characteristics' of the latter group due to the pooling process.

The main new and intriguing finding of our study is that for patients with a positive reaction to nickel sulfate the likelihood to have an additional positive reaction to fragrance mix is unequivocally and progressively increasing with an increasing strength of their nickel reaction, and that an increasing strength of a nickel reaction also raises the likelihood that an additional positive reaction to fragrance mix is stronger than +. Vice versa, the same holds true for patients with a positive reaction to fragrance mix regarding an additional reaction to nickel sulfate. These associations are statistically significant (Tables 3 and 4).

In our opinion these results support the notion that certain individuals may have a marked general disposition to acquire contact sensitization. This would imply that patients who develop a strong positive patch test reaction to one distinct contact allergen are more likely to acquire an additional contact sensitization to an unrelated second allergen than patients with only a weak reaction.

Because an analysis based on two allergens only is not representative for all contact allergens of the standard

series, we have also looked at those five standard patch test allergens that next to nickel sulfate and fragrance mix have the highest frequency of positive reactions and that are not related to the other two allergens. Due to the lower numbers of positive reactions to each allergen, the reactions to all five allergens were pooled for statistical analysis. Our results with these pooled allergens show that a strong reaction to nickel sulfate and particularly to fragrance mix is also significantly associated with further positive reaction(s) to at least one of these five pooled allergens. Interestingly, the number of such additional positive reactions rises continuously with an increasing strength of fragrance mix reactions, whereas an increasing strength of nickel reactions is accompanied by an increase of additional positive reactions that develops not so steadily. This observation relates well to previous observations that fragrance mix is more often coupled with other allergens than nickel (4). Furthermore, additional positive reactions are more likely to be stronger than + if the patient has a ++ or +++ reaction to nickel sulfate or to fragrance mix (Tables 5 and 6). The analysis of the five additional allergens therefore shows that the relation between positive reactions to them on the one hand and to nickel or fragrance mix on the other hand is very similar to the relation between the reactions to nickel sulfate and fragrance mix.

We feel that these corresponding findings for nickel sulfate, fragrance mix and five other contact allergens with high frequencies of positive reactions support our hypothesis that a strong allergic patch test reaction may indicate a general disposition for contact allergy. We are aware that this idea needs to be reviewed; it can raise new questions with regard to the conception that sensitization is in any case and throughout an exclusively allergen specific process. One may speculate, e.g. that distinct steps in the process of sensitization are easier for some 'predisposed' individuals.

The factors favoring an acquisition of polyvalent contact sensitization to unrelated allergens remain yet speculative. Our data do not indicate that the demographic parameters assessed including a history of atopic dermatitis are of importance in this context. A pronounced unspecific skin irritability and susceptibility, an impaired

epidermal barrier function (16), a particular capacity of epidermal enzymes to metabolize exogenous substances (17, 18), an enhanced immune reactivity of the skin (5, 19, 20), or other genetic or environmental conditions may be involved alone or in combination (15, 16, 21).

In conclusion, we suggest that some kind of factor(s) is likely to cause an allergen-independent disposition for contact sensitization in certain patients. The identification of separate contributing factors will take time, but patients with such a disposition need to be protected from further sensitization as effectively as possible. Therefore, as an immediate consequence from our findings we recommend that patients at risk should be adequately counseled. We suggest that patients with strong patch test reactions should not only be advised to strictly avoid their known allergen, but also to minimize exposure to further contact allergens.

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Appendix

The following centers contributed data to this analysis (in alphabetical order): Aachen (H. Dickel, S. Erdmann), Augsburg (A. Ludwig), Berlin B.-Frank. (B. Tebbe, R. Treudler), Berlin BWK (A. Köhler), Berlin Charité (B. Laubstein, T. Zuberbier, M. Worm), Berlin UKRV (J. Grabbe, T. Zuberbier), Bielefeld (I. Effendy), Bochum (C. Szliska, M. Straube, M. Freitag), Dortmund (P.J. Frosch, B. Pilz, C. Pirker, R. Herbst), Dresden (G. Richter, R. Aschoff), Duisburg (J. Schaller), Erlangen (K.P. Peters, T.L. Diepgen, M. Fartasch, M. Hertl, V. Mahler), Essen (H.M. Ockenfels, U. Hillen), Freudenberg (C. Szliska), Gera (J. Meyer), Göttingen (T. Fuchs, J. Geier), Graz (W. Aberer, B. Kränke), Greifswald (G. Bloss, M. Jünger), Halle (G. Gaber, D. Lübke), Hamburg (M. Kiehn, D. Vieluf, R. Weißbecher), Hannover (T. Schaefer, Th. Werfel), Heidelberg (A. Schulze-Dirks, M. Hart-

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