

Original article

A high-positive patch test load correlates with further positive patch test reactions irrespective of their location

Background: Patch testing is the standard clinical procedure to prove contact sensitization. It is a common practice to attach multiple patch tests at the same time. However, synchronous reactions to unrelated allergens may not be completely unassociated. If so, the reaction in a given test field might be influenced by other positive test reactions in a distance-related degree. This article analyses whether there is a distance-related effect of synchronous positive patch test reactions on the outcome of a target patch test.

Methods: Data collected from patients patch tested for diagnostic purposes with 15 standard allergens attached in a specific pattern between 1992 and 2004 in 20 centres in a Central European network were retrospectively evaluated. The association between the target patch test result (allergic vs negative reaction to the thiuram mix) and the number and cumulated strength of synchronous positive reactions (positive patch test load) to allergens placed in nearby or distant positions to the target patch was analysed by using logistic regression analysis.

Results: The likelihood of a positive reaction to thiuram mix significantly increased with an increasing synchronous positive patch test load generated by positive reactions to allergens unrelated to thiuram mix. The effect of allergens neighbouring the target allergen was not significantly stronger than that of allergens placed in distant positions.

Conclusion: For the interpretation of patch test results, the potentially enhancing effects of a synchronous positive patch test load should be considered. The local distribution of the patches on the back is, however, not critical.

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Patch testing is used to diagnose suspected contact hypersensitivity in patients presenting with a history of contact dermatitis (1). As standard clinical practice, a patch test series consisting of standard allergens is used for diagnosis, often supplemented with additional patch test series according to the individual history. It is common that > 20 (2, 3) and quite often > 50 allergens are attached to a patient's back at the same time. It is well-known that the effector phase of contact hypersensitivity (e.g. elicited by patch testing) is an immunological response involving blood cells (4) that can give rise to systemic effects like flare-up reactions or systemic contact dermatitis (5) remote from the primary allergen challenge. However, the established criteria for evaluating the patch test reaction to a specific contact allergen are exclusively confined to the morphology of the skin reaction occurring only at the application site (6, 7). Many clinicians feel that this procedure is inadequate and that it may also be necessary to consider synchronous reactions in other test fields for optimal interpretation of a patch test. The so-called 'angry back' (8, 9), 'spillover' (10) and 'noisy skin' (11) phenomena have been

discussed in this context. In previous studies, we found that an adjacent negative patch test does not modify a positive patch test reaction (12) and that a neighbouring positive patch test reaction does not enhance, but may possibly attenuate, a positive patch test reaction (13). On the contrary, a striking association between positive patch test reactions to a selected allergen and synchronous positive reactions to other unrelated allergens was found, particularly when the latter were strong reactions (14–17). We now examine whether the impact of synchronous positive patch test reactions on a given target relates to the distance between the target and synchronous reactions.

Materials and methods

The data files of the Information Network of Departments of Dermatology (IVDK; <http://www.ivdk.gwdg.de>) (18) were retrospectively evaluated. The period from January 1992 to December 2004 was chosen because the test concentration and arrangement of the first 15 allergens of the standard series used by all centres

remained unchanged during this time period. For this study, data were included only from those centres which had:

- used small Finn-chambers (total diameter 11 mm) on Scanpore™ tape attached for 2 days, and
- consistently placed the first 15 allergens of the German standard series on the upper left side of the back, as shown in Fig. 1.

Following these criteria, complete data sets from 49 096 patients collected in 20 centres fulfilling the above requirements were eligible for inclusion (Appendix). All patients were tested with the standard series in accordance with common guidelines (6, 7), including the complete set of the 11 allergens considered here (thiuram mix, five 'nearby' and five 'distant' allergens). Most patients were simultaneously tested with additional patch test series. Our evaluation used readings taken on day 3 of testing. Positive allergic reactions were classified as weak (+), moderate (++) or strong (+++) (6, 7). For statistical calculations, a numerical strength of 1, 2, and 3 was attributed to a +, ++, and +++ reaction respectively.

Thiuram mix was chosen as the target allergen because it was the only allergen for which distances to all neighbouring patch test allergens were definitely known (Fig. 1). The five allergens tested in the fields directly adjacent to the target field were pooled as 'nearby' allergens (*p*-phenylenediamine (PPD), nickel sulphate, colophony, *N*-phenyl-*N'*-isopropyl-*p*-phenylenediamine (IPPD), neomycin; see Fig. 1, Table 1). A potential cross-reactivity with thiuram mix was considered unlikely owing to the different chemical structures. Another set of five standard allergens, comprising substances unrelated to thiuram mix but attached > 50 mm away from the thiuram mix patch were pooled as 'distant' allergens (fragrance mix, methyl-dibromo glutaronitrile + phenoxyethanol (MDBGN + PE), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), ammoniated mercury and paraben mix; see Table 1). The distant allergens were never attached in positions occupied by the allergens listed in Fig. 1 and their test concentrations remained constant throughout the study period.

Questionable and irritant reactions were not considered because of their uncertain relevance in the context of our study. In order to achieve more stable estimates in the multifactorial analysis, all positive (+, ++, and +++) reactions were pooled for thiuram

Table 1. Allergens with test concentrations

Nearby allergens (%)	
<i>p</i> -Phenylenediamine (PPD)	1.0 (pet)
Nickel sulphate	5.0 (pet)
Colophony	20.0 (pet)
<i>N</i> -phenyl- <i>N'</i> -isopropyl- <i>p</i> -phenylenediamine (IPPD)	0.6 (pet)
Neomycin	20.0 (pet)
Distant allergens	
Fragrance mix (%)	8.0 (pet)
Methyldibromo glutaronitril + phenoxyethanol (MDBGN + PE) (%)	0.5 (pet)
Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI)	100.0 ppm (aq)
Ammoniated mercury (%)	1.0 (pet)
Paraben mix (%)	15.0 (pet)

mix, so that thiuram reactions were evaluated as either negative or positive without further grading of the latter. Both for the nearby and the distant allergens the cumulated strength of positive reactions (positive patch test load) was expressed by a score calculated from the numbers and the strengths of the positive reactions: score = number of reactions [1; 2; 3 etc.] × strength of reaction [1; 2 or 3]. For example, a + reaction to colophony, a + reaction to neomycin, and a +++ reaction to nickel sulphate add up to a score of 5 for the nearby allergens: (2 × 1) + (1 × 3) = 5. A score that is higher than the number of positive reactions used for its calculation indicates that at least one of these positive reactions is a strong one. The association between positive and nonpositive reaction to the thiuram mix and the number of positive reactions to nearby and distant allergens (with different scores) were analysed. Data analysis was controlled for age, gender and 'polysensitization' as a potential confounder. Polysensitization was defined as the number of positive reactions to other than the 11 allergens considered (excluding thiurams and dithiocarbamates), categorized into 0, 1, 2, 3, 4 and 5 or more reactions, as described in ref. (17). Odds ratios (OR) were derived from a binary logistic regression analysis, accompanied by 95% confidence intervals (CI).

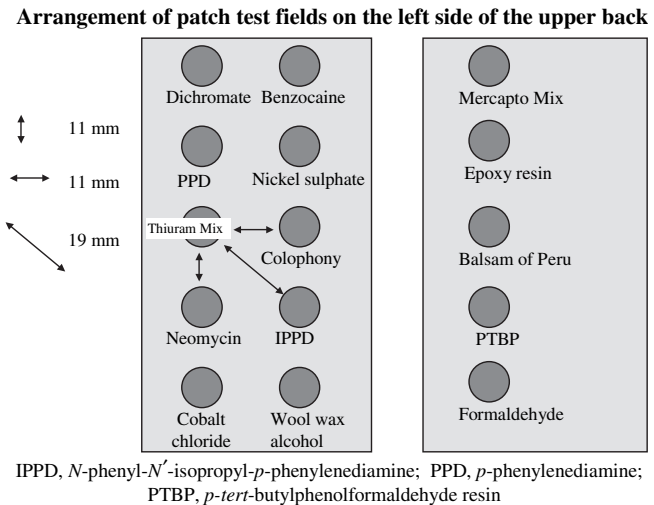


Figure 1. Schematic drawing of the arrangement of patch tests on the upper left side of the back. The allergens were attached with small Finn chambers on Scanpore™. Distances between test chambers are indicated by arrows.

Results

Complete data collected from 49 096 patients (63.5% female) was available for evaluation. Median age was 46 years (Q1: 31, Q3: 60). Altogether 1280 patients tested positive to thiuram mix (2.61%, exact 95% CI: 2.47–2.75). Patients (9071) had positive reactions to nearby allergens but no positive reactions to distant allergens. Of these, 335 (3.69%) showed positive reactions to thiuram mix. In contrast, 5500 patients showed positive reactions to distant allergens but no positive reactions to nearby allergens, of which 216 (3.93%) were positive to thiuram mix. The difference between these two subgroups regarding the proportion of patients positive to the thiuram mix is not significant (chi-squared test). In 31 505 patients, no positive reactions to the respective set of nearby and distant allergens were observed (1.59% positive to thiuram mix in this subgroup). Patients (3020) tested positive for both nearby and distant allergens (7.52% positive to thiuram mix in this subgroup). Scores in the higher range (≥3) calculated for nearby allergens were more often

Table 2. Odds ratios with 95% confidence interval (CI) for positive vs negative reactions to thiuram mix (patients with doubtful and irritant reactions excluded) in relation to the number of positive reactions and score to nearby allergens and to distant allergens. Data analysis is based on data of 49 096 patients and controlled for age, gender, and polysensitization

<i>n</i> positive	Score	OR for positive vs negative reactions to thiuram mix (95% CI)			
		Nearby allergens		Distant allergens	
		% Patients	OR (95% CI)	% Patients	OR (95% CI)
0	0	75.37	1.00 (ref.)	82.65	1.00 (ref.)
1	1	11.54	1.35 (1.15–1.59)	10.10	1.21 (1.03–1.43)
	>1	9.67	1.46 (1.23–1.72)	4.33	1.12 (0.89–1.39)
2	2	1.10	1.64 (1.13–2.37)	1.20	1.66 (1.19–2.30)
	>2	1.99	2.27 (1.78–2.90)	1.36	2.00 (1.51–2.64)
≥3	Score = number	0.09	2.04 (0.71–5.80)	0.004	n.c.
	Score > number	0.25	3.80 (2.35–6.33)	0.37	2.26 (1.43–3.56)

For explanation of score see Materials and methods.

n positive, number of positive reactions to nearby or distant allergens; % patients, percent of all patients (49 096 = 100%); OR, odds ratio n.c., not calculable.

because of strong positive reactions (+ + +) than similar scores calculated for distant allergens, which instead were more often based on higher numbers of weak positive reactions.

Table 2 shows the respective association, quantified as OR, between numbers of positive reactions with different scores (i.e. the positive patch test load) to nearby and distant allergens and a positive reaction to the target allergen thiuram mix. With an increasing number of positive reactions and increasing scores, respectively, the likelihood of a positive reaction to thiuram mix increased steadily and significantly (P for trend < 0.0001). While the OR calculated for ≥3 weak positive reactions may appear to deviate from this trend, these must be interpreted with particular care because they are based on extraordinarily low numbers of patients (Table 2). A detailed analysis of the relation between this additional enhancing effect exerted by strong reactions and rising scores revealed no further reliable information because of the rather low numbers of patients with different scores.

Table 2 also shows that the OR for equal numbers of positive reactions and comparable score for nearby allergens were slightly higher than the OR for distant allergens. An OR of 1.35 was calculated for 1 weak nearby reaction, compared with 1.21 for 1 weak distant reaction. For ≥3 positive reactions to nearby allergens, including strong reactions, an OR of 3.80 was calculated, compared with 2.26 for distant allergens. However, none of the differences between OR estimates for nearby and distant allergens proved to be significant.

Discussion

Our findings clearly indicate that the risk of a positive patch test reaction increases with the simultaneous occurrence of more and/or strong positive patch tests to other allergens, i.e. with an increasing positive patch test load. This corresponds very well to previous observations

that synchronous patch test reactions to distinct allergens occur more often than can be expected by chance (14), that strong patch test reactions appear to indicate an increased risk of further positive patch test reactions to other unrelated allergens (15), and that the risk of contact allergy to certain allergens, such as neomycin (17), bufexamac (19), or metals (20) increases with a rising number of additional positive reactions ('polysensitization'). Taken together, these results can in fact be interpreted as a confirmation of Moss et al.'s conclusion in their hallmark study 20 years ago that '...individual susceptibility is an important factor in the development of contact dermatitis, and occurs by a nonantigen-specific amplification of immune sensitization...' (21).

A novel finding of our study is that such enhanced reactivity is not significantly influenced by the distance that separates the target patch test from other positive reactions under normal patch test conditions. This means that a target patch test reaction with other directly adjacent positive reactions is not more markedly affected by these additional reactions than a target patch test with other more distantly occurring positive reactions. The finding that the OR for nearby allergens were slightly higher than the corresponding OR for distant allergens may in fact be because of the coupled exposure with thiuram mix-allergens and IPPD in certain occupational environments. Even when marginal distance-related differences might be proven in future analyses, such minor dissimilarities can hardly be considered clinically relevant. Our findings are consistent with previous observations (22), but definite proof for routine clinical patch testing was lacking until now.

In order to anticipate the positive patch test reactions most likely to exert an effect stronger than a weak positive reaction, we conceived a scoring system to weight the positive reactions as described in Materials and methods. This concept is considered a better representation of a 'positive patch test load' than the mere consideration of the number of positive reactions (irrespective of their

strength), or a focus merely on, e.g., +++ reactions. Our results now show that the number of positive reactions appears to be the most important parameter contributing to the positive patch test load, but that the strength of the reactions undoubtedly adds further power to it. The idea to define a patch test load that adequately reflects number as well as strength of positive reactions therefore appears to be justified.

With regard to pathophysiological considerations, we suggest that moderately enhanced and not locally confined skin reactivity involving unspecific trigger factors like cytokines and chemokines, upregulated by an initial inflammatory response, at least temporarily exists in patients with a high positive patch test load. This could very well correspond to enhanced skin reactivity in patients with current eczema or to what one may call 'excited skin' or 'individual susceptibility'. Interestingly, enhanced responsiveness appears primarily to be a systemic rather than a local event because it is not bound to the short distance between the allergen-exposed skin area (or a target patch test) and other positive patch tests (or localized eczema). In other words, although some kind of moderate, generalized 'skin excitement' is not uncommon, a purely local 'spillover' of positive reactions has not been proven.

Terms like 'excited skin' implicitly suggest a state of abnormally elevated reactivity that may potentially yield a certain number of false-positive reactions. Increased individual susceptibility to contact sensitization in general (21) is an alternative explanation for an apparently rather nonspecific association between reactivity to one particular allergen and other allergens, which we have termed 'polysensitization'. Polysensitization, as a clinical sign of heightened susceptibility, appears well-established in experimental (21) and clinical studies (17, 19). Although a deeper pathophysiological understanding of such susceptibility remains elusive, research on polymorphisms of functionally relevant enzymes (23) and cytokines (24, 25) in polysensitized patients shows great promise.

As a consequence of our findings, each positive patch test reaction should be evaluated with particular care in the presence of a high positive patch test load. The clinician must then critically ask whether a positive reaction truly reveals sensitization. The good news is that the arrangement of the patch tests is not critical and that positive patch tests have no enhanced effect on their direct neighbours. This is of considerable practical relevance as it is a necessary precondition to freely choose the positions of the allergens.

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Appendix

The following centres contributed data to this analysis (in alphabetical order):

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