

Patch-test reaction patterns in patients with a predisposition to atopic dermatitis

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Patients with a predisposition to atopic dermatitis often need to be patch tested in order to detect possible contact sensitization. However, it is unknown whether immunologic or other peculiarities of atopic skin are related to altered patch-test reaction patterns. Our study was aimed at answering this question, because patch-test reaction patterns are of considerable practical importance in the reading and interpretation of patch tests. Therefore, we compared patterns of patch-test reactions in patients with a predisposition to atopic dermatitis and in control patients matched for sex, age, reason for testing and test centre. Patch-test results from 9 centres (2322 patients with a disposition to atopic dermatitis and 2126 matched controls) were evaluated retrospectively. All patients were tested with nickel sulfate, fragrance mix, potassium dichromate, lanolin alcohol, formaldehyde and mercury ammonium chloride. Patch tests applied for 1 day with readings on days 1, 2 and 3 were evaluated in order to cover the early phase of the reactions. Not unexpectedly, we found that, compared to the matched controls, patients with a predisposition to atopic dermatitis tended to have more doubtful and irritant reactions on day 1. As a new observation, it turned out that they had less reactions of crescendo pattern and more strong reactions on day 3. All these differences were slight/insignificant. A higher skin irritability in patients with a predisposition to atopic dermatitis is a likely explanation. In conclusion, standard methods for patch testing can be applied in patients with a predisposition to atopic dermatitis, but minor differences in reaction patterns should be considered.

Key words: contact allergens; patch-test methods; reaction index; skin irritability. © Blackwell Munksgaard, 2003.

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Today, there is no doubt that individuals with a predisposition to atopic dermatitis can acquire allergic contact hypersensitivity (1–5). It is well known that skin of patients suffering from atopic dermatitis can be more susceptible to irritants than the skin of non-atopic individuals (6–8). Because many contact allergens are, at the same time, marginal irritants under patch-test conditions and can thus elicit some degree of skin irritation (9), the higher skin irritability of atopic patients could result in patterns of allergic patch-test reactions that are different from the patterns seen with the identical allergens in individuals without atopic dermatitis. In addition, the imbalance of Th1- and Th2-related processes in atopic patients (10) could have an influence on the development of allergic patch-test reactions. A pre-

vious study of ours indicated that the patterns of allergic patch-test reactions may be different in patients with and without a history of atopic dermatitis (11).

Relevant differences between patch-test reaction patterns in individuals with and without a predisposition to atopic dermatitis would be of practical importance for patch testing. Most patch testers feel that patients with atopic dermatitis have more weak patch-test reactions at early readings that fade by later readings. However, feelings can be misleading and need to be checked against the facts. Therefore, we now compared patterns of patch-test reactions with a set of 6 standard allergens between both groups of patients. To avoid confounding of this comparison by other factors that may be associated both

with patch-test reactivity to allergens and predisposition to atopic dermatitis, the two groups of patients were matched by possibly confounding factors. In order not to miss the early phase of the reactions, we chose to evaluate patch tests applied for 1 day and read on days 1, 2 and 3.

Methods

Data retrieved from January 1995 to June 2001 by the Departments of Dermatology cooperating in the German Contact Dermatitis Group (DKG) and the Information Network of Departments of Dermatology (IVDK) were retrospectively analysed. For this particular study, only patch tests that had been carried out by centres using small Finn Chambers[®] attached to the upper back for 1 day were evaluated, in order to achieve homogeneity concerning these important test conditions [9 centres: Berlin (Benjamin Franklin) (B. Tebbe, R. Treudler); Dresden (G. Richter); Duisburg (J. Schaller); Halle (G. Gaber); Homburg (P. Koch); Kiel (J. Brasch); Mannheim (C. Bayerl); Nürnberg (J. Müller); Rostock (H. Heise)]. Patch-test application for 1 day was chosen to make sure that the early stage of a reaction on day 1 was available for the assessment of the dynamic reaction pattern. Complete readings on days 1, 2 and 3 were required for this analysis, which had been taken according to common criteria (12, 13). Reactions to 6 distinct allergens were analysed separately: nickel sulfate 5% in petrolatum (pet.) and fragrance mix 8% in pet. (allergens with the highest numbers of positive reactions in test populations), potassium dichromate 0.5% in pet. and lanolin alcohol 30% in pet. (often considered as allergens with particular relevance to patients with atopic dermatitis) and formaldehyde 1% in water (aq.) and mercury ammonium chloride 1% in pet. (allergens supposed to have a particularly high irritant potential). All allergens were purchased from Hermal (Reinbek, Germany).

We focused on the impact a predisposition to atopic dermatitis might have on the development and course of patch-test reactions, by comparing patch-test reaction patterns to the 6 allergens between cases and controls. Cases were patients with previous or current atopic dermatitis (but no dermatitis on the back at the time of testing) as defined by common criteria (14), while patients without past or current atopic dermatitis served as control group.

For due consideration of the impact of potentially confounding factors, either adjustment techniques (like logistic or Poisson regression analyses or stratified analyses) or restriction techniques applied to a comparison group can, in

principle, be used. In our analysis, to descriptively illustrate the independent influence of atopic eczema (past or current) on reaction patterns, we opted for a frequency-matched case-control design, i.e. the latter possibility. The matched control group ultimately used was compiled in a stepwise process:

- (1) As potential confounders, the following factors were included: sex, age (40 and less years versus over 40 years), the department where patch testing had been carried out ($n=9$) and the reason for testing (suspected allergic contact dermatitis versus other indications, e.g. exclusion of allergic contact dermatitis).
- (2) The common distribution of 4 of these factors (72 theoretically possible, mutually exclusive combinations) in the case group was determined, arriving at proportions P_{case} .
- (3) The corresponding proportions were analysed for the unrestricted control group, i.e. all patients patch tested who were not cases, resulting in proportions $P_{\text{unrestricted control}}$.
- (4) A quotient $P_{\text{case}}/P_{\text{unrestricted control}}$ was calculated, and the largest value of this quotient was determined (i.e. the subgroup with the least number of controls in relation to cases).
- (5) In this subgroup, the number of unrestricted controls was divided by the number of cases. The result was used as a correction factor for all the other subgroups of factor combinations by multiplying the number of cases with it, arriving at the number of matched controls for the stratum (rounded to the nearest integer).
- (6) Subsequently, this required number of matched controls was randomly selected from the controls available in every stratum of the unrestricted control group.

For the case group, the unrestricted control group and the matched control group, the MOAHLFA index (15) was determined, and in addition, the parameters 'Reason for testing: suspected contact allergy', 'Allergic rhinitis' and 'Final diagnosis: allergic contact dermatitis' were compared.

Then, for each of the 6 allergens, the positive reactions on day 3 and the reaction indices (9, 16) were calculated for the case group and for the matched control group. Furthermore, the proportions of individuals in the case group and in the matched control group responding with a doubtful or irritant reaction on day 1 were calculated for the 6 allergens. For individuals of the case group and of the matched control group who had responded with an allergic reaction to an allergen, the ratio of crescendo reactions and of strong (++) or very strong (+++) reactions on

Table 1. MOAHLFA index and characteristics of cases ($n = 2322$), unrestricted control group ($n = 11804$) and matched controls ($n = 2126$)

	Cases		Controls (unrestricted)		Controls (matched)		
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Male*	706	30.4	4162	35.3	646	30.4	M
Occupational dermatitis	358	15.4	1531	13.0	366	17.2	O
Atopic dermatitis	2322	100	0	0.0	0	0.0	A
Hand dermatitis	794	34.2	2931	24.8	647	30.4	H
Leg dermatitis	68	2.9	1548	13.1	172	8.1	L
Face dermatitis	488	21.0	1677	14.2	298	14.0	F
Age ≥ 40 years*	936	40.3	8158	69.1	871	41.0	A
Reason for testing: suspected contact allergy*	802	34.5	3879	32.9	723	34.0	
Allergic rhinitis	813	35.0	298	14.0	1336	11.3	
Final diagnosis: allergic contact dermatitis	397	17.1	538	25.3	317	11.7	

*Matching variables.

day 3 was calculated. Crescendo reactions were defined as reactions with a progressive increase of intensity from day 1 to day 3; hence, on day 3, the highest score was read.

Owing to the frequency-matched case-control design, the variety of descriptive results detailed above can directly be compared between the case group and the matched control group without the need for adjustment.

Results

Altogether, 2322 patients qualified as cases in the 9 departments eligible for this analysis, 1829 stating that they had had previous atopic dermatitis and 1251 with current atopic dermatitis (both criteria fulfilled in 758 cases). The number of unrestricted controls was 11 804. The total number of patients patch tested in the 9 departments was 17 778, i.e. higher than the sum of cases and unrestricted controls, due to a certain number of cases with missing or invalid data for the case-defining variables. Matching resulted in a control group of 2126 patients with a MOAHLFA index similar to the MOAHLFA index of the case

group, with the exception, clearly, of the criterion 'atopic dermatitis' (Table 1). Somewhat more patients had face dermatitis in the case group than in the matched control group, which was characterized by a higher percentage of patients with leg dermatitis instead (Table 1). Allergic rhinitis was more common in the case group than in the matched control group, and a final diagnosis of allergic contact dermatitis was also made more often in the case group (Table 1).

In the case group and in the matched control group, somewhat similar percentages of allergic reactions to the distinct allergens were found (Table 2). However, the reaction index was lower for 5 of the 6 allergens in the case group than in the matched control group (Table 2). The number of doubtful and irritant reactions on day 1 was slightly higher for 5 of the 6 allergens in the case group than in the matched control group (Table 3). In the case group, 5 of the 6 allergens elicited a lower percentage of crescendo reactions than in the matched control group (Table 4) – this difference was largest for lanolin alcohol, followed by mercury ammonium chloride and

Table 2. Allergic reactions to the distinct allergens on day 3 and calculated reaction indices (RI) in cases and matched controls

	Cases			Controls (matched)		
	<i>n</i>	%	RI	<i>n</i>	%	RI
Nickel sulfate	329	14.2	0.72	295	13.9	0.80
Fragrance mix	214	9.2	0.49	167	7.9	0.68
Dichromate	92	4.0	0.39	55	2.6	0.39
Lanolin alcohol	47	2.0	0.41	50	2.6	0.56
Formaldehyde	57	2.5	0.25	45	2.1	0.27
Mercury ammonium chloride	34	1.5	0.36	40	1.9	0.45

n of cases = 2322; *n* of matched controls = 2126. Percentages are related to the number of cases and matched controls.

Table 3. Doubtful (+) irritant reactions to the distinct allergens on day 1 in cases and matched controls

	Cases		Controls (matched)	
	<i>n</i>	%	<i>n</i>	%
Nickel sulfate	54	2.3	39	1.8
Fragrance mix	98	4.2	83	3.9
Dichromate	88	3.8	60	2.8
Lanolin alcohol	14	0.6	13	0.6
Formaldehyde	51	2.2	40	1.9
Mercury ammonium chloride	15	0.6	11	0.5

n of cases = 2322; *n* of matched controls = 2126. Percentages are related to the number of cases and matched controls.

Table 4. Allergic crescendo reactions to the distinct allergens in cases and matched controls

	Cases		Controls (matched)	
	<i>n</i>	%	<i>n</i>	%
Nickel sulfate	145	35.2	129	36.5
Fragrance mix	63	17.5	60	23.9
Dichromate	33	15.3	20	14.8
Lanolin alcohol	21	23.9	26	35.1
Formaldehyde	29	22.0	26	24.5
Mercury ammonium chloride	14	20.3	17	28.3

n of cases = 2322; *n* of matched controls = 2126. Percentages are related to the number of patients with any type of reaction at days 1, 2 or 3.

fragrance mix. On the other hand, 4 allergens (fragrance mix, dichromate, formaldehyde and mercury ammonium chloride) yielded more strong or very strong reactions on day 3 in the case group than in the matched control group (Table 5).

Discussion

Today, there is no doubt that patients with atopic eczema can acquire allergic contact sensitization and often need to be patch tested (1–5). However, it is an open question of considerable practical importance as to whether immunologic or other peculiarities that may characterize atopic skin even during eczema-free periods are related to altered patch-test reaction patterns, because such patterns are crucial in the interpretation of test reactions as allergic or irritant. Therefore, in our study, we focused on a descriptive analysis of patterns of patch-test reactions in patients who had a predisposition to atopic eczema and matched controls.

Data in Table 1 show that, compared with the unrestricted control group, the matched control group is much better adapted to the characteristics of the case group by virtue of the matching process, particularly with regard to the crucial parameters age, sex and reason for testing. This similarity allows direct comparisons between these 2 groups. The fact that allergic rhinitis was more common in the case group than in the matched control group confirms the proper selection of cases, as atopic eczema and allergic rhinitis are associated parameters. The observation of a higher proportion of patients with face dermatitis in the case group, compared to the matched control group, may be explained by the common facial involvement in atopic dermatitis. The higher frequency of allergic contact dermatitis as a final diagnosis in the case group is interesting because there had been no higher suspicion of

allergic contact dermatitis in this group prior to testing than in the matched control group, as 'suspected allergic contact dermatitis' had been 1 of the 4 matching variables. This underlines the value of patch testing in appropriate patients with a predisposition to atopic dermatitis (1, 3).

The percentages of allergic reactions to the 6 allergens investigated were rather similar in our case group and in the matched control group. This result confirms that a predisposition to atopic dermatitis neither increases the risk factor for contact sensitization (17) nor diminishes the capacity to acquire contact allergy (18).

However, there appear to be some minor differences in the patterns of patch-test reactions shown by patients with a predisposition to atopic dermatitis as compared with control patients. First, the consistent tendency towards a lower reaction index and towards a higher percentage of doubtful and irritant reactions on day 1 of testing very well relates to the known higher skin irritability of patients with atopic dermatitis as compared with normal controls (6, 7), even if a panel of unrelated allergens with presumably different mechanisms of irritation is considered. Second, irritation is a factor that may enhance the early development of a pronounced allergic response. Irritation may thus boost allergic reactions in patients with a predisposition to atopic dermatitis. Such a mechanism could explain our finding of less crescendo reactions and of more strong positive reactions on day 3 in the case group as compared with the matched control group. This larger number of strong reactions in the case group on day 3 as compared with the matched control group is a new finding. A crescendo-type reaction pattern seems to be less related to a particularly strong irritant potential of an allergen than to the patients' disposition, because despite their irritative potentials, fragrance mix, formaldehyde and mercury ammonium chloride yielded lower percentages of cres-

Table 5. Strong (++) or very strong (+++) allergic reactions to the distinct allergens on day 3 in cases and matched controls

	Cases		Controls (matched)	
	<i>n</i>	%	<i>n</i>	%
Nickel sulfate	177	53.8	159	53.9
Fragrance mix	80	37.4	55	32.9
Dichromate	35	38.0	20	36.4
Lanolin alcohol	11	23.4	14	28.0
Formaldehyde	15	26.3	8	17.8
Mercury ammonium chloride	13	38.2	10	25.0

n of cases = 2322; *n* of matched controls = 2126. Percentages are based on the number of all positive reactions (+ to +++) on day 3.

cendo reactions in our case group as compared with the control group. Nevertheless, for these 3 allergens, the percentages of strong or very strong reactions on day 3 were markedly higher in the case group than in the matched control group (Tables 4 and 5). In contrast, lanolin alcohol yielded more crescendo reactions and more strong reactions in the control group as compared with the case group.

It is noteworthy that regarding crescendo patterns and strong reactions on day 3, the results with nickel sulfate and dichromate were rather similar in the case group and in the matched control group. This indicates that a predisposition to atopic dermatitis does not equally affect the development of patch-test reactions to different test allergens.

In conclusion, we found that a predisposition to atopic dermatitis, probably due to increased irritability, can slightly influence the patterns of patch-test reactions to distinct allergens. Not unexpectedly, more doubtful and irritant reactions were seen on day 1. However, it is a new observation that less crescendo reactions and more strong reactions on day 3 may occur. This shows that a detailed analysis of data can add valuable information to clinical experience. Although one should be aware of these minor differences in reaction patterns, we do not think that they make it necessary to develop a specially adapted patch-test procedure for patients with a predisposition to atopic dermatitis. Moreover, we underline that a patch-test application for 2 days may yield slightly different results and that late readings after day 3 may give additional information.

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