

Original article

Type-IV sensitization profile of individuals with atopic eczema: results from the Information Network of Departments of Dermatology (IVDK) and the German Contact Dermatitis Research Group (DKG)

The role of atopic eczema (AE) as risk factor for the development of allergic contact dermatitis is discussed controversially, as well as its influence on patch test results due to increased irritability. In this study, we analysed the pattern of positive patch test results to most frequent contact allergens in patients with AE ($n = 9020$) and age matched nonatopic ($n = 15\,263$) individuals. The pattern and the frequencies of the observed sensitizations did not differ greatly from nonatopic individuals. Bufexamac is an exception: in AE patients sensitization is observed three times more often. For the other substances tested only minor differences were detected. Moreover, the frequencies of single, double or polyvalent sensitizations were nearly identical between the two groups. The analysis of the anatomical sites of dermatitis shows differences between the groups: in AE patients, the face (7.2%) and hand dermatitis (6.6%) was more common, and leg dermatitis (4.0%) less common. Analysis of occupation, suspected allergen source, and accompanying factors revealed no major differences between the both groups. **Conclusion:** The chronic and long-term exposure to external drugs and emollients presumably carries a risk for sensitization against specific contact allergens in AE patients. However, the sensitization of contact allergens differs surprisingly little between patients with or without AE.

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For many years, there is an ongoing controversy about the role of atopic eczema (AE) as risk factor for the development of type IV sensitization and consecutive allergic contact dermatitis (ACD) (1). In the pathogenesis of both diseases, skin homing of T lymphocytes play a major role resulting in cutaneous inflammation. A complex interplay of cytokines have been observed in AE: T-cells involved in the initial cutaneous inflammation produce the cytokines interleukin (IL)-4, IL-5, and IL-13, whereas in chronic lesions interferon (IFN)- γ production can be detected from T cells (2). By contrast, in ACD, despite the involvement of several chemokines also cytokines like tumor necrosis factor (TNF)- α , IL-2, and IFN- γ play an important role. Interestingly, IL-4 production upon allergen triggering was observed, recently as well (3, 4). In terms of relevant pathophysiological

mechanism, TNF- α -polymorphisms were found in patients with ACD (5) but not with AE (6). IL-10 plays an important role for limiting the inflammatory processes in the skin (7, 8) and to date, type-IV allergen-induced IL-10 production was reported in nonatopic individuals only (9).

The clinical appearance of AE and ACD is comparable; both diseases present initially with papulovesiculae and later with dry erythematous lesions. The onset of AE occurs commonly during infancy or childhood (2) and concomitant ACD is described at that age, too (10). In ACD, a direct allergen contact is necessary for eliciting eczema, whereas in AE, the triggering allergen is not always easily to be determined due to more complex etiology. However, independently from the pathogenesis, the epidermal barrier of inflamed skin is disrupted.

Treatment involves mostly the topical use of ointments and emollients. This may be a risk factor for type-IV sensitization. On the contrary, it is not determined if the cytokine micromilieu or other factors playing a role in the pathogenesis of AE is rather protective to developing type-IV sensitization. As patch testing is an adequate method to determine type-IV sensitizations, in this study a retrospective analysis of the data collected by the IVDK from 1998 to 2003 was performed.

Patients and methods

Data collection

Data of the Information Network of Departments of Dermatology (IVDK, <http://www.ivdk.org>; accessed 20 December 2005) in Germany, which comprise results of patch tests and a standardized medical history were analysed, retrospectively. All IVDK members belong to the German Contact Dermatitis Research Group (DKG). IVDK surveillance is an instrument of clinical epidemiology, and its analysis being based on data of patients referred for the evaluation of suspected contact allergy, as opposed to population-based epidemiological approaches. All patch tests were performed for diagnostic purposes and according to international and DKG guidelines (11). A total of 53 892 patients from 40 clinics in Germany, Austria and Switzerland were patch tested from 1998 to 2003 from which 9020 individuals fulfilled the common criteria of AE (12), as diagnosed by a dermatologist. Furthermore, a detailed questionnaire for assessment of atopic diseases was evaluated in supervision of a dermatologist. As control group served data from patients without AE which was frequency matched for age to the age distribution in the case group (employing six age classes) was constituted ($n = 15\,263$).

To evaluate the role of data from patients with allergic asthma (AA) or allergic rhinitis (AR) in the control group, as well as the role of any atopic disease in the comparison group, a detailed analysis of the sensitization patterns was performed. All data was matched for age and sex of the patients. The comparison of data from (a) patients with AE, without AA or AR ($n = 4683$) vs patients without AE, AA or AR ($n = 31364$); and (b) patients with AE or AA or AR ($n = 15047$) vs patients without AE, AA or AR ($n = 31364$) did not show any significantly different results (data not shown).

Patch testing

Commercial allergens were used for patch testing (Hermal, Reinbek, Germany). Additional allergens to the standard series, which was applied to virtually all patients, were tested according to individual indications. Depending on the department's code of practice, test chambers had been applied for 24 h (7062 individuals, 41.0% of cases) or 48 h (17 221 individuals, 59.0% of cases); only the readings taken on day 3 (72 h) were evaluated for this study, based on previously published criteria (11, 13–15). Readings classified as +, ++ or +++ are summarized as allergic or positive (pos.), in contrast to all other readings (–, ?+ or IR) summarized as non-positive (nonpos.).

Statistical analysis

For descriptive characterization of the population, the MOAHLFA index (16) was used (see Table 1). Supplementary data used for analysis in our study included the indication for patch testing,

Table 1. The MOAHLFA-index

	AE	Control	Index
Male	34.7*	39.1	M
Occupation	21.6*	18.2	O
Hand dermatitis	38.4*	31.8	H
Leg dermatitis	2.6*	6.6	L
Face dermatitis	20.1*	12.9	F

*Significant difference ($P < 0.05$)

For descriptive characterization of the two groups of individuals with and without AE the MOAHLFA-index was modified (A = atopy and A = age were excluded).

history of AE, final clinical diagnosis and anatomical site of eczema. Data management and descriptive statistical analysis, which followed current guidelines (17) was performed with the program package SAS, version 8.2, SAS Institute, Cary, NC. In particular, sensitization prevalences in the two subgroups were sex-standardized (to 65% females and 35% males). To adjust for multiple statistical testing, P -values were alpha-adjusted following the method of Bonferroni–Holm.

Results

Anatomical site of eczema in ACD vs ACD and atopy

To characterize the two groups of age matched individuals with and without AE more precisely, the analysis of the MOAHLFA-index was performed initially. 'A' for AE was excluded, as this was the case definition, and 'A' for 'age 40 and above' was also excluded as by the age matching process the original age distribution of the comparison group was distorted. All other MOAHLFA factors differed significantly between the two groups of patients. As displayed in Table 1, in the AE group, a lower proportion of male patients was observed. Furthermore, occupational ACD was diagnosed more often in the AE group. Finally, the anatomical site of eczema differed significantly between the two groups: in the AE group, face dermatitis (7.2% in absolute terms) and hand dermatitis (6.6% in absolute terms) was observed more often, and leg dermatitis (4.0% in absolute terms) less often.

Frequencies of mono-, dual- or polysensitization in atopic and nonatopic individuals

The question, if AE is a risk factor for the development of ACD is still discussed controversially. To investigate this question, the overall sensitization frequencies in the two subgroups were analysed. As shown in Table 2, no association between the case status and the number of positive patch test reactions to allergens of the standard series was found.

Sensitization profile in atopic eczema patients

To get insight on the role of AE in the development of ACD, the pattern of type-IV sensitizations was analysed in the two groups. As displayed in Table 3, the frequency

Table 2. Frequency of none, one, two, three and four or more reactions, respectively, to allergens of the standard series in patients with vs without atopic eczema

	Individuals with AE		Controls	
	<i>n</i>	%	<i>n</i>	%
None	6043	74.63	10105	74.99
1	1500	18.53	2468	18.31
2	397	4.90	651	4.83
3	102	1.26	154	1.14
4 or more	55	0.68	98	0.73

Tested with at least 9 allergens.

Considering the following allergens of the standard series, included for at least 5 years during the study period: potassium dichromate (0.5%), *p*-phenylene diamine (1%), thiuram mix (1%), neomycin sulfate (20%), cobalt chloride (1%), benzocaine (5%), nickel sulfate (5%), colophony (20%), IPPD (0.1%), lanolin alcohols (30%), mercapto mix (1%), mercaptobenzothiazole (2%), epoxy resin (1%), balsam of Peru (Myroxylon Pereirae resin, 25%), *p*-tert. butylphenol formaldehyde resin (1%), formaldehyde (1% in water), fragrance mix (8%), ammoniated mercury (1%), oil of turpentine (10%), MCI/MI (100 ppm in water), paraben mix (16%), cetostearyl alcohol (20%), thiomersal (0.1%), zinc diethyldithiocarbamate (1%), MDBGN + PE (1%) – all allergens in pet, except where otherwise indicated.

of positive reactions to most allergens was similarly distributed between the two groups. Remarkably, the frequency of sensitization to bufexamac was almost three times higher in the AE group.

Next, we analysed the frequency of positive patch test results within common type-IV allergen groups in atopic

and nonatopic individuals. Common allergens were clustered and are displayed in Fig. 1. Statistical analysis partly revealed significant differences between atopic and nonatopic individuals (see asterisks in Fig. 1).

Occupation of atopic and nonatopic patients with ACD

To address the question whether occupation of the tested individuals was related to ACD in individuals with vs without AE, the frequencies of aggregated professions were compared between the two groups. The frequencies of ACD in office workers were significantly different between the two groups (AE: 6.2% vs control: 4.9%), as well as for nurses (4.6% vs 3.7%) but not cleaning staff (1.2% vs 1.5%). Other occupations like hairdressers (2.6% vs 2.3%, n.s.), chef (1.1% vs 1.3%, n.s.), dentist assistant (1.0% vs 0.9%, n.s.), and technical assistants (0.8% in both groups) were similarly distributed in the two subgroups.

Suspected allergen sources of ACD

In the routine patch test documentation within the IVDK, suspected contact allergen sources were identified. The frequency of common sources were compared between the group of individuals with or without AE. External drugs and ointments were most common allergen sources of ACD in patients with AE (58.6%), identified significantly more often than in the non-AE group (44.9%). The

Table 3. Most frequent contact allergens in individuals with or without atopic eczema [age-matched and sex-standardized sensitization prevalences with accompanying 95% confidence interval (CI)]

Allergen	Atopic dermatitis				Other patients			
	<i>n</i> (test)	<i>n</i> (pos.)	% (pos.)	95% CI	<i>n</i> (test)	<i>n</i> (pos.)	% (pos.)	95% CI
Nickel (II)-sulfate	8087	1422	17.6	16.8–18.4	13600	2438	18.9	18.2–19.5
Fragrance mix	8131	863	10.6	9.9–11.3	13618	1204	9	8.5–9.4
Oak moss abs.	1508	110	7.3	5.9–8.6	2038	104	5.1	4.1–6.1
Myroxylon pereirae resin (balsam of Peru)	8163	580	7.1	6.5–7.7	13626	968	7.2	6.7–7.6
Cobalt (II)-chloride	8132	572	7	6.5–7.6	13658	893	6.7	6.3–7.2
Potassium dichromate	8156	458	5.6	5.1–6.1	13686	550	4	3.7–4.3
Tetramethylthiurammonosulfide	2170	108	5	4.1–5.9	2997	114	3.8	3.1–4.5
Colophony	8153	335	4.1	3.7–4.5	13631	564	4.2	3.9–4.5
Lanolin alcohol	8161	332	4.1	3.6–4.5	13640	438	3.3	3.0–3.6
Amerchol L-101	6216	257	4.1	3.6–4.6	9040	354	3.9	3.5–4.3
Methyldibromoglutaronitrile + 2-phenoxyethanol	7860	311	4	3.5–4.4	13134	481	3.6	3.3–3.9
<i>p</i> -Phenylenediamine(CI 76060)	8068	315	3.9	3.5–4.3	13452	525	4	3.6–4.3
Compositae-mix	4363	166	3.8	3.3–4.4	7384	205	2.7	2.4–3.1
Thiuram-mix	8153	242	3	2.6–3.3	13621	297	2.2	1.9–2.4
4-(4-Hydroxy-4-methyl-pentyl)-3-cyclohexene carboxaldehyde (e.g. Lyrat®)	3558	99	2.8	2.3–3.3	5947	117	2	1.6–2.4
(Chloro)-methylisothiazolinone (MCI/MI)	8166	223	2.7	2.4–3.1	13646	268	1.9	1.7–2.2
Bufexamac	7026	188	2.7	2.3–3.0	11664	119	1	0.9–1.2
Ammoniated mercury	8107	203	2.5	2.2–2.8	13537	390	2.9	2.6–3.2
Propolis	6961	160	2.3	1.9–2.6	11609	211	1.8	1.6–2.1
Oil of turpentine	8164	182	2.2	1.9–2.5	13652	291	2.1	1.9–2.4
Formaldehyde	8171	156	1.9	1.6–2.2	13674	235	1.7	1.5–2.0
Neomycin sulfate	8162	133	1.6	1.4–1.9	13641	208	1.5	1.3–1.8

Allergens were described in Table 2.

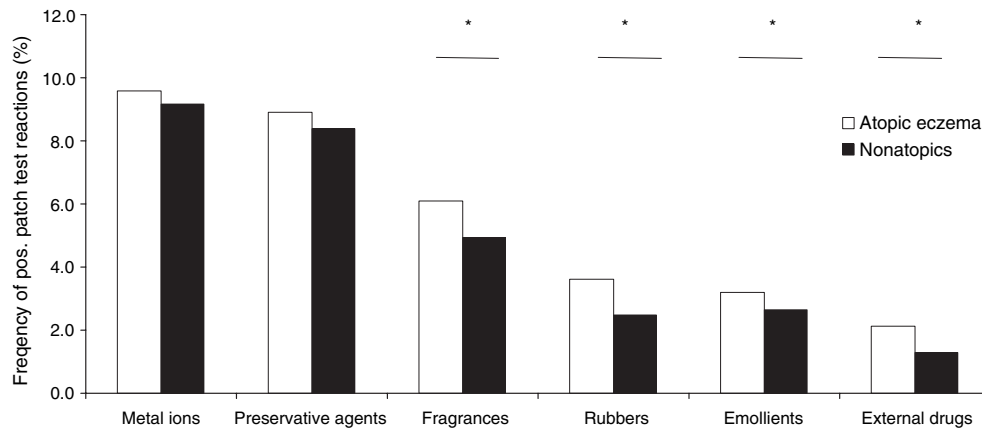


Figure 1. Frequency of clustered positive patch test results in patients with atopic eczema vs individuals without atopic eczema. The most frequent positive type-IV allergens were clustered in categories displayed on the x-axis. The total test numbers were summed up and % positive test reactions were calculated and are displayed on the y-axis. The light columns represent the data of atopic and the dark columns of the nonatopic individuals. Allergens in the different groups were: metal ions (nickel, cobalt, phenylmercuriacetate, and potassium dichromate), preservative agents (dibromocyanobutane and phenoxyethanol), rubbers (disulfirame and thiurame-mix), fragrances (fragrance-mix, oakmoss, Myroxylon pereirae resin, lyral, and propolis), emollients (lanoline and propylene glycol), external drugs (bufexamac and neomycine sulfate). *Statistical significance ($P < 0.05$).

frequency of dentistry as suspected contact allergen were in the AE group 4.1%, but in the non-AE group significantly more frequent (8.4%). Furthermore, other common sources of contact allergens such as rubbers and gloves (AE: 16.7% vs control: 13.8%), disinfectants (9.1% vs 7.4%), and fragrances (5.3% vs 3.8%) differed significantly between the two groups.

Cofactors for the development of ACD

Several factors are known to potentially promote the development of ACD. Analysis of these cofactors shows wet work (AE: 37.2% vs control: 31.9%) as most frequent circumstance, followed by occlusion (17% vs 19.3% – nonsignificant difference), dryness and dust (11.7% vs 5.3%), and chronic venous insufficiency (1.0% vs 8.7%), among other factors differing significantly between the two groups.

Coincidence of other atopic diseases

Atopy includes other clinical manifestations like allergic rhinitis or allergic asthma which may occur concomitantly in atopic individuals. In the tested patients, significantly more AE patients (39.0%) suffered from allergic rhinitis compared with the nonatopic individuals (15.3%). Similar results were obtained for the coincidence with allergic asthma (AE: 14.9% vs control: 4.1%).

Discussion

Still the role of AE in the development of ACD is not fully understood. Furthermore, the role of AE, even at

unaffected sites, on patch test results is discussed controversially.

This retrospective study is based on the comparison of two groups, defined by the presence and absence of underlying AE, respectively. Patients with AE are, on average, much younger than patients without AE. As age is an important (surrogate) marker for certain exposures, and contact allergy to many allergens is strongly age dependent, a confounding impact of the differing age distribution was anticipated. In contrast, while sex is an important surrogate risk factor for various contact allergies, such as nickel, there is no convincing association between sex and AE. Hence, to largely eliminate the confounding impact of age, the comparison group was matched to the AE group, while we refrained from an additional matching for sex, but took this factor into account by standardizing sensitization prevalences for sex. There are slightly more female patients in the AE group. Moreover, the more frequent involvement of facial and hand dermatitis in the AE group compared with the control group can be explained by the distribution pattern observed in this skin disease. Additionally, allergic rhinitis and allergic asthma was more frequent in the AE group, in accordance with previous data.

The analysis of occupation of patch tested individuals revealed a similar pattern of professions in both groups. The increased frequency of nurses is most probably related to the higher prevalence of occupational irritant contact dermatitis in these professions among persons with AE (18–20).

To get a better insight into the etiology of ACD in AE patients, the suspected allergen sources and risk factors were compared within the group of patients with or without AE. The high frequency of positive type-IV

reactions to external drugs and ointments in the AE group compared with the controls is indicating some sensitizing potential of the ointments and drugs in general, and additionally reflects the above-average exposure of AE patients. In line with this observation, the other common allergen sources were not significantly different in the study groups.

However, there were some differences in the contact allergen profile. The frequency of type-IV sensitization to the fragrance mix, composita mix, thiuram mix, MCI/MI, bufixamac, was significantly increased in the AE group compared with the control group. This observation is most probably related to the frequent use of scented moisturizing or skin protective creams and of bufixamac for the topical treatment of AE. The increase of sensitization to thiurame may be explained by the greater proportion of nurses in the group of AE (21). However, the increase in sensitization to MCI/MI is less easily to explain. This preservative is, apart from industrial applications, mainly used in rinse-off cosmetics, and may therefore be related to the group of hairdressers overrepresented in the AE group. Interestingly, in view of a assumed increased sensitivity to metals in AE, sensitization to potassium dichromate was increased, in contrast to the not increased frequency of sensitization to nickel. False positive irritative skin reactions of AE patients due to the marginally irritative potential of the potassium dichromate preparation as well as the susceptibility of the skin of atopic patients to irritation have to be considered and are in line with a recent report (22).

Taken together, this data indicate that the contact allergen profile in AE patients is quite similar to the spectrum found in patients without any atopic disease. Even if we can not rule out 'quiescent' atopic disease in the control group, due to the density of the data of this study, and the detailed analysis of the control group, we do not expect significant different results by serotyping of the included individuals for markers like total immunoglobulin (Ig)E or peripheral eosinophilia. Furthermore, there is no convincing evidence that inhaled antigens contribute to the development of ACD (1). Nevertheless,

the long-term use of topical drugs and ointments associated with the treatment of AE and Th2-like cytokine pattern may be regarded as risk factors of ACD. However, a generally increased or decreased risk of AE patients to be sensitized to contact allergens cannot be detected. A previous study on the frequencies of type-IV sensitizations to topical anti-microbial drugs did not show differences between atopic and nonatopic patients (23). Furthermore, more frequently used substances like bufixamac or ingredients of emollients which are often used may induce a type-IV sensitization and can trigger this chronic remittent skin disease by the addition of an ACD-component to the disease. However, further studies are needed to fully understand the complex interplay of atopic dermatitis and ACD in detail.

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