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SHORT COMMUNICATION

CONTACT HYPERSENSITIVITY IN ATOPIC DERMATITIS

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From January 1990 to December 1994, a total of 84 patients (56 men and 28 women) with atopic dermatitis (AD) were referred to our Clinic for patch testing. The European standard series of allergens was applied to all subjects together with any additional series indicated in the case history. Sensitization to at least one of the allergens was found in 57.1% of individuals with AD. Positive reactions were more frequently determined in adults than in children with AD. Women and men were equally positive in epicutaneous testing. The commonest sensitizer was nickel sulfate (discriminative in 28.6%). Adult patients with atopic dermatitis significantly differed from patients with chronic urticaria or healthy controls in patch test positive results. Our findings suggest that allergic contact dermatitis is more common in patients with AD than generally assumed and that patch testing is a practicable and clinically worthwhile procedure for determining allergic contact dermatitis in patients with AD.

Key words:
atopic dermatitis, contact allergens, contact dermatitis, contact hypersensitivity

Atopic dermatitis (AD, atopic eczema) is a genetically determined disease with manifold triggers and is characterized by pruritus (1).

Defective cell-mediated immunity is considered characteristic of AD patients. Patch testing is generally used to study allergy to low-molecule mass, haptenic contact sensitizers and is a clinical method for diagnosing allergic contact dermatitis and delayed hypersensitivity (2, 3).

Sensitization to contact allergens was found to be more common with a long-standing AD. The most frequently encountered allergens were nickel, fragrance mix, balsam of Peru, and neomycin (4).

This paper reports our cumulative clinical experience from patch testing of AD patients.

PATIENTS, MATERIALS AND METHODS

From January 1990 to December 1994, we tested a total of 84 AD patients (56 women and 28 men) aged between 5 and 68 years (mean age 29 years). The AD was diagnosed according to the criteria of *Hanifin and Rajka* (5). The patients were tested when their condition was under control. Patch tests were performed on the unaffected skin of the back which had not been treated with topical corticosteroids for at least 5 days. None of the patients were taking systemic steroids or antihistamines when tested. We also tested 50 healthy controls (39 women and 11 men) aged between 5 and 63 years (mean 20.7 years) and 3 patients with chronic urticaria.

The epicutaneous (patch) test was carried out with a standard series patch method for adult patients with AD and children over 5 years of age (6). We began our study using products supplied by the Institute of Immunology in Zagreb. Epicutaneous testing by patch method is performed by applying the allergen on a 1 x 1 cm patch of filter paper. One to two drops of the allergen are taken if in liquid base or 0.02 to 0.03 g of allergen if in Vaseline or other base. A cellophane patch sized 2 x 2 cm was laid over the allergen patch and the site was protected with a 5 x 5 cm adhesive bandage. Readings were graded according to ICDRG recommendations (24- and 48-hour readings). After a 24-hour application, the allergens were removed and the first reading took place, while the second reading occurred 48 hours later. Only in specific cases did the routine reading occur after 72 hours.

The test responses were graded according to the following criteria: negative; positive: +1 mild erythema and oedema; positive: ++ erythema, oedema, single papules and scattered vesicles; positive: +++ numerous papules and vesicles, single bullae, eroded surface and profuse moistening (6). Results of at least +1 were considered significant.

The obtained data were classified on the basis of criteria of positive and negative test results and on the basis of comparison with normal values. The statistical analysis used χ^2 test was while the significance was set at <0.05.

RESULTS

Patch tests of 84 patients with AD proved positive in 48 (57%). Patch tests proved negative in all three subjects with chronic urticaria and in all 50 controls.

Of 13 children with AD, nine (69%) were negative and four (31%) showed positive patch test results for contact testing ($\chi^2=1.89087$, df=1, $p=0.1691$).

Of 71 adult AD patients, 44 (62%) showed one or more positive patch test reactions to contact testing (Table 1). The difference between the non-AD and AD groups was found to be statistically significant ($\chi^2= 43.39799$, df=2, $p<0.01$).

The positive reactions in both women and men were comparable, that is, of 56 women with AD, 32 (57%) were positive and 24 (43%) negative, while of 28 men with AD, 16 (57%) were positive and 12 (43%) negative.

Table 1 *Results of epicutaneous test in adults*

Results	Epicutaneous test *	
	AD (n=71)	healthy control (n=40)
Positive	44 (62%)	0 (0%)
Negative	27 (38%)	40 (100%)

* the statistical test showed significance ($p < 0.05$)

Table 2 shows the most frequent allergens used in the epicutaneous test on 84 AD patients that caused positive response. Nickel sulfate was the commonest allergen, occurring in 24 of 84 AD patients, that is, with the frequency of 28.6%. The frequency of contact allergy for cobalt chloride was 25% and for potassium dichromate 20.2%. These were followed by fragrance mix, coal tar, balsam of Peru, and others.

Table 2 *The most frequent allergens with epicutaneous test positive results in 84 AD patients*

Allergen	No. of examinees with positive reactions	No. of examinees with intensity of reaction		
	Total (%)	+1	+2	+3
Nickel sulfate	24 (28.6)	15	7	2
Cobalt chloride	21 (25.0)	14	6	1
Potassium bichromate	17 (20.2)	14	0	3
Fragrance mix	16 (19.0)	10	5	1
Coal tar	15 (17.8)	12	3	0
Balsam of Peru	12 (14.3)	8	4	0
Black rubber mix	5 (5.9)	4	0	1
Rubel™ detergent	4 (4.8)	3	1	0
Čarli™ detergent	4 (4.8)	4	0	0
Carba - compounds	4 (4.8)	1	2	1
Colophony	3 (3.6)	2	0	1
Faks™ detergent	2 (2.4)	2	0	0
Vim™ detergent	2 (2.4)	0	2	0
Formaldehyde	2 (2.4)	1	1	0

Table 3 shows the frequency of positive reactions to contact allergens in 84 AD patients according to their profession. Most of the AD patients were students followed by a group of factory workers, clerks, salesmen, pensioners, housewives, etc.

Table 3 *Frequency of positive reactions to contact allergens in 84 AD patients according to their profession*

Professions	Tested	Positive	Negative	Nickel sulfate	Cobalt chloride	Potassium bichromate	Fragrance mix	Coal tar	Balsam of Peru	Black rubber mix
Students	8	3	5	1/8	1/8	2/8	2/8	2/8	1/8	0/8
Factory workers	7	5	2	1/7	0/7	2/7	2/7	3/7	1/7	1/7
Clerks	5	3	2	0/5	0/5	1/5	1/5	1/5	1/5	0/5
Salesmen	5	3	2	2/5	0/5	2/5	0/5	1/5	1/5	0/5
Pensioners	5	4	1	1/5	0/5	0/5	1/5	1/5	3/5	0/5
Housewives	5	2	3	2/5	2/5	0/5	1/5	1/5	1/5	1/5
Miners and workers in civil engineering	4	3	1	1/4	0/4	0/4	0/5	1/5	0/5	0/5
Traffic workers	4	1	3	1/4	1/4	1/4	0/4	1/4	0/4	0/4
Health workers	3	3	0	1/3	1/3	2/3	2/3	1/3	2/3	0/3
Others	38	21	17	14/38	16/38	7/38	7/38	3/38	2/38	3/38
TOTAL	84	48	36	24/84	21/84	17/84	16/84	15/84	12/84	5/84

The patient groups with highest yields of positive patch test were the health professionals (3/3), retired people (4/5), miners and workers in civil engineering (3/4), factory workers (5/7), clerks (3/5), salesmen (3/5), housewives (2/5), students (3/8) and professions related to traffic (1/4).

Table 4 *Occurrence of allergic patch test reactions in men and women with AD*

Allergen	Men (n=28)	Women (n=56)
Nickel sulfate	8 (28.5%)	16 (28.5%)
Cobalt chloride	10 (35.7%)	11 (19.6%)
Potassium bichromate	7 (2.5%)	10 (17.8%)
Fragrance	3 (10.7%)	13 (23.2%)
Coal tar	2 (7.1%)	13 (23.2%)
Balsam of Peru	3 (10.7%)	9 (16%)

Among AD patients, women manifested the most frequent positive response to nickel (28.5%), while more men reacted to cobalt (35.7%) (Table 4). Positive responses to nickel in the patch test were equally distributed between women and men (28.5% and 28.5%, respectively).

DISCUSSION

Histological and immunological characteristics of AD roughly correspond to type IV allergic reactions, indicating that type IV allergy plays an important role in the mechanism of AD pathology (7). Delayed hypersensitivity skin tests and patch tests are the most readily available methods for determining delayed hypersensitivity.

Since contact dermatitis may resemble other types of dermatitis, an allergen or irritant should be suspected as the cause or aggravating factor in any puzzling dermatitis. Typical skin changes and the history of exposure facilitate the diagnosis, but identification may require an exhaustive inquiry. A specialist should select test concentrations (particularly for industrial agents or cosmetics, in which case an industrial specialist should be consulted). A positive patch test reaction does not necessarily identify the agent causing the contact dermatitis. There must be a history of exposure to the test agent in the areas where the dermatitis originally occurred before a definitive diagnosis can be made. Moreover, a negative patch test does not rule out contact dermatitis: it may only mean that the particular agent was not included in the test.

The incidence of allergic contact dermatitis superimposed on atopic dermatitis is still controversial (4). While some authors report reduced incidence, others report similar or higher incidence than in non-AD population (8). An international study

revealed that individuals with AD are not more likely to develop allergic contact dermatitis than are the patients with other types of eczema (4). Its results show that exposure of AD skin to new potential contact allergens is less likely to result in acquisition of contact dermatitis than the skin of normal individuals. When diagnostic patch tests were investigated prospectively in AD and non-AD patients, positive tests were seen in 37% of AD patients vs. 57% of non-AD patients (4). Similar results were obtained by *Cronin and McFadder* (9). Based on the assessment of sensitivity to contact allergens, *Cronin and McFadder* believe that AD patients should be tested by epicutaneous test. Sensitization to ≥ 1 allergens occurred in 38% of 191 patient with existing atopic eczema, in 53% of 120 with the history of atopic eczema, in 54% of 156 with only mucous membrane atopy and in 50% of the 510 non-atopic patients. Sensitization to perfume, a common environmental allergen, was similar in all 4 groups, as was nickel among women. Patients with atopic eczema should be patch tested.

According to *Cronin and McFadder,* the sensitization to one or more allergens occurred in 38% of AD patients and in 50% of patients who were not atopic. *Lever and Forsyth* (8) found that 31 (42%) of 73 adult AD patients showed one or more positive patch test reactions on contact testing. We found contact sensitivity in 57% of AD patients. The incidence of AD manifested a progress in the number of cases with contact allergy at our department (10). It could be explained by the influence of environmental and stress factors during the war in Croatia (1990–1994) which are supposed to have significantly altered immunologic system activities in the atopics.

Positive reactions have been noticed to appear more frequently in adults than in children (62% vs. 31%, respectively). This confirms that the number of positive patch test reactions increases with age and environmental exposure (2, 11).

Ring and co-workers (12) patch tested AD patients and found that the commonest positive reactions were to nickel sulfate (15.2%), fragrance mix (9.5%), potassium dichromate (5.9%) and cobalt chloride (5.5%). *Lever and Forsyth* (8) found that the commonest allergens identified were fragrances (17.8%), nickel (9.5%), rubber (6.8%), lanolin (5.4%) and formaldehyde (4.1%). Our study showed that the commonest positive reactions were to nickel (28.6%), followed by cobalt (25%), chromate (20.2%), and fragrance (19%). The occurrence of sensitization to some allergens is mostly dependent on the level of industrialization and health culture in some countries. The most frequent allergens for the Croatian national pathology were chemical compounds with chrome, nickel, cobalt, rubber, ursol, mercury, artificial resins and others, also confirmed by our study.

The high prevalence of nickel allergy in the population might be due to the overwhelming environmental exposure (13). Nickel dermatitis may often be dry and closely resemble the eruption of atopic dermatitis (4). However, according to *Pambor and co-workers* (14), a positive reaction to nickel rarely correlates with clinical symptoms and relevant exposure in children.

Besides nickel being a component of coins, keys, handles, taps, machines, various devices and other objects, it may also be found in jewelry. Reactions to jewelry are commonly reported among atopics, but patch tests for notorious jewelry allergens result negative. Men who still suffer from atopic dermatitis are unlikely to go into the construction industry and are rarely sensitized to chromate. Perhaps such patients avoid wet jobs which require rubber gloves, thus avoiding exposure to thiurams (9).

Fragrances are almost ubiquitous in cosmetics and other proprietary preparations and they often cause contact hypersensitivity. The commonest sources of fra-

grance include toiletries, particularly shampoos, additives, washing powders and fabric conditioners. Where facial and braincase skin lesions are a particular problem, shampoos are often a significant factor. Appropriate advice as to what should be avoided can significantly alleviate the disease. Contact with wool and dust induces or exacerbates AD skin lesions.

Patch testing with topical medications and their preservatives is indicated in many chronic cases of atopic dermatitis (4). In atopic dermatitis, neomycin sensitivity is often obscured by a topical neomycin-corticosteroid preparation and is usually detected only by routine patch tests. Penicillin, quinine, sulfonamides, mercury, and arsenic can produce delayed contact reactions and immediate anaphylaxis.

In addition to standard series, testing is also made by epicutaneous test for professional allergens. Our study has shown that nickel allergy is not associated with a specific profession. Positive reaction to at least one of the allergens has also been noticed in all three health professionals who were AD patients. Positive reaction has often been reported in elderly retired persons tested with patch test (see above). In fact, our study does not allow precise hypothesis about the effect of occupational exposure on sensitization to a specific antigen because of wide distribution of patients in professional groups.

Hairdressers are particularly good for investigation being exposed to the same irritants and allergens, irrespective of their workplace. *Sutthipisal and co-workers* (15) have shown that, under the same conditions of exposure, eczematous atopics and non-atopics are equally sensitized. Positive patch test responses to hairdressing chemicals were found in 60% of the eczematous atopics, 53% of the mucous membrane atopics and 58% of the non-atopics. The commonest sensitizer in each group was glyceryl monothioglycolate, followed by paraphenylendiamine and related dyes. None of the men showed allergy to nickel, but 40% of women did. Jewelry, rather than equipment, was thought to be the cause. Sensitization capacity to hairdressing chemicals and to nickel show no significant difference between eczematous atopics, mucous membrane atopics and non-atopics. However, their (15) recent paper shows that AD patients are as frequently sensitized to common environmental allergens such as nickel and perfume as are the non-atopics.

There is a possibility that the skin of AD patients is more susceptible to irritation than is the normal non-atopic skin (8).

Recognition of contact allergy in AD patients is important in management (16). Patients should be aware that nickel, rubber and other allergens are common in our environment.

There is increasing evidence that exposure to organic allergens may induce or exacerbate skin lesions in AD patients (17).

In AD patients, patch test may often prove allergy to other antigens, for instance house dust particles (18). *Buckley and co-workers* confirm previous reports that the patch test reaction to aeroallergens and the lesions of AD patients exhibit characteristic features of a delayed type IV hypersensitivity reaction (17, 19). The close similarity between the cellular events after a patch test reaction to aeroallergens in AD patients and those present in AD lesions suggest that the patch test reaction may be a helpful *in vivo* model to study the pathogenesis of AD (19).

AD patients with defending specific IgE often show positive result to epicutaneous test. From a technical point of view, a simple application of allergic material to healthy skin yields best results. In epicutaneous tests to antigens of mites, *Castelain*

and co-workers often (20.8%) obtained positive results in AD patients, while rarely in non-atopics (0.76%) (20). The result show that the epicutaneous test with *Dermatophagoides pteronyssinus* extracts in atopics might contribute to better immunoallergic characterization.

Patients with positive patch tests did not necessarily show immediate response (20). It would be useful to test atopic patients systematically, even if it is not known what modern treatment to apply for the patient. Laboratories still do not provide other standardized preparations (like house mite). Measuring and codifying their type of test will lead to production of better test materials in syringes with homogeneous dispersion and concentration (20).

CONCLUSION

We have shown that contact sensitization in AD patients is considerably frequent. These data are in contrast with most other studies reporting contact allergy not to be predominant. Considering the clinical relevance of the results, patch testing is a useful supplement in examining patients with AD.

Recognition of associated contact sensitivity and appropriate medical advice as to what potentially toxic agents are to be avoided may alleviate the disease.

However, the remarkable frequency of differences between contact allergies in AD patients and healthy controls should initiate further prospective investigations, especially related to professional orientation of children and adolescents.

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Sažetak

KONTAKTNA PREOSJETLJIVOST U ATOPIJSKOM DERMATITISU

Od siječnja 1990. do prosinca 1994. godine, ukupno su 84 pacijenta (56 muškaraca i 28 žena) s atopijskim dermatitisom upućena u Kliniku za kožne i spolne bolesti Medicinskog fakulteta Sveučilišta u Zagrebu radi epikutanog (patch) testiranja. Standardne europske serije alergena aplicirane su svim ispitanicima zajedno s dodatnim serijama alergena na koje je uputila anamneza. Preosjetljivost na najmanje jedan od alergena bila je utvrđena u 57,1% osoba s atopijskim dermatitisom. Pozitivne reakcije dobivene su češće u odraslih (62%) nego u djece (30,8%) s atopijskim dermatitisom. Žene su pokazale podjednako često pozitivne reakcije (57,1%) kao muškarci u epikutanom testu. Među alergenima najčešće je pozitivne reakcije uzrokovao nikalski sulfat (28,6%), zatim kobaltni klorid (25%) te kalijski bikromat (20,3%). U muškaraca je najčešće pozitivnu reakciju uzrokovao kobaltni klorid (35,7%), a u žena nikalski sulfat (28,5%). Statistički značajna razlika nađena je kod pozitivnih

rezultata patch testa u odraslih između pacijenata s atopijskim dermatitisom, pacijenata s kroničnom urtikarijom ili zdrave kontrole. Prema zanimanjima najčešće su pozitivne reakcije uočene u zdravstvenih radnika, umirovljenika, radnika u rudarstvu i graditeljstvu. Rezultati naših istraživanja upućuju na to da je alergijski kontaktni dermatitis češći u pacijenata s atopijskim dermatitisom nego što se općenito smatra i da je patch testiranje praktičan i klinički vrijedan postupak kod njih.

Ključne riječi:
atopijski dermatitis, kontaktna preosjetljivost, kontaktni alergeni, kontaktni dermatitis

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