

## Contact Sensitivity in Patients with Atopic Dermatitis

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**ABSTRACT** Atopic dermatitis (AD) is a common chronic and relapsing, non-contagious inflammatory skin disorder, characterized by skin barrier impairment and baseline immune irregularities. The literature on the relationship between AD and cutaneous delayed-type hypersensitivity is inconclusive. There is an ongoing debate whether contact sensitivity (CS) is found more or less often among patients with AD. Aim of the study was to evaluate the incidence of contact sensitivity (positive patch test reactions) in patients with and without AD. We patch tested a total of 2143 patients (563 men and 1580 women). There were 226 patients with history of AD; 61 (27%) men and 165 (73%) women. The patient group without AD consisted of 1917 patients, 502 (26%) male and 1415 (74%) female patients, who were referred to our Department with clinical suspicion of allergic contact dermatitis (ACD). A patch test was performed with the baseline series, and readings were performed on days D2, D3, and D7. Among patients with AD, 109 (48.2%) had a positive patch test reaction to at least one allergen, whereas 1094 (57.1%) patients with no history of AD had a positive patch test reaction. The most common positive allergens in patients with AD were nickel (II) sulfate (13.3%), thimerosal (12.4%), cobalt (II) chloride (11.5%), methylisothiazolinone (MI) (8.4%), fragrance mix I (6.6%), potassium dichromate (5.3%), methyldibromo glutaronitrile (4.0%), and carba mix (4.0%). The results of our study agree with previous findings that there is no significant difference in prevalence of CS between the atopic and nonatopic populations.

**KEY WORDS:** atopic dermatitis, contact sensitivity, patch test

### INTRODUCTION

Atopic dermatitis (AD) is a common chronic and relapsing, non-contagious inflammatory skin disorder characterized by typical morphology/distribution of dermatitis, pruritus, and xerosis (1). Contact dermatitis (CD) is an inflammatory skin reaction caused by direct contact with noxious agents in the environ-

ment and typically develops following repeated or prolonged topical exposure to chemical allergens (2,3). Contact sensitivity (CS) is the term used to describe a positive patch test reaction and is characterized by induction of a specific T-lymphocyte response (3,4). To diagnose allergic contact dermatitis (ACD) in

a patient, the patient must have a contact sensitivity and clinical picture of dermatitis with clinically relevant exposure to the contact allergen (5). Induction of CS and elicitation of ACD depend on the sensitizing potential of the hapten, dose per unit area, presence of the irritants, race, gender, age, and genetic predisposition (6). The incidence of AD varies between 11% and 21% in Northern Europe (5), while CS affects up to 20% of the general population (7). Both diseases have a marked impact on quality of life (8,9). Experimental studies have clearly shown that individuals with AD have suppressed CS due to their disease (10). General population and clinical studies have found diverging outcomes, some suggesting a positive association between AD and CS (4,11-17). Clinical studies have shown that exposure to contact allergens used in topical products may result in CS, but sensitization trials have shown that especially moderate to severe AD is inversely associated with CS (18-20).

## OBJECTIVES

To evaluate the incidence of CS (positive patch test reactions) in patients with and without AD.

## PATIENTS AND METHODS

We patch tested a total of 2143 patients, 563 men and 1580 women, between March 2, 2015 and February 27, 2017. There were 226 patients with history of AD and 1917 patients without AD, who were referred to our Department with clinical suspicion of allergic contact dermatitis (ACD). Atopic dermatitis was diagnosed clinically, using Hanifin and Rajka criteria (21). We patch tested patients with AD when we suspected ACD (persistent and therapy refractory dermatitis especially on the face and hands and worsening of the dermatitis after application of local therapy). The patch test was performed with the baseline series (Imunološki zavod, Zagreb, Croatia; Chemotechnique, Vellinge, Sweden) using Finn Chambers on Scanapor tape, applied to the upper back area, and readings were performed on day (D) D2, D3, and D7.

## RESULTS

We patch tested 2143 patients: 563 men and 1580 women. Of the 2143 patients tested, 226 had AD. There were 61 (27%) men and 165 (73%) women with AD and 502 (26%) male and 1415 (74%) female patients without AD. Among patients with AD, 109 (48.2%) had a positive patch test reaction to at least one allergen, whereas 1094 (57.1%) patients with no history of AD had a positive patch test reaction (Figure 1). A total of 87 (52.7%) women and 22 (36.1%) men with AD had a positive patch test reaction to at

least one allergen, while 837 (59.2%) women and 257 (51.2%) men without AD had a positive patch test reaction. The median age of patients with AD was 24.6 years and 44.4 years in patients without AD. The most common positive allergens in patients with AD were nickel (II) sulfate (13.3%), thimerosal (12.4%), cobalt (II) chloride (11.5%), methylisothiazolinone (MI) (8.4%), fragrance mix I (6.6%), potassium dichromate (5.3%), methyldibromo glutaronitrile (4.9%), and carba mix (4.0%) (Figure 2, Table 1). In patients without AD, the most common positive allergens in the patch test were nickel (II) sulfate (21.4%), cobalt (II) chloride (14.0%), MI (12.9%), thimerosal (12.2%), potassium dichromate (6.6%), MCI/MI (6.3%), fragrance mix (6.2%), methyldibromo glutaronitrile (5.8%), and myroxylon pereirae (4.4%) (Figure 3, Table 1). A higher number of patients with AD had a positive patch test reaction to carba mix and to lanolin alcohol compared with patients without AD (Table 1). A lower number of patients with AD had a positive patch test reaction to potassium dichromate, cobalt (II) chloride hexahydrate, nickel (II) sulfate hexahydrate, myroxylon pereirae, neomycin sulfate, MCI/MI, and MI than patients without AD (Table 1). There were no differences between patients with and without AD for fragrance mix I, formaldehyde, thimerosal, tixocortol-21-pivalate, and budesonide (Table 1).

## DISCUSSION

There is ongoing debate in the literature regarding the relationship between AD and contact dermatitis. Several studies reported reduced CS (4,12,13), others found a positive relationship (4,11,14-17), while some studies found atopy and contact dermatitis to be independent (18). We found more positive patch test reactions in patients without AD (57.1%) compared with patients with AD (48.2%). The results of our study agree with previous findings that there is no significant difference in prevalence of CS between the atopic and non-atopic population (4,14,23). In a recent general population study that included 6161 patients, average prevalence of CS in patients with AD was 29.6%, while being 22.5% in those without AD (4). In the same study in a referred population group (n=50,544), the average prevalence of CS in patients with AD was 49.9%, which is the same as in our study (48.2%), and 54.9% in patients without AD (4). Results of a meta-analysis showed that patients with and without AD have similar prevalence of CS, with an inverse association in patients referred for patch testing (4). In studies on the general population, higher CS rates were found in individuals with AD (4). The higher proportion of positive patch test reactions in patients without AD could be explained

**Table 1.** Positive patch test results in patients with atopic dermatitis and patients without atopic dermatitis

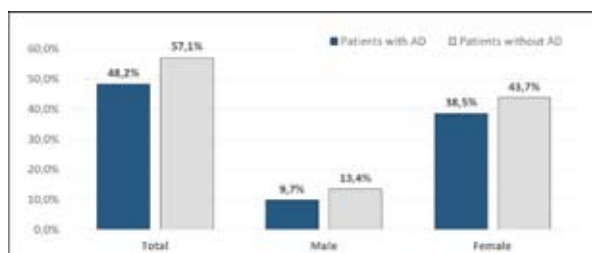
Allergen in baseline series	Patients with AD (N=226)	Patients without AD (N=1917)	p-value
1 Potassium dichromate	12 (5.3%)	127 (6.6%)	0.538
2 Cobalt(II) chloride hexahydrate	26 (11.5%)	269 (14.0%)	0.347
3 Nickel (II) sulfate hexahydrate	30 (13.3%)	410 (21.4%)	0.006
4 Fragrance mix I	15 (6.6%)	118 (6.2%)	0.89
5 Epoxy resin	0 (0.0%)	17 (0.9%)	0.245
6 p-phenylenediamine (PPD)	2 (0.9%)	29 (1.5%)	0.65
7 Myroxylon pereirae	2 (0.9%)	84 (4.4%)	0.007
8 N-Isopropyl-N-phenyl-4-phenylenediamine (IPPD)	0 (0.0%)	15 (0.8%)	0.392
9 Mercapto mix	4 (1.8%)	15 (0.8%)	0.132
10 Thiuram mix	3 (1.3%)	55 (2.9%)	0.274
11 Carba mix	9 (4.0%)	46 (2.4%)	0.23
12 Paraben mix	0 (0.0%)	7 (0.4%)	1
13 Coal tar	2 (0.9%)	70 (3.7%)	0.02
14 Neomycin sulfate	3 (1.3%)	79 (4.1%)	0.041
15 Benzocaine	1 (0.4%)	15 (0.8%)	0.484
16 Colophonium	1 (0.4%)	35 (1.8%)	0.17
17 Formaldehyde	3 (1.3%)	27 (1.4%)	1
18 Thimerosal	28 (12.4%)	234 (12.2%)	0.915
19 Phenyl mercuric acetate	2 (0.9%)	23 (1.2%)	1
20 Sesquiterpene lactone mix	4 (1.8%)	23 (1.2%)	0.521
21 Clioquinol	0 (0.0%)	6 (0.3%)	1
22 Quaternium -15	0 (0.0%)	10 (0.5%)	0.612
23 2-Methoxy-6-n-pentyl-4-benzoquinone	0 (0.0%)	7 (0.4%)	1
24 Budesonide	4 (1.8%)	36 (1.9%)	1
25 Tixocortol-21-pivalate	1 (0.4%)	8 (0.4%)	1
26 Methylisothiazolinone + methylchlorisothiazolinone	5 (2.2%)	121 (6.3%)	0.01
27 Fragrance mix II	3 (1.3%)	53 (2.8%)	0.27
28 Methylisothiazolinone	19 (8.4%)	247 (12.9%)	0.068
29 Methylidibromo glutaronitrile	11 (4.9%)	112 (5.8%)	0.656
30 Lanolin alcohol	8 (3.5%)	16 (0.8%)	0.001

by patients selection bias, since only patients with suspected CD are patch tested, and not the general population, while patients with AD were mostly referred to patch test just to rule out CS, therefore CS is less expected (4,13).

It is unclear whether patients with AD have an increased risk for CS or if they are at higher risk to become sensitized due to increased exposure to chemicals in topical products applied to the skin on

a daily basis along with impaired skin barrier function (4,11,19). However, the immune profile and suppression of cell-mediated immunity suggest lower risk (4,11). It is possible that AD not only results in CS but also that CS may result in AD in select individuals, or at least worsen the course of the disease (10,24). The risk to develop AD is increased in individuals with primary skin barrier impairment and primary immune dysregulation, and filaggrin gene mutations





**Figure 1.** Contact sensitivity in patients with and without atopic dermatitis.

(FLG *mut*) have the highest impact on impairment of barrier function (4,10,25,26). There is evidence of an almost 2-fold increase in absorption of irritants, chemicals, and contact allergens in the skin of patients with AD (27).

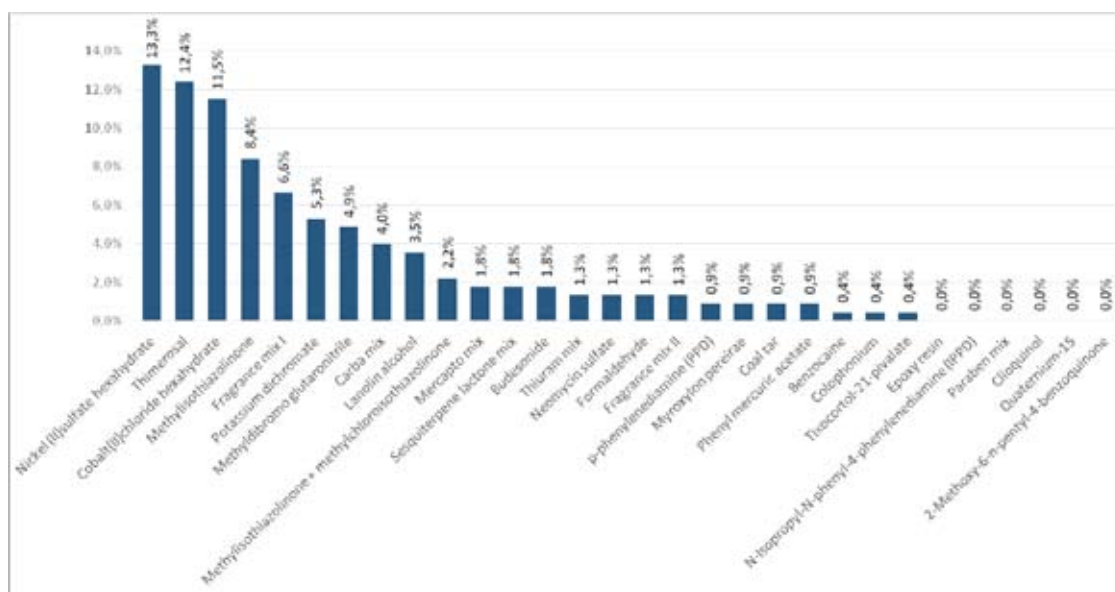
Patients with AD were much younger than patients without AD, which is a finding consistent with the results from previous studies (14,17,28). Contact allergy to the majority of allergens is strongly age dependent (10,15,17,18,27,29-31). The differences in the age are due to the differences in the exposure, frequency, type, and length of exposure required to induce sensitization to specific chemicals (14). AD predisposes a higher risk of ACD in children compared with adults (31). Risk factors for positive patch test reactions in a recent study were onset of dermatitis before 6 months of age and IgE-mediated sensitization, indicating that those that have been the most strongly exposed will have the higher incidence of CS (3,19). A higher frequency of positive patch test reactions and multiple sensitizations were found in patients with severe AD (16,23,32). Prevalence was higher in

patients with AD who had FLG loss of function mutation, when compared with individuals without AD and wild-type FLG, suggesting a severity of disease may increase a risk of CS (7,10,16,28,32). A general population study showed that patients with AD, especially those with FLG *mut*, had a higher prevalence of CS in topical products (3,6,18).

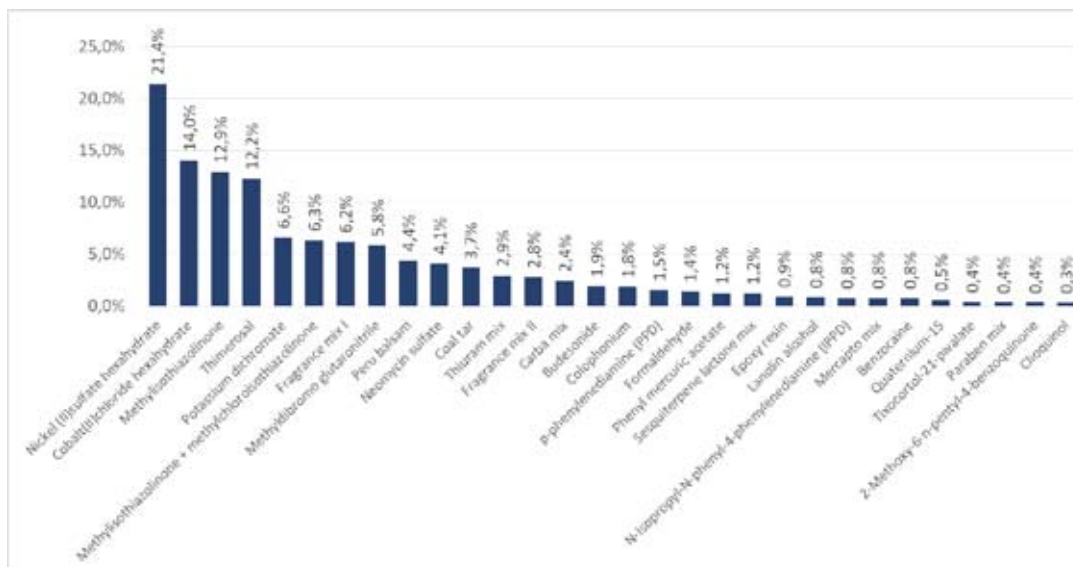
Although many studies have found chromium to be more statistically frequently positive in patients with AD (4,33) (which could be explained by a falsely positive patch test reaction due to the irritative potential of chromium) (3,7), our results showed lower positive reactions in patients with AD (5.3%) when compared with the group of patients without AD (6.6%), and this was similar to observations reported in other studies (23).

Previous epidemiological studies suggested an increased prevalence of nickel sensitization and ACD (14), although results of meta-analysis did not find a positive correlation (4). We found lower positive patch test reactions to nickel (II) sulfate in patients with AD, which is consistent with other reports (16). Ear-piercing is still considered to be the most important step in nickel-sensitization and it is speculated that nickel sensitivity is expected to be less dependent on skin barrier function impairment because barrier integrity is often violated by ear-piercing (25). A slight association of loss-of function FLG *mut* and CS to nickel has been found, with a strong association when analysis is restricted to female patients (25).

Our results showed that patients with AD were more likely to have a positive reaction to carba mix and to lanolin alcohol than patients without AD,



**Figure 2.** Positive patch test results in patients with atopic dermatitis.



**Figure 3.** Positive patch test reactions in patients without atopic dermatitis.

which could be explained by frequent usage of these substances in the emollients that they were using.

More patients with AD, compared with patients without AD, had fragrance CS, which is in correlation with results of other studies (6,10). However, there were some reports in which fewer patients with AD than patients without AD had fragrance allergy (23).

Many cosmetics and topical medications and hygiene products, including liquid soaps, shampoos, and conditioners, have a high water content and require chemical preservation (16). Parabens, formaldehyde, and formaldehyde releasers are commonly used as preservatives (16). Formaldehyde is a strong sensitizer, irritant, and potential carcinogen, and has therefore been mostly replaced by formaldehyde releasers (16). However, it is still used in some hair care and nail care products today (34). In our study, only 3 (1.3%) patients with AD were positive to formaldehyde, while formaldehyde releaser (quaternium-15) and parabens were negative, which is not in correlation with other reports (16) that demonstrated significantly higher allergic responses to formaldehyde releasers in patients with AD.

Contact allergy to biocides is still common throughout Europe. MI prevalence is 4.5%, and MCI/MI mixture prevalence is 4.1% (35). In our study, there was a relatively high percentage of both MI and MCI/MI (Table 1) in both studied groups, which can be explained as the result of using leave-on and rinse-off skin and hair care products containing those substances. There were 19 (8.4%) patients with AD positive to MI. Our study ended on February 27, 2017, and as of January 2017 MCI/MI and MI have been forbidden in leave-on cosmetics (36).

Methyldibromo glutaronitrile (MDBGN) was an allergen commonly used in cosmetics and personal care products, such as body lotions, facial lotions, hand lotions, sunscreen lotions, baby lotions, shower gels, shampoos, and massage oils (30,37). Since 2005, the European Union banned the use of MDBGN in stay-on products and then later in 2007 also in rinse-off products (30,37). We found a positive reaction to MDBGN in 4.9% patients with AD and in 5.8% patients without AD.

Coal tar is substance that can reduce inflammation, itching, and scaling and is mostly used in treatment of psoriasis, seborrheic dermatitis, and eczema (38). In our study, slightly higher positive reactions were found in patients without AD.

When the eczematous lesions do not respond properly to corticosteroid treatment or even worsen when topical corticosteroids are applied, patch testing with corticosteroid markers (tixocortol pivalate, budesonide, and hydrocortisone-17-butyrate) should be performed (39). Corticosteroids are not potent allergens, but CS to them is not that infrequent, since patients with AD are treated with corticosteroids since early childhood (39). More positive reactions can be expected on later patch test readings (day 7) (13). Although both of our tested groups were previously treated with corticosteroids, CS to corticosteroids was not a frequently positive allergen among our patients. We found positivity to tixocortol-21-pivalate in 0.4% of patients in both studied groups, and 1.8% positivity to budesonide in patients with AD compared with 1.9% positivity in patients without AD.

Thimerosal is used as an ophthalmic preservative, a topical anti-infective, and a topical veterinary

antibacterial and antifungal agent. It could be found in vaccines, antitoxins, skin testing allergens, antiseptics, contact lens solutions, and cosmetic products like eye make-up (40). A positive reaction to thimerosal was irrelevant to contact allergy in our patients. It may indicate exposure to vaccines during childhood.

While many studies reported significantly higher positive reactions to sesquiterpene lactone mix (4,6), which can cause worsening of AD during spring and summer months due to airborne dermatitis, in our study there was no difference between the two studied groups (1.8% of the patients with AD and 1.2% of the patients without AD had a positive reaction).

## CONCLUSIONS

CS in patients with AD should be always considered in cases of therapy-resistant AD and in cases of worsening of skin condition after application of local therapy. Patients with AD with suspected CS require careful evaluation of clinical and personal history, known allergies, hobbies and leisure activities, information on topical medication usage, and use of or exposure to cosmetics and skin care products.

## LIMITATIONS OF THE STUDY

Only patients with AD suspected of having ACD were patch tested, not the general population, while patients without AD were mostly referred to patch test just to rule out CS. We have data for contact allergy for all patch-tested patients, while data on relevance is missing. Another study limitation is the large differences between age groups. We did not evaluate the severity of the AD, which is expected to be an important risk factor in development of CS, and we do not have data on *FLG mut* in the group of patients with AD.

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