

Contact Hypersensitivity to Haptens of the European Standard Series and Corticosteroid Series in the Population of Adolescents and Adults With Atopic Dermatitis

Marek Kot, MD,* Jaroslaw Bogaczewicz, MD, PhD,* Beata Krecisz, MD, PhD,† and Anna Wozniacka, MD, PhD*

Background: Until recently, it was thought that in patients with atopic dermatitis (AD), contact hypersensitivity phenomenon occurs less frequently than in the general population because of the impaired cellular immune response.

Objective: The aim of this study was to evaluate the incidence of contact dermatitis in the population of patients with AD.

Methods: A total of 39 patients with clinical diagnosis of AD during remission were patch tested with 28 European Baseline Series allergens and 8 corticosteroids allergens in different concentrations and media. Twenty-nine (74.3%) patients were female and 10 (25.6%) patients were male. Thirty-three (84.6%) patients were older than 18 years. The mean duration of AD was 20 years.

Results: Nineteen (48%) patients had an allergic reaction to at least 1 European Standard Series allergen, and 5 (12.8%) patients had an allergic reaction to at least 1 corticosteroid. The most common allergens giving positive results were nickel sulfate (28.2%), potassium dichromate (20.5%), cobalt chloride (12.8%), and phenylenediamine, budesonide, betamethasone, clobetasol, and dexamethasone (7.7% each).

Conclusions: This study shows that allergic contact hypersensitivity is common among patients with AD and affects up to 40% of cases. Contact allergy to corticosteroids becomes a serious problem in the treatment of chronic inflammatory dermatoses such as AD.

Atopic dermatitis (AD) is a chronic inflammatory dermatosis that commonly presents during early infancy and childhood but can persist or start in adulthood. Atopic dermatitis affects 10% to 20% of children and 1% to 3% of adults and is considered to be one of the most common skin diseases.¹

Atopic dermatitis is the first manifestation of atopy in many patients who later develop another atopic disorder, such as allergic rhinitis, asthma, or food allergy. In the pathogenesis of AD, the imbalance among the populations of T_H1 and T_H2 lymphocytes is mentioned, with a predominance of T_H2 cells, which leads to reduced cellular immune responses. This phenomenon was considered to be the cause of the reduced contact hypersensitivity in patients with AD. Corticosteroids are drugs commonly used in

treating patients experiencing chronic inflammatory dermatoses such as eczema or AD. For many years, contact allergy to corticosteroids was regarded as impossible and was not diagnosed because their pharmacologic properties often masked their ability to induce contact allergy. Burckhardt² reported the first case of allergic contact dermatitis to hydrocortisone in 1959. In Poland, the first positive results were obtained in 1998; allergy to hydrocortisone was diagnosed in 1% of patients.³ We present our clinical experience with patch testing to the European Standard Series and corticosteroid haptens in the population of patients with AD.

MATERIALS AND METHODS

Thirty-nine patients with AD who were under the care of the Department of Dermatology and Venereology in the Medical University of Lodz between 2010 and 2013 were examined. The diagnosis of AD was set up on the basis of medical history, laboratory tests, and clinical signs. All patients fulfilled the criteria of Hanifin and Rajka.⁴ Twenty-nine patients were female, and 10 patients were male (age range, 13-57 years; mean age, 29.7 years). A total of 33 (84.6%) patients were older than 18 years. Detailed interviews about the previous course of the disease and the treatment

From the *Department of Dermatology and Venereology, Medical University of Lodz; and †Department of Occupational Diseases, Nofer Institute of Occupational Medicine, Lodz, Poland.

Address reprint requests to Jaroslaw Bogaczewicz, MD, PhD, Department of Dermatology and Venereology, Medical University of Lodz, Hallera 1, 91-647 Lodz, Poland. E-mail: jaroslaw.bogaczewicz@umed.lodz.pl.

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were collected before applying the patch tests to the patients. The disease duration covered the period of 1 to 45 years, with a mean of 20 years. In an interview especially drawing attention to the applicable topical corticosteroids, the time of using steroids topically (on and off) covered the period from 0 to 33 years, with a mean of 12.5 years. Thirty-two (82%) patients were using local therapy ointments containing corticosteroids from group A, 1 (2.6%) patient from group B, 6 (15.4%) patients from group C, 33 (84.6%) patients from group D1, and 20 (51.3%) patients were using topical corticosteroids from group D2. Two patients had never used the topical corticosteroids. No patient during the examination was taking corticosteroids, other immunosuppressive drugs, or antihistamines. For patch testing, patients who had used antihistamines in the previous 2 weeks or immunosuppressive drugs in the previous 3 weeks had these treatments stopped. Studies were performed after 3 weeks of intense sunlight. Unfortunately, after treatment discontinuation, a group of patients showed exacerbation of AD, which resulted in their disqualification and exclusion from the study. During patch testing, all patients were in remission (complete or incomplete). Skin lesions may have been present, but their severity and location allowed for doing the tests. Thirty-one (79.5%) patients experienced skin lesions on the

hands, 3 (7.7%) on the feet, 15 (38.5%) on the lower legs, 14 (35.9%) on the trunk, and 24 (61.5%) on the face. Several days before the patch testing, topical corticosteroids were stopped. Only use of moisturizing ointments was permitted during the patch testing. Patients were patch tested with 28 European Baseline Series allergens and 8 corticosteroid allergens in different concentrations and in different media. In our research, we used 8 corticosteroid allergens in petrolatum base; these are as follows: budesonide (with concentrations of 0.1% and 0.01%), betamethasone-17-valerate (0.1%), triamcinolone acetonide (1%), alclomethasone-17,21-dipropionate (1%), clobetasol-17-propionate (1%), dexamethasone-21-phosphate disodium salt (1%), tixocortol-21-pivalate (0.1%), and hydrocortisone-17-butyrate (1% in alcohol and in petrolatum). Patch tests were read in all patients 48 and 72 hours after application. Readings after 96 hours related to patients with positive reaction to corticosteroids and patients who demonstrated very strong positive reactions. Irritant reactions were not taken into account in calculating the prevalence of allergy.

RESULTS

A total of 19 (48%) patients had an allergic reaction to at least 1 European Standard Series allergen. The most common allergens

TABLE 1. Prevalence of Contact Allergy to European Baseline Series Haptens

Allergen	Positive Reactions, n (%)						
	Female	Male	Total	Age, y		Duration of AD, y	
				<25	25–50	<10	>10
0.5% Potassium dichromate	6 (20.7)	2 (20)	8 (20.5)	2 (13.3)	6 (27.3)	1 (7.7)	7 (26.9)
1% Phenylenediamine	3 (10.3)	0 (0)	3 (7.7)	2 (13.3)	1 (4.5)	1 (7.7)	2 (7.7)
1% Thiuram mix	1 (3.4)	0 (0)	1 (2.6)	1 (6.7)	0 (0)	0 (0)	1 (3.8)
20% Neomycin sulfate	1 (3.4)	0 (0)	1 (2.6)	1 (6.7)	0 (0)	1 (7.7)	0 (0)
1% Cobalt chloride	5 (17.2)	0 (0)	5 (12.8)	1 (6.7)	4 (18.1)	2 (15.4)	3 (11.5)
5% Benzocaine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
5% Nickel sulfate	11 (37.9)	0 (0)	11 (28.2)	5 (33.3)	6 (27.3)	4 (30.8)	7 (26.9)
5% Clioquinol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
20% Colophonium	2 (6.9)	0 (0)	2 (5.1)	1 (6.7)	1 (4.5)	1 (7.7)	1 (3.8)
16% Paraben mix	2 (6.9)	0 (0)	2 (5.1)	1 (6.7)	1 (4.5)	1 (7.7)	1 (3.8)
0.1% PPD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
30% Lanolin alcohol	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2% Mercapto mix	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1% Epoxy resin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
25% <i>Myroxylon pereirae</i> resin	1 (3.4)	0 (0)	1 (2.6)	0 (0)	1 (4.5)	1 (7.7)	0 (0)
1% Para tertiary butylphenol formaldehyde resin (PTBP)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2% 2-Mercaptobenzothiazole	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1% Formaldehyde	2 (6.9)	0 (0)	2 (5.1)	2 (13.3)	0 (0)	1 (7.7)	1 (3.8)
8% Fragrance mix I	2 (6.9)	0 (0)	2 (5.1)	0 (0)	2 (9)	1 (7.7)	1 (3.8)
0.1% Sesquiterpene lactone mix	1 (3.4)	1 (10)	2 (5.1)	0 (0)	2 (9)	0 (0)	2 (7.7)
1% Quaternium-15	1 (3.4)	0 (0)	1 (2.6)	1 (6.7)	0 (0)	1 (7.7)	0 (0)
0.01% 2-Methoxy-6-n-pentyl-4-benzoquinone	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.01% Methylisothiazolinone	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
0.01% Budesonide	2 (6.9)	0 (0)	2 (5.1)	0 (0)	2 (9)	1 (7.7)	1 (3.8)
0.1% Tixocortol-21-pivalate	2 (6.9)	0 (0)	2 (5.1)	1 (6.7)	1 (4.5)	2 (15.4)	0 (0)
0.5% Methyl dibromo glutaronitrile	1 (3.4)	0 (0)	1 (2.6)	0 (0)	1 (4.5)	1 (7.7)	0 (0)
14% Fragrance mix II	2 (6.9)	0 (0)	2 (5.1)	1 (6.7)	1 (4.5)	2 (15.4)	0 (0)
5% Lyrar	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

TABLE 2. Characteristics of Patients With Contact Allergy to Corticosteroids

Sex	Age, y	Disease Duration, y	Lesion Location	Time of Using Steroids Topically, y	Applied Substances Containing Steroids From Groups	Positive Tests
F	23	3	Hands, face	3	A, D1, D2	Cobalt chloride, nickel sulfate, fragrance mix II, tixocortol
F	25	5	Hands, face	4	A, D1	Cobalt chloride, nickel sulfate, paraben mix, tixocortol, hydrocortisone in 1% petr.
F	40	1	Hands, feet, face, trunk	1	A, D1	Potassium dichromate, colophonium, <i>Myroxylon pereirae</i> resin, fragrance mix I, methyl dibromoglutaronitrile, fragrance mix II, 0.01% budesonide, 0.1% budesonide, betamethasone, triamcinolone, clobetasol, dexamethasone, hydrocortisone in 1% alc. and in petr.
F	40	39	Hands, face	20	A, D1, D2	Cobalt chloride, nickel sulfate, 0.01% budesonide, 0.1% budesonide, betamethasone, triamcinolone, clobetasol, dexamethasone
M	25	22	Hands, feet, face	15	A, C, D1, D2	Potassium dichromate, 0.1% budesonide, betamethasone, clobetasol, dexamethasone

alc., alcohol; F, female; M, male; petr., petrolatum.

giving positive results were nickel sulfate (28.2%), potassium dichromate (20.5%), cobalt chloride (12.8%), and phenylenediamine (7.7%; Table 1).

The most common hypersensitivities among females were found to nickel sulfate (37.9%), potassium dichromate (20.7%), cobalt chloride (17.2%), and phenylenediamine (10.3%), whereas in males, mostly, hypersensitivity was observed to potassium dichromate (20%) and sesquiterpene lactone mix (10%).

In 15 patients younger than the age of 25 years, nickel sulfate (33.3%) and potassium dichromate, phenylenediamine, and formaldehyde (13.3% each) were the most common contact allergens.

In 22 patients between the age of 25 and 50 years, allergy to nickel sulfate and potassium dichromate was found in 27.3%, cobalt chloride in 18.1%, and fragrance mix I, sesquiterpene lactone mix, and budesonide each in 9%. In 13 patients with a duration of AD below 10 years, the most sensitizing allergens were nickel sulfate

(30.8%), cobalt chloride, fragrance mix II, and tixocortol-21-pivalate (15.4%).

In 26 patients experiencing AD for more than 10 years, the most sensitizing allergens were nickel sulfate and potassium dichromate (26.9% each), cobalt chloride (11.5%), and phenylenediamine and sesquiterpene lactone mix (7.7% each). Five (12.8%) patients had an allergic reaction to at least 1 corticosteroid (Table 2).

The most common haptens giving positive results were budesonide (0.1%) and betamethasone, clobetasol, and dexamethasone (7.7% each; Table 3).

Hypersensitivity to 1 corticosteroid has been observed in 1 patient, whereas hypersensitivity to more than 1 corticosteroid has been observed in 4 patients. All patients with hypersensitivity to corticosteroids were also sensitized to nonsteroidal haptens included in the European Baseline Series. Corticosteroids included in the European Baseline Series (0.01% budesonide and

TABLE 3. Prevalence of Contact Allergy to Corticosteroid Haptens

Allergen	Group	Positive Reactions, n (%)						
		Female	Male	Total	Age, y		Duration of AD, y	
					<25	25–50	<10	>10
0.1% Budesonide	B	2 (6.9)	1 (10)	3 (7.7)	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)
0.1% Betamethasone-17-valerate	D1	2 (6.9)	1 (10)	3 (7.7)	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)
1% Triamcinolone acetonide	B	2 (6.9)	0 (0)	2 (5.1)	0 (0)	2 (9)	1 (7.7)	1 (3.8)
1% Alclometasone-17,21-dipropionate	D1	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
1% Clobetasol-17-propionate	D1	2 (6.9)	1 (10)	3 (7.7)	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)
1% Dexamethasone-21-phosphate disodium salt	C	2 (6.9)	1 (10)	3 (7.7)	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)
Hydrocortisone 17-butyrate 1% alc	D2	1 (3.4)	0 (0)	1 (2.6)	0 (0)	1 (4.5)	1 (7.7)	0 (0)
1% Hydrocortisone	D2	2 (6.9)	0 (0)	2 (5.1)	0 (0)	2 (9)	2 (15.4)	0 (0)
0.01% Budesonide	B	2 (6.9)	0 (0)	2 (5.1)	0 (0)	2 (9)	1 (7.7)	1 (3.8)
0.1% Tixocortol-21-pivalate	A	2 (6.9)	0 (0)	2 (5.1)	1 (6.7)	1 (4.5)	2 (15.4)	0 (0)

TABLE 4. Prevalence of Contact Allergy to Corticosteroid Group

Steroid Group	Positive Reactions, n (%)				Total (n = 39)
	Age, y		Duration of AD, y		
	<25 (n = 15)	25–50 (n = 22)	<10 (n = 13)	>10 (n = 26)	
A	1 (6.7)	1 (4.5)	2 (15.4)	0 (0)	2 (5.1)
B	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)	3 (7.7)
C	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)	3 (7.7)
D1	0 (0)	3 (13.6)	1 (7.7)	2 (7.7)	3 (7.7)
D2	0 (0)	2 (9)	2 (15.4)	0 (0)	2 (5.1)

tixocortol-21-pivalate) allowed us to detect 80% of cases of allergy to steroids. Allergy to budesonide was observed in 3 patients; in 2 patients, a positive result of budesonide with concentrations of 0.1% and 0.01% was obtained; in 1 patient, a positive result was obtained only with budesonide with a concentration of 0.1%. Allergy to hydrocortisone was observed in 2 patients; in 1 patient, a positive result was observed with hydrocortisone in petrolatum and alcohol; in 1 patient, a positive result was obtained only with hydrocortisone in petrolatum.

Sensitivity to steroid groups B, C, and D1 occurred in 7.7% of patients, whereas in groups A and D2, sensitivity to steroid occurred in 5.1% of patients (Table 4).

The prevalence of allergy to the group of steroids according to topical steroid used is shown in Table 5.

DISCUSSION

Our research has shown that contact allergy is common in patients with AD, as it was diagnosed in 19 (48%) patients. For many years, in developed countries, nickel was regarded as the most common contact allergen, sensitizing women more often than men. In our study, patients who have sensitivity to nickel were 11 (28.2%) patients, females only. In Western Europe, the decline of the incidence of allergy to nickel is shown. It is explained and introduced in 1994 by the Parliament of the European Nickel Directive that reduced the allowable concentration of nickel in products authorized for sale. This trend is also visible in Poland, even though the nickel directive has not been implemented. A study conducted in the late 1990s in France on 137 patients with AD showed contact allergy in 43% of patients; the most frequent contact allergy was to nickel, which occurred in 19.3% of patients.⁵ In a Tunisian study conducted for a group of 63 children and 26 adults with AD, contact hypersensitivity occurred in 42.7% of patients and allergy to nickel in 24.7% of patients.⁶

In the 1960s, chromium was the most common contact allergen in developed countries; in Poland, this situation remained until 1997.^{7,8} Chrome belongs to the main contact allergens; however, in most developed countries, this metal sensitizes fewer individuals than in the Polish population. One of the significant features of

hypersensitivity to chromium, in general, is rare allergy in women in comparison with men. However, in the Polish population, this trend is not present. Allergy to chromium is also more common in the elderly and in poor people of low social position. Chromium is a strong sensitizer as a component of cement and leather.⁸ Regarding men, chrome allergy is very common in occupational eczema, especially in the construction industry workers. Poland is a country with intensive development of the construction industry, which unfortunately continues to apply cement-containing chromium.

Regarding women, a high incidence of allergy to chromium may reflect the phenomenon of “leather dermatitis” because leather products still contain small amounts of chromium. In our study, sensitivity to chromium was present in 8 (20.5%) patients; allergy to this hapten occurred in 20% of females and 20% of males; in the range of 25 to 50 years, allergy was reported in 27% of patients. In a study conducted by Belhadjali et al,⁶ allergy to chromium occurred in 7.9% of patients and the same percentage of patients were allergic to cobalt. In our study, allergy to cobalt occurred in 5 females, which is 12.8% of all patients and 17.2% of women. Isolated allergy to this metal is rare, described primarily in patients with metal implants. Sensitization to cobalt usually coexists with allergy to chromium in males and to nickel in females. In our research of 5 women allergic to cobalt, 4 (80%) women were simultaneously sensitized to nickel. In a study conducted by Czarnobilska et al,⁹ allergy to cobalt was found in 8.3% of 7-year-old patients and in 10.5% of 16-year-old patients with AD. Some patients in our study have reported exacerbation of skin lesions after contact with objects containing metal haptens, so they avoided these objects. Para-phenylenediamine (PPD) is a component of hair dyes and popularly called the *artificial henna*. Para-phenylenediamine is a major occupational allergen of hairdressers and gives cross-reactions of many textile dyes. A total of 7.7% of our patients were sensitized to PPD.

Contact allergy to corticosteroids becomes a serious problem in the treatment of AD because it occurs more frequently than previously appreciated. We present 5 (12.8%) patients with corticosteroid contact allergy; this allergy occurred in 4 (13.9%) females and 1 (10%) male. The most common haptens giving positive results were 0.1% budesonide, betamethasone, clobetasol, and dexamethasone. In patients who had positive results in patch testing for glucocorticoids previously, we observed exacerbation of

TABLE 5. Prevalence of Allergy to the Group of Steroids According to Topical Steroid Used

No. Patients in Steroid Group	Steroids Group, n (%)				
	A	B	C	D1	D2
A (32)	2 (6.2)	3 (9.4)	3 (9.4)	3 (9.4)	2 (6.2)
B (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
C (6)	0 (0)	0 (0)	1 (16.7)	1 (16.7)	0 (0)
D1 (33)	2 (6)	3 (9)	3 (9)	3 (9)	2 (6)
D2 (20)	1 (5)	2 (10)	2 (10)	2 (10)	0 (0)

skin lesions or no improvement after using topical treatment with corticosteroids to which they had been allergic.

Corticosteroids are drugs commonly used in treating patients experiencing chronic inflammatory dermatoses such as eczema or AD. For many years, contact allergy to corticosteroids was regarded as impossible and was not diagnosed because their pharmacologic properties often masked their ability to induce contact allergy. Clinical studies indicate that the incidence of hypersensitivity to corticosteroids is systematically increasing. The multicenter research carried out in the 1990s by Jappe et al¹⁰ showed an allergy to 17-hydrocortisone butyrate in 1.14% of patients and to budesonide in 0.87% of patients with AD. The research conducted on 641 children by Mailhol et al showed an allergy to tixocortol-21-pivalate in 2.5% of patients with AD.¹¹ Such a high percentage of patients with allergy to corticosteroids in our study may be explained by the fact that most of these patients were adults (84.6%) with long duration of AD (mean, 20 years) and several years of experience applying topical corticosteroids (mean, 12.5 years).

In our study, we used an extended number of corticosteroid haptens, which enabled a detailed diagnosis of allergy to these compounds. Corticosteroid haptens included in the European Baseline Series (0.01% budesonide and tixocortol-21-pivalate) allowed to detect 80% of cases of allergy to steroids. All patients with hypersensitivity to corticosteroids were also sensitized to nonsteroidal haptens included in the European Baseline Series. Hypersensitivity to 1 corticosteroid has been observed in 1 patient, whereas hypersensitivity to more than 1 corticosteroid has been observed in 4 patients. Positive reactions to several corticosteroids may be due to a multiple sensitization after the use of various different preparations in clinical practice, or it may also be due to a cross-reactivity mechanism. Because of the structure of the molecule and possible cross-reactions, corticosteroids were divided into 4 groups. Tixocortol pivalate is considered as a sensitive and specific allergy marker to group A, whereas budesonide tests for group B. In addition to cross-reactions between steroids in 1 group, cases of cross-reaction have also been reported between drugs from groups A and D and between drugs of groups B and D.¹² In the case of polyvalent allergy to steroids of different groups, topical corticosteroid should be used from the group for which there is no hypersensitivity or optionally a calcineurin inhibitor (tacrolimus and pimecrolimus).

Contact dermatitis has an important role in triggering exacerbations of AD. Allergic contact dermatitis affects up to 40% of patients with AD, which creates a significant clinical problem. Clinical studies indicate that the incidence of hypersensitivity to corticosteroids is systematically increasing and may become a serious problem in the treatment of chronic inflammatory dermatoses such as AD. The diagnosis of the hapten which is the cause of allergic contact dermatitis not only may significantly improve the quality of life and decrease the symptoms but also allows for the introduction of appropriate local treatment.

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