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Epicutaneous Patch Test Results in Children and Adults with Allergic Contact Dermatitis in Karlovac County: a Retrospective Survey

Ilko Kuljanac, Eva Knežević, Hrvoje Cvitanović

Department of Dermatology and Venereology, Karlovac General Hospital, Karlovac, Croatia

Corresponding author:
Ilko Kuljanac, MD, PhD
Department of Dermatology and Venereology
Karlovac General Hospital
Andrije Štampara 3
HR-47000 Karlovac, Croatia
ilko.kuljanac@ka.t-com.hr

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SUMMARY The aim of the study was to evaluate the results of epicutaneous patch testing with a standard series of contact allergens in children suspected to have allergic contact dermatitis (ACD), and to compare the results of patch testing between children and adults. Clinical records of children defined as patients aged ≤18 years and adults examined at Department of Dermatology and Venereology, Karlovac General Hospital, for suspicion of ACD during the 1994-2009 period were reviewed. Epicutaneous patch testing with a standard series of contact allergens, manufactured by the Institute of Immunology, Zagreb, Croatia, was performed in group 1 consisting of 412 children (274 female and 138 male, mean age 13.4 years, range 4-18 years) and group 2 consisting of 4440 adult patients (2918 female and 1522 male, mean age 40.3 years, range 19-81 years). The most common six allergens differed between the two groups. Adult subjects were divided into three age subgroups: 19-40 (n=1708), 41-60 (n=1570) and 61-81 (n=1162 subjects). The high sensitization rate in younger subgroup and lower sensitization rate in the oldest group compared to adult patient group as a whole was statistically significant ($P<0.05$). In children, the most common positive reactions were recorded to nickel sulfate (25.4%), thimerosal (17.8%), cobalt chloride (11.6%), fragrance mix (8.9%), white mercury precipitate (6.2%), formaldehyde (4.7%) and other allergens (25.4%). In adult patients, positive reactions were most common to nickel sulfate (32.6%), cobalt chloride (10.8%), fragrance mix (9.0%), wood tars (7.1%), potassium dichromate (6.6%), balsam of Peru (5.1%) and other allergens (28.8%). The group of children included 179 (43.4%) atopic subjects (according to Hanifin and Rajka criteria) and 233 (56.6%) non-atopic subjects. There was no statistically significant between-group difference and no statistically significant difference in nickel sulfate, cobalt chloride, fragrance mix and balsam of Peru sensitization between children and adult patients. A higher sensitization rate in children *versus* adults was recorded for thimerosal, white mercury precipitate and formaldehyde. Less frequent sensitization in children *versus* adults was found for wood tars and potassium dichromate. It is concluded that pediatric ACD exists and is more common than previously recognized. Sensitization to allergens differs between children and adults.

KEY WORDS: epicutaneous patch test, allergic contact dermatitis, children, adults

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INTRODUCTION

The term 'contact dermatitis' refers to inflammation of the skin caused by contact with external agents. There are two types of contact dermatitis: irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD). ICD and ACD are the most common dermatologic disorders in industrialized societies, with a prevalence usually reported to be 1%-10%. ICD predominates and accounts for 80% of all such reactions (1). ACD is an inflammatory reaction of the skin that follows percutaneous absorption of the antigen from the skin surface and recruitment of previously sensitized, antigen-specific T-lymphocytes into the skin (2). The reaction can be described as occurring in two phases, initial sensitization and then elicitation response (1). When the antigen contacts the skin, it is processed and presented with HLA-DR on the surface of Langerhans cells, which act as antigen presenting cells in the skin. They present antigen-HLA-DR complex to the helper T cells. The next step is the antigen-HLA-DR complex interaction with T cells. It leads to proliferation of specific T cell clones that circulate through the body and back into the skin (1). Although sensitivity to allergens is found in about 10% of the adult population, it is equally as likely in infancy as in adulthood, and represents 20% of all cases of dermatitis in children (3). The causes of ACD are usually small chemical substances, which must bind to carrier protein to become a complete antigen. It is a classical delayed hypersensitivity, or type IV immune reaction. Skin penetration of allergens is facilitated by skin barrier impairment due to dermatitis or trauma (4). Patch testing is the most useful diagnostic tool for evaluation of patients suspected to have ACD.

The aim of the study was to evaluate the results of epicutaneous patch testing with a standard series of allergens in children suspected to have ACD and to compare the results of patch testing between children and adults. Epicutaneous patch testing was performed at Department of Dermatology and Venereology, Karlovac General Hospital, during the 1994-2009 period.

PATIENTS AND METHODS

We reviewed clinical records of children, defined as patients aged ≤18 years, and adults examined at Department of Dermatology and Venereology, Karlovac General Hospital, for suspicion of ACD during the 1994-2009 period. Epicutaneous patch testing with a standard series of contact allergens (Table 1), manufactured by the Institute of Immunology, Zagreb, Croatia, was performed in 412 children (274 female and 138 male, mean age 13.4 years, range 4-18 years; group 1) and 4440 adult patients (2918 female and 1522 male, mean age 40.3 years, range 19-81 years; group 2). Group 1 was divided into two subgroups of atopic children (179/412, 43.4%) and non-atopic children (233/412, 56.6%) according to Hanifin and Rajka (5). Group 2 consisting of adult subjects was divided into three age subgroups: 19-40 (n=1708), 41-60 (n=1570) and 61-81 (n=1162).

Test substances were applied on the upper part of the patient's back, on clinically uninvolved, untreated, and without tape stripping skin with adhesive strips for patch test (Curatest, Lohmann Rauscher, Germany). All patients were free from therapy with oral antihistamines, steroids and immunosuppressants. The patch test was removed and reactions were evaluated after 48 h and 72 h. Grading of negative (-) to positive (+ to ++++) patch test was done according to the International Contact Dermatitis Research Group (ICDRG) rules (6). Parents were given information about the test and an informed consent was obtained.

Statistical data analysis was performed by using χ^2-test. The level of statistical significance was set at $P<0.05$.

RESULTS

During the study period (1994-2009), 412 children and 4440 adult patients suspected to have ACD were tested at our Department. The Croatian standard series of contact allergens was used. In the children group (group 1), there were 108 (26%) subjects with one or more positive tests and 146 positive tests were recorded. In adults (group 2), there were 1616 (36%) positive subjects and 2606 positive tests were recorded. Difference in sensitization between the groups was statistically significant ($\chi^2=8.35$, $P<0.05$).

The six most common allergens varied between the groups. In children, the most commonly observed positive reactions were to nickel sulfate in 37 (25.4%), thimerosal in 26 (17.8%), cobalt chloride in 17 (11.6%), fragrance mix in 13 (8.9%), white mercury precipitate in 9 (6.2%), formaldehyde in 7 (4.7%) and other allergens in 37 (25.4%) cases (Table 2). In adult patients, positive reactions were most frequently recorded to nickel sulfate in 850 (32.6%), cobalt chloride 281 (10.8%), fragrance mix in 235 (9.0%), wood tars in 186 (7.1%), potassium dichromate in 172 (6.6%), balsam of Peru in 133 (5.1%) and other allergens in 749 (28.8%) cases (Table 3).

There was no statistically significant between-group difference for nickel sulfate ($\chi^2=1.57$, $P>0.05$), cobalt chloride ($\chi^2=0.02$, $P>0.05$), fragrance mix ($\chi^2=0.01$, $P>0.05$) and balsam of Peru ($\chi^2=1.06$, $P>0.05$) sensitization. High sensitization rates in children *versus* adults were recorded to thimerosal ($\chi^2=57.1$,

Table 1. Standard series of allergens used in patch testing

Allergen	Dilution (%) vehicle	Allergen	Dilution (%) vehicle
Potassium dichromate	0.5 vaseline	PPD-black rubber mix	0.1 vaseline
Cobalt chloride	1.0 ¨	Thiuram mix	1.0 ¨
Nickel sulfate	5.0 ¨	Carba mix	3.0 ¨
Fragrance mix	8.0 ¨	Wood tars	12.0 ¨
Paraphenylene diamine	0.5 ¨	Neomycin sulfate	20.0 ¨
Balsam of Peru	25.0 ¨	Paraben mix	15.0 ¨
Epoxy resin	1.0 ¨	Lanolin alcohol	30.0 ¨
Colophony	20.0 ¨	Formaldehyde	1.0 aqua
White mercury precipitate	10.0 ¨	Detergent	2.0 ¨
Benzocaine	5.0 ¨	Thimerosal	0.1 vaseline
Mercapto mix	2.0 ¨	Vaseline	As it is

$P<0.05$), white mercury precipitate ($\chi^2=4.06$, $P<0.05$) and formaldehyde ($\chi^2=4.41$, $P<0.05$). Less frequent sensitization in children *versus* adults was recorded for wood tars ($\chi^2=5.76$, $P<0.05$) and potassium dichromate ($\chi^2=5.05$, $P<0.05$). In comparison with the adult group as a whole (group 2), higher sensitization rate was found in younger subgroup and lower sensitization rate in the oldest subgroup; these differences were statistically significant. However, there was no statistically significant difference between the subgroups of atopic and non-atopic children (64/179 (35.7%) and 82/233 (56.6%) positive tests, respectively).

Table 2. Results of epicutaneous patch testing in children

Allergen	n	%
Nickel sulfate	37	25.4
Thimerosal	26	17.8
Cobalt chloride	17	11.6
Fragrance mix	13	8.9
White mercury precipitate	9	6.2
Formaldehyde	7	4.7
Others	37	25.4
Total	146	100.0

n = number of positive test results

DISCUSSION

Epicutaneous patch tests along with history and clinical features are very important steps in the identification of a specific causative allergen in ACD patients. ACD is one of the most common inflammatory diseases of the skin regarded as a prototype of T cell-mediated delayed-type hypersensitivity reaction with a sensitization phase, generally asymptomatic, followed by the effector and resolution phases (7). However, in recent years, a large body of data support the idea that ACD may not be a traditional type IV hypersensitivity (8). In mice, neutrophil infiltration of hapten challenge sites is required for elicitation of contact dermatitis and suggests that neutrophils mediate recruitment of the specific CD8+ T cells that subsequently produce cytokines mediating the hypersensitivity response (9). Recent studies have shown that natural killer T cells, B-1 cells and TCRγδ T cells are involved in contact hypersensitivity (10). Today, about 3000 antigens are known to act as contact allergens. Most of them are small substances with a molecular weight of less than 500 daltons, called haptens (11). They bind to a carrier protein *via* covalent bonds or, in case of metals like nickel and cobalt, form a complex with protein (3,11). The term 'contact allergy' refers to a state of altered response of the immune system to a specific substance, which is not synonymous with the disease. Certain proportion of people with contact allergy will never develop clinical symptoms (12). The prevalence of contact allergy in the general population is estimated to 26%-40% in adults (13) and 21%-36% in children (14). In Europe and most of the world, most frequent contact sensitizers are nickel, thimerosal (methiolate) and fragrances (12).

Results of patch tests in children aged 6-15 years, performed in the 1990-1995 period at 22 centers by

Table 3. Results of epicutaneous patch testing in adult patients

Age (yrs) / Allergen	19-40		41-60		61-81		Summary	
	N	%	n	%	n	%	n	%
Nickel sulfate	430	33.5	308	34.8	112	23.2	850	32.6
Cobalt chloride	108	9.2	98	11.1	75	13.8	281	10.8
Fragrance mix	98	8.3	89	10.0	48	10.1	235	9.0
Wood tars	75	6.7	65	7.3	46	9.4	186	7.1
Potassium dichromate	72	6.3	59	6.7	41	8.4	172	6.6
Balsam of Peru	58	5.3	49	5.5	26	5.4	133	5.1
Others	391	30.7	218	24.6	140	29.7	749	28.8
Total	1322	100.0	886	100.0	488	100.0	2606	100.0

n = number of positive test results

Table 4. Epicutaneous patch test positive results in adult subjects according to age groups

Age group (yrs)		N	n	%
	19-40	1708	1322	77.4
	41-60	1570	886	56.4
	61-81	1162	488	41.9
Total	19-81	4440	2606	58.7

N = number of subjects; n = number of positive test results

the German Contact Dermatitis Research Group and filed by the Information Network of Departments of Dermatology, were analyzed and evaluated retrospectively, including epidemiological data (15). Children with positive tests (62 of 156 boys and 108 of 260 girls tested) had a higher prevalence of ACD and a lower prevalence of atopic dermatitis than the patch test negative ones (15). Reactions to nickel sulfate occurred in 15.9% of all children tested, i.e. in 25.0% of girls aged 14-15 and only 4.5% of boys aged 6-13. Mercury compounds ranked second (thimerosal: all children, 11.3%; children aged 6-13, 14.3%; and children aged 14-15, 8.0%), followed by fragrance allergens (15). Retrospective chart review of 100 children and adolescents aged 4-18 years that were patch-tested at the Ottawa Hospital Patch-Testing Clinic between 1996 and 2006 revealed 70% of children to have at least one positive patch test reaction; 55.8% of positive patch test reactions were relevant. The most common allergens were nickel sulfate (26%), cobalt (14%), fragrance mix (7%), neomycin (7%), colophony (6%), formaldehyde (4%), lanolin (4%), quaternium-15 (4%) and para-phenylenediamine (4%) (16). They conclude that the prevalence of positive and relevant allergens in children is similar to that in adults as compared with data from the North American Contact Dermatitis Research Group (NACDG) 2001-2002 study. Kuiters *et al*. evaluated the results of a five-year period of epicutaneous testing in children and teenagers younger than 16 (17). In the overall study population of 2671 persons, 67 were younger than 16. In these 16 (23.5%) children, a positive epicutaneous test was considered to be clinically relevant for the diagnosis of ACD. The most common allergen was nickel sulfate (18%), followed by balsam of Peru, carba mix, colophony and fragrance mix (6% each) (17). Results of patch tests in 337 children aged 1-15 years, performed at a pediatric unit during the past 3 years, were analyzed retrospectively in order to optimize patch test series and assess their relevance. The authors found a positive patch test rate of 66%, with a peak incidence among children less than 3 years of age (88% *vs*. 58.9%). The most common allergens were metals, especially nickel, fragrances, and less frequently rubber chemicals. Based on the results and their relevance, they propose a shortened standard series of patch tests for pediatric patients (18). The results of retrospective cross-sectional analyses of the NACDG data from January 1, 2001 through December 31, 2004, according to patch test reactions showed no significant difference in the overall prevalence of at least one relevant positive patch test reaction between children (51.2%) and adults (54.1%). The most common positive reactions in children were to nickel (28.3%), cobalt chloride (17.9%), thimerosal (15.3%), neomycin sulfate (8.0%), gold sodium thiosulfate (7.7%) and fragrance mix (5.1%). In adults, frequent positive reactions were to nickel sulfate (26.0%), cobalt (12.4%), neomycin

(4.4%), fragrance mix (4.1%), gold (3.6%) and quaternium-15 (3.6%) (19).

The next three studies investigated allergic contact sensitization in asymptomatic children. Weston *et al*. studied 314 children aged 6 months to 18 years and found a 20.3% prevalence of at least 1 positive reaction. In this group, 129 children were aged ≤5 years and 26 (20%) had positive skin test results. Neomycin, nickel and potassium dichromate were the most prevalent allergens in this study group. Sensitization occurred at less than 5 years of age for all but fragrance allergens (20). Barros *et al*. studied 562 schoolchildren aged 5-14 years and found that 13.3% were sensitized to 1 or more contact allergens (21). The most common allergens were neomycin, thimerosal, para-tertiary-butylphenol-formaldehyde resin and fragrance mix (21). In their study, Bruckner *et al*. examined 85 children aged 6 to 67.5 months and found a 24.5% prevalence of sensitization. They conclude that sensitization to contact allergens begins in infancy and continues to be common in older infants and young children (2).

During the study period (1994-2009), 412 children (mean age 13.4, range 4-18 years) and 4440 adult patients (mean age 40.3, range 19-81 years) suspected to have ACD were tested at our Department by use of the Croatian standard series of allergens. In the children group (aged ≤18 years), there were 108 (26%) subjects with one or more positive tests and 146 positive tests. In the group of adult patients, there were 1616 (36%) positive subjects (36%) and 2606 positive tests. Difference in sensitization between children and adults (26% *vs*. 36%) was statistically significant (χ^2=8.35; P<0.05). Our results differ from some earlier studies (19), but confirm the data reported by Goh (22) and Pevny *et al*. (23), who found a generally low rate of sensitization in children. Accordingly, it seems that the prevalence of contact sensitization in children and adults depends on genetic factors, allergen exposure, sex, race, age (22), atopic dermatitis (24), and even seasonal parameters can influence skin reactivity (25). The difference in these results depends on the subjects involved in patch testing and the number of allergens used. The most common localization of eczema in children was on the feet, face and hands, as also reported elsewhere (26). In our study, the most commonly observed positive reactions were to nickel sulfate (25.4%), thimerosal (17.8%), cobalt chloride (11.6%), fragrance mix (8.9%), white mercury precipitate (6.2%), formaldehyde (4.7%) and other allergens (25.4%). In adult patients, positive reactions were most frequently recorded to nickel sulfate (32.6%), cobalt chloride (10.8%), fragrance mix (9%), wood tars (7.1%), potassium dichromate (6.6%), balsam of Peru (5.1%) and other allergens (28.8%).

Positive patch test reactions were mostly the same as reported elsewhere (19,22,23). There was no statistically significant difference in nickel sulfate, cobalt chloride, fragrance mix and balsam of Peru sensitization between children and adult patients. High sensitization rates in children *versus* adults were found to thimerosal, white mercury precipitate and formaldehyde, but less frequent sensitization in children was recorded to wood tars and potassium dichromate. All results were statistically significant (P<0.05). There was a high rate of sensitization to thimerosal (an organic mercurial compound) in children. Its widespread use as a preservative in a variety of compounds including vaccine and preparations, eye drops and contact lens solutions may explain the high rate of positive patch test reactions (28). Sensitization rates to thimerosal decrease with age (29).

In our study, contact sensitization decreased with age. The lowest sensitization was recorded in the oldest subgroup. There are varying literature reports on the overall incidence of ACD with advancing age. Nevertheless, it has been clearly demonstrated that sensitivity to topical medicaments increases with age (30). According to sensitization in atopic patients, our results showed correlation with early studies (31).

The gold standard for definitive diagnosis of ACD is epicutaneous patch testing. Patch testing involves the application of chemical allergens under occlusion on the patient's back (4). The reactions are graded depending on the amount of erythema, induration or blistering that occurs at the site of allergen application (4). Patch tests are recommended whenever there is a clinical or history based suspicion of contact dermatitis, or when a child not only fails to benefit from the recommended treatment for a dermatologic disease such as atopic dermatitis but actually experiences worsening symptoms (29). Children's skin has a thinner stratum corneum than that of an adult, and the formation of the other layers of the epidermis is incomplete (32); it is only at the age of puberty that it acquires the thickness and trophism typical of adult skin (29). Previously, several authors have suggested that children should be tested with lower concentrations of allergens than adults due to the risk of irritant reactions leading to false-positive test results (33). Hjorth has suggested that patch test concentrations should be adjusted according to patient age and that all positive patch test reactions should be repeated using the half strength concentration (34). Recently, however, most authors speak in favor of testing children with the same concentrations as adults (14). Also, Pevny *et al.* recommend testing children with the same allergen concentrations as adults (23). *In vivo* diagnostic tests may cause side effects.

The well-known typical side effects of patch testing are active sensitization, irritant reactions, scars, alteration of pigmentation, pustular or microbial infection, reaction to plaster or test devices, and 'angry back syndrome' (35). Systemic symptoms are not unusual among patients undergoing patch tests; 5% of tested patients complain of rashes, high temperature and flare-up reactions (36).

CONCLUSION

It is concluded that pediatric ACD exists and is more common than previously recognized.

Sensitization to the allergens differs between children and adults. Children become sensitized to nickel sulfate, thimerosal, cobalt chloride, fragrances and white mercury precipitate. Thimerosal is one of the most common allergens in children, but its relevance seems to be low. Patch testing should be more frequently used in routine diagnosis of children with eczema.

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By rain, wind and snow use Nivea cream; year 1935.
(from the collection of Mr. Zlatko Puntijar)