ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine 2013, Vol 20, No 1, 55-60
www.aaem.pl

Prevalence of contact allergy in children suffering from atopic dermatitis, seborrhoeic dermatitis and in healthy controls

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Silny W, Bartoszak L, Jenerowicz D, Żukiewicz-Sobczak W, Goździewska M. Prevalence of contact allergy in children suffering from atopic dermatitis, seborrhoeic dermatitis and in healthy controls. Ann Agric Environ Med. 2013; 20(1): 55-60.

Abstract

Introduction: Atopic dermatitis is one of the most common skin disorders in children. There is only scarce literature data on the prevalence of contact allergy in children with atopic dermatitis.

Objectives: To assess the prevalence of contact allergy among children with atopic dermatitis, seborrhoeic dermatitis and in a population of healthy children.

Material and methods: Patch tests were performed in 104 children aged 1-20 years treated for atopic dermatitis in the Department of Dermatology, University of Medical Sciences, Poznań, and also in 2 control groups: 15 subjects with seborrhoeic dermatitis (15-20 years) and 36 healthy children (1-20 years).

Results: In children with atopic dermatitis, contact allergy was observed in 47/104 patients (45.2%). With regards to the 3 age subgroups, positive patch test results were detected in 30/43 in children aged 1-5 years (69.8%), 13/36 in children aged 6-14 years (36.1%) and in 4/25 adolescents 15-20 years of age (16%). The highest proportion of positive patch tests was detected in the youngest subgroup of healthy children. Comparative analysis revealed type IV hypersensitivity statistically significantly more frequent in children with atopic dermatitis than in the 2 control groups.

Conclusions: The statistically significant positive results in the highest proportion of patch tests in the youngest age subpopulation of children with atopic dermatitis, and detection of contact allergy most commonly in the youngest subgroup of healthy children, may suggest nonspecifically positive results associated with the immaturity of the epidermal barrier during the first years of life. Concentrations of contact allergens included in current pediatric sets of patch tests seems to be too high and should be verified.

Key words

contact allergy, atopic dermatitis, children, patch testing

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting a large number of children and adults, mostly in industrialized countries. Over the past 30 years, a worldwide increase in prevalence of AD has been observed (2–3-fold), and currently affects up to 18% of children and up to 5% of adults, depending on the analyzed population. In spite of systematically broadened research methods, the etiopathology of the disease has not yet been fully elucidated [1, 2, 3, 4].

In children suffering from AD, food allergens may play a noticeable role in the development of inflammation in the skin. Food allergy usually results from structural, functional and immunological immaturity of the gastrointestinal system, exposed to potent allergens, such as cow's milk proteins. Allergy to food is defined as a hyperreactive immunological response to particular components of a diet and it is also mediated by antibodies and cells. The antibodies most commonly involved in food allergy belong to the IgE class [4, 5, 6, 7, 8].

It has long been known that environmental substances such as aeroallergens (airborne allergens) may be the cause of flares in AD patients. Both perennial allergens (house dust mites, cockroach, animal dander) and seasonal allergens (pollens, moulds) are of high significance. In the case of AD patients, application of aeroallergens such as cat dander or house dust mites in the so-called atopy patch test shows that there is a possibility of eliciting eczematous skin lesions only by external application of aeroallergens to the skin. Literature data suggests that in patients showing positive results of atopy patch tests, a higher number of IgE-bearing dendritic cells can be found in the epidermis and dermis than in patients with negative atopy patch test reactions [8, 9, 10, 11, 12].

Allergic contact dermatitis (ACD) is an example of delayed-type hypersensitivity reaction, caused by skin contact with haptens, activating antigen-specific T cells in sensitized patients. ACD affects approximately 7% of the general population, between 13-24% of paediatric patients and 33-64% of the elderly population. Literature data suggests that approximately 85,000 chemicals are recognized in the human

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Received: 4 October 2012; accepted: 14 January 2013

environment, and among them, more than 3,700 compounds have been identified as contact allergens. Nickel is one of the most common contact allergens, causing ACD in about 4-8% of male subjects and 18-30% of female subjects in the industrialized world. Cosmetics, fragrances, and botanicals are also important causes of ACD [13, 14, 15, 16, 17].

AD and ACD are diseases manifesting clinically as dermatitis and pruritus. Due to identical morphology of skin lesions, diagnosing contact allergy in AD patients may be difficult. In case of suspicion of delayed-type hypersensitivity, the 'gold standard' in the diagnosis includes patch testing. Despite most researchers use patch tests series, consisting of the most common potentially sensitizing haptens, significant differences are observed in the incidence of delayed-type hypersensitivity in children suffering from AD. The percentage of patch tests positive results is defined in rather broad terms – 14.9- 64.2% [17, 18, 19, 20, 21, 22, 23, 24].

OBJECTIVES

The main objective of the paper was assessment of the prevalence of contact allergy among children with AD, and comparison of results with a group of patients with seborrhoeic dermatitis and a population of healthy children.

MATERIAL AND METHODS

During the period from October 2008 – March 2011, patch tests were performed in 104 children aged 1-20 years (mean 8.2 years) treated for AD in the Department of Dermatology, University of Medical Sciences in Poznan. The group consisted of 51 boys (49%) and 53 girls (51%). Diagnosis of AD was established on the basis of Hanifin and Rajka criteria [25]. Patients who presented with skin lesions on the upper part of the back were excluded from the study. Relatively stable clinical status allowed discontinuation of oral antihistamines and systemic corticosteroids for at least 2 weeks before the scheduled examination. Patch tests were also performed in the 2 control groups. The first control group consisted of 15 subjects suffering from seborrhoeic dermatitis, aged 15-20 years (mean 17.5 years): 8 girls (53.3%) and 7 boys (46.7%). The second control group consisted of 36 healthy children: 19 girls (52.8%) and 17 boys (47.2%) aged from 1-20 years (mean 8.1 years).

In children aged 1-5 years (belonging to the test group and control groups) who presented with a small skin area of the back, a paediatric set (established in our Department) consisting of 12 haptens was used (Tab. 1). In relation to older children and adolescents aged 6-20 years of age, a classic set of haptens belonging to the European standard series was used. Patch test substances (Chemotechnique Diagnostics, Vellinge, Sweden) were used mounted on the skin with the use of Finn chambers with Scanpore tape. Patch tests reading was performed after 48 and 72 hours in accordance with the guidelines of International Contact Dermatitis Research Group (ICDRG). Statistical analysis regarding differences in the incidence of contact allergy between examined populations was conducted using Fisher's exact test. Calculations were performed using the statistical package STATISTICA (data analysis software system), v 9.0. and Cytel Studio-package StatXact-8.

Table 1. Patch testing – paediatric set of haptens

Hapten	Substance	Base	Concentration [%]
Cobalt	Cobalt chloride (II) x 6 H_2O	Petrolatum	1
Sesquiterpene lactone	Sesquiterpene lactone mix	Petrolatum	0.1
Colophony	Colophony	Petrolatum	20
Epoxy resin	Epoxy resin	Petrolatum	1
Fragrance mixture I	Fragrance mixture I	Petrolatum	8
Mercaptobenzothiazol	2-mercaptobenzothiazol	Petrolatum	2
Nickel	Nickel sulfate x $6H_2O$	Petrolatum	5
Paraphenylenediamine	Paraphenylenediamine	Petrolatum	1
Potassium dichromate	Potassium dichromate	Petrolatum	0.5
Balsam of Peru	Balsam of Peru	Petrolatum	25
Parabens	Paraben mix	Petrolatum	16
Wool alcohols	Wool alcohols	Petrolatum	30

RESULTS

In the group of children suffering from AD, contact allergy was observed in 47 out of 104 patients (45.2%). With regards to the 3 age subgroups, positive patch tests results were detected in 30 out of 43 in children aged 1-5 years (69.8%), in 13 out of 36 children aged 6-14 years (36.1%) and in 4 out of 25 adolescents aged 15-20 years (16%). In 29 children (27.9%), delayed-type hypersensitivity was detected against at least 2 allergens. 15 children (14.4%) showed contact sensitization in relation to the 2 test substances, and 13 children (12.5%) to 3 test substances, while in one case (1%), sensitivity to 4 contact allergens was detected.

The highest number of positive patch tests results was found in relation to metal salts: 26 patients (25%) presented positive patch tests to nickel, 25 (24%) to cobalt and 22 patients (21.2%) to chromium (Tab. 2, 3). Repeatedly positive results of patch tests were detected in 5 cases (4.8%), both to nickel and chromium, in 4 cases (3.8%) to nickel and cobalt, in 3 (2.9%) to cobalt and chromium, while in 9 patients (8.7%) contact allergy was revealed to all 3 metals.

Table 2. Incidence of positive patch test results in the group of children suffering from atopic dermatitis and in control populations

		Age (years)			
		1-20	1-5	6-14	15-20
Atopic dermatitis patients	No. of patients	104	43	36	25
	No. of positive patch tests results	47	30	13	4
	Percentage of positive patch tests results (%)	45.2	69.8	36.1	16
Patients with seborrheic dermatitis	No. of patients	-	-	-	15
	No. of positive patch tests results	-	-	-	1
	Percentage of positive patch tests results (%)	-	-	-	6.7
Healthy controls	No. of patients	36	15	13	8
	No. of positive patch tests results	5	3	2	0
	Percentage of positive patch tests results (%)	13.9	20	15.4	0

Table 3. Incidence of sensitization to various contact allergens among children with atopic dermatitis

Allergen	No. and percentage of children with atopic dermatitis and results of positive patch tests	No. and percentage of children with atopic dermatitis (age 1-5) and results of positive patch tests	No. and percentage of children with atopic dermatitis (age 6-14) and results of positive patch tests	No. and percentage of adolescents with atopic dermatitis (age 15-20) and results of positive patch tests
Nickel	26 (25%)	19 (44.2%)	6 (16.7%)	1 (4%)
Cobalt	25 (24%)	18 (41.9%)	7 (19.4%)	0 (0%)
Chromium	22 (21.2%)	17 (39.5%)	5 (13.9%)	0 (0%)
Fragrance mix I	3 (2.9%)	0 (0%)	2 (5.6%)	1 (4%)
Mercaptobenzotiazole	2 (1.9%)	2 (4.7%)	0 (0%)	0 (0%)
Balsam of Peru	2 (1.9%)	0 (0%)	2 (5.6%)	0 (0%)
Paraphenylenodiamine	2 (1.9%)	1 (2.3%)	1 (2.8%)	0 (0%)
Epoxy resin	1 (1%)	1 (2.3%)	0 (0%)	0 (0%)
Mercaptans	2 (1.9%)	-	1 (2.8%)	1 (4%)
Neomycine	2 (1.9%)	-	2 (5.6%)	0 (0%)
Lyral	2 (1.9%)	-	0 (0%)	2 (8%)
Quaternium 15	1 (1%)	-	0 (0%)	1 (1%)
Fragrance mix II	1 (1%)	-	0 (0%)	1 (1%)
Formaldehyde	1 (1%)	-	1 (2.8%)	0 (0%)
Colophony	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Paraben mix	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Wool alcohols	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sesquiterpene lactone mix	0 (0%)	0 (0%)	0 (0%)	0 (0%)
4-phenylenediamine	0 (0%)	-	0 (0%)	0 (0%)
Thiuram mix	0 (0%)	-	0 (0%)	0 (0%)
Benzocaine	0 (0%)	-	0 (0%)	0 (0%)
Clioquinol	0 (0%)	-	0 (0%)	0 (0%)
N-Isopropyl-N-phenyl-4-phenylenediamine	0 (0%)	-	0 (0%)	0 (0%)
4-tert-butylphenolform-aldehyde resin	0 (0%)	-	0 (0%)	0 (0%)
Primin	0 (0%)	-	0 (0%)	0 (0%)
Budesonide	0 (0%)	-	0 (0%)	0 (0%)
Tixocortol	0 (0%)	-	0 (0%)	0 (0%)
Methyldibromo-glutarontrile	0 (0%)	-	0 (0%)	0 (0%)

Considering other allergens, 3 patients (2.9%) presented type IV hypersensitivity in the fragrance mix I, while in 2 children (1.9%) contact allergy was confirmed to mercaptobenzothiazole, paraphenylenodiamine, balsam of Peru, mercaptan, neomycin and lyral. In a few cases (1%) positive results were obtained with epoxy resin, formaldehyde, Quaternium 15, and allergens included in fragrance mix II. Other haptens included in standard series were negative.

In the group of children suffering from seborrhoeic dermatitis, 15 patients presented with a positive outcome of the patch tests (6.7%) with respect to nickel sulphate. In the control group of 36 healthy children, contact allergy was demonstrated in 5 cases (13.9%). With regards to the 3 age subgroups, positive patch tests were detected in 3 out of 15 children aged 1-5 years (20%), in 2 out of 13 children aged 6-14 years (15.4%), and in none of the adolescents aged 15-20 years (Tab. 2). Patch tests were positive to nickel in 5 subjects (13.9%), while in 3 cases (8.3%) to potassium dichromate.

Comparative analysis regarding prevalence of contact allergy in the population of children suffering from AD and control groups, revealed statistically significantly more frequent type IV hypersensitivity than in patients suffering from seborrhoeic dermatitis (p=0.0041, odds ratio – OR=11.5 with 95% confidence interval 1,463-91.1), and also in the population of healthy children (p=0.0007, odds ratio – OR=5.112 at 95% confidence interval 1.842-14.187). In the group of AD children, the chance for occurrence of delayed-type allergic reaction was therefore 5.1 times higher compared to healthy children, and 11.5 times higher compared with patients with seborrhoeic dermatitis.

The prevalence of contact allergy between analogous age subgroups in the study population and healthy children was also analysed. A statistically significantly greater number of patch tests positive results were found only in AD children aged 1-5 years than in healthy children of similar age (p=0.0017). However, there were no statistically significant differences between the other analogous age subgroups, belonging to the population of AD children and healthy children. Subsequently, a comparative analysis of the incidence of patch tests positive results between the control groups was carried out, which revealed no statistically significant differences. Afterwards, a comparative analysis of the incidence of contact allergy among the 3 age subgroups of the study population was conducted. Type IV hypersensitivity reaction significantly more often was detected among AD children aged 1-5 years than among patients aged 6-14 years (p=0.0034) and 15-20 years (p=0.0001). There was no statistically significant difference in the incidence of contact allergy among patients suffering from AD at the age of 6-14 years and 15-20 years. Comparative analysis of the incidence of contact hypersensitivity among the 3 age subgroups of the healthy population showed no statistically significant differences.

Another comparative analysis, relating to differences in the incidence of contact allergy detailing the differences in the incidence of contact allergy, particularly regarding the most common allergens, such as metal salts, between girls and boys in the population of atopic children and within the control groups showed no statistical significance.

DISCUSSION

Increasing attention has been paid lately to the occurrence of contact allergy in the paediatric population. A review of English-language scientific literature for 1999-2010 shows that the percentage of positive patch test results in selected populations of children with eczema or suspicion of contact allergy is estimated at 26.6-95.6% [26]. On the other hand, in the population of healthy children, the incidence of contact allergy is estimated at 13.3-24.5% [20, 27, 28, 29]. Regarding the population of AD children, the incidence of contact allergy is estimated at 14.9-64.2% [17, 18, 19, 20, 21, 22, 23, 24]. Some authors emphasize that atopy may be regarded as a predisposing factor for the development of type IV hypersensitivity reaction [18, 19, 20], while others indicate that there is no association between AD or other atopic diseases and increase of the risk of sensitization to contact allergens [21, 22, 23, 24]. In all the studies cited above, the

researchers used haptens for patch testing in concentrations suited for adult patients. The differences between these publications were associated primarily with the number of tested allergens, as well as the age of examined children.

As demonstrated in th presented study, a statistically significantly higher incidence of contact allergy was detected in the population of children suffering from AD, in comparison to healthy children and to the population of patients with seborrhoeic dermatitis. The described phenomenon may be associated with impaired epidermal barrier function in patients with atopy [30, 31, 32, 33, 34]. Filaggrin gene defect and excess serine protease activity that leads to a reduction in the thickness of the stratum corneum and the occurrence of disturbances in the production of ceramides, may affect the penetration of contact allergens into the skin. It seems that these disturbances have an impact on the development of delayed-type hypersensitivity, particularly in the youngest population of AD patients, as indicated by the statistically significantly higher incidence of delayed-type hypersensitivity detected only in atopic children aged 1-5 years, compared to healthy subjects being the same age. In relation to the other two age subgroups, there was no statistically significant difference detected in the incidence of contact allergy between the study population and the second control group.

These observations may indicate that in children suffering from AD, dynamic, age-related changes take place considering the skin-barrier dysfunction, which affect epidermal immune responses induced by contact allergens.

The most common contact allergens sensitizing children with AD were metal salts, especially nickel sulfate. The presented results are consistent with the literature [17, 20, 24, 35]. Nickel is commonly regarded as one of the most common contact allergens among children suffering from AD, as well as in the general paediatric population. Some authors suggest that AD, presenting with filaggrin gene mutations, are predisposed to the development of delayed-type hypersensitivity towards this metal [36, 37]. Thyssen draws attention to the fact that filaggrin gene mutations occur frequently in the population of patients with AD, lead to changes in the structure of filaggrin, which prevents penetration of nickel skin deep [37]. It should be noted that the literature includes studies showing no association between the presence of filaggrin gene mutations and an increased risk of contact produce an allergic reaction in relation to the nickel salt [38].

Both for the population of AD children as well as in relation to both control groups there was no statistically significant difference found in the incidence of delayed-type hypersensitivity between girls and boys. This observation is in accordance with the results published by some authors. Research conducted by Seidenari and Brasch [24, 39] among children in the general population of dermatological patients have shown an equal incidence of contact allergy between girls and boys. A similar observation conducted on a population of children suffering from AD was published by Gioradano-Labadie [35]. On the other hand, different observations were made by Dotterund who separated a group of children with a history of atopic diseases from a random population of students aged 7-12 years. The author found a statistically significantly higher incidence of positive patch test results in healthy girls (22.3%) than in healthy boys (14.4%) and also in girls with a history of atopic diseases (37.4%) compared to a similar population of boys (20%) [19].

What seems surprising, however, is revealing the largest number of positive patch tests results among the youngest age subgroups, both in the population of AD and in the group of healthy children. In addition, in the AD group the difference in the incidence of contact allergy in children aged 1-5 years compared to those aged 6-14 years and 15-20 years proved to be statistically significant. The predominance of contact allergy in the youngest age subgroup study population seems to be illogical, because the phenomenon of delayed-type hypersensitivity reaction is not characterized by spontaneous deterioration. Sensitized memory T cells remain in constant readiness to initiate the effector phase of an allergic reaction from contact with the sensitizing substance, even years after the last exposure, often for the entire life of the patient. Other authors, studying the incidence of contact allergy among children with AD, also showed the highest percentage of positive patch tests results among the youngest age groups. Both Roula and Seidenari observed statistically significantly higher incidence of delayed-type allergic reactions in children under 3 years compared to older patients [22, 24]. Similarly, Manzini showed the highest percentage of positive patch tests results in AD patients under 3 years of age, with no information of the statistical significance, however. It should be noted that authors of some publications have also shown increased incidence of contact allergy with increasing age of children with AD. Giordano-Labadie study showed, that contact allergy is detected statistically significantly more frequently above 5 years of age than in younger patients [35].

The reason for the highest number of positive patch tests results in the group below 5 years of age (both among healthy children and patients with AD), may be associated with immaturity within dermo-epidermal barrier in terms of both structure and function during the first years of life. Differences in the histological structure of epidermis between younger children and adults are now well known. Stratum corneum thickness, on average, is 30% lower, while the whole epidermis, on average, is 20% thinner in children aged 6 months to 2 years than in adults [40]. In addition, the study on the granular layer of the epidermis, conducted using a confocal laser scanning microscope, and the comparative measurements of cells collected by means of adhesive tape showed that the size of keratinocytes is significantly lower in children in the first years of life. Dynamic changes associated with aging skin is subject to the degree of hydration and lipid composition of the dermal-epidermal barrier. At birth, the skin of a baby is more dry, resulting in increased transepithelial water loss (TEWL) values, in comparison with adult skin. During the first months of life, TEWL decreases, and hydration of the body surface area increases, peaking at 12 months of age in a degree exceeding hydration of the adult skin. Moreover, younger children have a lower lipid content and lower level of natural moisturizing factor, as well as higher skin pH, compared to older children and adults [41, 42]. The above characteristics of the skin of a baby during the first years of life may significantly affect the penetration of haptens and facilitate the development of delayed-type immune response. Dynamic changes associated with maturation of the dermo-epidermal barrier may therefore be responsible for the occurrence of unspecifically positive reactions in patch tests, which become negative in later life.

For a long time there have been attempts to determine the appropriate concentrations of contact allergens used for testing children. Some authors have not found the need to

reduce the concentrations of the test substances [18, 21, 39, 43, 44]. Others indicate that concentrations of allergens used for the performance of patch tests in the youngest patient population should be reduced [45, 46, 47, 48]. Excessive reactivity of the skin of children under the age of 18 months of age, manifesting by transiently positive patch test results, has been demonstrated by Jøhnke who in 542 randomly selected children performed patch tests with fragrance mix and nickel sulphate in 3 different concentrations: 22 μg/cm², 66 μg/cm² and 200 μg/cm² [47]. In 304 out of 542 patients, the study was conducted both at 12 and 18 months of age. Particularly noteworthy was the fact that as many as 111 subjects had a single, temporary positive result with the highest patch tests concentration of nickel sulfate (as used in adults), while only in 26 children (8.6%) the results were repeatedly positive in both studies. The author suggests that for the performance patch tests in younger children the concentration of nickel sulphate is too high. On the contrary, other authors point to the need to use lower concentrations, also in relation to other allergen contact during patch tests conducted in children. Fisher proposed the use of 0.25% aqueous formaldehyde solution, and also the following concentrations with the use of petrolatum: Quaternium 0.5% and 0.25% potassium dichromate [45]. According to the author, in children over 10 years of age, mercaptobenzothiazole and tiuram mix may be used in concentrations used for testing in adults, but younger children should be tested using concentrations divided by half. Observation by Mobley suggest that children above 8 years of age may be patch tested with formaldehyde and nickel in concentrations used in adults [48]. According to the author, children aged under 8 years should be tested with concentrations lowered by half. Hjorth suggests that the concentration of patch test haptens should be tailored to the age of the children [46], and proposes that a positive patch test result in this case should be an indication for retesting with a concentration lowered by half.

CONCLUSIONS

It seems that concentrations of contact allergens included in the current patch tests sets for the paediatric population are too high and should be verified – the authors of the presented study plan to include reexamining patients aged 1-5 years after 5 years in order to determine incidence of nonspecifically positive results of patch tests, using the same set of haptens.

There is certainly a need to develop a paediatric set of patch tests differing in concentrations from those previously used; large-scale studies regarding this problem should engage research centers as well as companies producing patch tests allergen series.

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