TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 1207-1213
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doi:10.3906/sag-1309-62

The patterns and clinical relevance of contact allergen sensitization in a pediatric population with atopic dermatitis

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Received: 26.09.2013 • **Accepted/Published Online:** 13.01.2014 • **Printed:** 31.12.2015

Background/aim: Data about contact allergen sensitization (CAS) in children with atopic dermatitis (AD) are limited. The purpose of this study was to identify the frequency and patterns of CAS in children with AD by using a ready-to-use patch test system.

Materials and methods: After receiving the history of CAS in the patients, the severity of AD and IgE-mediated allergen sensitization were determined.

Results: Of 134 children with AD, 33.8% (n = 45) had at least 1 positive reaction. The most frequent positive reaction was to nickel sulfate (NS) (37.8%, 17/45), followed by methylchloroisothiazolinone (20.0%, 9/45) and thimerosal (15.6%, 7/45). The total Scoring Atopic Dermatitis (SCORAD) score was significantly higher in the NS-sensitized group (P = 0.036). The patients with NS sensitization had moderate–severe AD more frequently than those without any reaction (P = 0.020). When the SCORAD score was evaluated in detail, extent of eczema, score of sleep loss, and pruritus were significantly higher in the patients with NS sensitization than those without any reaction (P = 0.002, P = 0.001, and P = 0.002, respectively).

Conclusion: Our study confirms the necessity of CAS in the management of AD. In particular, NS sensitization should be considered for children with severe AD or larger extent of eczema and trunk involvement.

Key words: Atopic dermatitis, children, contact allergen sensitization

1. Introduction

Allergic contact dermatitis is an underestimated health problem in the pediatric population with atopic dermatitis (AD) (1). There are limited studies in the literature about the prevalence and clinical characteristics of allergic contact sensitization and dermatitis in children with AD (2–8). Allergic contact dermatitis is not rare in children with AD (9); they are exposed to more sensitizers because of the damaged epidermal barrier and the extensive use of topical medications (10).

The patch test is accepted as the gold standard for the detection of contact sensitization and allergy (11). The test provides the ultimate diagnose of allergic contact dermatitis, which is the result of delayed type hypersensitivity reactions. Additionally, it may detect contact sensitizations secondary to or complicating AD.

Different prevalence rates of contact allergens and patterns of sensitization reported by different studies may be due to variations in regional referral patterns, patch testing selection criteria, and patch test material used (12). Studies about contact dermatitis and allergen sensitization in Turkish children are limited (13).

The aim of this study was to identify the frequency of contact allergen sensitization (CAS) in children with AD, the most common sensitizers, the relation with specific comorbidities [coexisting asthma, allergic rhinitis, current household smoking, prenatal smoking, immunoglobulin E (IgE)-mediated allergic sensitization], and the rate of clinical relevance of CAS in a group of patients at our center.

2. Materials and methods

2.1. Patients

Children with AD treated at the Ankara Hematology-Oncology Children's Research and Education Hospital, Clinic of Pediatric Allergy, were enrolled in the study between September 2011 and March 2012. After receiving informed consent from the caregivers, the medical

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histories of the patients were evaluated for the status of CAS. The clinical diagnosis of AD was made according to the diagnostic criteria of Hanifin and Rajka (14). Patients who had a limited area on the back for a patch test, and those with comorbidities other than allergic diseases, were not included in the study. Data on prenatal smoking, current household smoking exposure, and family history of allergic diseases were obtained from the caregivers of the patients. All of the patients were evaluated for coexisting allergic diseases other than AD (asthma and allergic rhinitis). A skin prick test (SPT) for common food (cow's milk, egg white, wheat, peanut, soy, and fish) and aeroallergens (house dust mite, cockroach, animal dander, mold, and mixed grass pollen) was performed for all of the patients. According to sensitization to common allergens in the SPT, specific IgE tests were also performed. Total serum IgE and percentage of peripheral blood eosinophil tests were also performed for the whole study group. The severity of AD was defined according to the Scoring Atopic Dermatitis (SCORAD) score (15). The SCORAD index consists of A, B, and C scores. The A score grades the extent of eczema indicated as percent of the patient's total body surface, thus ranging between 0 and 100. The B score is the definition and grading of intensity items. Six items are selected: erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and dryness. Each item may be graded from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe). Thus, the B score may range between 0 and 18. The C score consists of subjective items such as sleep loss and pruritus. The caregivers, or the patients older than 7 years of age, were requested to rate each of the subjective items from 0 to 10 (15). The patients were grouped as having mild, moderate, or severe AD according to the cut-off points of 25 and 50 that had been defined before in the literature for SCORAD scores (15,16). The variables were compared for mild, moderate, and severe AD groups. Analyses were repeated for a unified group of moderate and severe AD cases. After this initial evaluation, a patch test was applied to the back of the patients. The patients and the caregivers were questioned about the presence of symptoms of contact dermatitis both before and after patch testing.

2.2. Procedure of patch testing

Oral treatments with antihistamines and systemic steroids were stopped 7 days before patch testing. The use of topical steroids and topical immunomodulators was prohibited on the test area for 7 days before patch testing. The presence of sensitization for contact allergens was evaluated by using a ready-to-use patch test system (TRUE test, Mekos Laboratories AS, Hillerød, Denmark). It includes 29 standardized test substances including the most common allergens or allergen mixes selected in accordance with the recommendations of the International Contact Dermatitis Research Group. Patch test plasters were applied on the upper back of the patients and removed after 2 days. The first reading was performed on day 2 at least 20 min after removing the patches. On day 3, the routine final reading was made for all patients. If necessary, later readings on days 5 and 7 were performed. The clinical relevance of the positive reactions was considered if the patient or the caregiver described symptoms related to cutaneous exposure to a product known to contain the allergen to which the patient had reacted.

2.3. Data analysis and statistical analysis

Results were expressed as percentile (absolute numbers), as mean and standard deviation, or as median and interquartile range (IQR) as required. SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. To compare variables, the chi-square test and Mann–Whitney U test were used. A 2-tailed P-value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study group

The caregivers of 145 patients with AD were asked for permission to enroll the patients in the study, and 134 of them signed informed consent forms and accepted the patch testing procedure. The average age of the study group was 21 (9–59) months [median (IQR)], ranging between 2 and 206 months. Boys accounted for 58.1% (n = 79) of the patients. Coexisting allergic diseases other than AD (asthma and/or allergic rhinitis) were defined for 28.9% (n = 39) of the patients, while 19.9% (n = 27) had family history of allergic diseases. The median SCORAD index was 29.5 (18–45.5). According to SCORAD scores, 38.2% of the patients were grouped as having mild, 39.7% as moderate, and 20.6% as severe AD. Regarding the results of SPT and allergen specific IgE, 53.0% (n = 71) of the study population had sensitization to common allergens. Of these, 32.1% (n = 43) of patients had sensitization to food and 26.1% (n = 35) to inhalant allergens.

Of the study group, 33.8% (n = 45) had at least 1 positive patch test reaction on the TRUE test. Sixteen of them (35.6%) had more than 1 positive patch test reaction. Only 1 patient described having symptoms of contact dermatitis without a positive patch test reaction. The most frequent positive patch test reaction was to nickel sulfate (NS) (37.8%, 17/45), followed by reaction to methylchloroisothiazolinone (MCI) (20.0%, 9/45) and thimerosal (15.6%, 7/45). The other positive reactions were 4 patients for black rubber mix; 3 patients for each of potassium dichromate, cobalt chloride, p-tert butyl phenol formaldehyde resin, and thiuram mix; 2 patients each for neomycin sulfate, fragrance mix, formaldehyde, and mercapto mix; 1 patient each for wool alcohols, colophony, balsam of Peru, ethylenediamine dihydrochloride, paraben mix, carba mix, quaternium-15, mercaptobenzothiazole,

p-phenylenediamine, diazolidinyl urea, and tixocortol 21-pivalate. The frequency of the clinical relevance of positive reactions was as follows: 7/17 of the patients with positive reaction to NS, 5/9 of those with positive MCI reaction, 2/7 with positive thimerosal reaction, 1/3 with positive potassium dichromate reaction, 1/2 with positive fragrance mix reaction, 1/1 with positive colophony reaction, 1/1 with positive ethylenediamine reaction, 1/3 with positive cobalt chloride reaction, 2/3 with positive p-tert butyl phenol formaldehyde resin reaction, 1/1 with positive paraben mix reaction, 1/1 with positive quaternium-15 reaction, 1/2 with positive mercapto mix reaction, and 1/1 with positive diazolidinyl urea reaction had symptoms of contact dermatitis related to patch test results. The positive reactions with neomycin sulfate, balsam of Peru, carba mix, black rubber mix, mercaptobenzothiazole, p-phenylenediamine, formaldehyde, thiuram mix, and tixocortol 21-pivalate were not related to any clinical symptoms. Of all patients with positive patch test reactions, 40.0% (n = 18) had symptoms related to the positive reaction on patch test.

3.2. Patients with and without positive patch test reactions

There was no difference in the distribution or frequency of age, sex, age of eczema onset, coexisting allergic diseases, family history of allergic diseases, history of current household smoking, total IgE, and percentage of peripheral blood eosinophils between the groups with and without positive patch test reactions. There were no differences in the total SCORAD scores or in the frequency of severity grade of AD. When the SCORAD score was evaluated in detail, the scores of sleep loss and pruritus were significantly higher in the group with a positive patch test reaction than in patients without (P = 0.004 and P = 0.018, respectively) (Table 1).

Some of the substances on the TRUE test may be found in emollients, antiseptics, cosmetics, and toiletries, such as wool alcohols, neomycin sulfate, fragrance mix, colophony,

Table 1. Features of the patients with and without positive patch test reactions. Data are shown as percentiles (absolute numbers) or medians (interquartile ranges), and statistically significant data are shown in bold.

Patch test reactions	Positive (n = 45)	Negative (n = 89)	P
Age (months)*	15 (6–63)	24 (12–58)	0.255
Age of AD onset (month)*	5 (1–12)	9 (2–22)	0.218
Sex, male†	62.2 (28)	55.7 (49)	0.470
Prenatal smoking†	11.1 (5)	6.8 (6)	0.404
Current household smoking†	44.4 (20)	52.3 (46)	0.393
Consumption of cow milk in the first year of life†	35.6(16)	33.0 (29)	0.764
Coexisting allergic disease (asthma, allergic rhinitis)†	22.2 (10)	32.2 (28)	0.231
Familial history of allergic diseases†	15.6 (7)	21.6 (19)	0.406
Allergen sensitization			
Food allergen†	33.3 (15)	30.7 (27)	0.756
Inhalant allergen†	17.8 (8)	29.5 (26)	0.141
IgE*	53 (18–125)	37 (16–190)	0.411
Percent of eosinophils*	3 (1–5)	4 (1–7)	0.139
Localization of eczema			
Face†	62.2 (28)	61.4 (54)	0.923
Trunk†	37.8 (17)	22.7 (20)	0.067
Moderate–severe AD†	66.7 (30)	58.4 (52)	0.453
Total SCORAD score*	30 (21–48)	30 (16–42)	0.258
Extent of eczema (involved percent of total body surface)*	6 (4–16.5)	4 (2–8.8)	0.113
Score of B symptoms*	6 (3–9)	6 (3–9)	0.703
Score of sleep loss*	**5 (0–8)**	**0 (0–5)**	**0.004**
Score of pruritus*	**8 (4–10)**	**6 (3–8)**	**0.018**

* Median (interquartile range).
† Percent (absolute number).

balsam of Peru, ethylenediamine dihydrochloride, cobalt chloride, formaldehyde resin, paraben mix, carba mix, MCI, quaternium-15, formaldehyde, thimerosal, thiuram mix, diazolidinyl urea, and tixocortol pivalate. Of the study group, 25.4% (n = 34) patients had contact sensitization to the ingredients of these products. Only 1 patient had sensitization to tixocortol pivalate, but had no clinically relevant symptoms. These patients had more than 1 positive reaction on patch tests more frequently than the participants with positive reactions to other materials that were not in these products (P = 0.009). There was no difference in age, onset of AD, sex, coexisting allergic diseases other than AD, severity of AD, and IgE mediated allergen sensitization between the patients sensitized to ingredients of these products and those sensitized to other allergens in the TRUE test, or those without any sensitization. There was no patient sensitized to steroids like budesonide and hydrocortisone-17-butyrate.

3.3. Patients with NS sensitization

Of the study group, 12.7% (n = 17) of the patients were sensitized to NS. The distribution and frequency of age, sex, age of eczema onset, IgE, and percent of peripheral blood eosinophils were similar for the patient group with NS sensitization and those without patch test reaction. Regarding the localization of eczema, trunk involvement was significantly more frequent in the group with NS sensitization than those without any patch test reaction (P = 0.016) (Table 2). Total SCORAD score was significantly higher in the NS-sensitized group (P = 0.036). The patients with NS sensitization had moderate–severe AD more frequently than those without any patch test reaction (P = 0.020). When the SCORAD score was evaluated in detail, extent of eczema, score of sleep loss, and pruritus were significantly higher for the patients with NS sensitization than those without any reaction, as well (P = 0.002, P = 0.001, and P = 0.002, respectively).

The patients with MCI and thimerosal sensitization, which were the second and third most prevalent positive patch test reactions in our study, were compared separately with negative patch test reactions. There was no difference in assessed variables between these 2 groups and the group without any patch test reaction.

Table 2. Comparison of the patients with nickel sulfate sensitization and those without any patch test reactions. Data are shown as percentiles (absolute numbers) or medians (interquartile ranges), and statistically significant data are shown in bold.

Patch test reactions	Negative (n = 89)	Nickel sulfate (+) (n = 17)	P
Age (months)	24 (12–58)	20 (6–52)	0.333
Age of AD onset (month)	9 (2–23)	2 (1–18)	0.213
Sex, male	56.2 (50)	58.8 (10)	0.840
Prenatal smoking	6.7 (6)	17.6 (6)	0.155
Current household smoking	52.8 (47)	47.1 (8)	0.664
Consumption of cow's milk in the first year of life	32.6 (29)	41.2 (7)	0.493
Coexisting allergic disease (asthma, allergic rhinitis	31.8 (28)	17.6 (3)	0.241
Familial history of allergic diseases	22.5 (20)	5.9 (1)	0.184
Allergen sensitization	55.1 (49)	58.8 (10)	0.774
Food allergen	31.5 (28)	41.2 (7)	0.475
Inhalant allergen	30.3 (27)	23.5 (4)	0.773
IgE	37 (16–190)	92 (30–382)	0.076
Percent of eosinophils	3 (1–5)	4 (2–11)	0.070
Localization of eczema			
Face	61.8 (55)	58.8 (10)	0.818
Trunk	**22.5 (20)**	**52.9 (9)**	**0.016**
Moderate–severe AD	**58.4 (52)**	**88.2 (15)**	**0.020**
Total SCORAD score	**30 (16–43)**	**43 (27–59)**	**0.036**
Extent of eczema (involved percent of total body surface)	**4 (2–9)**	**14 (5–44)**	**0.002**
Score of B symptoms	6 (3–9)	8 (4–11)	0.303
Score of sleep loss	**1 (0–5)**	**6 (4–8)**	**0.001**
Score of pruritus	**6 (3–8)**	**8 (6–10)**	**0.002**

4. Discussion

In this study, children with AD were evaluated for the prevalence of CAS and clinically relevant symptoms of contact dermatitis. The patients with positive patch test reactions had higher scores of sleep loss and pruritus than those without any reaction. Furthermore, the patients with NS sensitization had significantly higher SCORAD scores, wider extent of eczema, higher scores of sleep loss and pruritus, and a higher frequency of trunk involvement. These may be taken into account as warning points for investigating children with AD for possible contact sensitization.

In the literature, the frequency of contact sensitization of children with AD was reported as 6.2% to 89% in different countries worldwide (2–7). This wide range of frequency may be due to the usage of different contact allergen panels and inclusion of different age groups of children in different studies. In our study, the positive patch test reaction rate was 33.8%. The frequency in our study was less than the frequency in some of the other studies, and this may be attributed to the younger age of our patients as compared to the ages of the children in those studies (12,17).

The frequency of CAS has been demonstrated to be higher in severe AD groups than those with mild and moderate disease, both in adults and in children (5–7). In the present study, although there was no relation between contact sensitization and severity of AD, when the components of the SCORAD index were evaluated, scores of sleep loss and pruritus were significantly higher in the patients with positive patch test reaction. Giordano-Labadie et al. (2), who used a European standard series including 25 allergens as patch test material in children with AD, found that the age of onset of AD and its severity were not associated with CAS and symptoms of contact dermatitis. In accordance with the study by Jacob et al. (12), exposure to current household smoking did not differ for allergic contact sensitization in our study group. Other clinical characteristics were similar between the groups with and without sensitization.

In their study, conducted with children with AD, Giordano-Labadie et al. (2) demonstrated that the risk of developing a contact allergy was significantly elevated in children after the age of 5 years. In the literature, prevalence of CAS is generally thought to increase with age and environmental exposure (18). However, in our study population, no statistically significant difference was found for the frequency and pattern of CAS between patients older or younger than 24 months of age, in accordance with the results found by Fortina et al. (10). Children younger than 2 years old may be sensitized to contact allergens (10,19), even children as young as the 1-week-old infant that Fisher et al. reported (20). In our study, of 17 patients younger than 6 months old, 7 were sensitized, and of 69 patients younger than 2 years old, 27 were sensitized to 1 or more contact allergens.

In the literature, most studies stated NS as being the most common contact allergen, at a frequency of 14.9%–59.1% in patients with positive patch test reactions (2–3,5,7,17). Accordingly, in our study population, NS was the most common positive reaction with a frequency of 37.8% (17/45). NS sensitization was also shown to be the most common contact allergen in a group of Turkish children admitted to a tertiary hospital with complaints of eczema (13). Ear piercing, which may be the main nickel source, is a common tradition in Turkey that is performed even in the first years of life. Other sources of nickel may be wrist straps, snaps, belt buckles, nickel-releasing clothing fasteners, and the use of cleansing products containing nickel (3). To our knowledge, there are no data available about the association of NS sensitization with the severity and extent of AD in the literature. In our study population, NS sensitization was significantly related to moderate–severe AD, higher SCORAD score, wider extent of eczema, trunk involvement, and higher scores of sleep loss and pruritus when compared with children with other sensitizations and without any sensitization. Similarly, Fortina et al., who studied children with AD and other types of eczema, demonstrated that the prevalence of NS sensitization was higher among children with truncal and widespread dermatitis (10).

In our study, the second most common sensitization was to MCI, with a frequency of 6.7% (9/134) in the patch-tested population. MCI is a chemical preservative that can be found in infant products, such as wet wipes and moisturizing creams. In different studies conducted with children with eczema, the frequency of MCI was stated as between 1.5% and 4.9% of the patch-tested population (21–26). These studies also included children with AD, but none of them were entirely composed of patients with AD. Tosti et al. (27) found MCI as the third most common sensitization in pediatric patients, including those with and without AD, with a frequency of 7.3%. According to the literature, it may be stated that MCI sensitization is more frequent in younger patients (21–26). This high frequency may be explained by the history of frequent use of personal skin care products containing this ingredient, especially by patients with eczema.

Sensitization to thimerosal is reported to be frequent in different studies from different countries, with rates varying from 1% to 37% (28–29). In studies conducted with children with AD, the frequency of thimerosal sensitization was reported as between 1.5% and 12.2% in the patch-tested population (10,17,30). In our study, the thimerosal sensitization rate was 5.2% (7/134). Thimerosal (merthiolate) is an organic mercurial derivative widely used as a preservative, which has been added to various products for medical use, such as vaccines, solutions

for intracutaneous skin testing, thimerosal-containing antigenic extracts for hyposensitization therapy, immunoglobulin preparations, cleansing solutions, and topical medicaments (31). In Turkey it was sold as a skin disinfectant in the past.

Mailhol et al. (6) patch-tested 641 children diagnosed with AD with the 6 active components of their topical AD treatment and with their current emollient, and they found a positive reaction in 40 (6%) children. In their study, while younger age at the time of study, onset of AD before 6 months of age, and IgE sensitization were risk factors for contact sensitization, sex and history of asthma were not associated with the risk of sensitization to topical AD treatment. In our study, 25.4% (34/134) patients tested had contact sensitization to the test substances that may be found in emollients, antiseptics, cosmetics, and toiletries. No patient was sensitized to steroids like budesonide and hydrocortisone-17-butyrate. Only 1 patient had sensitization to tixocortol pivalate, but no clinically relevant symptoms. These patients had more than 1 positive reaction on patch testing more frequently than the participants with positive reactions to other materials that were not in emollients. There was no difference in analyzed clinical characteristics between the patients sensitized to ingredients of emollients and those sensitized to other materials on TRUE test or those without any sensitization.

There are some limitations of this study. The absence of a control group consisting of children without AD makes no data available for comparing the frequency of contact sensitization of AD patients with the general population. Additionally, there may be referral bias of a tertiary care center with a patient population having relatively refractory eczema.

In conclusion, the results of our study confirm the necessity of performing patch tests in the management of AD, especially for NS sensitization in children with severe AD with a larger extent of eczema and trunk involvement.

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