Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.14744/TurkPediatriArs.2020.79577

Contact allergen sensitivity in children with contact dermatitis

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What is already known on this topic?

- *Allergic contact dermatitis is a late hypersensitivity reaction that develops after re-contact with an allergen that has previously developed sensitivity. The incidence is increasing in children.*
- *The most common allergen that causes allergic contact dermatitis is nickel sulfate and other metals. Nickel allergy is more common in girls*
- *One of the most important steps of the treatment is to detect the responsible allergen and prevent recurrent contact.*

What this study adds on this topic?

- *Our study has shown that contact allergen sensitivity can also be detected at an early age.*
- *Our study has shown that nickel sensitivity is the most common allergen in both genders at the same rate.*
- *Our study showed that CI + Me-Isothiazolinone (MCI / MI) sensitivity, which is found in cosmetic products such as wet wipes, moisturizers, shampoos, and diaper rash creams used at all ages from the newborn period, is common in children, and there may also be different contact allergen sensitivities.*

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Received: 16.12.2019
Accepted: 02.07.2020
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ABSTRACT

Objective: Irritant contact dermatitis and Allergic contact dermatitis are two distinct forms of contact dermatitis. Allergic contact dermatitis is a Type 4 (delayed-type) hypersensitivity reaction that occurs during subsequent contact with an allergen to a previously sensitized person. The number of allergens that cause allergic contact dermatitis is increasing day by day. Although it is not the gold standard for the detection of these allergens, skin patch testing is a very helpful method. This study aimed to determine the most common contact allergens in the pediatric age group.

Material and Methods: All patients with the diagnosis of contact dermatitis who underwent a skin patch test (TRUE TEST) in the department of Pediatric Allergy and Immunology between March 2017- February 2018 were enrolled in this study. The patch test was evaluated 72 hours later by the same physician and interpreted as recommended by the American Academy of Dermatology. In addition to the patient files, demographic and clinical characteristics, localization of lesions, and itch score according to visual analog scale were recorded.

Results: A total of 80 children enrolled in the study; 45 (56.3%) were girls and 35 (43.7%) were boys. The mean age of the children was 7.37±3.84 years and 57.5% of the patients who underwent skin patch testing had a positive response to at least one or more allergens. The most common allergens were Nickel sulfate, CI + Me-Isothiazolinone, Thiuram Mix, Formaldehyde, and P-tert-butylphenol formaldehyde resin (14.8%, 10%, 6.3%). There was no difference in terms of age, sex, duration of complaints, and pruritus score according to nickel sensitization.

Conclusion: In the presence of chronic dermatitis in children, allergic contact dermatitis should be considered in the differential diagnosis. The culprit allergen should be determined. Also, the most common contact allergen is Nickel Sulphate in the world and the increased sensitization to other allergens is due to the increased contact of children with cosmetics and different contact allergens.

Keywords: Allergic contact dermatitis, children, nickel sulphate, patch test

Introduction

Inflammatory dermatoses caused by substances in contact with the skin are called contact dermatitis and when evaluated etiologically, it is classified as allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). Allergic contact dermatitis is defined as an allergic or inflammatory skin reaction due to a late type of hypersensitivity reaction that occurs in subsequent contact of the previously sensitized person with a chemical, physical or biological allergen substance (1).

Although it is less common than adults, it is increasingly common in childhood as a result of ear piercing, piercing, temporary and permanent tattooing at an early age, and increased use of cosmetic products, and even in adolescence, it is almost as common as adults (2).

Cite this article as: Yücel E, Özçeker D. Contact allergen sensitivity in children with contact dermatitis. Turk Arch Pediatr 2021; 56(1): 51-6.

In studies evaluating the prevalence of ACD in children, patch test positivity rates between 14.5-70.7% were reported (3-5). In a study by Heine et al. (6) evaluating a large case series, the rate of sensitization in childhood and adolescents was found to be similar to adults. A significant increase in the rate of patch test positivity is noticed in children, and it is thought that this may be related to both increased allergen sensitivity and more widespread use of patch testing.

In patients with allergic contact dermatitis, early detection of the sensitive allergen helps to reduce the long-term use of topical steroids by preventing exposure, because allergen avoidance results in an improvement in clinical findings. In our study, we aimed to determine the frequency of contact allergen sensitivity and the allergens most frequently detected in our patients.

Material and Methods

Patient selection

The file data of all patients between the ages of 1-17 who were diagnosed with contact dermatitis and admitted to Pediatric Allergy and Immunology outpatient clinics between March 2017 and February 2018 were evaluated. Patients with concomitant atopic dermatitis, contact urticaria, and other chronic dermatosis were excluded from the study. The diagnosis was made based on the location of the lesions, clinical features, and clinical improvement by avoiding the allergen if detected.

Laboratory tests

Demographic characteristics, presence of atopy in the family, location of the lesions, itching score according to visual analog scale, skin patch test results, serum total IgE, blood eosinophilia percentage, skin prick test results for respiratory and food allergens were recorded.

Patients with serum specific Ig E antibodies and/or positivity to at least one allergen in the skin prick test were evaluated as atopic. A blood eosinophil percentage ≥4% and /or >450/mm^3 was considered as eosinophilia.

Skin Prick Test

A skin prick test (SPT) was performed using standard methods. As allergen extracts (Stallergenes-France) Dermatophagoides pteronyssinus (DP), Dermatophagoides farinae (DF), Blattella germanica, Felis domesticus, Canisis, Aspergillus fumigatus, familiar Penicillium mixture (P.digitatum, P.expansum and P.notatum) mix, Cladosum (C. cladosporioides, C. herbarum, A.niger), Rumex acetosa (Sorrel), Urtica dioica (Common nettle), Plantago (Plantain), Artemisia vulgaris (Wormwood), Chenopodium album (White goosefoot), Parietaria oficinalis (Upright pellitory), Lolium perene (Perennial ryegrass), Anthoxantum odoratum (Sweet vernal grass), Dactylis glomerata (Cat grass), Festuca elatior (fescue grass), 7 grain mix (barley, corn, oats, rice, rye, wheat, wheat flour), Alnus glutinosa (Black alder), Fagus sylvatica (Common beech), Betula alba (Silver birch), Corylus avellena (Common hazel), Quercus robur (English Oak), Olea europea (Olive), Populus alba (White poplar), Salix caprea (Goat willow), False acacia (Black locust), latex, cow's milk, egg white, egg yolk, cocoa and banana so a total of 34 allergen extracts were used, Histamine (10 mg/mL) was used as positive control and saline solutions were used as negative control. One drop (0.01-0.02 mL) of allergens, positive and negative control extracts were dropped to the inner surface of the forearm at 2 cm intervals, the skin was pierced with a lancet at a 90° angle over each drop. Evaluations were made 20 minutes after the test was administered; detection of ≥3 mm wheal diameter compared to negative control was considered positive.

Skin Patch Test

Skin patch test consisting of 36 allergens (Nickel sulfate, Wool alcohols, Neomycin sulfate, Potassium dichloramate, Caine mix, Fragrance mix, Colophony, Paraben mix, Blank patch, Balsam of Peru, Ethylenediamine dihydrochloride, Cobalt chloride, p-tert- butylphenol formaldehyde resin, Epoxy resin, Carba mix, Black rubber mix, CI + Me- Isothiazolinone, Quarternium-15, Methyldibromo glutaronitrile, P-Phenylenediamine, Marcapto mix Formaldehyde, Thiomersal, Thiuram mix, Diazolidinyl urea, Quincoroline mix, Diazolidinyl urea, Quincoroline mix, Gold sodium thiosulphate, Imidazolidinyl urea, Budesonide, Hydrocortisone-17-butyrate, mercaptobenzothiazole, Bacitracin, Parthenolide, Disperse blue 106, 2-Bromo-2-nirtopropane 1,3 diol) as ready-to-use tape "TRUE test (Albio© Ltd) "was applied. Before the patch test, patients were warned not to use systemic steroids and antihistamines, and not to use topical steroid creams and ointments in the test area. The standard envelope was opened and the ready-made test material inside was attached directly to the back skin. The patients were warned that the test area should not get wet (bathing, sweating, excessive physical activity, etc.) and that activities that could cause the tapes to come off their places should not be performed. The patch test was removed after 48 hours by two allergists and the test area was evaluated after 30 minutes. The test site was reevaluated at 72 or 96 hours to detect late reactions. The results were interpreted as negative if there was no reaction, erythema, and infiltration (+), erythema, infiltration, papule, vesicle (++), erythema, infiltration, bulla (+++) as recommended by the American Academy of Dermatology (7). Written consent was obtained from the patient and their parents before the patch test. According to the test result, a list was given to the family about the things to avoid for the allergens with sensitivity detected.

Our study was conducted following the Helsinki Declaration principles. Okmeydanı Training and Research Hospital Ethics committee approval was obtained from the Training and Research Hospital Ethics Committee with the letter number 2017/756.

Statistical analysis

When evaluating the findings obtained in the study, IBM SPSS Statistics 22 for statistical analysis (SPSS IBM, Turkey) program was used. The suitability of the parameters to the normal distribution was evaluated with the Shapiro Wilks test while evaluating the study data. Besides descriptive statistical methods (mean, standard deviation, frequency), the Student t-test was used for comparing normally distributed parameters between two groups, and Mann-Whitney U test was used for comparisons of parameters that did not show normal distribution between two groups while evaluating the study data. Fisher's Exact test, Fisher Freeman Halton Test, and Yates's correction for continuity were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Results

A total of 80 children, 45 (56.3%) girls, and 35 (43.7%) boys, aged between 1 and 17 were included in the study. The mean age of the children was 7.37±3.84 years (1-17) and the longest duration of complaints was 15 years (1.86±2.73). The clinical and demographic characteristics of the patients are given in Table 1. The median serum total IgE value of the patients was 125 kU/L (36-251), and the mean percentage of eosinophils was 4.06±3.00 (0.1-14). Positive response to at least one or more allergens was detected in 57.5% (n=46) of the patients who underwent a skin patch test. Among the patients who were found to be positive, the location of the allergen and the lesion was compatible with 76% (n=35). The most common allergen is Nickel sulfate 14.8% (n=12) and the results of the allergens detected in the skin patch test are given in Table 2.

When the patch test-positive patients were compared with the negative ones, the age values of those with positive patch test results were found to be significantly lower than those with negative patch test results (p:0,008; p<0.05) (Table 3).

No statistically significant difference was found when the age, gender, duration of complaints, pruritus score, IgE, and eosinophil parameters of patients with negative and positive nickel results were compared (p>0.05) (Table 4).

Discussion

A positive response to one or more allergens was detected in 57.5% of the skin patch test in our study. This rate was reported as 14.5-70.7% in other studies conducted with children (8-11). Önder et al. (12) from our country reported this rate as 32% in our country. In a study conducted in Iran from the nearby geography, the patch test positivity was reported as 46.8% and 60% in Greece (13, 14). The highest patch test positivity rate was found to be 95.6% (15).

Table 1. Clinical, demographic and laboratory features of the patients

		Min-Max	Mean±SD
Age (year)		1-17	7.37±3.84
Duration of complaint (year)		0.1-15	1.86±2.73
Pruritus score		0-10	4.9±2.14
		N	%
Gender	F	45	56.3
	M	35	43.7
Location	Hand	33	41.3
	Face	18	22.5
	Foot	2	2.5
	Other	27	33.8
Atopy in the family	No	69	86.2
	Yes	11	13.8
Additional allergic disease	No	54	66.3
	Asthma	15	18.7
	Allergic rhinitis	10	12.5
	Drug allergy	1	1.2
Skin Prick Test	Negative	58	72.5
	Respiratory	18	22.5
	Food	4	5

The mean age of patients with positive patch test was found to be lower than those with negative in our study. Although contact allergen sensitivity is expected to increase with age, this finding may be an indication that contact allergen sensitivity can start at an early age and can be detected at a young age.

The most common allergen was Nickel sulfate with 14.8% in our study, and Nickel sulfate is reported to be the most common contact allergen in adults and children worldwide (16-22). According to European Union regulations, it is recommended that the nickel release rate in products should not exceed 0.5µg/cm²/week (22). Although Nickel sensitivity is expected to decrease with this regulation, the presence of a tradition of ear piercing at an early age in our country, the widespread use of metal accessories and piercings, as well as hairpins, metallic fabric prints, coins, lip paint, watches, zippers, rings, earrings, studs, metal buttons, belt buckles, nickel-containing batteries, metal toys, kitchen, and bathroom items still cause nickel sensitivity to be detected most frequently with the increasing contact in daily life. It has been reported that nickel allergy is more common in girls (12, 23, 24). Nickel positivity was found at a similar rate in both genders in our study, unlike other studies. We think that this may be due to the low number of patients or the increase in the use of daily items containing both accessories and nickel among boys.

Table 2. Allergens sensitized in patch test

Allergens	% (N)
Nickel sulfate	15 (12)
CI+Me- Isothiazolinone	10 (8)
Thiuram mix	6.3 (5)
P-tert-butylphenol formaldehyde resin	6.3 (5)
Formaldehyde	6.3 (5)
Epoxy resin	5 (4)
Paraben	5 (4)
Fragrance mix	5 (4)
P-Phenylenediamine	5 (4)
Wool alcohols	3.8 (3)
Thimerosal	3.8 (3)
Potassium Dichromate	3.8 (3)
Colophony	3.8 (3)
Mercapto mix	3.8 (3)
Diazolidinyl urea	3.8 (3)
Imidazolidinyl urea	3.8 (3)
Balsam of Peru	2.5 (2)
Black rubber mix	2.5 (2)
Disperse blue 106	2.5 (2)
Carba mix	2.5 (2)
Ethylenediamine dihydrochloride	2.5 (2)
2-Bromo-2 nitropropane-1,3-diol	2.5 (2)
Neomycin sulfate	1.3 (1)
Caine mix	1.3 (1)
Tixocortol-21-pivalate	1.3 (1)
Gold sodium thiosulfate	1.3 (1)
Budesonide	1.3 (1)
Bronopol	1.3 (1)
Mercaptobenzothiazole	1.3 (1)
Bacitracin	1.3 (1)

CI + Me- Isothiazolinone (MCI/MI) is the second most common contact allergen detected in our study with a rate of 10%. MCI/MI is present as a preservative as a mixture of 3:1 ratio in moisturizers, powders, sunscreens, shampoos, liquid soaps, toilet paper, wet wipes, non-rinsing cleaning materials. It is considered a weak contact allergen, but as a result of the increase of the legal permission limits from 3.7 ppm to 100 ppm since 2010, cases of ACD localized in the face and perineal region have been reported in children due to MCI/MI (25). Cosmetic products such as wet wipes, moisturizers, shampoos, diaper rash creams are used at all ages since the newborn period and this use is increasingly common. As a result, sensitivity to cosmetic ingredients is also detected at earlier ages. MCI sensitivity was found to be 4.4% in babies between 3-36 months in a study

Table 3. Comparison of patients with positive patch test with negative ones

	Patch test result		
	Negative	Positive	
	Mean±SD (median)	Mean±SD (median)	p
Age (year)	8.74±4.24	6.33±3.23	[a]0.008*
Duration of complaint (year)	2.35±3.21 (1)	1.49±2.31 (1)	[b]0.055
Pruritus score	5.06±2.37 (5)	4.83±1.97 (5)	[b]0.859
IgE	287.69±473.1 (79)	190.88±281.97 (118.5)	[b]0.744
Eosinophil	4.71±3.76 (3.4)	3.28±2 (2.9)	[b]0.231
	N (%)	N (%)	
Gender			
F	19 (55.9)	25 (54.3)	[c]1.000
M	15 (44.1)	21 (45.7)	
Atopy in the family			
No	25 (73.5)	44 (95.7)	[d]0.007*
Yes	9 (26.5)	2 (4.3)	
Additional allergic disease			
No	20 (58.8)	33 (71.7)	[c]0.333
Yes	14 (41.2)	13 (28.3)	
Prick result, n (%)			
Negative	25 (70.6)	33 (71.7)	[e]1.000
Respiratory	8 (23.5)	10 (23.9)	
Food	2 (5.9)	2 (4.3)	
Additional allergic disease, n (%)			
No	21 (61.8)	33 (71.7)	[e]0.425
Asthma	6 (17.6)	9 (19.6)	
Allergic rhinitis	6 (17.6)	4 (8.7)	
Drug allergy	1 (2.9)	0 (0)	

[a]Student t-test, [b]Mann-Whitney U Test, [c]Yates's Correction for Continuity, [d]Fisher's Exact Test, [e]Fisher-Freeman-Halton Test, *p<0.05

Table 4. Evaluation of patients according to nickel positivity

	Nickel Sensitivity		
	Negative	Positive	p
	Mean±SD (median)	Mean±SD (median)	
Age (year)	7.41±3.87	7.17±3.86	[a]0.844
Duration of complaint (year)	1.97±2.93 (1)	1.23±0.81 (1.4)	[b]0.784
Pruritus score	4.88±2.22 (5)	5±1.65 (5)	[b]0.978
IgE	232.79±363.62 (120)	214.78±444.81 (66)	[b]0.536
Eosinophil	3.95±3.11 (3)	3.45±1.6 (2.9)	[b]0.878
	N (%)	N (%)	
Gender			
F	38 (55.9)	7 (58.3)	[c]1.000
M	30 (44.1)	5 (41.7)	
Location			
Hand	28 (40.6)	3 (25)	[d]0.259
Face	17 (24.6)	2 (16.7)	
Foot	1 (1.4)	1 (8.3)	
Other	19 (27.5)	6 (50)	

[a]Student t-test, [b]Mann-Whitney U Test, [c]Yates's Correction for Continuity, [d]Fisher-Freeman-Halton Test, *p<0.05

conducted in Italy (26). In a study conducted in Europe, MCI/MI sensitivity was detected at a rate of 6% and it was observed that the history of ACD started after 2013 in 80% of the cases with sensitivity in this study. In 2013, the American Contact Dermatitis Association chose MCI/MI as the allergen of the year to raise awareness (27-29).

Thiuram mix is a substance used in the production of rubber. It is associated with occupational ACD in adults working in the food, health, and sanitation sector. It causes face and hand dermatitis (30). Sensitivity with Thiuram mix was found to be 2.7% in an adult study conducted in Denmark. In a study, it has been shown that its frequency has decreased over the years, while 4% sensitivity was detected in 1995, this rate decreased to 2% in 2004 (31). In our study, Thiuram Mix, Formaldehyde, and P-tert-butylphenol formaldehyde resin were the third most common allergens. Personal products such as raincoats, boots, shoes, gloves, balloons, pacifiers and baby bottles, rubber bands, erasers, socks, and elastic bands on underwear, which children frequently use in their daily lives, include Thiuram Mix. Skincare products, hair dyes, varnishes, gums, disinfectants, nail polishes, creams, shampoos, deodorants, skin cleansing products contain Formaldehyde and P-tert-butylphenol formaldehyde resin. In a study evaluating the patch tests applied to children and adolescents in Europe, sensitivity to metals and neomycin was detected most frequently, while Formaldehyde, P-tert-butylphenol formaldehyde resin, and Thiuram Mix were not reported in children with this frequency (18). We think that the widespread use of these products among children may increase this sensitivity.

Allergic contact dermatitis localization was most frequently detected in the hand and face (41.3% and 22.5%) in our study. Önder et al. (12) reported ACD location in children as hand and face (37.7% and 30.3%) similar to our study. Allergic contact dermatitis causes serious deterioration in the quality of life of the person, especially when it is localized on the hand and face. Since the distribution of positive allergens in our study was wide, stratification could not be performed, so the frequency of allergens could not be evaluated according to lesion localization. When the test results were evaluated, it was observed that the sensitized allergen and localization of the lesions were consistent in the majority of the patients.

In the studies conducted, the European standard patch test series, pediatric standard patch test, and TRUE test were used as patch test panels in children (18). Frequently detected allergens are common in all three panels. Jacob et al. (32) reported that the TRUE test can be used safely and easily in childhood.

As a result, Nickel is the most frequently sensitized contact allergen similar to other studies. However, unlike other studies, the sensitivity of CI + Me- Isothiazolinone, Thiuram Mix, Formaldehyde, and P-tert-butylphenol formaldehyde resin was shown at a higher rate in our study. It was thought that this situation was due to the increase in children's contact with more cosmetics and different contact allergens in their daily lives compared to previous years. In our study, the fact that boys were as sensitive to nickel as girls, was attributed to the gradual increase in nickel contact in boys' daily life.

Allergic contact dermatitis and allergens that cause sensitization are found with increasing frequency in children and the younger age group. The awareness of physicians on this issue should increase, and to determine the responsible allergen with the skin patch test should be tried. Avoiding the responsible allergen will ensure the control of lesions and prevent their recurrence, avoiding long-term use of topical steroids and thus increasing the quality of life of patients.

Ethical Committee Approval: Ethics committee approval was received for this study from the ethics committee of Okmeydanı Training and Research Hospital (2017/756).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.Ö.; Design – D.Ö.; Supervision – D.Ö., E.Y.; Funding – D.Ö., E.Y.; Data Collection and/or Processing – D.Ö., E.Y.; Analysis and/or Interpretation – D.Ö., E.Y.; Literature Review – D.Ö., E.Y.; Writing – D.Ö., E.Y.; Critical Review – D.Ö., E.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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