

ORIGINAL ARTICLE

Results of the patch tests with European baseline series in children: Five years of experience from a single center in Turkey and a review of the literature

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Abstract

Background: Pediatric allergic contact dermatitis (ACD) is increasingly prevalent. Patch testing is the gold-standard diagnostic method.

Aims: Our study aimed to identify common contact-sensitizing allergens in Turkish children.

Patients/Methods: We retrospectively analyzed the patch test results and characteristics of 191 pediatric patients [114 (59.7%) females, 77 (40.3%) males], who received the diagnosis of allergic contact dermatitis between 2015 and 2019.

Results: The mean age of the patients was 12.2 years (range 4–18 years). Thirty-six (18.8%) of the patients in the study group had positive patch test outcomes with 56 positive allergens. Girls had a significantly higher rate of total positive patch test results than boys (75%/25%; $p = 0.003$, $p < 0.05$). The most frequent four allergens were nickel sulfate ($n = 20$, 10.4%), cobalt chloride ($n = 6$, 3.14%), p-phenylenediamine ($n = 5$, 2.61%), Methylchloroisothiazolinone/methylisothiazolinone ($n = 5$, 2.61%), respectively.

Conclusions: In our study, we discovered that in addition to the frequently encountered metal allergens such as nickel and cobalt, p-phenylenediamine and Methylchloroisothiazolinone/methylisothiazolinone sensitivities were frequent in the Turkish population. p-phenylenediamine sensitization can cause serious systemic dermatitis during the lifetime of children. We suggest that in Turkey personal care and hygiene products containing Methylchloroisothiazolinone/methylisothiazolinone should be legally regulated. Since childhood contact dermatitis may have an impact on the quality of life by influencing family and social life, suspected allergens should be detected as early as possible.

KEYWORDS

allergic contact dermatitis, patch testing, pediatric dermatology

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1 | INTRODUCTION

ACD is a type-4 hypersensitivity reaction. Contact allergy is an altered status of the immune system which is sensitized by a contact allergen. This process has two phases the first of which is the clinically latent induction phase. During the induction phase, at first contact with the allergen, a clone of allergen-specific T-cells rapidly multiplies and creates a sensitized immune system. Upon re-exposure, the elicitation phase is initiated, during which specific T-cell stimulation begins. This leads to a clinically evident skin disorder called allergic contact dermatitis. In our study, we opted to use the terms contact allergy and contact sensitivity synonymously. Allergic contact dermatitis is an inflammatory skin disorder which is characterized by erythema, edema, vesiculation, and itching.¹

Previously, due to less frequent exposure to allergens and the immature immune system, allergic contact dermatitis was thought to have been an adulthood disease. However, nowadays the incidence of allergic contact dermatitis in children has been on the rise.²

The studies in which the prevalence of allergic contact dermatitis was investigated documented high positive patch test rates (14.5%–70.7%).^{3,4} In the pediatric population, exposure to allergens at early ages and increasing patch test applications are proposed to be the reasons for the high positivity rates.²

In this study, we aimed to investigate the outcomes of the European baseline series patch test of Turkish children diagnosed with allergic contact dermatitis and to review the pediatric literature.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

We conducted a mono-centric, retrospective study. Ethical approval was obtained from the local ethics committee (date: 29/01/2020, number: 2020/0103). The study group comprised 191 pediatric patients between the ages of 4 and 18. A European standard series patch test was applied with a history of exposure to contact allergen accompanied by atypically distributed, treatment-recalcitrant, relapsing-and-reoccurring contact dermatitis lesions. Broadly, for preschool and school children, topical cosmetic and medical products and toys were considered sources for contact allergens; therefore, a patch test indication, whereas for adolescents jewelry, hair dyes, nail polish, henna tattoos, and cosmetics were considered source of allergens, between the years 2015 and 2019. Patients had treatment-recalcitrant dermatitis located on their hands, faces, trunk, and feet. The allergic contact dermatitis was diagnosed clinically with patient history, dermatologic examinations, and follow-ups. The patch test was performed on the patients, who had not applied any topical steroid drugs in the previous 10 days on the application area, and those who had not used any systemic corticosteroids, non-steroidal anti-inflammatory drugs, and anti-histaminic drugs in the previous 4 weeks. An extensive history, including age, sex, profession, and contact with a suspected allergen, was obtained.

2.2 | Patch testing process

For the cases, 29 allergens were utilized which were prepared with recommended concentrations and vehicles standardized by the ICDRG-International Contact Dermatitis Research Group. Subjects were tested using European baseline patch test series of 29 allergens (Chemotechnique Diagnostics) with Finn Chambers (IQ Ultra patch test units). The back of the patient was cleaned with 70% alcohol and let dry. Allergens were either installed in the boxes or absorbed into drying papers and applied to the back area of the patient using ten-spot chambers (Q Chamber®) with hypoallergenic plasters. Patients were advised to avoid bathing or engaging in activities that could cause excessive sweating. The first reading was obtained at the 48th hour and the second reading was obtained at the 72nd hour, according to the schema recommended by ICDRG. Positivity at 48 h, which recedes or disappears at 72 h is evaluated as irritant contact dermatitis. The patch tests were scored according to the ICDRG guidelines; (–) no reaction, (–/+) mild erythema/uncertain reaction, (+) erythema, infiltration, (++) erythema, infiltration, papule, vesicle, (+++) erythema, infiltration, and bulla.¹ Before the test, an informed consent form from the legal guardian of the patient was obtained.

2.3 | Statistical analysis

The Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analysis. Descriptive statistics were presented as numbers and percentages for categorical variables. The chi-square test was used to compare the rates. *p*-values <0.05 were considered statistically significant.

3 | RESULTS

We collected data from 191 consecutive pediatric patients at our Allergy Unit. The study group consisted of 114 girls (59.7%) and 77 boys (40.3%) with a mean age of 12.2 years (range 4–18 years). Ninety-four patients were under 10 years old, and ninety-seven patients were between 10 and 18 years old. The patch tests were positive for 36 (18.8%) patients. Out of 36 patients, 34 were students and two were apprentices to hairdressers. There was no statistically significant difference in the mean age between the allergen sensitivity positive and negative group (Mean age 12.17 vs. 12.22, *p* > 0.05). Girls had a significantly higher rate of total positive patch tests than boys (75.0%/25.0%; *p* = 0.003, *p* < 0.05). Frequencies of encountered allergens according to sex are seen in Table 1.

A total of 56 positive allergens were detected in 36 patients with positive patch test results. The most frequent four allergens were nickel sulfate (*n* = 20, 10.4%), cobalt chloride (*n* = 6, 3.14%), phenylenediamine Base (PPD) (*n* = 5, 2.61%), Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (*n* = 5, 2.61%), respectively. Out of 36 patients with a positive patch test, 21 (58.3%) patients manifested sensitivity to one allergen, 10 (27.8%) to two allergens, and

TABLE 1 Positive allergens according to sex.

Allergen	Female (n = 114)		Male (n = 77)		Total (n = 191)		p
	n	%	n	%	n	%	
Nickel sulfate	14	9.72	6	7.79	20	10.47	0.074
Cobalt chloride	5	3.47	1	1.30	6	3.14	0.102
Phenylenediamine base	5	3.47	0	0.00	5	2.62	NS
Cl + Me-isotiazolinone	5	3.47	0	0.00	5	2.62	NS
N-isopropyl-N'-phenyl-4-Phenylendiamine	3	2.08	1	1.30	4	2.09	0.317
4-tert-butylphenol formaldehyde recine	3	2.08	0	0.00	3	1.57	NS
Balsam of peru	1	0.69	1	1.30	2	1.05	NS
Primin (2-methoxyl-6-N-pentyl-4-benzoquinon)	2	1.39	0	0.00	2	1.05	NS
Sesquiterpene lactone mix	1	0.69	1	1.30	2	1.05	NS
Textile dye mix	1	0.69	1	1.30	2	1.05	NS
Thiuram mix	1	0.69	0	0.00	1	0.52	NS
Formaldehyde	1	0.69	0	0.00	1	0.52	NS
Colophony	1	0.69	0	0.00	1	0.52	NS
Mercapto mix	0	0.00	1	1.30	1	0.52	NS
Fragrance mix I	0	0.00	1	1.30	1	0.52	NS
Total	43	2.86	13	1.88	56	29.32	0.000

Note: Chi square; NS, Not signification.

five (13.9%) to three allergens. The list and frequency of positive allergens with the European baseline series are seen in Table 2. The most common sensitivity to a single allergen was nickel sulfate with 12 patients (60%). In a single patient, the most encountered concomitant sensitivity was to nickel and cobalt in three patients (15%) and nickel and MCI/MI in three patients (15%). Three different types of allergen sensitivity in a single patient were detected in five patients.

Nickel sulfate was the most common allergen with 20 patients (10.4%). Fourteen females (70%) and six males (30%) exhibited nickel positivity. The difference between the sexes was not statistically significant ($p = 0.074$, $p < 0.05$). A statistically significant correlation between nickel sulfate sensitivity and cobalt chloride sensitivity was detected ($p = 0.011$ $p < 0.05$, respectively) (Table 3).

4 | DISCUSSION

ACD is a type-4 delayed hypersensitivity reaction and occurs when a patient who is previously sensitized by an allergen, encounters the same allergen.¹

Recent studies suggest that the frequency of contact sensitization in children is rising.⁵ However, children are not patch-tested as often as adults.⁶

The limitations of the application of patch testing in childhood are that children are required to visit the hospital three times a

week, the application area is narrow, and the cooperation of children is limited as it is hard to sustain 48 h of contact with the test to the back of children. Contact sensitization rates during childhood in North America and European countries are reported to be 16%–25% whereas studies from other parts of the world have reported higher sensitization prevalence in children.^{5,6} Toys, hobbies, and personal care products contribute to the rise of new allergens in pediatric patient groups.⁷ Studies from Turkey report that contact sensitization rates in the pediatric population are 32%–57%.^{8,9} In our study, we established that the contact sensitization rate in the Turkish pediatric population is 18.8%. The small percentage in our study compared with others in Turkey might be due to the fact that we only used European baseline series allergens in our patch test. Our data revealed the most common allergen was nickel with 10.4% consistent with the data from the rest of the world.¹⁰ As a traditional behavior in Turkey, the high prevalence of wearing earrings might explain this high percentage of nickel sulfate sensitivity. Jewelry, sports equipment, metal zippers on clothes, toys containing metal, music instruments, cell phones, iPads, and such electronics comprise nickel sulfate resources.¹⁰ The European Union (EU) Nickel Directive was introduced in 1994 to limit nickel content in products.¹¹ Even though the EU restriction on nickel induced a decrease in the prevalence of nickel allergy, nickel is nonetheless the most common allergen (23.7%).¹² There are reports from Turkey indicating that pediatric nickel sensitization rates are 14.8%–21.5%.^{8,9} Nickel sensitization is shown to

TABLE 2 List and frequency of 56 positive allergens with European baseline series.

	1 Positivity		2 Positivity		3 Positivity		Total	
	n	%	n	%	n	%	n	%
Nickel sulfate	12	60	7	35.0	0	0.0	20	35.7
Cobalt chloride	1	4.8	4	20.0	1	6.7	6	10.7
Cl + Me-isotiazolinone	2	9.5	3	15.0	0	0.0	5	8.9
Phenylenediamine base	2	9.5	1	5.0	2	13.3	5	8.9
N-isopropyl-N'-phenyl-4-phenylenediamine	0	0.0	1	5.0	3	20.0	4	7.1
4-tert-butylphenol formaldehyde resin	0	0.0	2	10.0	1	6.7	3	5.4
Balsam of peru	1	4.8	1	5.0	0	0.0	2	3.6
Primin (2-methoxyl-6-N-pentyl-4-benzoquinon)	1	4.8	0	0.0	1	6.7	2	3.6
Sesquiterpene lactone mix	0	0.0	0	0.0	2	13.3	2	3.6
Textile dye mix	0	0.0	0	0.0	2	13.3	2	3.6
Mercapto mix	1	4.8	0	0.0	0	0.0	1	1.8
Fragrance mix I	0	0.0	1	5.0	0	0.0	1	1.8
Thiuram mix	0	0.0	0	0.0	1	6.7	1	1.8
Formaldehyde	0	0.0	0	0.0	1	6.7	1	1.8
Colophony	0	0.0	0	0.0	1	6.7	1	1.8
Total	21	100.0	20	100.0	15	100.0	56	100.0

Abbreviation: n, number.

TABLE 3 Correlation between Nickel sulfate and Cobalt chloride sensitization.

		Nickel sulfate						χ^2	p
		Negative		Positive		Total			
		n	%	n	%	n	%		
Cobalt chloride	Negative	168	98.2	17	85.0	185	96.9	6430	0.011
	Positive	3	1.8	3	15.0	6	3.1		
	Total	171	100.0	20	100.0	191	100.0		

Note: χ^2 (Chi square). Bold values indicate $p < 0.05$ considered as statistically significant.

be more frequent in females both in Turkey and in the world.^{8,13} On the contrary, consistent with the study of Yücel et al., we detected a similar rate between males and females.⁹ This conclusion might be related to male subjects rising exposure to nickel due to the increased popularity of nickel-containing earrings, accessories, and clothing. When we compared pre-adolescent and adolescent groups, both groups showed the most common sensitivity is nickel in both sexes. However, Yücel et al. demonstrated that under the age of 10 the most common sensitizations are nickel and thiomersal, whereas over the age of 10 the most common ones are nickel and PPD.⁹ A study out of Israel, showed in girls nickel sensitization frequency decreases from infancy to childhood and increases during adolescence, whereas in boys there is not such variation.¹⁰ In Turkey, according to The Regulation of Chemicals, nickel release is restricted to 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ in products intended to come into

direct contact with the skin (published on June 23, 2017).¹⁴ Nickel remains to be the most commonly-encountered allergen in Turkey.

A review in which 50 studies from Europe, North America and Asia were investigated outlined that the most encountered allergens are cobalt, thiomersal, fragrance mix and potassium dichromate, respectively.¹⁰ In our study, cobalt was the second most common allergen (3.14%). Likewise in the literature, cobalt is often the second most common allergen after nickel.^{9,10} A study from Turkey by Önder et al., in 2007 showed the sensitization rate as 9.5%.¹⁵ Yet, a recent study from Yılmaz et al revealed the rate as 1.6%.⁸ Because of the similar constitutional atomic structure of cobalt and nickel, cobalt positivity might be explained by cross-sensitivity. Nonetheless, it should be considered that one could develop a sensitivity to these metals concurrently or sequentially.¹⁶ Children can be exposed to cobalt via jewelry, make-up,

tattoo inks, school chairs, cleaners, and detergents.⁹ In our study, six participants showed cobalt allergy. Three of them also had nickel sensitivity while the other three did not. Our study supported that cobalt sensitization can be a standalone sensitization without the presence of nickel sensitivity. Novel sources of cobalt reservoirs such as jewelry, dental alloys, and pigmented cosmetics should not be overlooked.¹⁷

PPD is a tinting chemical, which is found in body coloring substances such as hair dyes and black henna tattoos. In our study, sensitization prevalence was 2.61%. Recent studies from European countries estimated the rate of PPD allergy in childhood at 2.3%–6%.^{5,18} Additionally, studies out of Turkey determined the rate at 5%–8.4% and it was also among the top 10 allergens.^{8,9} Five patients in our study showed PPD allergy. Out of five positive cases two worked as hairdresser apprentices and had occupational exposure to PPD. We detected no differences in the prevalence of PPD sensitivity between preadolescent and adolescent groups. Our country shows an uptrend in the use of semi-permanent henna tattoos and hair dyes. Many patients allergic to PPD can be reactive to semi-permanent dyes of darkly-colored synthetic clothes.¹⁹ There are case reports in the literature illustrating children who had a history of localized reaction to black henna tattoos developing severe generalized reactions when they encountered hair dyes.²⁰ Another point to take into consideration is that cross-reaction between PPD and drugs such as benzocaine, diuretics (hydrochlorothiazide), and sulfonamides might trigger lifelong sensitization resulting in generalized contact dermatitis upon drug intake.²¹ Therefore, PPD sensitization of children is of utmost importance.

MCI/MI and MI alone are common preservatives in cosmetics and hygiene materials such as wet wipes, moisturizers, shampoos, and diaper rash creams. MCI/MI and MI sensitization increased globally between 2010 and 2015, especially in 2013/2014.²² The prevalence of MI allergy has recently reached 11.1% in recent years.²³ Our study was conducted between 2013 and 2019. The MCI/MI sensitization rate was at 2.61%. A study from Turkey revealed between the years 2007 and 2017 the incidence of pediatric MCI/MI-associated allergic contact dermatitis increased five times compared to the prior decade.⁸ This sensitization rate can be explained by the change of the legal limit in 2010 from 3.7 ppm to 100 ppm despite having weak antigenic properties.²⁴ Recent regulations by the European Commission have banned MCI/MI in all body products such as creams (published on April 16, 2015). The preservative can still be used in rinse-off products such as shampoos and shower gels at a maximum concentration of 0.0015% of a mixture in the ratio of 3:1 of MCI/MI. The MCI/MI prevalence has been plummeting in countries with adequate legal regulations, however the absence of a legislation in Turkey against exposure to MCI/MI in cosmetic and personal care products might lead to alarming rates. Additionally, the rise in the use of personal care and hygiene products in Turkey might facilitate the rise of MCI/MI allergy.

The limitation of our study was that due to the retrospective structure of the study design, we could not determine the clinical relevance of patients showing allergen sensitization. However, the

fact that our study is a single-center study, and that tests were applied and evaluated by the same doctor, makes our study valuable.

In conclusion, according to the data of our study, nickel, cobalt, PPD, and MCI/MI are the most common culprits in contact sensitization during childhood. While the prevalence of metal allergies is consistent with the rest of the world, relatively higher rates of PPD and MCI/MI allergies are remarkable. PPD sensitivity is important due to the risk of developing systemic dermatitis throughout the lifespan of an individual. We believe that there is a necessity for legislation for personal care and hygiene products in Turkey because of the high rates of MCI/MI allergy. Allergic contact dermatitis can lead to the deterioration of quality of life and negatively influence future life decisions such as hobbies and career choices. Therefore, patch tests should be applied on patients with treatment-recalcitrant dermatoses without further delay.

AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript.

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S.A.K. gathered data, reviewed the literature, writing the manuscript; F.C.K. supervised the study, N.A. diagnosed the patients and evaluated the patch tests, T.Ö. helped in writing the manuscript and gathered data.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICAL APPROVAL

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