Dermatology Practical & Conceptual

The Contact Sensitivity of Turkish Children and Adolescents to European Baseline Series Allergens between 2013 and 2023

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ABSTRACT

Introduction: Increasing the numbers of patch testing in suspected children increases the rate of diagnosis of allergic contact dermatitis and the identification of clinically relevant allergens.

Objective: The aim of this study was to identify the most frequently observed allergens among Turkish children and adolescents patch-tested in 2013–2023.

Methods: The patch test results of 160 patients (age ≤18) were analyzed retrospectively. The frequency of contact allergens and distribution of positive results in terms of sex, age group (children and adolescents), and the presence of atopic dermatitis (AD) were identified.

Results: Forty-nine patients (30.6%) (34 girls and 15 boys) exhibited positive patch test reactions to a minimum of one allergen, and contact sensitivity was statistically significantly higher in girls (P=0.034). The five most frequent allergens were nickel sulfate (10.6%), MCI/MI (8.1%), cobalt chloride (5.6%), p-phenylenediamine (PPD) (5%), and MI (3.5%). No significant association was observed between patch test positivity and age groups (P>.05). Nickel sulfate sensitivity was significantly higher in girls than in boys (P=.043). A positive reaction was detected in 31.3% of patients with AD and in 33.7% of those without (P>.05), and a statistically significant relationship was observed between contact sensitivity to fragrance allergens and AD (P=.046).

Conclusion: Metals and preservatives represent the most frequent allergens in Turkish children and adolescents. Metal sensitivity is expected to decrease as legislation is enforced. Regulatory measures are now required to reduce MI and MCI/MI contact allergy in Turkey.

Introduction

The prevalence of pediatric allergic contact dermatitis (ACD) was previously underestimated because traditional ACD was regarded as very rare in children. This derived from the belief that children have an immature immune system and are less frequently exposed to contact allergens [1]. However, recent studies have confirmed an increase in positive patch test results in children [2]. The meta-analysis by Bonitsis et al. [3] reported a higher proportion of positive reactions in studies published after 1995 [4]. The rate of positive patch test reactions in the pediatric age group ranges from 27% to 95.6% in recent studies, while relevance ranges from 30.5% to 92.6% [5]. Variations in the prevalence of contact sensitivity to allergens are observed between countries due to differences in allergen exposures, legislations, and local cultures. In previous studies from Turkey, the patch test positivity rate in children ranged between 32% and 57.5% [6-10].

Objective

Limited data are available for patch test results among Turkish children. The aim of this study was to determine the prevalence of ACD and the most common allergens in children and adolescents attending our referral patch testing center in Turkey.

Materials and Method

Approval was granted by the Ankara University Faculty of Medicine ethical committee (n. 02-133-19). One hundred and sixty children and adolescents with clinically suspected ACD who underwent patch testing based on the European Baseline Series (EBS, Chemotechnique Diagnostics, Vellinge, Sweden) at the Ankara University School of Medicine Dermatology Department in 2013–2023 were enrolled. Demographic characteristics, personal and family histories of atopy, duration, and localization of lesions, and patch test findings were retrieved retrospectively from chart reviews. Localizations were classified as the hands, face/head/neck, leg, trunk, or generalized. Allergen groups were classified as metals, fragrances, preservatives, rubber additives, and topical treatments. The patients were divided into two age categories: children (≤10 years) and adolescents (11–18 years).

The allergens were applied to the upper back using Van der Bend chambers. These were removed on Day 2, and reading was conducted after 30 minutes. A final reading and evaluation were conducted on Day 4. The results were assessed based on the scoring system recommended by the International Contact Dermatitis Research Group (ICDRG) [11]. Reactions of 1+ or more were regarded as positive. Irritant, doubtful, and negative responses were recorded as negative.

The EBS underwent several modifications during the study period. Test results based on the EBS applicable during the study period were included in the analysis.

SPSS software (SPSS for Windows, Version 15.0, SPSS Inc., USA) was used for statistical analyses. Qualitative variables are expressed as number and percentage values at a 95% confidence interval, while quantitative variables are expressed as mean ± standard deviation (SD). Categorical variables were compared using the chi-square and Fisher's exact tests, while the Mann-Whitney U and Student's t tests were applied to compare parametric values. *P* values <0.05 were considered statistically significant.

Results

One hundred and sixty children and adolescents aged 2–18 were patch-tested during the study period. The study group consisted of 91 girls (56.9%) and 69 boys (43.1%), with a mean age of 12.4± 4.1 years (median 13 years, range 2–18 years). Sixty-eight (42.5%) patients reported a history of atopy, with a family history of atopy being reported in 31 (19.4%) patients, and personal atopy in 51 (31.9%). Atopic dermatitis (AD) based on the Hanifin and Rajka criteria was present in 36 (22.5%) patients [12].The median duration of symptoms was 12 months (mean 22.6±23.9, range 1–120 months). The most common primary site of dermatitis was the hands (n=77, 48.1%), followed by the face/head/neck (n=35, 21.9%), the leg/foot (n=18, 17.4%), and generalized lesions (n=18, 17.4%).

Forty-nine patients (30.6%) (34 girls and 15 boys) exhibited positive patch test reactions to a minimum of one allergen (range 1–7). Thirty-one patients (19.4 %) were positive to one allergen, 13 (8.1%) to two, three (1.9%) to three, one (0.8%) to four, and one (0.8%) to seven. Overall, there were 77 positive reactions to EBS allergens. The distribution of frequencies of contact sensitization to EBS allergens is presented in Table 1. The five most common allergens were nickel sulfate (n=17, 10.6%), MCI/MI (n=13, 8.1%), cobalt chloride (n=9, 5.6%), p-phenylenediamine (PPD) (n=8, 5%), and MI (n=4, 3.5%). Metal allergens were the most common group (n=22, 13.8%), followed by preservatives (n=16, 10%), dyes (n=10, 6.2%), and fragrances (n=7, 4.4%). A significantly higher prevalence of contact sensitivity to cobalt chloride was observed among patients with positive responses to nickel sulfate *(P*=.008). Four patients with positive reaction to MI and three with positive reaction to MDBG exhibited concomitant sensitivity to MCI/MI (*P*<.001).

The frequencies of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age groups are given in Table 1. Prevalences of contact sensitivity were 21.7% in boys and 37.4% in girls. Contact sensitivity was statistically significantly higher

Table 1: Frequency of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age group.

	Number of positive reactions/ total number of tested patients	Prevalence %(95% CI)	Sex N(%)		P value	Atopic Dermatitis N(%)		P value	Age Group N(%)		P value
			Boy	Girl		AD	Non-AD		Children	Adolescent	
Potassium dichromate 0.5% pet	0/160	-	-	-	-	-	-	-		-	-
p-Phenylenediamine 1.0% pet	8/160	5.8%	3 (4.3)	5 (5.5)	>.99	1 (2.8)	7 (5.6)	.685	1 (1.9)	7 (6.5)	.272
Thiuram mix 1.0% pet	1/160	0.6%	-	1 (1.1)	-	-	1 (0.8%)	-	-	1 (0.9)	-
Neomycin sulfate 20.0% pet	0/160	-	-	-	-	-	-	-	-	-	-
Cobalt chloride 1.0% pet	9/160	5.6%	4 (5.8)	5 (5.5)	>.99	1 (2.8)	8 (6.5)	.685	1 (1.9)	8 (7.5)	.274
Benzocaine 10.0% pet	0/160	-	-		-	-	-	-	-	-	-
Nickel sulfate 5.0% pet	17/160	10.6%	2 (2.9)	15 (16.5)	**.008**	5 (13.9)	12 (9.7)	.539	4 (7.5)	13 (12.1)	.429
Clioquinol 5.0% pet	0/93	-	-	-	-	-	-	-	-	-	-
Colophony 20.0% pet	3/160	1.9%	1 (1.4)	2 (2.2)	>.99	0	3 (2.4)	>.99	2 (3.8)	1 (0.9)	.255
Paraben mix 16.0% pet	1/160	0.6%	0	1 (1.1)	-	0	1 (0.8)	-	0 (0)	1 (0.9)	-
N-Isopropyl-N-phenyl-4-phenylenediamine 0.1% pet	1/160	0.6%	1 (1.4)	0	-	0	1 (0.8)	-	1 (1.9)	0	-
Lanolin Alcohol 30.0% pet	0/160	-	-	-	-	-	-	-	-	-	-
Mercapto mix 2.0% pet	0/160	-	-	-	-	-		-	-	-	-
Epoxy resin 1.0% pet	1/160	0.6%	0	1 (1.1)	-	0	1 (0.8)	-	1 (1.9)	0 (0)	-
Myroxylon pereirae resin 25.0%pet	3/160	1.9%	1 (1.4)	2 (2.2)	>.99	3 (8.8)	0	**.011**	0	3 (2.8)	.555
4-Tert-Butylphenol formaldehyde resin 1.0% pet	1/160	0.6%	0	1 (1.1)	-	1 (2.8)	0	-	0	1 (0.9)	-
2-Mercaptobenzothiazole (MBT) 2.0% pet	0/160	-	-	-	-	-	-	-	-	-	-
Formaldehyde 2.0% aq	2/160	1.3%	0	2 (2.2)	.506	0	2 (1.6)	>.99	0	2 (1.9)	>.99

Table 1. Frequency of contact sensitization to EBS allergens and distributions of positivity according to sex, atopic dermatitis, and age group. *(continued)*

	Number of positive reactions/ total number of tested patients	Prevalence %(95% CI)	Sex N(%)		P value	Atopic Dermatitis N(%)		P value	Age Group N(%)		P value
			Boy	Girl		AD	Non-AD		Children	Adolescent	
Fragrance mix I 8.0% pet	1/160	0.6%	0	1 (1.1)	-	1 (2.8)	0	-	0	1 (0.9)	-
Sesquiterpene Lactone mix 0.1% pet	0/160	-	-	-	-	-	-	-	-	--	-
Quaternium 15 1.0% pet	1/160	0.6%	0	1 (1.1)	-	0	1 (0.8)	-	0	1 (0.9)	-
Primin 0.01% pet	0/93	-	-		-	-		-			
Methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) 0.02% aq	13/160	10.7%	3 (4.3)	10 (11)	.153	4 (11.1)	9 (7.3)	.491	4 (7.5)	9 (8.4)	>.99
Budesonide 0.01% pet	0/160	-	-	-	-	-	-	-	-	-	-
Tixocortol-21-pivalate 0.1% pet	1/160	0.6%	1 (1.4)	0	-	0	1 (0.8)	-	1 (1.9)	0	-
Methyldibromo glutaronitrile 0.5% pet	3/160	1.9%	0	3 (3.3)	.260	0	3 (2.4)	>.99	0	3 (2.8)	.551
Fragrance mix II 14.0% pet	3/160	1.9%	1 (1.4)	2 (2.2)	>.99	0	3 (2.4)	>.99	2 (3.8)	1 (0.9)	.255
Hydroxyisohexyl 3-cyclohexene carboxaldehyde 5.0% pet	0/160	-	-	-	-	-	-	-	-	-	-
Methylisothiazolinone 0.2% aq	4/113	3.5 %	1 (2.2)	3 (4.5)	.645	1 (5)	3 (3.2)	.547	2 (5.7)	2 (2.6)	.586
Textile dye mix 6.6% pet	2/91	2.1%	1 (6.3)	1 (2.8)	.525	1 (8.3)	1 (2.5)	.412	0	2 (5.1)	>.99
2-Hydroxyethyl methacrylate 2.0% pet	0/67	-	-		-						
Propolis 10.0% pet	0/67	-	-		-						

CI: Confidence interval Significant results ($P < 0.05$) are shown in bold.

in girls (*P*=0.034). The prevalence of contact allergy to nickel sulfate was significantly higher in girls than in boys (2.9% vs 16.5%) (*P*=.008*)*. However, there was no significant association between positive reactions to other allergens and sex (*P*>.05).

The mean age of the patients with contact sensitivity to EBS allergens was 12.7±4.2 years. No significant association was found between age and patch test positivity (*P*=.496). Contact sensitivity to at least one allergen was observed in 28.3% (n=15) of the children and 31.8% (n=34) of the adolescents, although the difference was not statistically significant (*P*=.654). There was also no significant association between the distribution of contact sensitivity rates to each EBS allergen and age groups (*P*> .05).

Positive reactions to at least one allergen were determined in 29.4% (n=15) of individuals with a personal history of atopy and in 33.3% (n=12) of those diagnosed with AD. No significant difference in positive patch test rates was observed between patients with and without atopy (*P*>.05). The presence of AD also exhibited no significant effect on contact sensitivity rates (P>.05). However, contact sensitivity to Myroxylon pereirae resin was significantly higher in patients with atopy (*P*=0.031) and AD (*P*=.011), and a significant relationship was observed between contact sensitivity to fragrance allergens and individuals with AD (*P*=.046).

Conclusions

The frequency of positive reactions to EBS allergens in Turkish children and adolescents in this study was 30.6%. Five studies from Turkey reported patch test positivity in 32% to 57.5% of children [6-10]. Zafrir et al. reviewed 50 series from 48 studies from Europe, North America, South America, and Asia. Patch test reaction positivity in children ranged from 14.5% to 70.7% in Europe, 61% to 95.6% in North America, and 45.4% to 80% in Asia [13]. Our result is consistent with some European studies involving EBS allergens, but substantially lower than in the North American studies, which report high sensitization rates. In contrast to contact sensitivity rates, the most common allergens do not differ significantly. Zafrir et al. reported nickel sulfate as the most common allergen, followed by cobalt nitrate, thimerosal, fragrance mix, and potassium dichromate in 48 different international studies [13]. The five most common allergens in the present study were nickel sulfate (n=17, 10.6%), MCI/MI (n=13, 8.1%), cobalt chloride (n=9, 5.6%), p-phenylenediamine (PPD) (n=8, 5%), and MI (n=4, 3.5%).

The prevalence of pediatric nickel-induced ACD in previous studies ranged between 6.8% and 80.4% [13]. The prevalence of contact sensitization to nickel sulfate among Turkish children varied between 7.2% and 46%, and nickel sulfate is also the most common allergen in studies from Turkey [7-10]. The frequency of nickel sensitivity in the pediatric population rises with age, the risk being significantly greater among girls [14]. Nickel allergy prevalences of 13% in girls with pierced ears compared to 1% in those without were reported in one study [15]. The prevalence of contact allergy to nickel sulfate in the present study was also significantly higher among girls (*P*=.008*)*. Ear piercing in the first 2–3 years of life is a common tradition in Turkey, the holes being kept open by imitation or gold jewelry that may also contain nickel [7]. Turkish legislation limits nickel release to 0.5 µg/cm²/week in items intended for direct contact with the skin [16]. The regulation was fully enforced by the end of 2021, and positive effects on metal sensitivity are anticipated.

Cobalt chloride was another common metal allergen with a 5.6% sensitivity rate and significantly higher in our patients with a positive response to nickel sulfate (*P*=.008). Positive patch test reactions to cobalt chloride in the pediatric age group ranged between 4.4% and 11.1% [13]. Concomitant nickel and cobalt sensitization may be a result of cross-sensitivity due to the similar atomic structures, or dual sensitization may result after separate or coupled exposure to nickel and cobalt [17].

Preservatives constituted two of the five principal allergens in this study (MCI/MI 8.1%, and MI 3.5%). MCI/ MI and MI are isothiazolinone preservatives frequently employed as skin care agents for babies and children as well in cosmetics, household products or water-based paints, glues, and slime. MCI/MI sensitivity rates in children in previous studies ranged from 2.4% in asymptomatic infants to 11.7% in children referred for patch testing [18,19]. Zafrir et al.'s review of 48 studies reported that MCI/MI was not among the five most common allergens in children; however, it has been identified as one of the most common allergens in Turkish children, with 12%–20% sensitivity rates [6,8,10]. Yılmaz et al. reported a low sensitivity rate of MCI/MI (1.9%), but also stressed that the number of patients with MCI/MI-induced ACD rose five-fold in 1996–2006 compared to 2007–2017 [9]. The sensitivity rate of MI in the present study was 3.5%. Turkish cosmetic regulations permit MCI/MI to be used in rinse-off products at a maximum concentration of 15 ppm, while MI can be employed at up to 100 ppm [20]. The presence of MCI/MI and MI in leave-on products in Turkey until 2015 and 2017, respectively, may have caused the high sensitivity rates in our study. Sensitivity to MCI/MI and MI is a major public health problem in Turkey, and regulations are needed to reduce the permitted level of MI in rinse-off cosmetics.

PPD is a significant component of chemical hair dyes and black henna tattoos. In the present study, the contact sensitivity of PPD was 5%, and ranged from 7.1% to 9.5% in other studies from Turkey. These results are slightly higher

than in other studies from the literature, which reported 3.5% and 4.2% contact sensitivity rates to PPD [21]. Temporary tattoos containing high concentrations of PPD constitute a major cause of sensitivity in Turkish children and adolescents.

The question of whether children with AD are particularly prone to allergic contact dermatitis (ACD) is controversial. A systematic review and meta-analysis reported similar prevalences of contact sensitization in individuals with and without AD, recommending that clinicians should consider patch testing on suspicion of ACD [22]. In a review of 21 studies comparing the patch test results of children with and without AD, the prevalence of contact allergy was significantly higher among children without AD (overall, 41.7% vs 46.6%) [23]. Patch testing may be useful as a screening tool in the management of pediatric AD. It should always be considered in recalcitrant AD or if ACD is indicated by a previous medical history [23]. The allergens to which children with AD react differ significantly from those in children without AD. All children with AD are inevitably chronically exposed to topical agents, and epidermal barrier defects in AD may facilitate sensitization to medications and fragrances. In this study, the contact sensitivity rate to Myroxylon pereirae resin was significantly higher in patients with AD (P=.011), and a significant relationship was found between the fragrance allergens group and patients with AD (P=.046). A study of 1012 Dutch children reported that individuals with AD reacted significantly more frequently to fragrances (fragrance mix I and Myroxylon pereirae resin) [24]. Personal care products containing fragrances should also be considered as potential causes of ACD in children, especially those with AD. A recent study found that 89% of 187 surveyed products labeled as "hypoallergenic," "dermatologist recommended/tested," "fragrance-free," or "paraben-free" contained at least one contact allergen [25].

In conclusion, metals and preservatives are the main allergens in Turkish children. Legislation that was enacted in 2022 would lower the high nickel sensitivity rates. However, regulations are required to reduce the permitted level of MI in rinse-off cosmetics. The principal limitation of this study is that the clinical relevance of allergens was not investigated.

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