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Short title: Patch test results of children and adolescents from Turkey

Patch test results in terms of the recently recommended allergens in children and adolescents:

a retrospective cohort study over 22 years from Turkey

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Abstract

Background: An European pediatric patch test series was suggested recently.

Objectives: To evaluate the patch test results in children (<10 years old) and adolescents (10-18 years old) in Turkey, focusing on the clinical/occupational relevance, and the diagnostic value of the recently suggested series.

Patients and Methods: A retrospective cohort study on 317 consecutively patch tested patients aged ≤ 18 years, between 1996-2017.

Results: The contact sensitization rate was 46.1%. Allergic contact dermatitis (ACD) was diagnosed in 30.9%, comprising non-occupational (84.7%) and occupational (15.3%) ACD. Nickel was the leading allergen in almost every age group.

Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) was the clinically most relevant allergen, followed by p-phenylenediamine (PPD), ammonium persulfate, fragrance mix I, nickel sulfate, and mercury/mercury(II)amidochloride. Occupational ACD was most frequently seen in hairdresser apprentices (adolescents only) who were sensitized with PPD $\pm$ ammonium persulfate. ACD from MCI/MI increased to 5-fold, ammonium persulfate, mercurial compounds to-2 fold, and PPD to 1.7-fold after 2007. Almost 1/3 of patients would be missed by testing only with the recommended allergens.

Conclusions: For patch testing in Turkish children and adolescents, we would suggest additionally to test with ammonium persulfate, mercury/mercury(II)amidochloride, toluenesulfonamide formaldehyde resin, and polyethylene glycol, the latter as marker for nitrofurazone allergy, in appropriate patients.

Key words: allergic contact dermatitis, patch test, pediatric, COADEX, atopy, nickel, occupational, hairdresser, hand eczema, p-phenylenediamine

1. Introduction

During the last three decades, positive patch test results and allergic contact dermatitis (ACD) in children have been increasingly reported worldwide.¹ The exposure patterns of the allergens differ depending on the individual and geographical variability.² An evidence-based, standardized patch test series for the pediatric age group is still lacking.³ There have been several attempts to create a baseline allergen series for this age group.³⁻⁶ In a position paper of the European Academy of Allergy and Clinical Immunology (EAACI) in 2015, a baseline and an additional list of allergens, the latter for specific indications, were suggested for pediatric patients with suspected ACD.³

This study aimed to evaluate the patch test results in patients aged ≤ 18 years from a tertiary referral center in Turkey, with regard to positive patch test findings, their clinical/occupational relevance, the characteristics of ACD/occupational ACD, and with special emphasis on whether the relevant allergens were covered by the recently suggested European pediatric patch test series.

2. Patients and Methods

In this retrospective cohort study, the medical files of 317 patients aged ≤ 18 years who were consecutively patch tested in our allergy unit with the suspicion of ACD between 1996 and 2017, were reviewed. Of these, 146 patients who had at least one positive patch test reaction comprised the main study group.

Demographic features (gender, age, atopy in terms of atopic dermatitis⁷ or atopic skin⁸), patch test findings, the clinical/occupational relevance of positive patch test reactions, and characteristics of patients with non-occupational and occupational ACD as well as the temporal changes over the years were recorded. Regarding the possible immunological and exposure differences among age groups, positive patch test reactions were evaluated in terms of two age groups, namely patients aged < 10 years old (children) and ≥ 10 years old

(adolescents). The MOAHLFAP index (male-occupational dermatitis-atopic dermatitis-hand eczema-leg eczema-face eczema-age ≥ 40 years-at least one positive reaction to baseline series)⁹ was calculated. Positive patch test reactions with current clinical/occupational relevance were further analyzed whether they were covered by the recently suggested European pediatric patch test series.

The verbal or written consent of patients aged 18 years and of the legal guardians for patients aged <18 years were taken prior to patch testing. Patch tests were performed with the extended European baseline series (n=300) and/or additional test series (n=130) such as hairdresser series or cosmetic series including preservatives and emulsifiers, if necessary. Our extended baseline patch test battery included palladium chloride 1-2% pet., 4,4'-diaminodiphenylmethane (MDA) 0.5% pet., oil of turpentine 10% pet., thimerosal 0.1% pet., mercury(II)amidochloride 1% pet., toluensulfonamide formaldehyde resin 10% pet., carbamix 1% pet. (changed to zinc diethyldithiocarbamate 1% after 2010), ethylenediamine dihydrochloride 1% pet., polyethylene glycol (PEG) 400 'as is', propylene glycol 5% pet. (between 1996 and 2013) and 30% aq. (since 2014). Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) was tested at 0.01% aq. between 1996-2014, and at 0.02% aq. in 2015 and later. Patients were additionally patch tested with MI 0.2% aq. in 2016 and later. The test allergens were obtained from Chemotechnique Diagnostics (Vellinge, Sweden), Brial Allergen (Greven, Germany), and Hal-Brial (Leiden, the Netherlands), and applied in IQ Chambers® (Chemotechnique Diagnostics) on the upper back for 48 hours. The same allergen concentrations were used as in adults. Primin was not tested in any patient. p-Phenylenediamine (PPD) was only tested if ACD from black henna and/or hair dye was suspected. In severe cases, the patch test concentration of PPD was diluted by 50% in petrolatum and was applied as open test as the first step.¹⁰ When testing with ammonium persulfate, open test was performed prior to patch testing to exclude immediate-type allergies

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in suspected cases. Patient's own materials such as leave-on cosmetics and topical medicaments were patch tested 'as is'. Shoes, rubber, leather and paper samples were tested in pieces of 2x2 cm, soaked in water, with an occlusion period of 72 hours. Rinse-off cosmetics and permanent wave solution were open tested at 1% aq. Patient's own materials were tested in serial dilutions or by repeated open application test (ROAT), if appropriate. Orthopedic cast powder was patch tested at 1% pet. Nickel release from metals was confirmed by the dimethylglyoxime test (Chemo Nickel Test, Chemotechnique Diagnostics), if necessary. The test areas were evaluated on days (D) D2, D3 and D4 in patients who were patch tested between 1996-2009, and additionally on D7 in patients who were tested in 2010 and later according to the ESCD guidelines.¹¹ The COADEx system was used for the assessment of the clinical relevance of the positive patch test reactions.³

IBM SPSS® Statistics Version 22 was used to store and analyse the data. Descriptive statistics were calculated as median, minimum and maximum values for continuous variables, and as frequency and percentage for categorical variables. The differences in the distribution of categorical variables between independent groups were assessed by the chi-square test or Fisher's exact test. A 2-tailed *P*-value less than .05 was considered statistically significant. The study was approved by the Ethical Committee of Istanbul University, Istanbul Faculty of Medicine (approval number: 2017/08) and conducted in accordance with the Declaration of Helsinki.

3. Results

The characteristic features of the patients are shown in Table 1.

3.1 Demographic features

Among 317 patch tested patients, 146 (46.1%) had one or more positive reactions. The male:female ratio of these 146 patients was 1:2.9. The age range was 1-18 years (median: 14 years), while 34 patients (23.3%) were <10 years old. Of 13 patients aged ≤3 years, 6 patients

had positive patch test reactions. The distribution of patients regarding their age at the time of patch testing was shown in Figure 1. Atopic dermatitis was present in 20 patients (13.7%) whereas 23 (15.8%) had atopic skin diathesis. The MOAHLFAP index in % was 25.3/10.3/13.7/24.0/0.7/16.4/0/74.

3.2 Patch test findings

The most frequent positive patch test allergens are shown in Table 2. Regarding our extended baseline series, nickel sulfate was the most frequent sensitizer (21.5%) showing concomitant positive reactions to palladium chloride and/or cobalt chloride, whereas patch testing with potassium dichromate was negative in all of the patients. Thimerosal came in the second range (14.8%), followed by PPD (8.4%), mercury(II)amidochloride (5.8%), MCI/MI (1.9%), fragrance mix I (1.3%), neomycin (1.3%), and colophonium (1%). Two of the patients with a positive patch test reaction to MCI/MI were also tested with MI, that was negative in both of them. Ammonium persulfate from the hairdresser series, tested only in selected patients (n=22) had a high share of sensitivity (31.8%) as well as metallic mercury (28.6%) from the metal series. In 28 patients, patch test positivity was observed with patient's own materials, while ROAT was positive in four of these patients with five products (Table 2).

Nickel and thimerosal were the leading allergens in almost all age groups, including the very young (≤ 3 years old) (Table 3). PPD and ammonium persulfate were positive exclusively in adolescents.

Nickel sensitivity was significantly more frequent among females ($P < .05$, odds ratio: 4.4; 95% confidence interval [CI]: 1.9-10.6), and in adolescents ($P < .05$, odds ratio: 2.6, 95% CI: 1.1-5.8). Atopic patients (patients with atopic dermatitis/atopic skin) were more frequently sensitized with nickel (55.8%) in comparison to non-atopic patients (42.7%), however, the difference was statistically not significant. Similarly, patch test was positive in 46.7% (n=43/92) of the atopics, and in 45.8% (n=103/225) of the non-atopics.

3.3 Clinical relevance

Among 317 patients, ACD was diagnosed in 98 (30.9%) according to confirmed current clinical relevance (CCR) of positive patch test reactions (Table 1). Interestingly, among 6 patients aged ≤ 3 years with a positive patch test reaction, 5 were found to have CCR, mainly to nickel. The allergen with the highest rate of CCR was MCI/MI (100%) mainly from rinse-off cosmetics (shampoos, n=4) or leave-on cosmetics (wet wipe, n=1, and hair wax, n=1), followed by PPD (90.5%) from hair dye (n=16) or black henna (n=3), ammonium persulfate (85.7%) from hair bleach (n=6), fragrance mix I (75%) from cosmetics/household products (n=3), and nickel sulfate (57.4%) mainly from metal jewelry and clothing accessories (n=24) (Figure 2a-b) (Table 2). The CCR rates of mercury(II)amidochloride and metallic mercury were 40% and 50%, respectively. None of the patients developed ACD due to thimerosal (Table 2 and 4) (Figure 3). Thimerosal showed past clinical relevance in two patients who had developed eczematous reaction at the vaccination site in the past (Table 4).

Eight of 20 patients with atopic dermatitis had ACD. Nickel sulfate was the leading causative agent (n=5), followed by tin chloride in clothing accessories (n=1), nitrofurazone-PEG in a topical antibacterial ointment (n=1), and lavender oil in a moisturizer (n=1). Of these, two patients with systemic allergic dermatitis from nickel-rich diet and one patient with ACD from a moisturizer containing lavender oil presented with widespread lesions which healed after avoiding the relevant allergens.

ACD was predominantly located on hands (n=35). Systemic allergic dermatitis (n=11) presented with dietary nickel-induced dyshidrotic hand&foot eczema (n=4) as well as nummular (n=2), and papular/follicular eczema (n=2), and Baboon syndrome (n=3). The latter was observed due to the inhalation of metallic mercury vapour from broken thermometer in children primarily sensitized with mercury(II)amidochloride through umbilical cord antisepsis (Figure 2c-d) (Table 5). Positive patch test reaction with nickel induced a flare of eczema in

two of these patients, one in the form of dyshidrotic hand dermatitis and one as generalized dermatitis, which was a supporting finding for the CCR as well.

3.4 Occupational relevance

Occupational ACD was diagnosed in 15 patients (Table 1) which comprised 15.3% of patients with ACD. Most of the patients with occupational ACD were hairdresser apprentices (n=13) with relevant sensitizations mainly to PPD (n=11), six of them with additional sensitization to ammonium persulfate in hair bleach. Although the primary sensitizer was black henna tattoo in 10 of the 21 patients with positive patch test reaction to PPD, hairdresser apprentices were primarily sensitized with PPD through hair dyes (n=9), and only rarely through black henna tattoos (n=2). Occupational ACD was additionally diagnosed in a cleaning worker from fragrances in a detergent (n=1), and a shoe painter (n=1) from shoe dye. All of the patients with occupational ACD had hand eczema whereas additional airborne ACD was observed in a hairdresser apprentice from ammonium persulfate in hair bleach dust (Table 5).

3.5 Time trends

When compared in two consecutive 10 year periods (1996-2006 and 2007-2017), the number of patients with MCI/MI-induced ACD increased to 5-fold, whereas ACD from ammonium persulfate and mercurial compounds increased to 2-fold and PPD to 1.7-fold after 2007.

Interestingly, nickel-and fragrance mix I-induced ACD decreased by 50% after 2007 (Table 2) (Figure 4).

3.6 Diagnostic patch test series

ACD was diagnosed in 73.5% of the patients by testing with the extended European baseline series alone, with patient's own material (topical drugs, cosmetics, permanent wave solution, shoe dye, orthopedic cast powder) in 11.2%, with the extended baseline series + additional series in 10.2%, and with additional series in 5.1% (Figure 5).

3.7 The diagnostic value of the recommended pediatric patch test allergens

The recommended European pediatric baseline patch test series and additional allergens (Table 6) could successfully identify ACD in 63.2% of our patients (Figure 6). The diagnosis of ACD would not have been established in 28.6% of the patients by testing with the recommended allergens only (Figure 6).

4. Discussion

Reports on pediatric patch test results are increasing worldwide. However, there are difficulties in comparing the results mainly because of variations in the selection criteria of the patients such as age groups, allergen exposure in different geographical regions, allergens chosen for patch testing, and the patch test methodology.¹ Therefore, some methodologic changes and baseline series were suggested for patch testing in the pediatric age group.³⁻⁶ A limited number of allergens were recommended to be tested due to the smaller body surface areas of pediatric patients and the risk of active sensitization.⁶ The same test concentration and a 48-hour occlusion time as in adults were generally accepted,³ while some authors suggested a 24-hour occlusion time.⁶ PPD was recommended to be tested only in suspected cases, and after diluting the original test concentration by 50%.^{3,6}

The reported contact sensitization rates among children varied between 24.5-69.3% in major European studies.^{14,15} In a multicenter analysis of patch test results of patients aged between 1-16 years from 11 European countries between 2002–2010, patch test positivity rate was reported as 36.9%.¹⁶ In our study, the patch test positivity rate was 46.1% that was similar¹⁷ or a little higher¹⁸ than the previously reported rates in Turkish patients from similar age groups. The high sensitization rate in our study might be due to lack of regulatory legislations in our country (use of mercurial antiseptics and thermometers containing mercury until recently, the currently allowed level of 100 ppm for MI in rinse-off cosmetics, and the lack of regulatory directives for nickel-containing jewelry) or due to the high positivity rates of some major allergen groups. For instance, mercurial compounds (other than thimerosal), a major allergen

group in our study, have not been mentioned in the studies reported from European countries, except Spain¹⁹. Moreover, the majority of the positive patch test reactions to PPD in our series was related to occupational ACD from hair dyes in hairdresser apprentices, while PPD sensitization was mainly related to non-occupational contact with black henna in Europe.^{14,19,20}

Atopic dermatitis is a major point of attention in pediatric ACD. There is no consensus on the role of atopic dermatitis in ACD as a risk factor and there are conflicting data in the literature.²¹ Atopic dermatitis was proposed to contribute to the development of contact sensitization due to increased allergen penetration from impaired skin barrier and frequently used moisturizers with various potentially allergenic ingredients.^{1,22} On the other hand, there is a counter-argument that the use of moisturizers would support the enhancement of the epidermal barrier, and prevent allergen penetrance.²³

Some recent studies showed similar sensitization rates among atopic and non-atopic pediatric patients,^{24,25} while metals and fragrances were among the remarkable allergen groups in atopic patients,²⁴ which was in line with our findings. The high rate of nickel sensitization in atopic individuals was found to be related to filaggrin mutation.^{26,27}

Distinguishing between questionable/weak positive and irritant reactions may be a problem in the pediatric age group, especially among atopics as the atopic skin is more prone to irritant reactions.³ Two questionable patch test reactions to nickel sulfate and lavender oil with confirmed CCR were detected in our patients with atopic dermatitis, further underlining the importance of interpreting the clinical relevance.

Nickel was the leading allergen in most of the studies^{2,28} as well as in the present study. The prevalence of nickel-induced ACD among pediatric patients varied between 6.8%-80.4% in the literature.^{29,30} In the present series, nickel-induced ACD (mainly due to metal jewelry and clothing accessories) was diagnosed in 57.4% of patients with nickel sensitization whereas

20.6% had past clinical relevance (Table 4). Alternative nickel sources reported in the literature such as coins, dental braces and nickel-containing cosmetics²¹ were also found to be culprit allergen sources in some of our patients. Consistent with previous reports,^{14,28} girls were significantly more frequently sensitized with nickel which was mainly related to ear piercing in early childhood in our study. Cobalt was reported as a frequent metal allergen in the literature and it was mainly associated with nickel sensitization in pediatric patients^{2,28}, whereas it was also reported to cause ACD from leather items such as shoes.²⁵ In the present study, however, cobalt positivity was exclusively related to coupled exposure of cobalt with nickel in metals.

Similar to our findings, thimerosal, fragrance mix I, neomycin, PPD, MCI/MI, colophonium, cobalt, wool alcohols and rubber allergens were the mainly reported allergens in the pediatric age group in the literature.^{1,2,28} Potassium dichromate, thiuram mix and *Myroxylon pereirae*, other important allergens in pediatric patients,^{2,28} however, were not observed in our series. A higher share of sensitization to MCI/MI was observed (4.5-7.9%) in recent Turkish studies on pediatric patients^{17,31,32} conducted after 2011 in comparison to our results (1.9%).

Although the overall share of MCI/MI allergy was low in our series, the sensitizations were detected almost exclusively after 2007, corresponding to the increasing period of MCI/MI allergy in Turkey in accordance with the global epidemic.³³ Furthermore, MCI/MI-induced ACD increased to 5-fold in the second decade of our study. In contrast to a previous report from Turkey³⁴, none of the children had slime dermatitis resulting from a popular sort of play material prepared with household products that might contain MCI/MI.²¹

The overall prevalence of occupational ACD among adolescent patients was almost equal to those in adult patients (unpublished data). Hairdresser apprentices were the leading group. There was a strikingly high share of sensitivity (n=7/22, 31.8%) to ammonium persulfate in hairdresser apprentices which was only rarely mentioned in the literature regarding the same

age group.^{5,35,36} It usually accompanied PPD allergy³⁵, as was the case in the present series.

Occupational exposure was high to this hairdresser chemical in our study in accordance with the popularity of blonde hair among Turkish women. Ammonium persulfate was an important occupational allergen for pediatric patients including hairdresser apprentices in a previous study from Australia.⁵

Thimerosal, the contact (non)allergen of the year 2002,³⁷ was the second leading allergen in our series, without showing a CCR in any of the patients. Studies on pediatric patch testing showed similar high shares of sensitivity with a low clinical relevance rate.^{30,38,39} Thus, it was suggested to remove thimerosal from the screening trays.³⁷ Thimerosal is used as a preservative in eye/ear/nose drops and vaccines, mainly against tetanus or hepatitis B.^{37,40,41}

Children as well as adults are usually sensitized to thimerosal through vaccinations.^{30,37}

History of thimerosal-containing vaccinations was present in a majority of our patients, while thimerosal showed a past clinical relevance in two of them, presenting with ACD on the vaccination site. The inorganic mercurial compound mercury(II)amidochloride was an important allergen during our study period, mainly between 1997 and 2016, although its current relevance seems to be decreasing. Until recently, it has been used in Turkey for antiseptics of wounds, and especially of the umbilical cord in the neonates. The contact sensitization to this mercurial compound through umbilical cord antiseptics is still a valid history for many patients admitting to our allergy unit. Correspondingly, according to information gathered through patient history, umbilical cord antiseptics was the main route of sensitization with mercurial compounds in our series, whereas wound antiseptics was the eliciting factor for ACD in six of these patients.

Concomitant sensitization to nitrofurazone and PEG from topical nitrofurazone-containing preparations for wound care is still a major problem in Turkey. PEG, which is a widely used vehicle in topical medications enhances the penetration of nitrofurazone through the skin,

while nitrofurazone allergy facilitates contact sensitization to PEG in affected individuals.⁴²

Thus, PEG was reported to serve as a marker for nitrofurazone allergy in Turkey.⁴² In our series, the lesions of a patient with recalcitrant atopic dermatitis, using topical nitrofurazone-containing ointment for her wounds and additional PEG containing moisturizers were observed to heal significantly after identification of the culprit allergens.

Hands were the major involved site in patients with ACD in our series. Hairdresser chemicals (PPD± ammonium persulfate), nickel sulfate and MCI/MI were the main elicitors of hand eczema. Interestingly, more than one third of the patients with hand eczema were hairdresser apprentices who were occupationally sensitized mainly with PPD and/or ammonium persulfate, which was only rarely reported for pediatric patients.^{5,35,36} In a multicenter study from Spain conducted between 2005-2009 on pediatric patients with hand eczema, the most common clinically relevant allergen was MCI/MI, followed by fragrance mix I and nickel sulfate.⁴³ In another report, nickel was the leading relevant allergen in pediatric patients with ACD on hands.⁴⁴

Persistent foot eczema in the pediatric population may be associated with ACD to footwear.³ Mercapto derivatives and potassium dichromate were the leading allergens,^{15,19,44-47} followed by PPD, nickel, p-tert-butylphenol-formaldehyde resin and thiuram derivatives.^{30,44-46} ACD on foot was detected in two patients in our series with only one of them sensitized to mercapto derivatives in her rubber sports shoes. (Figure 2e-f)

Face/periorbital ACD was mainly induced by PPD in hair dyes in the present study, presenting with eczema along the hairline and angioedema-like periorbital edema that is a well-known phenomenon for PPD allergy. One patient had airborne ACD from henna stone powder, as described previously.¹² Topical drugs and moisturizers were other frequent causes of ACD on the face. Ectopic eyelid eczema in our series was observed in patients using toluensulfonamide formaldehyde resin-containing nail varnish for cosmetic purpose as was in

line with previous reports,^{30,48} or rarely against nail-biting.⁴⁹ Besides, metal contact sites might be hidden localizations for toluensulfonamide formaldehyde resin allergy since patients with metal allergy might use nail varnish for coating metal jewelry.⁵⁰

Systemic allergic dermatitis from dietary ingestion of nickel was occasionally reported among children, presenting with generalized eczema,^{51,52} or dyshidrotic hand/foot eczema, the latter being the main type in our series. The nickel-rich diet was very prominent in these patients who were consuming considerable amounts of iced tea, chocolate, canned food, nuts, and in particular, tap water. Baboon syndrome through inhalation of metallic mercury vapour from a broken thermometer was another important presentation of systemic allergic dermatitis in our study. Even though thermometers containing mercury have not been sold in pharmacies for the last 10 years in our country, it is still present in many houses. It was observed in children primarily sensitized with mercury(II)amidochloride through umbilical cord antisepsis in the past. Systemic allergic dermatitis had regressed after removal of the mercury vapour source from childrens' environment. This systemic allergic dermatitis occurred only once and did not recur after cessation of the exposure. According to our observations, some children find mercury droplets exciting and play with them once a thermometer is broken. A similar case of Baboon syndrome was previously reported.⁵³

Several exposures related to school and fun activities were identified in the literature with nickel (in musical instruments, toys and electronic devices such as mobile phones, tablets), MCI/MI (in slime), compositae mix (in flowers), PPD (in temporary black henna tattoos), rubber allergens and thiourea derivatives (in protective shin guards used in sports activities).^{1,21} In our series, PPD allergy was diagnosed in three cases due to temporary black henna tattoo which has been gaining popularity among children and adolescents in our country in the recent years. Another allergen, N-isopropyl-N-phenyl-4-phenylenediamine has been detected in a child suffering from palmar hyperhidrosis as the culprit allergen for hand

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eczema due to prolonged contact with bicycle grip.¹³ Mercury (exposed from a broken thermometer used in the science laboratory and caused Baboon syndrome) and colophonium (found in glues that had been used in school activities related to hand eczema in the past) were two school activity related allergens detected in our series.

The rising trend in the number of ACD from MCI/MI and hairdresser chemicals (ammonium persulfate and PPD) after 2007 was striking in the present study. The increase of MCI/MI allergy to 5-fold was consistent with the global epidemic of isothiazolinone allergy that affected Turkey as well.³³ It was mainly presented with non-occupational ACD from rinse-off cosmetics. The majority of PPD allergy was related with occupational ACD in adolescents who were primarily sensitized with PPD through hair dyes. However, the increase of PPD-induced ACD after 2007 was mainly related to non-occupational contact with black henna tattoos or hair dyes. Similar to our recent findings, the share of non-occupational PPD sensitization among children increased to two-fold in the United Kingdom during 2005-2014 when compared with the period of 1995-2004.²⁰

Testing with the extended European baseline series could successfully diagnose ACD in a majority of our patients, however, more than one-fourth of the patients would have been missed without testing with additional series/patient's own materials. Similarly, previous studies on pediatric patch testing showed that a remarkable number of patients with ACD would not be identified without testing with the additional series, and patient's own materials such as cosmetics and healthcare products.^{19,54,55}

Regarding the smaller size of the patch test area in children in comparison to adults and potential active sensitization risk with various irrelevant allergens,^{3,6} the suggested pediatric baseline series and additionally suggested allergens by EAACI³ appear concise and practical. However, according to our results, almost 1/3 of patients would be missed by testing only with the recommended allergens. Therefore, the recommended European list of allergens

warrants a modification for the Turkish child and adolescent population. We would suggest to include ammonium persulfate (for adolescents), mercury/mercury(II)amidochloride, toluenesulfonamide formaldehyde resin, and PEG as an indicator of nitrofurazone allergy in Turkey,⁴² to the additional list of recommended allergens for child and adolescent patients, to be selectively tested only in patients with suspected ACD from these allergens. Testing with the patient's own materials seems also to be essential to make a correct diagnosis of ACD. The main limitation of our study was its retrospective nature. On the other hand, the fact that the study was conducted in a single-center over a long period, the evaluation of the patch test results by the same observer team preventing interobserver variability, and the use of standardized forms for documenting the results were the main strengths of this study.

5. Conclusion

Standardization of a pediatric patch test series is more difficult than it seems. A remarkable number of the relevant allergens in our study were not covered by the recommended European pediatric patch test series. Non-occupational ACD from mercury compounds and occupational ACD from hairdresser allergens were common. As recently suggested,³ it seems reasonable to extend the recommended list of allergens according to history, clinical findings, and exposure patterns in a given geographic region. For patch testing in Turkish children and adolescents, we would suggest ammonium persulfate, mercury/mercury(II)amidochloride, toluenesulfonamide formaldehyde resin, and PEG, the latter mainly as a marker for nitrofurazone allergy, to be tested in selected patients.

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Table 1. Characteristic features of child and adolescent patients with positive patch test reaction between 1996 and 2017 (n=146)

Patient characteristics	Patients with positive patch test reactions
Gender (male:female)	37:109 (1:2.9)
Age (years)	1-18 (median: 14) (34 patients aged <10 years old, 112 patients aged 10-18 years old)
	Atopic skin (n=23), atopic dermatitis (n=20)
[†] Overall prevalence of sensitization	46.1% (146/317)
Degree of patch test reactions	?+ (n=22), + (n=95), ++ (n=156), +++ (n=86)
Current clinical relevance of ?+ reactions	2/22 (nickel sulfate and lavender oil) [‡]
Patients diagnosed with ACD	30.9% (98/317)
Duration of eczema	40 weeks (range: 1 day - 884 weeks)
Anatomic localization of patients with ACD [§] (see also Table 5)	Hands (n=35), metal contact sites (n=32), face/periorbital (n=24), topical drug contact sites (n=15), generalized (n=11), feet (n=4), temporary tattoo sites (n=3), other sites (n=3)
Non-occupational ACD / male:female ratio / age / atopy	84.7% (83/98) / 1:3.4 / 2-18 years (median: 13 years) / atopic skin (n=11), atopic dermatitis (n=8)
Relevant non-occupational allergen/material	see Table 5
Occupational ACD / male:female ratio / age / atopy	15.3% (15/98) / 1:1.1 / 14-18 years (median: 17 years) / atopic skin (n=2)
Relevant occupational allergen/material for	
• Hairdresser apprentices (n=13)	p-Phenylenediamine (n=11) ± ammonium persulfate (n=6) ± fragrance mix I-II (n=1), MCI/MI (n=1) in hair wax, permanent wave (n=1)
• Shoe painter (n=1)	Shoe dye (n=1)
• Cleaning worker (n=1)	Fragrance mix I (n=1) in detergents
MOAHLFAP	25.3/10.3/13.7/24.0/0.7/16.4/0/74

ACD: allergic contact dermatitis, MCI/MI: methylchloroisothiazolinone/methylisothiazolinone, MOAHLFAP: Male-occupational dermatitis-atopic dermatitis-hand eczema-leg eczema-face eczema-age ≥40 years-at least one positive reaction to baseline series

[†]number of patients with positive patch test reaction/number of patients who were patch tested

[‡]observed in patients with atopic dermatitis

[§] The total number of localizations are >98 as some patients presented with more than one involved site.

Table 2. The most frequent positive and current relevant allergens in the study group

Allergen	Rate of sensitization in % (n _{positive} /n _{tested})	Rate of current clinical relevance in % (n _{current relevant} /n _{positive})	Current relevant reactions between 1996-2006 n	Current relevant reactions between 2007-2017 n
From the extended baseline series				
Nickel sulfate 5% pet. /	21.5 (68/317) /	57.4 (39/68)	26	13
palladium chloride 1-2% pet. /	9.5 (30/317) /	/ 63.3 (19/30)	/ 15	/ 4
cobalt chloride 1% pet.	1.6 (5/317)	/ 60 (3/5)	/ 2	/ 1
Thimerosal 0.1% pet.	14.8 (40/270)	0 (0/40)	0	0
†p-Phenylenediamine 1% pet.	8.4 (21/251)	90.5 (19/21)	7	12
Mercury(II)amidochloride 1% pet.	5.8 (15/261)	40 (6/15)	3	3
‡MCI/MI	1.9 (6/317)	100 (6/6)	1	5
Fragrance mix I 8% pet.	1.3 (4/317)	75 (3/4)	2	1
Neomycin 20% pet.	1.3 (4/317)	25 (1/4)	0	1
Colophonium 20% pet.	1.0 (3/317)	33.3 (1/3)	0	1
From additional series				
Ammonium persulfate 2.5% pet.	31.8 (7/22)	85.7 (6/7)	2	4
Metallic mercury 0.5% pet.	28.6 (6/21)	50 (3/6)	0	3
Patient's own materials¶	20.3 (28/138)	100 (28/28)	10	18

MCI/MI: methylchloroisothiazolinone/methylisothiazolinone

† tested as 0.5% pet. in four patients (with open test technique in two of them)

‡ tested as 0.01% aq. between 1996-2014 and 0.02% aq. between 2015-2017

¶ Repeated open application test was positive in four patients with five products, i.e. topical drug (n=2) and moisturizer cream (n=3).

Table 3. The most frequent positive allergens in different age groups

≥ 10 years (n)	< 10 years [†] (n)	≤ 3 years (n)
Nickel sulfate (58)	Thimerosal (14)	Nickel sulfate (4)
Thimerosal (26)	Nickel sulfate (10)	
p-Phenylenediamine (21)	Mercury(II)amidochloride (5)	
Mercury(II)amidochloride (10)	MCI/MI (2)	
Ammonium persulfate (7)	Metallic mercury (1)	
Metallic mercury (5)		
MCI/MI (4)		

MCI/MI: methylchloroisothiazolinone/methylisothiazolinone

[†]including patients aged ≤ 3 years

Table 4. The distribution of the most frequently positive allergens according to COADEx system³

Allergen	Number of positive reactions, n	C <i>current</i>	O <i>old</i>	A <i>active sensitization</i>	D <i>doubtful</i>	E <i>exposed</i>	X <i>cross-reaction</i>
From the extended baseline series							
Nickel sulfate /	68	39	14	0	4	11	0
potassium dichromate /	30	19	6	0	0	5	0
cobalt chloride	5	3	1	0	0	1	0
Thimerosal	40	0	2	0	0	25	13
p-Phenylenediamine	21	19	1	0	0	0	1
Mercury(II)amidochloride	15	6	0	0	0	7	2
MCI/MI	6	6	0	0	0	0	0
Fragrance mix I	4	3	0	0	1	0	0
Neomycin	4	1	0	0	3	0	0
Colophonium	3	1	2	0	0	0	0
From additional series							
Ammonium persulfate	7	6	0	0	1	0	0
Metallic mercury	6	3	1	0	0	0	2

MCI/MI: methylchloroisothiazolinone/methylisothiazolinone

Table 5. The localizations of allergic contact dermatitis (n=98) in relation with the culprit allergens and allergen sources (occupational sources are highlighted in bold)

Localization	†No. of patients (%)	Culprit allergen (n)	Allergen source (n)
Hands	35 (35.7)	p-Phenylenediamine (12) ± ammonium persulfate (6) ± fragrance mix I (1) ± fragrance mix II (1)	Hair dye (11) ± hair bleaching powder (6) ± eau de cologne (1) Henna stone powder ¹² (1)
		Nickel sulfate (10)	Prolonged contact of hands with metals (keyholder, chain, coin) (4) Metal jewelry (2) Dietary ingestion (4) as part of systemic allergic dermatitis (dyshidrotic hand±foot eczema)
		Methylchloroisothiazolinone/methylisothiazolinone (6)	Rinse-off cosmetics (shampoo) (4) Hair wax (1) Wet wipe (1)
		Patient's own material (2)	Shoe dye (1) Permanent wave (1)
		Formaldehyde (1)	Rinse-off cosmetic (liquid soap) (1)
		Toluenesulfonamide formaldehyde resin (1)	Nail varnish (1)
		Mercury(II)amidochloride (1)	Mercurial antiseptic (1)
		Fragrance mix I (1)	Cleaning detergent (1)
		n-Isopropyl-n-phenyl-4-phenylenediamine (1)	Bicycle handgrip ¹³ (1)
Metal contact sites	32 (32.7)	Nickel sulfate (30)	Metal jewelry (19) (mainly earlobe) Clothing accessories (5) Metal goods (keyholder, chain, coin) (4) Eyeglass frame (1) Dental brace (1)
		Copper sulfate (1)	External fixator on the leg (1)
		Tin chloride (1)	Clothing accessories (1)
Face / periorbital	24 (24.5)	p-Phenylenediamine (7)	Hair dye (5) Black henna (1) Henna stone powder ¹² (1) (airborne eczema)
		Patient's own material (7)	Topical drug (4) Leave-on cosmetics (moisturizer cream) (3)
		Methylchloroisothiazolinone/methylisothiazolinone (2)	Rinse-off cosmetic (shampoo) (1) Wet wipe (1)
		Toluenesulfonamide formaldehyde resin (2)	Nail varnish (2) (ectopic eyelid eczema)
		Nickel sulfate (2)	Eyeglass frame (1) Leave-on cosmetic (eyeliner) (1)
		Colophonium (1)	Wound plaster (1)
		Neomycin + bacitracin (1)	Topical drug (1)
		Fragrance mix I (1)	Leave-on cosmetic (rose water) (1)
		Ammonium persulfate (1)	Hair bleaching powder (1) (airborne eczema)
Topical drug contact sites	15 (15.3)	Mercury(II)amidochloride (6)	Mercurial antiseptic (6)
		Patient's own material (5)	Topical drug (ointment, eye drop) (5)
		Nitrofurazone (2) ± polyethylene glycol (1)	Topical drug (2)
		Neomycin+bacitracin (1)	Topical drug (1)
		Wool alcohols (1)	Topical drug (1)
		Nickel sulfate (4) • generalized papular/follicular eczema (2) • generalized nummular eczema (2)	Dietary ingestion (4) as part of systemic allergic dermatitis
Generalized	11 (11.2)	Metallic mercury vapour (3) • Baboon syndrome (3)	Broken thermometer (3) as part of systemic allergic dermatitis
		Mercury(II)amidochloride (1)	Mercurial antiseptic (1) (generalized from a primary contact area)

		Patient's own material (1)	Moisturizer (1) (generalized from a primary contact area)
		Lavender oil (1)	Moisturizer (1) (generalized from a primary contact area)
		Paraben (1)	Rinse-off cosmetic (shampoo) (1) (generalized from a primary contact area)
		Wool alcohols (1)	Topical drug (1)
Feet	4 (4.1)	Mercapto mix and mercaptobenzothiazole (1)	Rubber sports shoes (1)
		Nickel sulfate (2)	Dietary ingestion (2) as part of systemic allergic dermatitis (dyshidrotic hand±foot eczema)
Temporary tattoo sites	3 (3.1)	p-Phenylenediamine (3)	Black henna (3)
Other sites	3 (3.1)	Colophonium (1)	Wound plaster (1)
		Patient's own material (1)	‡Orthopedic cast on the arm (1)
		Copper sulfate (1)	External fixator on the leg (1)

†The total number of localizations are >98 as some patients presented with more than one involved site.

‡Benzalkonium chloride was negative in this patient.

Table 6. Lists of allergens recommended by EAACI position paper (Number of allergens with current clinical relevance in our study group are shown in parenthesis, and the relevant allergens are highlighted in bold) [adapted from reference de Waard-van der Spek FB et al. (2015)]³

Recommended allergens for baseline pediatric patch test series	Recommended allergens for additional testing	Clinical/occupational relevant allergens in the present series not covered by the recommended list
Nickel sulfate (39)	p-tert-butylphenol formaldehyde resin	Ammonium persulfate (6)
Thiuram mix	Potassium dichromate	Mercury(II)amidochloride (6)
Colophonium (1)	Wool alcohols (1)	Metallic mercury (3)
Mercaptobenzothiazole (1)	p-Phenylenediamine (19)	Nitrofurazone (2)
Fragrance mix I (3)	Disperse blue 106	Toluenesulfonamide formaldehyde resin (2)
Fragrance mix II (1)	Tixocortol pivalate	Polyethylene glycol (1)
Mercapto mix (1)	Budesonide	Formaldehyde (1)
Methylchloroisothiazolinone/	Bufexamac	n-Isopropyl-n-phenyl-4-phenylenediamine (1)
methylisothiazolinone (6)	Neomycin (1)	Copper sulfate (1)
Sesquiterpene lactone mix	Dibromodicyanobutane	Tin chloride (1)
	Compositae mix	Bacitracin (1)
	Lyrall®	Lavender oil (1)
		Paraben (1)

Figure legends

Figure 1. The distribution of patients regarding their age at the time of patch testing.

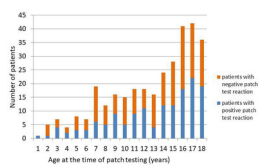
Figure 2. (A) Nickel-induced allergic contact dermatitis (ACD) in a girl at the contact site of the metal part of her bra, **(B)** ++ positive patch test reaction to nickel sulfate (5% pet.) on day 3, **(C)** Baboon syndrome in a girl induced by the inhalation of metallic mercury vapour from a broken thermometer, **(D)** strong positive patch test reactions to thimerosal (0.1% pet.) (cross allergen), metallic mercury (0.5% pet.) (current allergen), and mercury(II)amidochloride/ammoniated mercury (1% pet.) (cross allergen and the primary sensitizer through umbilical cord antiseptics) on day 2, **(E)** ACD on the plantar surfaces of the feet in a girl from rubber sports shoes, **(F)** ++ positive patch test reactions to rubber additives mercapto mix (2% pet.) and 2-mercaptobenzothiazole (2% pet.) on day 3.

Figure 3. The most frequently diagnosed allergens in the study group (grey bars) and their current clinical relevance (orange bars).

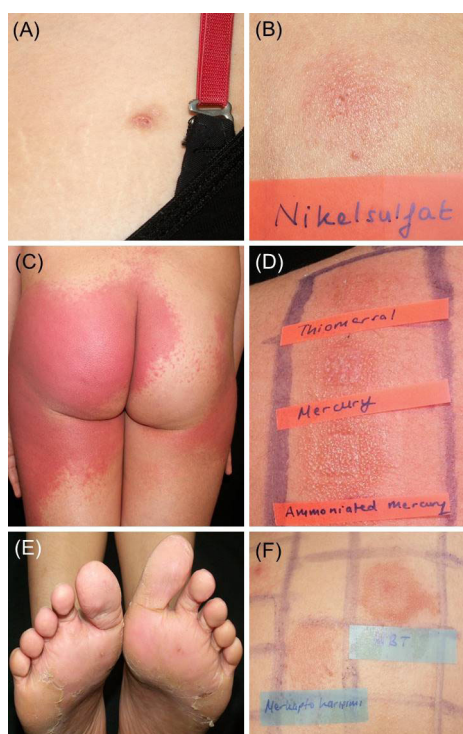
Figure 4. Distribution of patients with allergic contact dermatitis to major allergens between 1996-2006 and 2007-2017.

Figure 5. The distribution of the diagnostic patch test series/material in child and adolescent patients with allergic contact dermatitis.

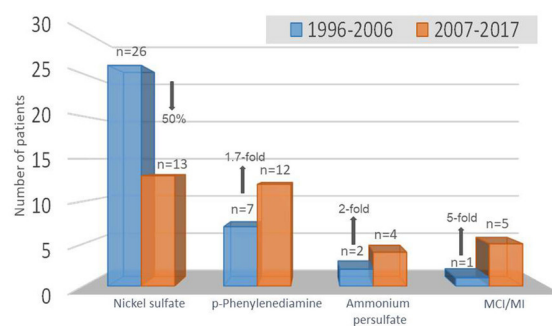
Figure 6. The diagnostic value of the recommended pediatric patch test allergens.



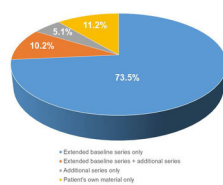
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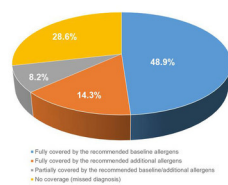
COD_13842_Figure 2.jpg



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COD_13842_Figure 5.jpg



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