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Contact allergy in a pediatric population observed in a tertiary referral center in Belgium

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Disclosures

The authors declare no conflict of interests.

Running head

contact allergy in children

Summary

Background: Contact allergy is increasingly recognized as being important in children with eczema.

Objectives: To retrospectively analyze the patch-test results in them over the past 10 years, aiming to (i) evaluate demographic characteristics and lesion locations, (ii) describe frequencies of positive patch-test reactions, and (iii) investigate the relationship with atopic dermatitis (AD).

Patients and methods: 329 children were patch tested between January 2010 and December 2019 with the European (children) baseline series and/or other series, and the personal product(s) used.

Results: 119 (36%) children presented with at least one positive reaction. Children with AD had a higher prevalence of positive reactions compared to the non-AD group ($P = .002$), but without statistically

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significant difference regarding sensitization to more than one hapten ($P = .39$). The face (20.2%), hands (19.3%), feet (16.8%), arms (12.6%), and body folds (10.9%) were the most common primary localizations. The most frequent contact allergens were nickel sulfate and linalool hydroperoxide (both 16%), limonene hydroperoxide (13.5%), and para-phenylenediamine (10.9%). No statistically significant difference for nickel sulfate was found between the AD and non-AD group ($P = .20$).

Conclusions: Contact allergy in children with eczema was frequently observed in our tertiary referral center in Belgium as well, confirming the need for patch testing.

Key words

Allergic contact dermatitis; contact allergy; children; pediatric; patch testing; atopic dermatitis

1. Introduction

Data from the past decades indicate that contact allergy is highly relevant in the pediatric population, contrary to what previously was assumed (1), however, the exact incidence and prevalence of which are still unknown since research on this topic is limited. When interpreting the published data, it is important to consider whether it concerns a selected population (as described below), for which patch testing is performed because there is suspicion of allergic contact dermatitis (ACD), or a general (unselected) population, the latter for which even a point prevalence of contact allergy of 13.3-23.3% was reported (2). Conflicting data have been reported about the role of contact allergy in children with atopic dermatitis (AD) in selected populations. Indeed, there is uncertainty about a possible discrepancy in prevalence and variations in the most common allergens in children with or without AD (3–8). For instance, some publications suggest that patients with AD who have function mutations in the gene encoding filaggrin are predisposed to develop sensitization to nickel, in particular (9,10). A recent case-control study has indicated that contact allergens show age-specific patterns (11), which is due to variations in specific exposures to sensitizers. Small children are not often referred for patch testing, have a smaller patch-test area; moreover, many parents are reluctant to it (12,13). Further investigation of contact allergy and ACD in the pediatric population is necessary though to perform more accurate testing in the future.

This study involves a retrospective analysis of the data obtained during the past 10 years in our tertiary referral center regarding children suffering from dermatitis and suspected of having ACD. These results have been collected from an extensive standardized database containing demographic data, patch-test results, and corresponding sensitization sources, which creates a unique and privileged position to (i) evaluate demographic characteristics and lesion locations, (ii) describe frequencies of positive patch-test reactions, and (iii) investigate the relationship with AD.

2. Methods

All data were retrieved from, and evaluated with, a patient database developed in-house in the Contact Allergy Unit of the University Hospitals of Leuven (14). This database contains socio-demographic variables and results of all contact allergy investigations for patients suspected of ACD, or with other diseases such as irritant dermatitis, or other forms of eczema for which an allergenic cause needed to be excluded. Atopic constitution was defined as AD and/or asthma and/or rhinitis. The AD subgroup consists of patients with clinically confirmed atopic eczema. During the 10-years' period from January 1st, 2010 until December 31st, 2019, 5258 patients presenting with an eczematous dermatosis were patch tested with an extended European baseline series (i.e. with Belgian additions) and/or other series, the products used, and, whenever possible, also the respective ingredients; 329 of them, i.e., 6.3 %, were children (aged below 18 years). Only when the size of the child's back did not allow to test with the extended European baseline series, a modified 'children' baseline series was used (**Supplemental Table S1**). The test substances were obtained from Trolab Allergens (previously Almirall Hermal GmbH, Reinbek, Germany; currently SmartPractice Europe, Barsbüttel, Germany), and/or Chemotechnique Diagnostics (Vellinge, Sweden), or self-prepared *lege artis* according to the concentrations proposed by De Groot (15), and stored at 4°C. The patch tests were applied on the patient's back with Van der Bend patch test chambers (Van der Bend, Brielle, the Netherlands) applied to Micropore® (3M Health Care, Borken, Germany), later with IQ Ultra chambers (Chemotechnique Diagnostics, Vellinge, Sweden); they were fixed initially with Fixomull® (Beiersdorf, Hamburg, Germany) and later with Mefix® (Mölnlycke Health Care, Göteborg, Sweden). The patch-test readings were performed according to the international guidelines by the European Society of Contact Dermatitis (16) at 2, 3 (exceptionally), and 4 days, and often also later. A +, ++ or +++ reaction at either reading was recorded as an allergic patch-test reaction; an irritant, doubtful, or no response was recorded as a negative result. Patients with at least one positive patch test were considered for further analysis. To study the statistical significance of differences in the characteristics and test results, the data were presented in 2x2 contingency tables and analyzed using the Chi-square test in an Excel (Microsoft) spreadsheet, with *P*-values ≤ .05 considered to be significant. The study was approved by the ethical research committee of our hospital.

3. Results

Among the 329 children investigated for contact allergy, 136 (41%) were boys and 193 (59%) were girls, with a mean age of 10.9, with 119 (36%) of them showing a positive reaction to at least one of the allergens tested, i.e., 42 (35%) boys and 77 (65%) girls. The median and mean age were both 8.5 years. 75 children were sensitized to more than 1 hapten, with 48 of them having at least three positive

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reactions and one child presenting with 13 positive patch tests, the mean number per patient being 2.8. When dividing this pediatric population into 6 age categories, the highest percentage (41.7%) of positive tests was observed in the age group from 9 to 11 years, and the lowest (17.1%) in children from 3 to 5 years old, as illustrated in **Table 1**. The number of boys and girls with a positive patch test within each age group was very similar, except for the 15–17-year-olds, for whom a predominance of girls was noted due to the higher total number of them in this age group tested. In the group with at least one positive test, 96 were tested with the extended European baseline series, 7 with the modified ‘children’ baseline series and 16 children were tested only with the products and their ingredients to which they had been exposed. 5 of the 7 children tested with the modified ‘children’ baseline series belonged to the 3 lowest age categories (and thus had an age under 9 years).

A total of 205 pediatric patients having an atopic constitution were tested, of whom 179 suffered from AD. Among the latter patient group 78 presented with at least 1 positive patch test (**Table 1**). Significantly more children with AD had a positive test than those without ($P = .002$). Of the 75 children with sensitization to more than 1 hapten, 47 suffered from AD, for whom no statistically significant difference in sensitization to more than 1 hapten versus those without AD was observed ($P = .39$).

The top 5 most frequent primary locations were the face (20.2%), hands (19.3%), feet (16.8%), arms (12.6%), and body folds (10.9%) (**Figure 1**), with some of the children showing multiple lesion locations. The ten most frequent contact allergens identified were nickel sulfate and linalool hydroperoxide (HP) (both 16%), limonene hydroperoxide (13.5%), para-phenylenediamine (PPD) (10.9%), cobalt chloride (9.2%), rosin/colophony (8.4%), textile dye mix (7.6%), fragrance mix (6.7%), and potassium dichromate, sodium tetrachloropalladate (palladium, cross-reacting with nickel) and para-toluene diamine (PTD, cross-reacting with PPD) (all 5%). The 5 responses (4.2%) to isobornyl acrylate, i.e. in all of the 5 children with diabetes tested because of suspicion of ACD to glucose sensor or insulin pumps, were also remarkable (**Table 2**).

Within the age group up to, and including the 8-year-olds, the most common allergens were limonene hydroperoxide, nickel sulfate, and cobalt chloride (all three 11.5%). The top 4 most common allergens in the age group of 9 to 17 years old were linalool hydroperoxide (19.4%), nickel sulfate (17.2%), limonene hydroperoxide and para-phenylenediamine (14%).

In total, 19 positive tests were observed to nickel sulfate, 10 of which in children with AD but without statistically significant difference between the AD group and the non-AD group ($P = .20$).

Own material/products were tested 107 times, of which 34 reacted positively (31.7%), with 7 cases reacting to those only. An overview of the causal factors of the positive patch tests can be found in **Table 3**.

4. Discussion

Thirty-six % out of 329 children tested presented with a positive result to at least one allergen, which is consistent with the percentage, i.e. 36.9%, as reported in the ESSCA (European Surveillance System on Contact Allergies) Network study, in which data had been collected from 6008 pediatric patients with suspicion of AD observed in 11 different European countries (17). Other recent European studies show even higher rates in their selected patient population, i.e. 46.7% and 46%, respectively (3,18), while the prevalence rates in North America are even significantly higher (12,17,19). The mean age of our patch-tested children was 10.9, which is younger than reported in some other recent studies, i.e. 13.3 and 14.5 y, respectively (18,20).

A female predominance (ratio almost 2:1) was noted in children with a positive patch test, which confirms most previous studies (12). Within our study population, about half of the children were known with pre-existing AD (54.4%), a significant figure in contrast to other recent European studies (3,17,18). This high ratio can be explained by the fact that many children with refractory AD were referred for patch testing to investigate a contact-allergic component as a potential aggravating factor. Children with AD are more prone to come in contact with topical agents (emollients and topical medications), applied on an impaired skin barrier, which makes them more susceptible to skin penetration (18). (Of note, 17 children reacted positively to their own products used, i.e. 7 emollients and 10 topical medications, of whom 11, i.e. 4 and 7 within the group of children with AD, respectively). On the other hand, sensitization to more than 1 hapten was not higher than in non-atopic children.

The most frequent primary locations of ACD in our study group were roughly those body areas generally clinically suspected of ACD in children (21). On the other hand, it has already been shown that primary dermatitis sites in them cannot predict the diagnosis of ACD (22), therefore any child with persistent or atypical eczema should be referred for patch testing regardless the affected primary locations.

The 10 most frequent contact allergens observed in our population (**Table 2**) are consistent with the literature in this regard, being metals, fragrances, PPD, ingredients of topical pharmaceutical products and cosmetics, and *compositae* plants (12). Nickel sulfate is the most frequent reported allergen in children worldwide (21), despite the EU Nickel Directive since 2001 (23), possibly because of nickel-containing toys imported from non-European countries that do not have to comply with these restrictions (12). Co-sensitization to both nickel and cobalt occurred in 7 children, as frequently reported. Moreover, the prevalence of positive patch-test reactions to nickel sulfate was similar in both AD and non-AD children, hence, the proposed predisposition of children with AD, who have function mutations in filaggrin, to develop contact allergy to nickel sulfate could not be confirmed (9,10). Nickel sulphate frequently provokes pustular reactions especially on an eczematous skin, which however are not reproduced when repeated on intact skin and hence are irritant. It can thus be concluded that the relationship between AD and contact allergy remains dubious based on our results, but also according

to the current literature (2). Other frequent allergens were fragrances (fragrance mixes, linalool- and limonene HPs), being obviously omnipresent in the daily life of children. Frequent sources are perfumes, cosmetics even commercialised as toys, personal care products (including shampoo and (wet) wipes), essential oils, diffusers, scented candles, and incense (21,24).

Contact dermatitis due to PPD is common in teenagers (12), the main exposure sources being hair dyes and black henna tattoos (25). In our study group there were no children with a positive test to PPD under the age of 9 years, and for PTD not even under the age of 15. In Belgium hairdressing courses are organized from the third year of secondary school, which corresponds to the age at which we observed PPD positives, however, some of them may have been primarily sensitized at a younger age by black henna tattoos (12,25).

Finally, we would like to underline the high ranking of isobornyl acrylate in our study results, which is a relatively 'new kid on the block' within the contact allergens, being present in glucose sensors and insulin pumps. This allergen should therefore always be tested if ACD from a medical device is suspected in a child with diabetes (26).

5. Limitations of the study

Our study population consisted of a selected cohort from a tertiary referral patch test center, meaning only children suffering from dermatitis and/or suspected of having ACD were included. Moreover, the study population is rather small. Therefore, the findings have to be carefully interpreted and will need further confirmation in a bigger (prospective) study.

Given the retrospective nature of the study, we were not able nor allowed to investigate the relevances of all positive patch tests separately. However, whenever a clear relevance was obtained, the 'causal factor(s)' were registered for each patient.

6. Conclusion

To our knowledge, this is the first retrospective study of contact allergy in children from Belgium published, showing that it is a frequent phenomenon as well. Hence, patch testing should always be considered in children with atypical and/or recalcitrant eczema. Future continued data collection of ACD in children will allow us to identify relevant allergens and sensitization sources, so that these can be (preventively) avoided.

7. Tables

Table 1: Demographic characteristics of our pediatric study population

Characteristic	Number of children tested <i>n</i>			Number of children with ≥ 1 positive patch test <i>N (%)</i>		
Total	329			119		
Sex						
Female	193			77		
Male	136			42		
Age group (years)	Total	Female	Male	Total	Female	Male
0 to ≤ 2	28	10	18	10 (35.7%)	5	5
3 to ≤ 5	35	16	19	6 (17.1%)	3	3
6 to ≤ 8	32	16	16	10 (31.3%)	5	5
9 to ≤ 11	60	29	31	25 (41.7%)	11	14
12 to ≤ 14	65	38	27	25 (38.5%)	15	10
15 to ≤ 17	109	84	25	43 (39.4%)	38	5
Atopic constitution	205			103		
Atopic dermatitis	179			78		

n = absolute number

% = % of children with at least 1 positive patch test of the total number of children tested within this age category

Table 2: most common contact allergens in the study group

Most common contact allergens (tested positive ≥ 3)			n
Linalool hydroperoxide	1%	pet.	19
Nickel sulfate	5%	pet.	19
Limonene hydroperoxide	0.3%	pet.	16
Para-phenylenediamine	1%	pet.	13
Cobalt chloride	1%	pet.	11
Rosin/colophonium	20%	pet.	10
Textile dye mix	6.6%	pet.	9
Fragrance mix I	8%	pet.	8
Potassium dichromate	0.5%	pet.	6
Sodium tetrachloropalladate	2%	pet.	6
Para-toluene diamine	1%	pet.	6
Ammonium persulfate	2.5%	pet.	5

Isobornyl acrylate	1%	pet.	5
Fragrance mix II	14%	pet.	4
2-Ethylacrylate	1%	pet.	4
Sesquiterpene lactone mix	0.1%	pet.	4
Sodium metabisulphite	1%	pet.	3
Amerchol L 101	50%	pet.	3
Benzoyl peroxide	1%	pet.	3
Benzalkonium chloride	0.1%	aq.	3
Wool alcohols	30%	pet.	3
Propylene glycol	30%	aq.	3
Formaldehyde	1% (*2% from 2018 onwards)	aq.	3
Quaternium-15	1%	pet.	3
Methylisothiazolinone	0.05% (*0.2% from 2018 onwards)	aq.	3
Gold sodium thiosulfate	2%	pet.	3
Bromonitropropanediol	0.5%	pet.	3
Mercaptobenzothiazole	2%	pet.	3
Compositae mix	2.5%	pet.	3
Chloorhexidine acetate	0.5%	aq.	3

n = absolute number

pet. = in petrolatum

aq. = in aqua

Table 3: Overview of the causal factors of the positive patch tests

Causal factors	n
Cosmetics	39
Cross reaction	33
Textiles and accessories	28
Iatrogenic	27
Medical materials	8
Occupational	8
Hobbies	7
Concomitant	5

Plant/Flowers/Trees	3
Systemic medication	2
Airborne	2
Ectopic	2
Domestic work	2
Utensils	2
Industrial products	2
Protein	1

n = absolute number registered

8. Figure legends

Figure 1: lesion locations in our pediatric study group with at least one positive patch test

n = absolute number

9. Appendices

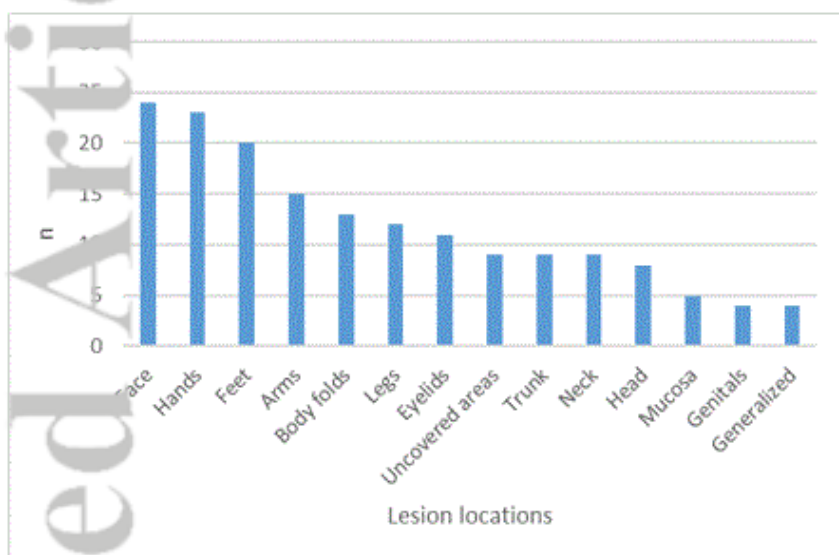
Supplemental Table S1: Modified 'children' baseline series, only used when the size of the child's back does not allow to test with the extended European baseline series.

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Supplemental Table S1. Modified ‘children’ baseline series, only used when the size of the child’s back does not allow to test with the extended European baseline series.

Potassium dichromate	0.5%	pet.
Neomycin	20%	pet.
Thiuram-mix	1%	pet.
Paraphenylene diamine	1%	pet.
Cobalt chloride	1%	pet.
Formaldehyde	1%	aq.
Colophony	20%	pet.
Baume of peru (<i>Myroxylon perei</i>)	25%	pet.
Wool alcohols	30%	pet.
Mercapto-mix	2%	pet.
Paraben-mix	15%	pet.
P-tert-butylphenolformaldehyde resin	1%	pet.
Fragrance mix I	8%	pet.
Nickel sulphate	5%	pet.
Methylchloroisothiazolinone	0.01%	aq.
Mercaptobenzothiazole	2%	pet.
Tixocortol pivalate	0.1%	pet.
Budesonide	0.01%	pet.
Hydrocortison-17-butyrate	0.1%	alc.
Methylisothiazolinone	0.05%	aq.
Hydroxymethylpentylcyclohexenecarboxaldehyde (Lyr)	5%	pet.
Fragrance mix II	14%	pet.
Compositae -mix	5%	pet.
Hydroperoxides of linalol	1%	pet.
Hydroperoxides of limonene	0.30%	pet.
Epoxy resin	1%	pet.

pet. = in petrolatum

aq. = in aqua

alc. = in alcohol