

Contact Sensitization in Children: A Retrospective Study of 2,614 Children from a Single Center

Anna Belloni Fortina, M.D.,* Elena Fontana, M.D.,* and Andrea Peserico, M.D.†

*Pediatric Dermatology Unit, †Dermatology Unit, Department of Medicine, University of Padova, Padova, Italy

Abstract

Background: Contact sensitization in children is more common than previously thought, but few studies have been performed on a large population assessed by the same team. The objective was to evaluate contact sensitization in children with suspected contact dermatitis, the relationship with atopic dermatitis (AD), and the most common allergens.

Methods: The same team patch tested 2,614 children younger than 11 years old with a standard series of 30 allergens.

Results: A total of 1220 children (46.7%) developed at least one positive reaction, 606 of which were clinically relevant (49.7%). The most frequent reactions were to nickel sulfate (22.7%), cobalt chloride (11.1%), potassium dichromate (9.9%), neomycin sulfate (5.2%), thimerosal (4.2%), cocamidopropyl betaine (3.4%), and methylchloroisothiazolinone/methylisothiazolinone (3.2%). The prevalence of contact sensitization was similar in children with (47.3%) and without (46.1%) AD. Children with AD had a higher prevalence of positive reactions to potassium dichromate ($p < 0.001$), Compositae mix ($p = 0.01$), and disperse blue ($p = 0.03$).

Conclusions: Contact sensitization is quite common in young children. This study adds some information on the most common contact allergens. A similar prevalence of positive patch test reactions was found in children with and without AD, but children with AD had a greater prevalence of positive patch test reactions to potassium dichromate, Compositae mix, and disperse blue.

Contact sensitization in children is more common than previously thought (1,2), but few studies have been performed in large cohorts, and most have been

multicenter studies and thus may have had limitations because of the interinstitution variations in patch test methodologies and interpretation (3).

Address correspondence to Anna Belloni Fortina, M.D., Pediatric Dermatology Unit, Department of Medicine, University of Padova, Via C. Battisti, 206, 35128 Padova, Italy, or e-mail: belloni@pediatria.unipd.it.

The aim of our study was to describe the frequency and relevance of positive patch test reactions and to assess the most common allergens in a large population of children with and without atopic dermatitis (AD) evaluated for suspected allergic contact dermatitis (ACD) by the same team of experienced dermatologists at a single referral center.

MATERIALS AND METHODS

Our retrospective analysis was based on data from the Pediatric Dermatology Unit of Padua, a referral center for a large part of northeast Italy. From January 2002 to December 2013, 2,614 children 1 to 10 years old (mean age $5.3 \pm \text{SD } 2.5$ years; 1,188 boys, 1,426 girls) were patch tested with our screening pediatric series of 30 allergens (Chemotechnique Diagnostics, Malmö, Sweden) (4).

At the beginning of the study, there was no standard screening pediatric series. The series was chosen on the basis of the European Standard Series; it includes some allergens not present in the proposed Pediatric North American Standard Series (5) (benzocaine, disperse red 1, disperse yellow 3, epoxy resin, ethylenediamine dihydrochloride, *N*-isopropyl-*N*-phenyl-para-phenylenediamine [I-PPD], 2-mercaptobenzothiazole [2-MBT], methyl dibromoglutaronitrile + 2 phenoxyethanol [MDGN+2PE], 4-tert butylphenol formaldehyde resin, paraben mix, paraphenylenediamine [PPD], and thimerosal) and does not include some allergens present in the proposed Pediatric North American Standard Series (bacitracin, formaldehyde, fragrance mix 2).

All patients were referred with a clinical suspicion of ACD.

The study population was divided into three age groups, reflecting the different exposures during daycare (group 1: <3 yrs; $n = 409$), kindergarten (group 2: 3–5 yrs; $n = 1,049$), and primary school (group 3: 6–10 yrs; $n = 1,156$) (Table 1).

Patch tests were performed using Finn Chambers on Scanpore tape. All substances were applied on the upper back (day 0) and removed 48 hours after application (day 2). The sites were examined at day 2 and day 4 according to the International Contact Dermatitis Research Group guidelines (6).

At the time of testing, patients did not have active dermatitis at the test application site and had not taken systemic corticosteroids or applied topical corticosteroids on the test areas for at least 1 week.

General information regarding age, sex, location of dermatitis, personal or family history of atopic diseases, sports, hobbies, and use of cosmetics was

TABLE 1. Demographic Characteristics of the Study Population

Characteristic	Study population <i>n</i> (%)	Atopic dermatitis
Patients tested	2,614	1,283 (49.1)
Age, yrs		
<3	409 (15.6)	187 (45.7)
3–5	1,049 (40.1)	574 (54.7)
6–10	1,156 (44.2)	522 (45.2)
Sex		
Male	1,188 (45.4)	575 (48.4)
Female	1,426 (54.6)	708 (49.6)
Location of suspected allergic contact dermatitis		
Head and neck	729 (27.9)	406 (31.6)
Lower limbs	408 (15.6)	142 (11.1)
Upper limbs	264 (10.1)	128 (10)
Hands	312 (11.9)	120 (9.4)
Widespread	169 (6.5)	86 (6.7)
Trunk	277 (10.6)	91 (7.1)
Feet	106 (4.1)	25 (1.9)
Intertriginous folds	333 (12.7)	279 (21.7)
Not reported	16 (0.6)	6 (0.5)

Mean age 5.3 ± 2.5 yrs.

obtained. AD was evaluated according to the Hanifin and Rajka criteria (7).

Reactions were designated as 1+ (weak positive reaction; erythema, infiltration, possibly papules), 2+ (strong positive reaction; erythema, infiltration, papules, vesicles), or 3+ (extreme positive reaction; intense erythema and infiltration and coalescing vesicles) according to the International Contact Dermatitis Research Group (6). We calculated the overall prevalence of at least one positive reaction to an allergen in our pediatric series for each age group with AD and without. Because nickel sensitization may introduce a bias in the analysis if not addressed separately (8), we also calculated the overall prevalence of at least one positive reaction excluding nickel.

Clinical relevance was assessed for all positive reactions on the basis of the clinical history and skin examination. The relevance of a positive patch test reaction was considered to be present when related to the current clinical symptoms and past when associated with previous clinical events. Relevance data were combined to include present and past relevance; only definite relevance was considered for the aim of this study.

Data were stored using Excel 2010 (Microsoft, Redmond, WA), and statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL). The ordinal data and associations between positive patch test reactions were analyzed using the Pearson chi-square test and, in situations with low cell counts, Fisher's exact test. For all tests, $p < 0.05$ was assumed to indicate statistical significance.

RESULTS

Of the 2,614 children tested, 1,220 (46.7%) developed at least one positive reaction, 606 (49.7%) of which were relevant; 484 children were polysensitized, with 308 of these having only two positive reactions. Few irritant reactions were seen, and no child had “excited skin syndrome.”

The overall prevalence of at least one positive reaction to an allergen of our pediatric standard series disregarding nickel was 35.7% (933 patients).

There were 215 (52.6%) children with at least one positive reaction in group 1 (55.8% relevant), 476 (45.4%) in group 2 (46.2% relevant), and 529 (45.8%) in group 3 (50.3% relevant).

The prevalence of at least one positive reaction in children of group 1 was statistically significantly greater than in children of groups 2 ($p = 0.01$) and 3 ($p < 0.001$). This difference in prevalence did not reach statistical significance when calculated excluding nickel.

The 10 most common allergens in our study population were nickel sulfate (22.7%), cobalt chloride (11.1%), potassium dichromate (9.9%), neomycin sulfate (5.2%), thimerosal (4.2%), cocamidopropyl betaine (3.4%), methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) (3.2%), *Myroxylon pereirae* (2.6%), disperse yellow (1.9%), and carba mix (1.5%). Of the 291 patients with a positive patch test to cobalt, 135 (46.4%) had a positive reaction also for nickel. The 10 most relevant allergens were cocamidopropyl betaine (68.5%), fragrance mix I (66.7%), paraben mix (55.6%), nickel sulfate (54.9%), *M. pereirae* resin (54.4%), Compositae mix (53.7%), budesonide (50%), wool alcohols (50%), MCI/MI (48.2), and 2-mercaptobenzothiazole (2-MBT) (44.4%). All the allergens and their respective relevance are shown in Table 2 in alphabetical order.

Of all allergens present in our series but not present in the proposed pediatric North American standard series (5), only the following were positive in more than 0.5% of patients tested: thimerosal (4.2% positive, of which 11.8% were relevant), disperse yellow (1.9% positive, 20.4% relevant), 4-tert butylphenol formaldehyde resin (1.5% positive, 30.8% relevant), and disperse red (1.4% positive, 24.3% relevant).

The prevalence of positive patch test reactions to some allergens was higher in group 3 than in group 1 and reached statistical significance for carba mix (group 3: 2.2%; group 1: 0.5%; $p = 0.02$), cobalt chloride (group 3: 12.2%; group 1: 8.3%; $p = 0.03$),

and thimerosal (group 3: 7.9%; group 1: 1%; $p < 0.001$). The prevalence of positive patch test reactions to nickel sulfate was higher in group 1 (35%) than in group 2 (24%; $p < 0.001$) and group 3 (17.3%; $p < 0.001$) (Table 2).

Five hundred sixty-six of 1,188 (47.6%) boys and 654 of 1,426 (45.9%) girls developed at least one positive reaction ($p = 0.36$). No difference between sexes was found when considering each age group separately. Boys had a statistically significantly greater prevalence of positive patch test reactions to carba mix, cocamidopropyl betaine, Compositae mix, I-PPD, neomycin sulfate, and propylene glycol.

One thousand two hundred eighty-three children (49.1%; 708 girls, 575 boys) had a past or current diagnosis of AD, and 1331 (50.9%; 613 boys, 718 girls) had no past history of AD. Six hundred of 1,283 (47.3%) children with a past or current diagnosis of AD had at least one positive reaction and 613 of 1,331 (46.1%) with no past history of AD had at least one positive reaction, ($p = 0.52$).

There were 234 polysensitized children with AD and 250 without ($p = 0.72$). There was no difference in the frequency of 1+ reactions between children with ($n = 627$) and without ($n = 608$) AD ($p = 0.54$). The overall prevalence of at least one positive reaction to an allergen in our pediatric series excluding nickel was 36.2% in children with AD and 35.2% in those without ($p = 0.62$). Children with AD had a statistically significantly greater prevalence of positive patch test reactions to potassium dichromate, Compositae mix, and disperse blue, and those without had a statistically significantly greater prevalence of positive patch test reactions to the MCI/MI, thimerosal, and 4 tert-butylphenol formaldehyde resin.

The most frequent locations of suspected ACD were the head and neck (27.8%), lower limbs (15.6%), intertriginous folds (12.7%), hands (11.9%), and trunk (10.6%). Information about the location of ACD was missing in 16 patients (0.6%), who were excluded from the calculations on location. The contact sensitization rate was highest when suspected ACD was on the trunk (53.1%), feet (51.9%), or intertriginous folds (51.1%).

DISCUSSION

Our retrospective study conducted in 2,614 children with suspected contact dermatitis confirms that contact sensitization in children is frequent. The overall prevalence of a positive reaction to at least one allergen in our pediatric standard series in the study population was high (46.7%), confirming recent

TABLE 2. Prevalence of Positive Patch Test Reactions and Corresponding Relevance for Each Allergen in the Total Study Population and Stratified According to Age

Allergen	Total study population	Relevance	Group 1 (<3 yrs)	Relevance	Group 2 (3–5 yrs)	Relevance	Group 3 (6–10 yrs)	Relevance
	n (%)							
Benzocaine 5% pet	6 (0.2)	0	3 (0.7)	0	3 (0.3)	0	0	0
Budesonide 0.01% pet	2 (0.1)	1 (50)	1 (0.2)	0	0	0	1 (0.1)	1 (100)
Carba mix 3% pet	38 (1.5)	5 (13.2)	2 (0.5)	0	11 (1)	4 (36.4)	25 (2.2)	1 (4)
Cobalt chloride 1% pet	291 (11.1)	104 (35.7)	34 (8.3)	17 (50)	116 (11.1)	37 (31.9)	141 (12.2)	50 (35.5)
Cocamidopropyl betaine 1% aq	89 (3.4)	61 (68.5)	26 (6.4)	20 (76.9)	31 (3)	19 (61.3)	32 (2.8)	22 (68.8)
Colophony 20% pet	15 (0.6)	2 (13.3)	1 (0.2)	0	6 (0.6)	1 (16.7)	8 (0.7)	7 (87.5)
Compositae mix 5% pet	41 (1.6)	22 (53.7)	3 (0.7)	2 (66.7)	16 (1.5)	9 (56.3)	22 (1.9)	11 (50)
Disperse blue 124 1% pet	19 (0.7)	6 (31.6)	8 (2)	3 (37.5)	7 (0.7)	1 (14.3)	4 (0.3)	2 (50)
Disperse red 1 1% pet	37 (1.4)	9 (24.3)	21 (5.1)	6 (28.6)	12 (1.1)	2 (16.7)	4 (0.3)	1 (25)
Disperse yellow 3 1% pet	49 (1.9)	10 (20.4)	12 (2.9)	2 (16.7)	19 (1.8)	6 (31.6)	18 (1.6)	2 (11.1)
Epoxy resin 1% pet	9 (0.3)	2 (22.2)	2 (0.5)	0	2 (0.2)	1 (50)	5 (0.4)	1 (20)
Ethylenediamine dihydrochloride 1% pet	8 (0.3)	1 (12.5)	3 (0.7)	0	3 (0.3)	1 (33.3)	2 (0.2)	0
Fragrance mix I 8% pet	12 (0.5)	8 (66.7)	0	0	5 (0.5)	4 (80)	7 (0.6)	4 (57.1)
2-mercaptobenzothiazole 2% pet	9 (0.3)	4 (44.4)	1 (0.2)	0	1 (0.1)	1 (100)	7 (0.6)	3 (42.9)
Methyldibromo glutaronitrile + 2 phenoxyethanol 0.5% pet	8 (0.3)	3 (37.5)	1 (0.2)	1 (100)	4 (0.4)	1 (25)	3 (0.3)	1 (33.3)
Methylchloroisothiazolinone/methylisothiazolinone 0.01% aq	83 (3.2)	40 (48.2)	18 (4.4)	8 (44.4)	28 (2.7)	14 (50)	37 (3.2)	18 (48.6)
<i>Myroxylon pereirae</i> resin 25% pet	68 (2.6)	37 (54.4)	7 (1.7)	3 (42.9)	23 (2.2)	12 (52.2)	38 (3.3)	22 (57.9)
<i>N</i> -isopropyl- <i>N</i> -phenyl-para-phenylenediamine 0.1% pet	13 (0.5)	4 (30.8)	2 (0.5)	0	7 (0.7)	3 (42.9)	4 (0.3)	1 (25)
Neomycin sulfate 20% pet	135 (5.2)	51 (37.8)	22 (5.4)	9 (40.9)	45 (4.3)	15 (33.3)	68 (5.9)	27 (39.7)
Nickel sulfate 5% pet	594 (22.7)	326 (54.9)	143 (35)	83 (58)	251 (23.9)	123 (49)	200 (17.3)	120 (60)
Paraben mix 12% pet	9 (0.3)	5 (55.6)	1 (0.2)	1 (100)	3 (0.3)	1 (33.3)	5 (0.4)	3 (60)
Paraphenylenediamine 1% pet	11 (0.4)	2 (18.2)	3 (0.7)	0	3 (0.3)	2 (66.7)	5 (0.4)	0
Potassium dichromate 0.5% pet	259 (9.9)	91 (35.1)	45 (11)	16 (35.6)	111 (10.6)	38 (34.2)	103 (8.9)	37 (35.9)
Propylene glycol 5% pet	4 (0.2)	0	3 (0.7)	0	1 (0.1)	0	0	0
Quaternium-15 1% pet	12 (0.5)	1 (8.3)	1 (0.2)	0	5 (0.5)	0	6 (0.5)	1 (16.7)
4-tert butylphenol formaldehyde resin 1% pet	39 (1.5)	12 (30.8)	4 (1)	0	16 (1.5)	6 (37.5)	19 (1.6)	6 (31.6)
Thimerosal 0.1% pet	110 (4.2)	13 (11.8)	4 (1)	0	15 (1.4)	2 (13.3)	91 (7.9)	11 (12.1)
Tixocortol-21-pivalate 0.1% pet	10 (0.4)	4 (40)	4 (1)	2 (50)	3 (0.3)	1 (33.3)	3 (0.3)	1 (33.3)
Wool alcohols 30% pet	40 (1.5)	20 (50)	6 (1.5)	2 (33.3)	18 (1.7)	11 (61.1)	16 (1.4)	7 (43.8)

Petrolatum is the vehicle in which most allergens are dispersed and should cause no positive reactions. Thus it is tested in our patients but is generally negative. It is a kind of negative control. aq, water; pet, petrolatum.

studies from a nearby geographical area (9) and from different areas and continents (1,2). The high prevalence was seen in a selected study population with a suspicion of contact dermatitis. The relevance was lower than in other similar studies (1,10,11), probably because we considered only definite relevance, as it is often difficult to know what children have come into contact with during their daily activities, especially small children.

In the youngest group of children (group 1), the overall prevalence of at least one positive reaction to an allergen in our pediatric standard series was statistically higher than in older children (groups 2 and 3), although this difference was not statistically significant when excluding nickel.

The 10 most frequent allergens in our pediatric population were nickel sulfate, cobalt chloride, potassium dichromate, neomycin sulfate, thimerosal,

cocamidopropyl betaine, MCI/MI, *M. pereirae* resin, disperse yellow, and carba mix. These results are in agreement with recent findings and reflect the most frequent and likely exposures in our geographic area (12,13), although some of these allergens do not seem to have great relevance (e.g., disperse yellow 20.4% relevant, carba mix 13.2% relevant, and thimerosal 11.8% relevant).

The very high prevalence of contact sensitization to nickel was mostly due to the high prevalence in younger patients, which was significantly higher than in older children (Table 2). Contact sensitization to nickel in children may result not only from jewelry, belt buckles, and clothing fasteners, but also from toys and technological devices such as laptops and mobile telephone cases (14,15); however, positive nickel patch test reactions in children may sometimes not be reproducible (16).

Of 291 patients with a positive patch test to cobalt, 135 (46.4%) also had a positive reaction to nickel, confirming that contact sensitization to cobalt is often but not always associated with contact sensitization to nickel and challenging the traditional view of cobalt as a concomitant allergen (17). Contact sensitization to cobalt in children may result not only from jewelry, but also from toys (13) and leather footwear (17,18), as underlined by the association with foot dermatitis.

The contact sensitization rate to neomycin sulfate (5.2%) was also high, probably because it is still widely used as a topical antibiotic and as eye and ear drops in children (19,20). Contact sensitization to thimerosal was very low in very young children (1%) and higher in older age groups, probably as a result of the recent limitation of its use as a preservative in vaccines (10,12,20).

No statistically significant difference between the sexes was found considering each age group, including when nickel was excluded, although the prevalence of positive reactions to some allergens was significantly higher in boys (Compositae mix, carba mix, neomycin sulfate, cocamidopropyl betaine), possibly because of greater exposure (e.g., outdoor activities, use of rubber shoes and sportswear such as soccer shin guards, topical medications for small skin injuries).

Because conflicting data have been reported in the literature about contact sensitization in children with and without AD (21), we compared the prevalence of positive patch test reactions of children with and without AD. We found a slightly higher prevalence of positive reactions for children with AD (47.3%) than those without (46.1%), but this difference did not reach statistical significance, even when nickel was excluded, in accordance with the findings of other authors (9,13,22). However, when taking into account single allergens, children with AD had a significantly greater prevalence of positive reactions to potassium dichromate, disperse blue, and Compositae mix, partly confirming some recent studies. The higher incidence of positive reactions to Compositae mix in AD could be partly related to the use of Compositae-based emollients (e.g., calendula) (9,12,23,24).

A 1+ reaction might be an irritant response and not a true positive, especially in children with AD. Thus we calculated the prevalence of 1+ reactions and 2+/3+ reactions separately and found no statistically significant difference in the prevalence of 1+ reactions between children with AD and children without.

The most common sites of dermatitis were the head, lower limbs, intertriginous folds, and hands. The site of dermatitis may help clinicians identify the offending allergens. In our study, for instance, head

dermatitis suggested contact sensitization to nickel, cobalt, or neomycin, and foot dermatitis correlated with contact hypersensitivity to nickel, chromium, or cobalt.

CONCLUSIONS

Contact sensitization is frequent in young children and patch testing is the criterion standard for diagnosis of ACD. It should always be performed when there is a suspicion of contact allergy or when dermatitis does not respond to conventional therapies. Children with recalcitrant AD should be evaluated for ACD and, when appropriate, be patch tested, with special attention given to metals, disperse dyes, and Compositae.

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