SHORT REPORT

The most important contact sensitizers in Polish children and adolescents with atopy and chronic recurrent eczema as detected with the extended European Baseline Series

Ewa Czarnobilska[1], Krystyna Obtulowicz[1], Wojciech Dyga[1] & Radoslaw Spiewak[2]

[1]Department of Clinical and Environmental Allergology, Jagiellonian University Medical College, Krakow, Poland; [2]Institute of Dermatology, Krakow, Poland

To cite this article: Czarnobilska E, Obtulowicz K, Dyga W, Spiewak R. The most important contact sensitizers in Polish children and adolescents with atopy and chronic recurrent eczema as detected with the extended European Baseline Series. *Pediatr Allergy Immunol* 2011; **22**: 252–256.

Keywords
contact allergy; contact hypersensitivity; hapten; patch testing; eczema; atopy; children; adolescents

Correspondence
Dr habil. med. Radoslaw Spiewak, ul. Lentza 6 M 17, 31-312 Krakow, Poland
Tel.: +48 60 122 48 13
Fax: +48 12 416 62 62
Email: spiewak@onet.eu

Accepted for publication 31 March 2010

DOI:10.1111/j.1399-3038.2010.01075.x

Abstract

The differential diagnostic work-up of children with chronic eczema should involve patch testing, also in cases with confirmed atopy. In our previous study, contact allergy was detected in every second child with chronic eczema. The aim of the present study was to identify the most important sensitizers in atopic children with eczema. During an allergy screening program, 103 consecutive children aged 7–8 and 93 adolescents aged 16–17 were enrolled. The inclusion criterion was chronic recurrent eczema as detected with the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and atopy, defined as positive skin prick test to one or more common airborne or food allergens. The children were patch-tested with the newly extended European Baseline Series (EBS, 28 test substances) supplemented with propolis, thimerosal, benzalkonium chloride, and 2-phenoxyethanol. In total, 67.0% children and 58.1% adolescents were found patch test positive. Among children, 35.9% reacted to nickel, 16.5% propolis, 11.7% thimerosal, 9.7% cobalt, each 6.8% fragrance mix (FM) I and chromium, and 5.8% to FM II. Among adolescents, 37.6% reacted to thimerosal, 19.4% to nickel, 6.5% to cobalt, and 5.4% to propolis. We demonstrate the advantage of using FM II – a new addition to the EBS that detects a relatively high proportion of contact hypersensitivity among children. An important sensitizer from outside EBS is propolis, which according to the frequency of sensitization occupies rank 2 in children and rank 4 in adolescents. These data show that propolis should be included into routine patch testing in children.

Although it may appear tempting and seemingly justified to settle for the diagnosis of atopic eczema in children with chronic recurrent dermatitis and confirmed atopy, the differential work-up should also include patch testing. Patch test (PT) is gold standard in the detection of contact allergy (1). The test may either detect contact sensitizations secondary to and complicating atopic eczema or indicate that the ultimate diagnosis is allergic contact dermatitis – another frequent type of eczema, which is primary clinical expression of contact allergy (2). Contact allergy is among the most frequent types of allergy, affecting 26–40% of all adults (3–5) and 13–25% children (6). Atopy and contact allergy are independent phenomena, which means that the presence of atopy does not exclude the possibility of contact sensitization (5). We have recently demonstrated that contact allergy can be found in every second child with chronic eczema, and in every third such child the ultimate diagnosis is allergic contact dermatitis (7). However, the mentioned study was based on a test series of 10 substances only. Results in adults indicate that the diagnostic effectiveness of PT depends on the number of test substances used (8–11), which inspired the question, to what extent would the positivity rate in children increase when using an extensive PT series and what would be the most important sensitizers. The aim of the present study was, therefore, to analyze the rates of contact hypersensitivity among schoolchildren with symptoms of chronic recurrent eczema and atopy, with the use of an extensive PT series of 32 substances, including the newly extended European Baseline Series (EBS) and 4 additional haptens.

Patients and methods

During an allergy screening program in Krakow (Poland) in 2008–2009, 103 consecutive children aged 7–8 and 93 adolescents aged 16–17 – all with history of chronic recurrent eczema and atopy – were qualified for patch testing. The qualification was based on affirmative answers to questions in the eczema modules of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (12). Atopy was defined as at least one positive skin prick test reaction (wheal diameter equal or larger than 3 mm) to the following allergens: house dust mites, storage mites, grass/rye pollen, hazel, alder, birch, weeds, molds, dog and cat dander, egg white, cow milk. PTs were carried out with 28 substances present in the new EBS of 2008 (13), supplemented with propolis 10% in petrolatum (pet.), thimerosal 1% pet., benzalkonium chloride 0.1% in aqua (aq.), and 2-phenoxyethanol 1% pet. The addition of propolis was based on our previous observation that this substance is a frequent sensitizer in Poland (14). The preservative benzalkonium chloride was included because it replaces thimerosol in cosmetic products, external drugs, and contact lens fluids, whereas 2-phenoxyethanol is used as a replacement for thimerosol in preserving vaccines. Therefore, we were interested whether the exchange of preservatives is reflected in sensitization rates.

Altogether 32 test substances (Chemotechnique Diagnostics, Vellinge, Sweden) were applied in IQ Ultra Chambers for 48 h. Reading and scoring of the test results were carried out after 48 and 72 h, according to standard procedures (15). The positivity rates with 95% confidence intervals (95%CI) were calculated for each substance tested, along with the overall hypersensitivity rate. Comparisons were made between age groups (7–8 year old vs. 16–17 year old) and gender (males vs. females) using the Chi-square test with $p < 0.05$ considered as statistically significant.

Results

The results of PTs in 196 schoolchildren with atopy and chronic recurrent eczema are shown in Table 1. Altogether, 62.7% subjects with eczema were found PT positive, including 67.0% children (7–8 year old) and 58.1% adolescents (16–17 year old). The most frequent contact sensitizer in children was nickel, followed by propolis, thimerosal, cobalt, chromium, fragrance mix (FM) I, and FM II. In adolescents, the most frequent PT reactions were found to thimerosal, followed by nickel, cobalt, propolis, chromium, FM I, FM II, and colophonium. Children were more frequently than adolescents sensitized to nickel and propolis (each $p = 0.01$) and less frequently to thimerosal ($p = 0.0001$). Regarding the differences between gender, the frequency of nickel allergy was significantly higher in adolescent girls than in boys ($p = 0.05$), with similar tendency among children.

Discussion

Contact allergy may begin in infancy and continue to be more common in toddlers and young children; therefore, patch testing is indispensable in the diagnosis of eczema, also in children with confirmed diagnosis of atopic dermatitis (16). The tests enable the diagnosis of primary or secondary allergic contact dermatitis and the identification of offending haptens, which helps in their avoidance and thus improves quality of life (17). There is no generally accepted strategy for patch testing in children – some authors propose 'shortened' test series for children (18), while other use the same series as in adults (19). In a previous study based on patch testing with 10 sensitizers only, we were able to detect contact allergy in 42.8% children and adolescents with chronic recurrent eczema (7). The expansion of the test series to 32 substances resulted in an increase in the overall detection rate up to 62.7%. This confirms that the diagnostic effectiveness of patch testing improves with the number of substances tested. Obviously, the composition of the series is also of importance. The selection of substances for PT series is a complicated and continuous process reflecting changes in epidemiology, appearance of new sensitizers in the environment, and availability of appropriate test formulations (20). In 2008, European standard series was renamed to EBS and extended through the addition of FM II and Lyral (13).

FM II is a new six-ingredient test substance proposed in 2002 by Frosch et al. (21). Further on, the authors demonstrated that 32% of all patients with positive reactions to FM II were negative to FM I (22). Our results confirm the usefulness of FM II, which has been recently introduced into EBS: Among 17 children and adolescents allergic to fragrances observed in our study, 7 (41%) reacted exclusively to FM II (Table 2). Overall sensitization rates to FM I and FM II were higher among children (6.8% and 5.8%, respectively) than among adolescents (3.2% and 2.2%). The higher frequency of contact allergy to FM I in younger children was also observed in our previous study, which unfortunately did not include FM II (7). A possible explanation for the higher sensitization rates to fragrances in the younger generation is increasing exposure of young children to perfumed products (toys, books, cosmetics, etc.). Moreover, perfumes for children and toys containing large amounts of fragrances, like 'perfume science laboratories' or 'perfume dragons', are sold without any control through the Internet. Another possible source of infantile exposure to fragrances may be the mother's perfumes and cosmetics transferred onto child's skin during baby care routines or close physical contact.

In this study, nickel sensitization was significantly more frequent among children than among adolescents, which confirmed our observation from the previous study (7). This difference can hardly be explained by changed exposure patterns to the hapten, as nickel has been omnipresent in human environment for many decades. This difference may, however, reflect the general increase in allergies observed in the younger generation of Polish children – a phenomenon that is thought to be a consequence of the 'westernization' of lifestyle in Poland (23). The female predominance of nickel allergy observed in our study is a well-known phenomenon, which most probably reflects the exposure patterns with early ear piercing among girls and use of cheap, nickel-releasing earrings (24, 25).

Table 1 Frequency of positive patch test reactions in children (7–8 y.o.) and adolescents (16–17 y.o.) with atopy and history of chronic recurrent eczema

	7–8 y.o. (%)			16–17 y.o. (%)		
	Total (N = 103)	♀ (N = 52)	♂ (N = 51)	Total (N = 93)	♀ (N = 54)	♂ (N = 39)
European Baseline Series (EBS) supplemented with propolis, thiomersal, benzalkonium chloride, 2-phenoxyethanol (32 substances): At least one test positive	67.0 (57.9–76.1)	69.2 (56.7–81.8)	64.7 (51.6–77.8)	58.1 (48.0–68.1)	57.4 (44.2–70.6)	59.0 (43.5–74.4)
EBS only (28 substances): At least one test positive	48.5 (41.5–55.5)	60.2 (50.7–69.6)	67.3 (54.6–80.1)	52.9 (39.2–66.6)	35.5 (25.8–45.2)	38.9 (25.9–51.9)
Nickel sulfate 5% pet.	35.9 (26.7–45.2)	42.3 (28.9–55.7)	29.4 (16.9–41.9)	19.4 (11.3–27.4)	27.8 (15.8–39.7)	7.7 (0–16.0)
Propolis 10% pet.	16.5 (9.3–23.7)	15.4 (5.6–25.2)	17.6 (7.2–28.1)	5.4 (0.8–10.0)	1.9 (0–5.4)	10.3 (0.7–19.8)
Thimerosal 1% pet.	11.7 (5.5–17.8)	5.8 (0–12.1)	17.6 (7.2–28.1)	37.6 (27.8–47.5)	31.5 (19.1–43.9)	46.2 (30.5–61.8)
Cobalt chloride 1% pet.	9.7 (4.0–15.4)	13.5 (4.2–22.7)	5.9 (0–12.3)	6.5 (1.4–11.4)	3.7 (0–8.7)	10.3 (0.7–19.8)
Potassium dichromate 0.5% pet.	6.8 (1.9–11.7)	1.9 (0–5.6)	11.8 (2.9–20.6)	3.2 (0–6.8)	3.7 (0–8.7)	2.6 (0–7.5)
Fragrance mix (FM) I 8% pet.	6.8 (1.9–11.7)	3.8 (0–9.1)	9.8 (1.6–18.0)	3.2 (0–6.8)	1.9 (0–5.4)	5.1 (0–12.1)
FM II 14% pet.	5.8 (1.3–10.3)	5.8 (0–12.1)	5.9 (0–12.3)	2.2 (0–5.1)	3.7 (0–8.7)	2.6 (0–7.5)
Neomycin sulfate 20% pet.	4.9 (0.7–9.0)	3.8 (0–9.1)	5.9 (0–12.3)	0	0	0
Myroxylon pereirae (balsam of Peru) 25% pet.	4.9 (0.7–9.0)	7.7 (0.4–14.9)	2.0 (0–5.8)	1.1 (0–3.2)	0	2.6 (0–7.5)
4-Phenylenediamine base (PPD) 1% pet.	1.9 (0–4.6)	1.9 (0–5.6)	2.0 (0–5.8)	1.1 (0–3.2)	0	2.6 (0–7.5)
Colophonium 20% pet.	1.9 (0–4.6)	3.8 (0–9.1)	0	2.2 (0–5.1)	0	5.1 (0–12.1)
Tixocortol-21-pivalate 0.1% pet.	1.9 (0–4.6)	3.8 (0–9.1)	0	1.1 (0–3.2)	1.9 (0–5.4)	0
Paraben mix 16% pet.	1.0 (0–2.9)	1.9 (0–5.6)	0	1.1 (0–3.2)	0	2.6 (0–7.5)
Lanolin (wool alcohols) 30% pet.	1.0 (0–2.9)	0	2.0 (0–5.8)	0	0	0
2-Mercaptobenzothiazole (MBT) 2% pet.	1.0 (0–2.9)	1.9 (0–5.6)	0	1.1 (0–3.2)	1.9 (0–5.4)	0
Formaldehyde 1% aq.	1.0 (0–2.9)	0	2.0 (0–5.8)	1.1 (0–3.2)	1.9 (0–5.4)	0
Sesquiterpene lactone mix 0.1% pet.	1.0 (0–2.9)	1.9 (0–5.6)	0	1.1 (0–3.2)	1.9 (0–5.4)	0
Budesonide 0.01% pet.	1.0 (0–2.9)	1.9 (0–5.6)	0	0	0	0

95% confidence intervals are given in brackets.

aq., aqueous; pet., petrolatum; y.o., years old.

Composition of FM I: cinnamic alcohol 1%, cinnamic aldehyde 1%, eugenol 1%, isoeugenol 1%, geraniol 1%, hydroxycitronellal 1%, oak moss absolute 1%, amylcinnamaldehyde 1%.

Composition of FM II: Lyral 2.5%, citral 1%, farnesol 2.5%, citronellol 0.5%, hexyl cinnamaldehyde 5%, coumarin 2.5%.

Remaining substances tested (thiuram mix 1% pet., benzocaine 5% pet., clioquinol 5% pet., N-isopropyl-N-phenyl-4-phenylenediamine 0.1% pet., mercapto mix 2% pet., epoxy resin 1% pet., 4-tert-butylphenolformaldehyde resin 1% pet., 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride 1% pet., 2-methoxy-6-n-pentyl-4-benzoquinone 0.01% pet., 5-chloro-2-methyl-4-isothiazolin-3-one 0.01% aq., methyldibromoglutaronitrile 0.5% pet., Lyral 5% pet., benzalkonium chloride 0.1% aq., 2-phenoxyethanol 1% pet.) were all negative in the tested groups.

Table 2 Hypersensitivity to fragrance mix (FM) I and FM II in children (7–8 y.o.) and adolescent (16–17 y.o.) with atopy and history of chronic recurrent eczema

Test substance	Total (N)	7–8 y.o. (N)	16–17 y.o. (N)
FM I (+)	10	7	3
FM II (+)	8	6	2
FM I (+) and FM II (–)	9	6	3
FM I (–) and FM II (+)	7	5	2
FM I (+) and FM II (+)	1	1	0
FM I (+) and/or FM II (+)	17	12	5

A reverse trend – significantly lower sensitization rates to thimerosal among children than among adolescents can be explained by changing exposure patterns: The adolescents have received six thimerosal-preserved vaccines during their life course, with the last immunization taking place 2–3 years before the PTs. The children received only four thimerosal-preserved vaccines, with the last one applied 5 years before the tests, while further immunizations were performed with new thimerosal-free vaccines. In our study, we have not observed any positive PTs to the alternative preservatives benzalkonium chloride and phenoxyethanol.

A new finding from our study was the relatively high sensitization rate to propolis, which is the second most frequent sensitizer in children after nickel. We have found positive PT reactions to propolis in 16.5% of 7–8-year-olds and 5.4% of 16–17-year-olds with chronic/recurrent eczema. The first figure is close to the positivity rate of 15% recently observed in adult Polish patients (14). The frequency of contact allergy to propolis in Italian children with eczema amounted to 5.9% (26). Altogether these results suggest that propolis is indeed among the most frequent contact sensitizers and should be included in routine patch testing. In many countries (including Poland), propolis is widely advocated as a 'steroid-free', 'chemical-free' natural remedy for all kinds of diseases, from burns to allergy and eczema. Propolis-based products are accessible free of prescription at pharmacies and herbal shops. They have been popular with the elderly for a long time. Now it appears that with ever-increasing steroid-phobia, many parents choose propolis for any skin conditions of their children, including eczema, which may lead to secondary sensitization to this substance.

Conclusions

- Contact allergy can be found in two-thirds of atopic children and adolescents with atopy and chronic recurrent eczema.
- Increasing the number of test substances in the baseline series improves the diagnostic effectiveness of patch testing.
- The newly introduced FM II detects a considerable number of cases with fragrance allergy that would have been missed if using only FM I.
- Propolis seems to be one of the most frequent contact sensitizers and should be included in routine patch testing in children and adolescents.
- Patch testing is an indispensable element of eczema diagnosis in children.

Acknowledgments

This study was financed from the statutory grant No. K/ZDS/000659 of the Jagiellonian University Medical College, Krakow. Preliminary results of this study were presented at the XXVIII EAACI Congress in Warsaw 2009 (27).

References

1. Mowad CM. Patch testing: pitfalls and performance. *Curr Opin Allergy Clin Immunol* 2006: **6**: 340–4.
2. Spiewak R. Contact allergy – diagnosis and treatment. *Alergia Astma Immunol* 2007: **12**: 109–26. (In Polish).
3. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult, population: a population-based study from Northern Norway. *Contact Dermatitis* 2007: **56**: 10–5.
4. Schäfer T, Böhler E, Ruhdorfer S, et al. Epidemiology of contact allergy in adults. *Allergy* 2001: **56**: 1192–6.
5. Spiewak R. Atopy and contact hypersensitivity: a reassessment of the relationship using objective measures. *Ann Allergy Asthma Immunol* 2005: **95**: 61–5.
6. Spiewak R. Allergic contact dermatitis in childhood – a review and meta-analysis. *Allergologie* 2002: **25**: 374–81. (In German).
7. Czarnobilska E, Obtulowicz K, Dyga W, Wsolek-Wnek K, Spiewak R. Contact hypersensitivity and allergic contact dermatitis among schoolchildren and teenagers with eczema. *Contact Dermatitis* 2009: **60**: 264–9.
8. Francalanci S, Giorgini S, Ricci L, Sertoli A. Patch testing by additional series of allergens: results of further experiences. *Am J Contact Dermat* 2001: **12**: 203–7.
9. Larkin A, Rietschel RL. The utility of patch tests using larger screening series of allergens. *Am J Contact Dermat* 1998: **9**: 142–5.
10. Cohen DE, Rao S, Brancaccio RR. Use of the North American Contact Dermatitis Group Standard 65-allergen series alone in the evaluation of allergic contact dermatitis: a series of 94 patients. *Dermatitis* 2008: **19**: 137–41.
11. Lach K, Odrzywolek L, Sliwa L, Obtulowicz K, Czarnobilska E, Spiewak R. Diagnosis of contact allergy: the effectiveness of patch testing depends on the composition of the diagnostic series. *Allergy* 2009: **64** (Suppl. 90): 117.
12. Asher MI, Keil U, Anderson HR, et al. International study of asthma and allergies in childhood (ISAAC): Rationale and methods. *Eur Respir J* 1995: **8**: 483–91.
13. Bruze M, Andersen KE, Goossens A; ESCD; EECDRG. Recommendation to include fragrance mix 2 and hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) in the European baseline patch test series. *Contact Dermatitis* 2008: **58**: 129–33.
14. Pietowska J, Czarnobilska E, Spiewak R. The most frequent contact sensitizers and atopic diseases among consecutive patients of a Polish patch test clinic. *Allergy* 2008: **63** (Suppl. 88): 320.
15. Spiewak R. Patch testing for contact allergy and allergic contact dermatitis. *Open Allergy J* 2008: **1**: 42–51.
16. de Waard-van der Spek FB, Oranje AP. Patch tests in children with suspected aller-

gic contact dermatitis: a prospective study and review of the literature. *Dermatology* 2009: **218**: 119–25.
17. Rajagopalan R, Anderson R. Impact of patch testing on dermatology-specific quality of life in patients with allergic contact dermatitis. *Am J Contact Dermat* 1997: **8**: 215–21.
18. Romaguera C, Vilaplana J. Contact dermatitis in children: 6 years experience (1992–1997). *Contact Dermatitis* 1998: **39**: 277–80.
19. Manzini BM, Ferdani G, Simonetti V, Donini M, Seidenari S. Contact sensitization in children. *Pediatr Dermatol* 1998: **15**: 12–7.
20. Bruze M, Conde-Salazar L, Goossens A, Kanerva L, White IR. Thoughts on sensitizers in a standard patch test series. The European Society of Contact Dermatitis. *Contact Dermatitis* 1999: **41**: 241–50.
21. Frosch PJ, Johansen JD, Menné T, et al. Further important sensitizers in patients sensitive to fragrances. *Contact Dermatitis* 2002: **47**: 78–85.
22. Frosch PJ, Pirker C, Rastogi SC, et al. Patch testing with a new fragrance mix detects additional patients sensitive to perfumes and missed by the current fragrance mix. *Contact Dermatitis*. 2005: **52**: 207–15.
23. Samolinski B. Epidemiology of Allergic Diseases in Poland (ECAP). A study report for 2006–2008. Warsaw: Medical University, 2008. (In Polish).
24. Jensen CS, Lisby S, Baadsgaard O, Volund A, Menne T. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002: **146**: 636–42.
25. Czarnobilska E, Spiewak R, Dyga W, Obtulowicz A, Wsolek-Wnek K, Obtulowicz K. Contact allergy among Polish children and adolescents with dermatitis. *Alergia Astma Immunol* 2008: **13**: 100–9. (In Polish).
26. Giusti F, Miglietta R, Pepe P, Seidenari S. Sensitization to propolis in 1255 children undergoing patch testing. *Contact Dermatitis* 2004: **51**: 255–8.
27. Czarnobilska E, Obtulowicz K, Dyga W, Sak-Rusek D, Spiewak R. The most important contact allergens in children and adolescents with eczema. *Allergy* 2009: **64** (Suppl. 90): 13.