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Influence of environment exposures on the frequency of contact allergies in children and adolescents

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Abstract

Contact allergy is detected in every second child with the symptoms of chronic or recurrent eczema, and in every third child the final diagnosis is allergic contact dermatitis. Haptens responsible for the majority of contact sensitizations in children are substances ubiquitous in our environment, e.g. metals, preservatives, fragrances, propolis, and balsam of Peru. Much concern is provoked by the higher rates of sensitization to fragrances in younger children, compared to adolescents, which may be attributed to the higher exposure nowadays of infants and children to fragrant products. On the other hand, a limitation of exposure to the preservatives thimerosal and Kathon CG has resulted in decreased rates of sensitization to these haptens. Altogether, these observations demonstrate that the rates of contact sensitizations in children reflect changes in their environment, and limitations imposed on the use of haptens with strong sensitizing properties, may be an effective tool in the prevention of contact allergy.

Key words

contact allergy, patch tests, nickel, propolis, fragrance mix, thimerosal, Kathon CG, children

INTRODUCTION

Contact allergy is a type of specific immunological hypersensitivity which develops in the cell type mechanism (type IV of hypersensitivity according to Gell and Coombs, so-called delayed type allergy). The sensitizing factors are chemical substances with a low molecular weight (haptens), which induce hypersensitivity reaction by direct contact with the skin [1-3]. Allergic contact dermatitis (ACD) is the most common clinical form of contact allergy; nevertheless, contact allergy can also be manifested as allergic contact stomatitis, rhinitis, bronchitis, conjunctivitis, vaginitis, and also as systemic reactions [4-9]. In the diagnosis of allergic contact dermatitis, the patch test is the method of choice. It is both a screening and a provocation test in the target organ [10-13]. According to the latest recommendations, in people with the suspicion of contact allergy, the patch tests are to be performed with the European Baseline Series containing 28 substances (haptens or haptens mix) [14], which in Poland should be supplemented with propolis and palladium. In a group of younger children, patch tests with all 28 substances are not always possible because of the limited area of the back. Roul *et al* proposed a 'Shortened European Standard' for children under 6 years of age that consists of 18 substances [15].

ACD is an acquired disease and its development depends on the time and intensity of the exposure to haptens, sensitive and irritant potential of haptens, and also on the functional state of skin protective barrier – both physical and immunological. Recently, the number of reports on children's ACD has increased. This situation may be caused by the increased frequency of its occurrence or increased allergologists' awareness of the problem and, as a consequence, the increased number of patch tests carried out on children. Identification of the responsible hapten and avoiding contact with it, increases the effectiveness of the treatment and, what is more, leads to a full withdrawal of disease symptoms. On the other hand, repeated exposure to unidentifiable haptens may result in chronic, recurring eczema episodes, quite often of increasing intensity.

Similar to adults, children also become allergic to haptens which are present all around [16, 17]. Table 1 shows the most frequent allergic substances among a group of European children with eczema (according to metaanalysis conducted by Śpiewak in 2002) [18], as well as the results of own studies in children living in Krakow with recurring and chronic eczema in 2007-2009 [19-21]. The most frequent substances causing allergy were: nickel, cobalt, chromium, fragrance mix, propolis, balsam of Peru, as well as preservatives such as thimerosal and Kathon CG.

Factors which have an influence on the increase of frequency of contact allergy to nickel, palladium, fragrance substances: fragrance mix I and II, balsam of Peru, and propolis

Nickel. Nickel, chromium and cobalt are still the major contact sensitizers among children [22-24]. Nickel can be found in many everyday appliances and allergy to nickel is therefore common. Facing the fact that as many as 65 million EU citizens – 54 million women and 11 million men – are

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Table 1. The most frequent substances sensitive for schoolchildren and adolescents

Schoolchildren with eczema from EU [18]	Schoolchildren with eczema from Kraków (2007)			Schoolchildren with eczema from Kraków (2008-2009)		
		7-8 y.o.	16-17 y.o.		7-8 y. o.	16-17 y. o.
Kathon CG 21%	Nickel sulfate	30.2%	25.9%	Nickel sulfate	35.9%	19.4%
Nickel sulfate 19%	Thimerosal	10.4%	25.0%	Propolis	16.5%	5.4%
Mercury ammonium chloride 15%	Cobalt chloride	8.3%	11.6%	Thimerosal	11.7%	37.6%
Thimerosal 14%	Fragrance mix I	7.3%	0%	Cobalt chloride	9.7%	6.5%
Cobalt chloride 13%	Potassium dichromate	6.3%	7.1%	Potassium dichromate	6.8%	3.2%
Potassium dichromate 12%	Kathon CG	6.3%	0.9%	Fragrance mix I	6.8%	3.2%
Wool alcohols 12%	Balsam of Peru	3.1%	0.9%	Fragrance mix II	5.8%	2.2%
Fragrance mix 12%	Mercury ammonium chloride	2.1%	1.8%	Neomycin sulphate	4,9%	0%
Balsam of Peru 11%	Colophony	1.0%	0%	Balsam of Peru	4.9%	1.1%
Colophony 10%	Wool alcohols	0%	0%	Phenylenedia-mine	1.9%	1.1%

allergic to nickel [3], legal regulations were issued in an attempt to reduce the rates of new sensitization, so far, however, with only partial success. In 1994, the European Commission introduced limitations on the nickel content of objects exposed to constant contact with human skin to 0.5 ug /cm^2 per week (the so-called Nickel Directive) [11, 25, 26]. It is worth considering that despite the EU restrictions and regardless of the country and age of the population tested, the consistency of nickel in everyday objects still remains the main contact for hapten. Nickel is absolutely the hapten which most frequently causes allergy in all age groups [2, 3, 8, 27]. Nickel-releasing earrings have been identified as the major single risk factor for developing nickel allergy [28]. A ban on nickel-releasing earrings in Denmark resulted in a decrease in rates of nickel allergy among girls from 17.1% down to 3.9% [29]. A similar EU-wide 'Nickel directive', in full force since 2001, seems to have failed to protect European consumers, evidenced by the fact that 15-18% of earrings purchased in London and Warsaw in 2010 still released nickel in amounts capable of inducing contact allergy [30, 31]. This is not very surprising due to the large scale of uncontrolled private import of jewellery in both countries from areas outside EU jurisdiction. The Nickel Directive officially came into force in 2004 in Poland, and a survey carried out 2 years later showed that it still remained at the planning stage, with no practical implementation [32].

Typically, hypersensitivity to nickel is demonstrated by eczema on the auricle or in the navel area, the areas most exposed to nickel found in jewellery, press studs or buckles. Eczema on the face can also be caused by nickel elements found in mobile phones [33].

Data on the prevalence of nickel allergy among the general Polish population are limited to 2 studies, both concluded before the introduction of the Nickel Directive, which show a sensitization rate of 8% among 13-15 year-olds in 1999 [34], and 18.5% among 18-19 year-olds in 2002 [35]. However, the possible impact of the Nickel Directive might be assessed by comparing the reports on the prevalence of nickel allergy among adolescents who were patch tested before and after the introduction of the legislation. In a study of patch tests in adolescents (12–16 year-olds) carried out between 1970-1994, the prevalence of nickel allergy reached 15.3% in girls and 5.5% in boys [36, 37], compared with 27.8–31.8% in girls and 6.7–7.7% in boys aged 16–17 years patch tested in 2007–2009 [19, 38]. In our research in 2007, carried out on children with eczema, contact allergy to nickel was found at the rate of 30% among 7-8 year-olds and, in 2008/2009 appeared at the rate of 35.9% among 7-8 year-olds. However, in teenagers with eczema in 2007, nickel was the cause of allergy in 26 % of 16-17 year-olds, and in 2008/2009 in 19.4% contact allergy to nickel was diagnosed. Regarding the group of teenagers (16-17 year-olds), contact allergy to nickel appeared characteristically more often among girls than boys (p=0.013) [19, 20, 39]. The increased frequency of nickel allergy in females may be the result of wearing earrings already in childhood [2, 40-42]. This can also be confirmed in our study: the highest frequency of nickel allergy (31.8%) was observed in 16-17 year-old girls, i.e. in the group with the highest number of people wearing earrings (Tab. 2).

Table 2. Percentage of children with piercings in a group examined with eczema [39]

Group	% of children with piercings	Age of first piercing [years]	
		Range	Median
Girls 7-8 y.o	42.6%	0.5-7	3
Boys 7-8 y.o.	0%	-	-
Girls 17-18 y.o.	64.8%	1-16	7
Boys 17-18 y.o.	4.2%	-	15

A surprising result of our analysis is the more frequent nickel allergy in 7-8 year old boys, compared to 16-17 year old boys [20, 39]. Similar differences were observed by Vigan [43]. It is difficult to explain the reason for this difference owing to the fact that nickel has been omnipresent in our environment for a century and, what is more, children are exposed to it from the first days of their lives. This phenomenon probably illustrates the general tendency of increasing frequency of allergy among children.

In the case of nickel, it becomes apparent that the initial route of exposure to the hapten may play an important role, as people drinking water with high nickel contact seem less prone to developing nickel allergy, despite constant exposure. This tendency was observed in people who live in the vicinity of Russian nickel refineries in Nikel and Zapolyarny, with heavy environmental pollution with nickel, and who drink nickel-contaminated water [28]. Wearing nickel-releasing orthodontic appliances, which also cause a constant oral exposure to nickel, seems to have similar protective effects against the development of nickel sensitization [44]. The dependency between the route of exposure and the risk of contact sensitization to various haptens (increase risk in the case of primary skin contact, decrease in the case of primary oral or systemic exposure), along with therapeutic attempts at utilizing this phenomenon, was recently reviewed in detail by Spiewak [45].

Palladium. Following the changes in epidemiology of contact sensitization in Poland, the palladium (Pd) was among 2 relevant environmental haptens that have been recently added to the Polish Baseline Series [46, 47]. Two decades ago, positive patch tests to palladium were regarded as a cross-reactivity with nickel, as there was no environmental exposure to this then rare metal [36]. Nowadays, palladium is present in every automobile catalytic converter, computer, mobile phone, or LCD television, Pd alloys are used in dentistry and orthopaedics. Following EU restrictions on nickel (Ni) used in jewellery, Pd has replaced Ni in 'white gold' alloys. This has led to a rapid increase in sensitization rates, and in a recent study 19.6% of all patients tested to the new Polish Baseline Series were detected with Pd allergy, including 5.4% of those sensitive to Pd, but not to Ni [32].

Fragrances: fragrance mix I and II, balsam of Peru. Fragrance substances belong to a hapten group the avoiding of which is particularly difficult. They are present in cosmetic products such as balsams, fluids, sun-filters, clothes, toys, books, detergents, toilet paper, handkerchiefs, and other everyday products. Children can also be allergic to perfumes used by people in their vicinity and, what is more, the Internet promotes special cosmetics and perfumes for children. Due to this mass exposure, allergy to fragrance substances is common in children. As in the case of adults, contact eczema often come out on one's face, nape, armpits, and a generalized reaction can also appear [48]. Contact allergy to fragrance substances can be detected with the help of patch tests (European Baseline Series) which consists of fragrance mix I, fragrance mix II, and balsam of Peru. Fragrance mix I consists of 9 haptens, which are: Cinnamic alcohol 1.0%, Cinnamic aldehyde 1.0%, Eugenol 1.0%, Isoeugenol 1.0%, Geraniol 1.0%, Hydroxycitronellal 1.0%, Oak moss absolute 1.0%, Amylcinnamaldehyde 1.0%, and Emulgator Sorbitan sesquioleate 5%. In 2008, in response to the increased frequency of allergy to fragrance substances, fragrance mix II was added to the EBS, which consists of 6 haptens: Citronellol 0.5%, Hydroxyisohexyl 3-cyclohexene carboxaldehyde (Lyral) 2.5%, Hexyl cinnamal 5.0%, Citral 1.0%, Coumarin 2.5%, and Farnesol 2.5%. An alarming finding of our research (2007) was the more frequent allergy to fragrance substances (Fragrance mix I) among 7-8 year-olds, compared with teenagers aged 16-17 (Tab. 1, Fig.1) [20, 39].

These results were confirmed during our further research carried out in 2008-2009 on children with eczema, although this time fragrance mix II was used. Among 17 children and adolescents allergic to fragrances observed in the present study, 7 (41%) reacted exclusively to fragrance mix II (Tab. 3).

Table 3. Hypersensitivity to fragrance mix I and fragrance mix II in children (7-8 y.o.) and adolescent (16-17 y.o.) with atopy and history of chronic recurrent eczema [12]

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

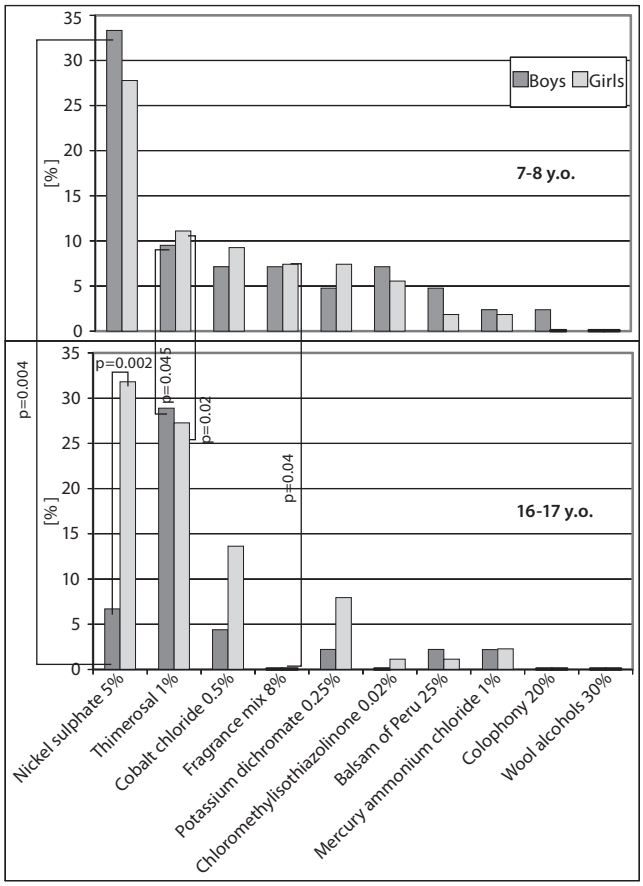

Figure 1. Frequency of positive patch test reactions in children (7-8 y.o.) and adolescents (16-17 y.o.) with atopy and history of chronic recurrent eczema in 2007 [20].

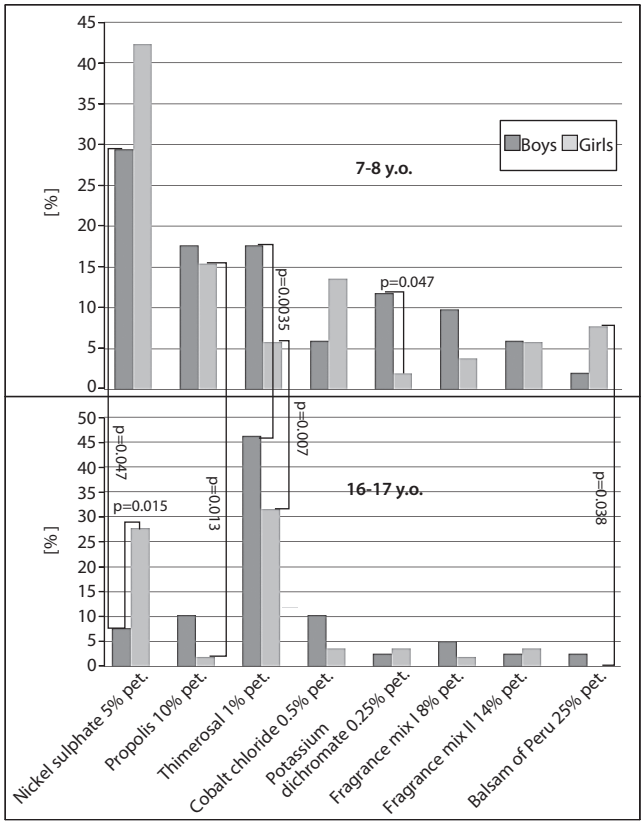

Figure 2 Frequency of positive patch test reactions in children (7-8 y.o.) and adolescents (16-17 y.o.) with atopy and history of chronic recurrent eczema in 2008-2009 [19].

Overall sensitization rates to fragrance mix I and II were higher among children (6.8% and 5.8%, respectively), than among adolescents (3.2% and 2.2%) (Tab. 1, Fig. 2) [19].

Balsam of Peru. In population screenings, allergies to this fragrance substance is also used owing to its common usage and provoking cross-reactions with other fragrance substances [48]. Balsam of Peru is one of the most frequent haptens causing isolated hand eczema. Apart from cosmetic products, balsam of Peru or chemical compounds provoking cross-reactions are used in toothpastes and mouthwashes, which can be the cause of allergic stomatitis or cheilitis. Balsam of Peru is also a favorite medicament for surgeons, used for difficult wounds and ulcerations. It is also a component of flavored alcoholic or non-alcoholic drinks, balsamic sauces, as well as confectionery products and flavor additives, such as cinnamon, vanilla, cloves or curry. Regarding our research carried out in 2007 on students with eczema allergy to balsam of Peru, it occurred more often in children 7-8 years old (3.1%), compared with 16-17 year-olds (0.9%) (Tab. 1, Fig. 1). Continuation of the same research in 2008-2009 confirmed the significance of allergy to balsam of Peru in 7-8 year-olds (4.9%) and 16-17 year-olds (1.1%) (Tab. 1, Fig. 2) [19, 20, 39].

According to the presented results, allergy to fragrance substances (Fragrance mix I & II, balsam of Peru) is increasing and is higher in the case of children (7-8 year-olds), compared to teenagers (16-17 year-olds). This illustrate the increase in exposing children to perfumed products (books, toys, cosmetics for children, etc.) and, what is more, proves the need to test children with fragrance substances.

Propolis. Propolis is another interesting example of how changes in exposure may lead to increased contact sensitization to haptens. Propolis is a resinous mixture collected by honey bees from tree buds, sap flows, or other botanical sources. Its composition varies depending on the geographical location: in Central Europe, the sensitizing compounds of propolis are caffeates derived from the sticky exudates of poplar buds. Patients from countries where poplar trees do not grow, become allergic to other propolis constituents as the caffeates are not present in local propolis [49]. In Poland, an increase in contact sensitization to propolis has been observed recently, which seems to result rather from the intensity of exposure than from changes in the composition of this complex sensitizer. For the last 20 years, propolis has been promoted in Poland as a 'pure, natural', 'steroid-free', 'chemical-free' remedy for a wide range of diseases, including allergies. In every pharmacy and herbal shop there is a variety of propolis preparations for oral and external use on sale. It is used in biocosmetics, such as face creams, ointments, balsams, solutions, varnishes, toothpastes, mouthwashes, pills, chewing gums, etc. It is also used as violin wax. As a result of the increased exposure, sensitization to propolis has emerged as a major public health problem. In recent studies, 15.1% of seven-year-old children and 15.1% of adults diagnosed for allergic contact dermatitis turned out sensitive to propolis, which places it among the most frequent sensitizers in Poland [19, 50]. In 2008-2009, in a study of children, we demonstrated the relatively high sensitization rate to propolis, which is the second most frequent sensitizer in children after nickel. (Tab.1, Fig.2) [19]. It now appears that with an ever-increasing steroid-phobia, many parents choose propolis for any of their children's skin conditions, including eczema, which may lead to secondary sensitization to this substance. We have found positive patch tests reactions to propolis in 16.5% of 7-8 year-olds and 5.4% of 16-17 year-olds with chronic/recurrent eczema (Tab.1, Fig.2) [19]. During earlier research, positive patch test with propolis was observed in 15 % of adult patients [50]. Altogether, these results suggests that propolis is indeed among the most frequent contact sensitizers and should be included into routine patch testing.

Features influencing the termination of contact allergy to thimerosal, Kathon CG.

Thimerosal is a preservative adsorbent which contains mercury, which used to be added to many products, including cosmetics and medicines. Exposure to this hapten occurred while using eye droplets, contact lens fluids, disinfectants and cosmetics. Eyelid eczema was therefore the reaction. It is also known that thimerosal is one of the vaccine preservatives. In 2007, in our study, in the case of 7-8 year-olds, contact allergy to thimerosal occurred less frequently than in the case of 16-17 year-olds (p=0.007) (Tab.1, Fig.1). In most of their papers, authors emphasize the fact that a possible cause for the frequent hypersensitivity to this hapten among teenagers may be the compulsory prophylactic vaccinations [51, 52]. This is also confirmed by our research, which revealed that the 16-17 year-olds participating in the study had received 6 thimerosal-preserved vaccines, with the most recent immunization 2-3 years before patch testing. The 7-8 year-olds received only 4 vaccines with thimerosal, the last one 5 years before testing. The new acellular DTPa vaccines (Infanrix, Tripacel, Pentaxim) given to 7-8 year-olds a year earlier, did not contain thimerosal (Tab.4) [20, 39]. Because boys and girls received the same number of vaccines containing tiomersal, this method of immunization does not explain the more frequent occurrence of allergy to this preservative in 16-year-old girls (27.3%) than in 7 year-old girls (11.1%), with the absence of such difference among boys (Tab.1, Fig.1). The difference might result from the fact that teenage girls use more cosmetics and intimate hygiene fluids preserved with thimerosal. Many authors suggest that thimerosal allergy is not clinically relevant, which might be caused by the different routes of exposure to hapten (intramuscular injection). Therefore, the presence of positive patch test with thimerosal does not constitute any contraindication against applying vaccines preserved with thimerosal [53, 54]. Because of the low clinical relevance of contact allergy to thimerosal, this substance is not included in the EBS [14]. The less frequent allergy to thimerosal in 7-8 year-olds can result from withdrawing this preservative from vaccines, which limits the risk of hypersensitivity to this hapten.

Table 4. Immunization with use of vaccinations preserved with thimerosal with which examined children were vaccinated [39]

Type of vaccine	Group of 7-8 y.o.	Group of 16-17 y.o.
DTP	4 inj. until 2 y.o.	4 inj. until 2 y.o.
DT	-	1 inj. in 6 y.o.
DT	-	1 inj. in 13-14 y.o.

D – Diphteria, T – Tetanus, P – Pertussis

Kathon CG (MCI/MI chloromethyloisotiazolinone/ metyloisotiazolinone). According to the results of the meta-analysis carried out by Spiewak (1980- 2001) [18], this was the substance which mostly caused allergy to children with eczema (21%). In 2007, however, positive reactions to Kathon CG were noted only in 3% of tested children with eczema (Tab.3, Fig. 1) [1]. This distinctive difference results from the fact that this preservative has been withdrawn from cosmetics in recent years, which has possibly limited the frequency of sensitization to this hapten. This assumption is confirmed by a study carried out in 1995-2001 by Seidenari *et al.* [55] on Italian children with eczema: in this group, 4.2% were allergic to Kathon CG. The results of this study are similar to ours. The decrease of allergy to Kathon CG has resulted in the fact that it has not been taken into consideration in the most recent investigations [22, 23, 24].

CONCLUSIONS

The frequency of contact allergy among children illustrates the changes taking place in their environment.

Contact allergy among children is most often caused by substances commonly found in the environment. The most common haptens causing allergy to children are metals (particularly nickel), preservatives (thimerosal), fragrance substances, propolis and balsam of Peru.

The increase of frequency of contact allergy to fragrance substances among young children seems to illustrate increasing exposure of children to these substances from miscellaneous sources.

The decrease in frequency of contact allergy to withdrawn preservatives like thimerosal and Kathon CG seems to prove that restricting the environmental exposure to haptens with proved allergic potential, seems to be an effective tool for contact allergy prevention.

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