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CLINICAL REPORT

Nickel Sensitization in Adolescents and Association with Ear Piercing, Use of Dental Braces and Hand Eczema.

The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS)

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The prevalence of nickel allergy (sensitization) and the associations with ear piercing, use of dental braces and hand eczema were assessed in a cohort of 1,501 8th grade schoolchildren (aged 12–16 years) in Odense, Denmark. Nickel allergy was found in 8.6% and was clinically relevant in 69% of cases. Nickel allergy was found most frequently in girls and the association with ear piercing was confirmed. Application of dental braces (oral nickel exposure) prior to ear piercing (cutaneous nickel exposure) was associated with a significantly reduced prevalence of nickel allergy. In adolescents a significant association was found between hand eczema and nickel allergy. A follow-up study of this population is planned in order to assess the course and development of contact dermatitis, hand eczema and atopic diseases in adulthood and after choice of occupation. ***Key words: schoolchildren; atopic dermatitis; inhalant allergy; hand eczema; multivariate graphical analysis.***

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Studies in children and adolescents visiting dermatological clinics as well as population-based studies have repeatedly shown that nickel allergy is the most common contact allergy (1–13). The prevalence of nickel sensitization in children and adolescents in the general population varies from 0.9 to 14.9% (2, 14, 15). The most common cause of sensitization appears to be ear piercing (16–19), and the risk for nickel allergy is increased with the number of piercings (16, 17). Other sources of sensitization include jewellery, belt buckles, metal fasteners on clothing and eyeglass frames.

Few reports have suggested that treatment with nickel-containing metallic orthodontic appliances (oral nickel exposure) before ear piercing (cutaneous nickel exposure) may reduce the frequency of nickel allergy (20, 21). However, more clinical studies are needed to confirm this hypothesis.

Nickel allergy in adults has been shown to increase the risk of development of hand eczema (22). However it is not known whether this relationship exists already in childhood and adolescence.

The aims of this study were 1) to estimate prevalence measures of nickel sensitization in an unselected population of adolescents, 2) to identify groups of nickel sensitized persons with a weak, moderate or strong degree of nickel allergy in order to evaluate in future studies if the degree of nickel allergy is correlated with later development of dermatitis, 3) to confirm the relationship between nickel allergy and ear piercing and the use of dental braces, and 4) to study the relationship between nickel allergy and atopic diseases and nickel allergy and hand eczema.

METHODS

Population and study design

The Odense Adolescence Cohort Study (TOACS) is an epidemiological follow-up study. Phase one (1995–1996) was conducted as a cross-sectional study among 1,501 8th grade schoolchildren in 40 schools in the Municipality of Odense. Phase one included questionnaires, interviews and clinical examinations, blood samples for IgE measurement and patch tests. Phase two (1996–1997) was conducted as a case-control study in selected groups of schoolchildren. The population and study design has been described already (23).

Definitions and description of terms

Atopic dermatitis, inhalant allergy and allergic contact dermatitis. The criteria for the diagnoses have already been reported in detail (23, 24).

Hand eczema. The lifetime prevalence of hand eczema was evaluated from the questionnaire, as already reported (23, 24). At the clinical examination, hand eczema was defined as eczema localized to the fingers or finger webs, backs of hands or palms, characterized by itching, erythema, vesicles and/or papules and scaling. More chronic erythematous, scaling, fissuring and/or lichenified types of dermatitis were also included. The eczema should have a duration of at least 2 days.

Allergic contact dermatitis caused by metal contact. The lifetime prevalence of self-reported eczema caused by metal skin contact was evaluated from the question: ''Do you get eczema (rash) from jeans buttons, metal fasteners, metal costume jewellery (e.g. earrings) or other metal parts of clothes next to your skin (excluding under the ring)?'' (25).

Ear piercing and use of dental braces. The questions were: (i)

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Have you ever had your ears pierced or had any other piercing of your skin?", (ii) "Have you ever had dental braces?" The time for both events should be given.

Contact allergy/Type IV sensitization. This was defined as at least one positive patch test reaction to allergens in the TRUE Test® including a nickel dilution series.

Patch tests

The TRUE Test® panels 1 and 2 (Pharmacia & Upjohn, Hillerød, Denmark) was used together with a TRUE Test patch dilution series consisting of nickel sulphate ($NiSO_4$, $6H_2O$) in 3 concentrations (200, 10, 1 $\mu g/cm^2$) and one placebo (26, 27). The patch test method has been described previously (24). Briefly, the patch tests were applied to the upper back for 2 days, removed by the investigators and scored after 3 days (28). The relevance of a positive test result was evaluated in relation to exposure history, dermatitis history and present dermatitis pattern.

Ethics

The ethics committee for Vejle and Funen County (proj. no. 95/22) approved the study. Informed consent was obtained both from the school children and from their parents.

Data handling and statistics

All data were entered twice in the databases. When differences were found, a comparison with raw input forms was made and corrections done accordingly. Statistical analyses were performed using Stata 5.0 (Stata corporation, TX, USA), with the exception of in graphical models.

The prevalence proportion was defined by the number of positive answers divided by the total number of schoolchildren questioned. The 95% confidence intervals are shown in parentheses (95% CI). The prevalence proportions for boys and girls are given and if a significant sex difference is found, the *p*-value is given or significance is indicated. Comparisons were made by χ^2-based table analysis.

Odds ratio (OR) is given as the Mantel Haenzel odds ratio stratified by sex, with associated confidence intervals in parentheses (95% CI). Differences by sex are noted, when the stratum-specific estimates indicate significant "effect modification". Statistical significance was defined as $p < 0.05$.

Because of the close association between the investigated diseases, a multivariate analysis was performed, which at the same time could account for the interdependence and possible association with external factors (control for all associations at the same time). The analysis was performed using specialized software (Digram®) following the procedure as described by Klein et al. (29). The results are expressed in the form of a graph on which non-random associations between variables are represented by a line (further description in (24)). Because the variables are binary or ordinal, the strength and degree of statistical significance of an association can be measured by Kruskal and Goodman's gamma coefficient in the form of a conditional or partial gamma (30). Gamma coefficients numerically less than 0.15 indicate weak associations, those between 0.15 and 0.30 indicate moderate associations, and more than 0.30 strong associations. Because of the many statistical tests in these analyses, a significance level of 0.01 was used to compensate for false associations (Type I error).

RESULTS

Prevalence of nickel sensitization

The pattern of participation, patch test characteristics and frequencies of individual patch test reactions have been described previously (23, 24). Patch testing was performed in 76.3% (1,146/1,501) of the schoolchildren.

Nickel sensitization was found in 8.6% using results from both patches with nickel sulphate 200 $\mu g/cm^2$ (Table I). In the TRUE Test patch dilution series 2.8% reacted to nickel sulphate 10 $\mu g/cm^2$ and 0.3% to nickel sulphate 1 $\mu g/cm^2$. Significantly more girls than boys had nickel allergy (Table I). No reactions to nickel sulphate 10 $\mu g/cm^2$ and 1 $\mu g/cm^2$ were obtained without a reaction to 200 $\mu g/cm^2$ and no reactions to the placebo were seen.

Nickel allergy in relation to atopic dermatitis, inhalant allergy and hand eczema

Nickel allergy was significantly associated with hand eczema (OR 2.36, 95% CI 1.39–4.01, $p < 0.002$ stratified for sex). The association was still significant when those with concomitant atopic dermatitis and inhalant allergy were excluded from the hand eczema group (OR 4.01, 95% CI 1.82–8.84, $p < 0.001$ stratified for sex).

Of those with present or past hand eczema, 18.2% had nickel allergy (girls 23.5%, boys 7.5%, $p < 0.04$ for sex difference) compared with 7.4% of those without hand eczema (girls 12.2%, boys 2.1%, $p < 0.001$ for sex difference). On the other hand, 22.4% of nickel allergic schoolchildren had present or past hand eczema (girls 22.4%, boys 23.1%) compared with only 9.4% of those without nickel allergy (girls 11.6%, boys 7.2%, $p < 0.02$

Table I. *Prevalence of nickel sensitization, ear piercing, use of dental brace and hand eczema (lifetime prevalence measures)*

	Total population	Girls	Boys
Nickel sensitization			
200 $\mu g/cm^2$	8.6% (98/1,146)	13.7% (85/620)*	2.5% (13/526)
10 $\mu g/cm^2$	2.8% (32/1,146)	5.0% (31/620)*	0.2% (1/526)
1 $\mu g/cm^2$	0.3% (4/1,146)	0.6% (4/620)	0% (0/526)
Ear piercing	50.8% (731/1,438)	81.5% (581/713)*	20.7% (150/725)
Dental brace	31.7% (456/1,438)	39.3% (280/713)*	24.3% (176/725)
Hand eczema	9.2% (133/1,438)	12.2% (87/713)*	6.3% (46/725)

*$p < 0.001$ for sex difference.

for sex difference). Furthermore, we also found an association between clinically relevant nickel allergy and hand eczema by analysing self-reported metal-contact-related eczema verified by a positive patch test to nickel (OR 2.39, 95% CI 1.27–4.50, $p < 0.006$, stratified for sex). There was no association between contact allergy to other compounds than nickel and hand eczema.

Among the adolescents, 1.6% (13 girls, 9 boys) had current hand eczema. Twenty-one of the 22 were patch-tested and 2 girls, both with pierced ears, had positive reactions to nickel. One of the girls had nickel allergy of current relevance and a strong reactivity down to 10 μg/cm^2. The other girl had a reaction only to 200 μg/cm^2 and had no history of dermatitis from metal skin contact.

There were no significant associations between nickel allergy and atopic dermatitis or inhalant allergy (data not shown).

A multivariate analysis with nickel sensitization as the outcome is illustrated in Fig. 1 and Table II. All those with other contact allergies were excluded from the analysis. The 3 different boxes in Fig. 1 indicate outcome variable (nickel sensitization), investigated diseases and background variables. The figure should be read from the right to the left. Arrows indicate associations between different levels (boxes) and lines indicate associations within the same level (box). As expected, the analysis shows a strong association between atopic dermatitis and inhalant allergy, between atopic dermatitis and hand eczema, and also an association between nickel allergy and hand eczema. However, conflicting gamma and χ^2 values were found for the relationship between nickel allergy and hand eczema (gamma 0.36 vs. χ^2 7.7). This analysis shows no association between nickel allergy and atopic dermatitis or inhalant allergy.

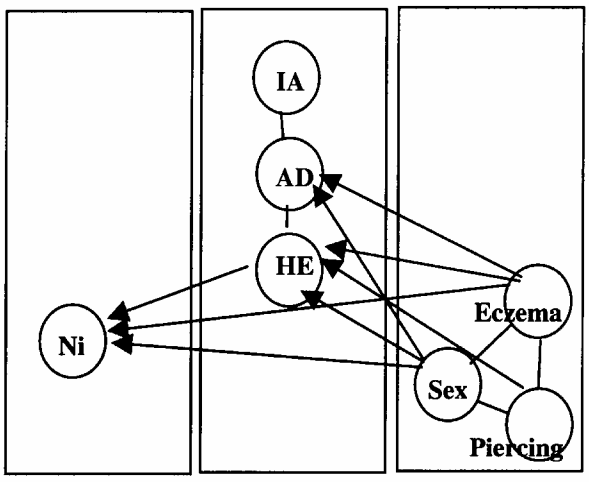

Fig. 1. Summary of results from a multivariate graphical analysis with nickel sensitization as outcome ($n = 1{,}070$). In this analysis all those with other contact allergies have been excluded. See also Table II. Ni: Nickel sensitization – positive patch test for nickel; AD: present or past atopic dermatitis; IA: present or past inhalation allergy (allergic asthma and/or allergic rhinitis); HE: present or past hand eczema; Eczema: present or past eczema caused by metal contact; Piercing: present or past ear piercing.

In a multivariate analysis for contact allergy excluding nickel sensitization, no association was found between contact allergy and hand eczema, atopic dermatitis or inhalant allergy (data not shown).

Nickel allergy by patch testing in relation to clinical relevance

The association between reported eczema caused by metal skin contact and nickel allergy by patch testing adjusted for sex was highly significant (OR 9.33, 95% CI 5.62–15.47, $p < 0.001$). In the questionnaire a total of 15.5% (223/1,438) of schoolchildren reported eczema caused by metal skin contact (girls 23.4%, boys 7.7%, $p < 0.001$ for sex difference), and among those participating in patch testing 17.9% (205/1,146) reported metal-contact-related eczema (girls 24.8%, boys 9.7%, $p < 0.001$ for sex difference). Of those with a history of eczema from metal skin contact, 30.7% (girls 37.7%, boys 9.8%, $p < 0.001$ for sex difference) showed a positive nickel patch test, compared with 3.7% (girls 5.8%, boys 1.7%, $p < 0.002$ for sex difference) in those with a negative history of eczema from metal skin contact.

The clinical relevance of a positive patch test to nickel sulphate was assessed by exposure history, dermatitis history and present dermatitis pattern immediately after patch testing. 69.4% (68/98) of the nickel allergic cases had a clinical relevance (girls 74.1%, boys 38.5%, $p < 0.01$ for sex difference) and only 5 of these 68 cases were not identified from the questionnaire.

The clinical relevance of nickel allergy was found in 87.5% of those with reactions to nickel sulphate 10 μg/cm^2 and in all 4 reacting to nickel sulphate 1 μg/cm^2.

Nickel allergy in relation to ear piercing and wearing of dental braces

In this study 50.8% of the adolescents had their ears pierced, and 31.7% had used dental braces (Table I).

As expected, nickel allergy was significantly associated with ear piercing adjusted for sex (OR 3.18, 95% CI 1.43–7.08, $p < 0.004$). However, there was a significant effect modification by sex. A significant association was found between nickel allergy and ear piercing in girls (OR 5.12, 95% CI 1.82–14.44, $p < 0.002$). Of the girls with pierced ears, 15.9% had nickel allergy compared with 3.6% of girls without ear piercing. Among girls with nickel allergy, 95.3% had ear piercing, while 79.8% of the girls without nickel allergy had ear piercing. In boys, nickel allergy was not associated with ear piercing (OR 0.88, 95% CI 0.24–3.23, $p = 0.841$).

The occurrence of nickel allergy in relation to different time sequence combinations of use of dental braces and ear piercing is presented in Table III. None of the boys

Table II. *Summary of results from the multivariate graphical analysis with nickel sensitization as outcome (n = 1070). In this analysis all those with other contact allergies have been excluded. See also Fig. 1*

Hypothesis	χ^2	Df	Exact *p*-value	Gamma	Exact *p*-value (one-sided)
Ni vs. HE ⊥ sex, eczema	7.7	4	0.094	0.36	0.006
Ni vs. sex ⊥ HE, eczema	23.5	4	0.000	− 0.61	0.000
Ni vs. eczema ⊥ HE, sex	103.2	4	0.002	0.81	0.002
AD vs. IA	94.3	1	0.000	0.62	0.000
AD vs. HE ⊥ sex, eczema	81.5	4	0.000	0.68	0.000
AD vs. sex ⊥ HE, eczema	8.5	4	0.068	− 0.18	0.010
AD vs. eczema ⊥ HE, sex	12.5	4	0.018	0.27	0.002
HE vs. sex ⊥ AD, eczema, piercing	15.8	8	0.042	− 0.26	0.060
HE vs. eczema ⊥ AD, sex, piercing	27.6	8	0.004	0.41	0.002
HE vs. piercing ⊥ sex, eczema	12.1	4	0.020	− 0.19	0.082
Sex vs. eczema ⊥ piercing	14.5	2	0.000	− 0.38	0.000
Sex vs. piercing ⊥ eczema	433.9	2	0.000	− 0.87	0.000
Eczema vs. piercing ⊥ sex	22.3	2	0.000	0.48	0.000

The Table contains the statistical- or user-specified non-random associations.
Ni vs. HE ⊥ sex, eczema, e.g. Ni is associated with hand eczema conditional (⊥) on sex and eczema.
Conditional in this context means "sex and eczema", plus all other information in the analysis.
Ni: Nickel sensitization – positive patch test for nickel; AD: present or past atopic dermatitis; IA: present or past inhalation allergy (allergic asthma and/or allergic rhinitis); HE: present or past hand eczema; Eczema: present or past eczema caused by metal contact; Piercing: present or past ear piercing.

Table III. *Relations between use of dental brace, ear piercing and nickel allergy*

Dental brace	Pierced ears	Group size			Percentage of nickel patch test positive		
		Total	Girls	Boys	Total	Girls	Boys
		(*n* = 1,438)	(*n* = 713)	(*n* = 725)	(*n* = 1,146)	(*n* = 620)	(*n* = 526)
+*	+	266	227	39	15.7% (36/230)	18.0% (36/200)	0% (0/30)
+ first	+	67	51	16	1.7% (1/60)	2.1% (1/48)	0% (0/12)
+	+ first	177	160	17	20.4% (31/152)	22.5% (31/138)	0% (0/14)
+ same year	+ same year	22	16	6	22.2% (4/18)	28.6% (4/14)	0% (0/4)
–	–	517	79	438	2.9% (11/382)	4.5% (3/66)	2.5% (8/316)
+	–	190	53	137	2.7% (4/150)	2.2% (1/46)	2.9% (3/104)
–	+	465	354	111	12.2% (47/384)	14.6% (45/308)	2.6% (2/76)

*Those with both dental brace and ear piercing were separated into 3 groups, depending on whether the dental brace was the first event, the ear piercing was the first event or the two events occurred during the same year.

with both dental braces and ear piercing had nickel allergy, while 18.0% of the girls with both conditions had nickel allergy. The application of dental braces prior to ear piercing was significantly associated with a reduced frequency of nickel allergy in girls compared to the use of dental braces after ear piercing (OR 0.07, 95% CI 0.01–0.59, $p < 0.002$). Only 2.1% of the girls who acquired dental braces before their ears were pierced had nickel allergy, compared with 22.5% of the girls who had ear piercing before acquiring the dental braces.

Considering the question about self-reported metal-related eczema, 17.4% of the girls who had ear piercing prior to using dental braces reported eczema caused by metal skin contact and had a positive patch test to nickel, while none of the girls with dental braces before piercing reported metal-related eczema and had a positive patch test to nickel ($p < 0.003$).

DISCUSSION

The study confirmed that the prevalence of nickel allergy was high in adolescents (8.6%) in accordance with other population-based studies in this age group (0.9% to 14.9%) (2, 14, 15), and, as expected, nickel allergy was significantly more frequent in girls than boys (girls 13.7% vs. boys 2.5%) (5, 6, 11, 12, 31).

The European Union (EU) regulation on nickel exposure (94/27/EEC) is now in effect in 2001 whereas it was implemented in Denmark in 1991 (32). The reduction of nickel release from jewellery seems to reduce the frequency of nickel allergy in young people (33).

A possible relationship between the level of skin reactivity to nickel sulphate and the presence of hand dermatitis has not been studied in a prospective protocol. Two retrospective studies revealed no relationship (27,

34). Furthermore, an inverse correlation between skin reactivity to nickel and the effect of a low nickel diet on activity of dermatitis has been published (35). In our study, patch testing was performed with 3 different concentrations of nickel sulphate to identify groups of people with varying degrees of nickel sensitization. Reactions to nickel sulphate concentrations of 10 $\mu g/cm^2$ were seen in 2.8% and to 1 $\mu g/cm^2$ in 0.3%. The concentrations were selected from a previous dose-response study in selected nickel-sensitive patients (27). The 3 groups of nickel-sensitized persons will be followed prospectively to determine whether those with moderate or strong sensitization are more likely to develop hand eczema.

Nickel allergy was considered clinically relevant in 69.4% of the nickel sensitized, and those reacting to the 2 lower concentrations were almost all of clinical relevance. Recall bias could explain some of the reactions without a positive history. However, the frequency of relevance of a positive nickel patch test was higher in this study than in two other studies including schoolchildren (16, 17), and was in agreement with a Danish study among veterinary students (36).

Of those reporting metal-related eczema, only 30.7% had a positive nickel patch test, as also reported by Kieffer (36). Possible explanations for the difference could be irritant skin reactions under wristwatch cases, buckles and rings or false negative patch test reactions. It has also been suggested that a positive history but a negative nickel patch test indicates atopy (37).

The most common cause of sensitization to nickel appears to be ear piercing (16, 17) and the risk for nickel allergy is increased with the number of piercings (17). However, we could not confirm the association in men as reported by others (38).

Explanations for the more frequent occurrence of nickel allergy in girls compared with boys include the fact that more girls than boys have their ears pierced, and boys may have ear piercing at a later age, have piercing only in one ear, or they use jewellery containing less nickel (28). However, it has also been suggested that women are sensitized by a lower exposure than men (39).

There is no method of desensitization. However, some studies have shown that treatment with nickel-containing metallic orthodontic appliances before ear piercing (cutaneous nickel exposure) may reduce the frequency of nickel hypersensitivity (20, 21). Studies have verified that nickel-containing alloys undergo degradation and small quantities of free metals (ions) are released in the oral cavity (40). We also found that the use of dental braces before ear piercing was associated with a lower prevalence of nickel allergy compared to ear piercing before the use of dental braces. These results support the view that oral administration of a contact allergen prior to attempted sensitization induces immune tolerance.

Several studies in adults have shown an association between hand eczema and nickel allergy (22, 39, 41, 42). In a previous report we found a significant association between contact allergy and hand eczema in adolescents (24), and it was nickel allergy that was responsible for this association. Those with nickel allergy had a higher prevalence of hand eczema (22.4%) compared with those without nickel allergy (9.4%). The risk assessment cannot be evaluated in this cross-sectional design, but will be evaluated in a follow-up study in this population.

The association between nickel allergy and atopic dermatitis, inhalant allergy and hand eczema was evaluated in a simple model using the Mantel Haenzel analysis, stratified for sex. Because of the association between the 3 diseases, analyses have also been performed for each disease alone, excluding schoolchildren with one or both of the other diseases. This is a simplification of real life, and more complicated statistical approaches were performed for verification of the results. Because of the association between all three diseases, a logistical regression model was not considered appropriate and a multivariate graphical analysis was used as an alternative. This gave similar results, as the simpler stratified analyses, for example, verified the association between nickel allergy and hand eczema.

In the future this cohort of schoolchildren will be followed with regard to the course and development of atopic diseases, hand eczema and contact dermatitis.

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