

Received Date : 11-Feb-2016

Revised Date : 01-Apr-2016

Accepted Date : 14-Apr-2016

Article type : Original

Low patch test reactivity to nickel in unselected adolescents tested repeatedly with nickel in infancy

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Running title: Low patch test reactivity to nickel sulphate.

Conflicts of interest: Klaus E. Andersen is an advisor and Charlotte G. Mortz is an investigator for SmartPractice A/S, Denmark. For other co-authors there are no conflicts of interest.

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Low patch test reactivity to nickel in unselected adolescents tested repeatedly with nickel in infancy

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Pediatr Allergy Immunol

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:

10.1111/pai.12578

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Abstract

Background: It is questionable how repeated patch tests with nickel sulphate in infancy affect nickel patch test reactivity at a later age.

Methods: The DARC cohort encompasses 562 infants invited to a clinical examination including patch tests with nickel sulphate 6 times during the first 36 months of life. At the follow-up investigation at 14 years of age (2013-14) participants were offered re-patch tests with nickel sulphate.

The TOACS cohort encompasses 1501 schoolchildren evaluated for the first time at 14 years of age (1995-96) including clinical examination and nickel sulphate patch tests. The prevalence of nickel sensitization in the DARC cohort was compared to the prevalence in the TOACS cohort at 14 years of age.

Results: Nickel sulphate sensitization was found in 1.2% of the participants from the DARC cohort tested repeatedly with nickel sulphate in early childhood and retested at 14 years of age compared to 8.6% of the participants from the TOACS cohort patch tested for the first time at 14 years of age using the same patch test system and test concentration

Conclusion: The significant difference in nickel patch test reactivity comparing the two cohorts may reflect an immunologic effect or the effect of nickel regulation.

Key words: patch test, nickel sulphate, cohort study, infancy, adolescence, allergic contact dermatitis.

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Introduction

Nickel sulphate is regarded as one of the contact allergens with the highest frequency of reproducible positive patch tests (1). However, a Swedish study retested 30 nickel sensitive females with a dilution series 4 times over 7 months and found a considerable variation in the individual level of nickel sensitivity over time (2). In 2013, we reported a very low reproducibility of nickel sensitization at 3 and 6 years of age in children from the DARC cohort patch tested with nickel sulphate repeatedly during the first 18 months of life and having reproducible positive reactions at both 12 and 18 months of age (3). The positive reactions during infancy were interpreted as being of irritant or non-specific nature. The question emerges if an alternative explanation is possible. Several studies have shown that peroral nickel exposure may induce nickel unresponsiveness or tolerance (4-7). It is questionable how repeated epicutaneous patch tests with nickel sulphate in infancy affect nickel patch test reactivity at a later age. Lowney exposed human volunteers to dinitrochlorobenzene (DNCB) epicutaneously and concluded that it is possible to manipulate the level of contact sensitivity in man by manipulating the circumstances under which sensitization is induced (8). The aim of this study is to compare the frequency of positive nickel sulphate patch tests in the 2 unselected cohorts of adolescents tested with the same patch test system and scoring methods 18 years apart.

Methods

Study population

The Danish Allergy Research Center (DARC) birth cohort is a population-based birth cohort including children born between November 1998 and November 1999 in Odense, Denmark. Inclusion criteria were: Born between the 1st and 14th of every month and gestational age ≥ 37 weeks. A total of 1095 infants fulfilled the inclusion criteria. The parents of 435 infants declined and 98 were excluded by investigator, leaving 562 children in the study for future follow-up investigations. The group that declined participation did not differ significantly from the study population regarding maternal age, parity, gender, birth weight, gestational age and the prevalence of atopic dermatitis at 12 months (9). The parents answered a questionnaire and the children were examined clinically at 0, 3, 6, 9, 12, 18 month and 3, 6, 14 years of age. Furthermore, patch tests were performed at 0, 3, 6, 12, 18 month and 3 years with nickel sulphate and fragrance mix I. At the 72 month follow-up investigation a selected group of 21 children with a positive patch test to nickel sulphate at 12 and 18 month were re-patch tested. A more detailed description of the follow-up investigations is published (9, 10).

At the 14 years follow-up investigation in 2013-14 all participants (372) were offered re-patch tests with TRUE Test[®] panel 1, 2 and 3, encompassing nickel sulphate 200 $\mu\text{g}/\text{cm}^2$.

The other population based cohort is the Odense Adolescence Cohort Study (TOACS) established in 1995-1996 as a cross sectional study among 1501 eight grade school children (mean age 14 years) and including a questionnaire, clinical examination and patch tests with TRUE Test panel 1 and 2 (11).

Patch Test

Nickel sulphate 200 $\mu\text{g}/\text{cm}^2$ and Fragrance Mix I 430 $\mu\text{g}/\text{cm}^2$ (TRUE Test[®], SmartPractice A/S, Hillerød, Denmark) were applied for testing the DARC cohort the first 6 years. At the 14 years follow-up investigation all participants were offered retest with TRUE Test[®] panel 1, 2 and 3 including nickel sulphate 200 $\mu\text{g}/\text{cm}^2$. In the TOACS cohort patch tests were performed with TRUE Test[®] panel 1 and 2 in 1995-1996. In both cohorts testing were performed according to International Contact Dermatitis Research Group (ICDRG) guidelines (12).

Atopic dermatitis

Current atopic dermatitis was based on the Hanifin and Rajka criteria (13) and symptoms within the previous 12 months. Severity was assessed by SCORAD index (14).

Hand eczema

The lifetime prevalence of hand eczema was determined using the NOSQ-2002 questionnaire (15); in the DARC cohort as part of an interview and in the TOACS cohort as a questionnaire. The criteria for a history of hand eczema were eczema (rash) on the fingers, finger webs, palms or back of hands, which had appeared once and continued for at least 2 weeks or had appeared several times or had been persistent.

Ethics

The Regional Scientific Ethical Committee for Southern Denmark approved both studies: DARC cohort (S-VF-19980101) and TOACS cohort (S-VF-19950022). The risk of a primary sensitization by patch testing with nickel sulphate was considered extremely low.

Statistics

Statistical analysis was performed with STATA/SE 11.0 (Stata Corporation, College Station, TX, U.S.A). The results are given as a prevalence proportions and 95% confidence intervals. Comparisons between positive patch test to nickel sulphate in the two cohort studies were made by Fisher's exact test. Comparison of the lifetime prevalence of hand eczema and atopic dermatitis in the two cohorts was made by χ^2 -test.

Statistical significance was defined as $P < 0.05$.

Results

From the DARC cohort a total of 372/562 participated in the clinical examination at the 14 years follow-up investigation in 2013-2014 and 249 were patch tested, (148 females and 101 males). Of the 190 from the original cohort that did not participate in the 14 years follow-up investigation: 113 participants dropped-out before and at the 14 years follow-up investigation, 11 did not respond to the invitation, and 66 participated only in a telephone interview. Comparing those participating with those not-participating showed few differences in baseline characteristics i.e. children of mothers who smoked during pregnancy and at birth tended not to participate.

A positive nickel sulphate patch test was seen in three females giving a point prevalence of 1.2%, and two of the three reactions were clinically relevant (Table 1).

In the TOACS cohort a total of 1340/1501 participated in a clinical examination in 1995-1996, and 1146 were patch tested (620 females and 526 males). A total of 98 (8.6%) had a positive nickel sulphate patch test (85 females and 13 males) (Table 1).

In both cohorts the number that had ear piecing and the prevalence of current atopic dermatitis was comparable whereas the lifetime prevalence of atopic dermatitis was significantly higher in the DARC cohort (Table 2). In the DARC cohort 53.3 % of those with current atopic dermatitis were type I sensitized to either inhalant and/or food allergens while it was 52.2% in the TOACS cohort. The lifetime prevalence of hand eczema in the DARC cohort was significantly lower than in the TOACS cohort (Table 2).

Discussion

The data presented here is an interesting observation. We chose to compare results from the DARC cohort with the results from the TOACS cohort because the two cohorts are comparable regarding test method, age and geographical region. The use of TRUE® tests in both studies have ascertained complete technical uniformity, as dosage and bioavailability is up to pharmaceutical standard.

A factor 7 difference in the prevalence of positive nickel patch tests observed in the DARC cohort (1.2 %) compared to the TOACS cohort (8.6%) is unexpected.

There is an 18 years interval between the 2 investigations which may partly explain the difference in nickel reactivity. The participants in the DARC cohort were born after implementation of the Danish nickel regulation (1990) in contrast to the participants in the TOACS cohort who were born between 1980 and 1982. The effect of the nickel regulation is supported by epidemiological studies showing that the occurrence of nickel allergy is decreasing in the younger age group (16-21). However, a follow-up study of the TOACS cohort in 2010 showed a surprisingly high incidence of new nickel allergy among participants tested both in 1995 and 15 years later in adulthood and that suggested that the effect of the nickel

regulation was limited (22) and a recently published study from the population-based Swedish BAMSE (Children, Allergy, Milieu, Stockholm, Epidemiological Survey) cohort found that the prevalence of nickel sensitization was 7.5% among 16 years old adolescents (23). Other studies have shown that a large proportion of inexpensive earrings, jewelry items and hair clasps stills release nickel in concentrations that may lead to nickel allergy despite of the EU nickel directive entering to full force in 2001 (24-26). The difference in frequency of positive nickel patch tests may partly be explained by the difference in the lifetime prevalence of hand eczema but it cannot be explained by difference in occurrence of ear piercing and atopic dermatitis.

The participants in the DARC cohort were tested repeatedly during infancy and the question is if this could explain the low patch test reactivity to nickel sulphate. Lowney (27) applied different and multiple doses of dinitrochlorobenzene (DNCB) to different groups of human volunteers, and in some there was evidence of low reactivity to DNCB later, and that could not be broken by exposure to a higher dose. Mitchel (28) reviewed the literature in 1969 and reported that repeated applications of topical agents to a sensitized individual could reduce or remove reactivity to the agent. A recent animal experiment conducted in C57BL/6 mice showed that repeated exposure to a hair dye induced an inflammatory response that peaked at the fourth epicutaneous exposure to hair dye and subsequently an upregulation of regulatory T cells and IL-10 producing cells induced anti-inflammatory mechanisms (29). A study among poison ivy sensitized workers in a cashew nut shell oil processing factory also showed decreased reactivity to poison ivy after working in the factory for several months (30).

Our observation has considerable limitations: the 2 cohorts are tested 18 years apart and the nickel regulation may have had different impact on the participants. Further, the children in the DARC cohort were tested several times through infancy that may have increased parents awareness regarding nickel avoidance. A total of 1146 from the TOACS cohort were tested in contrast to only 249 from the DARC cohort. The limited number of the participants patch tested in the DARC cohort is explained by several factors: Age, performing sports activities 5-6 times a week and that patch tests required more than one visit. However, the confidence intervals support that the difference in nickel reactivity is convincing, and the difference may be an effect of the nickel regulation, and an immunologic effect cannot be ruled out. The participants in the DARC cohort will be followed-up in the future revealing possible clinical effects of the low frequency of nickel reactivity.

Acknowledgement

We thank the participants in the DARC cohort and their parents for their cooperation, and nurses Lis Lykkegaard and Joan Kramer and laboratory technicians Anni Larsen and Ulla Johannesen for skillful technical help. This work has been performed at The Department of Dermatology and Allergy Center, Odense University Hospital, Odense Denmark. The TOACS cohort used technical facilities of OPEN (Odense Patient Exploratory Network), Odense University Hospital, Odense, Denmark. This work has received funding from University of Southern Denmark, Odense University Hospital and SmartPractice A/S, Denmark donated TRUE® test and supplied the nickel dilution series.

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Table 1: Prevalence of sensitization to nickel sulphate and fragrance mix I in the DARC (tested in 2013-2014) and TOACS cohorts (tested in 1995-1996).

	DARC			TOACS		
	Total n=249	Girls n= 148	Boys n=101	Total n=1146	Girls n=620	Boys n=526
Positive patch to nickel 200 µg/cm²	1.2% (3)*	2.0% (3)	ND	8.6% (98)*	13.7% (85)	2.5% (13)
95% CI	0.25-3.47			6.98-10.22		
Positive patch test to fragrance mix I	ND	ND	ND	1.8 % (21)	1.6% (10)	2.1% (11)

* P<0.00, ND (not detected)

Table 2: Prevalences of ear piercing, atopic dermatitis and hand eczema in the DARC cohort and the TOACS cohort.

	DARC			TOACS		
	Participants N=372	Girls n=194	Boys n=178	Participants N=1438	Girls n=713	Boys n=725
Ear Pierced (% proportions)	50.2(187/372)	86.6(168/194)	10.7(19/178)	50.8 (731/1438)	81.5 (581/713)	20.7 (150/725)
Current Atopic Dermatitis (%, proportions)	8.1 (30/372)	9.3 (18/194)	6.7 (12/178)	6.7(90/1340) ¹	7.7 (53/684)	5.6 (37/656)
Lifetime prevalence of Atopic Dermatitis (% proportions)	28.5(106/372)*	23.2(45/194)	34.3(61/178)	21.3(306/1438)*	25.7 (183/713)	17.0(123/725)
Hand Eczema life time prevalence (% proportions)	4.8(18/372)*	6.2 (12/194)	3.4 (6/178)	9.2(133/1438)*	12.2(87/713)	6.3(46/725)

*P<0,05

¹ In the TOACS cohort 1438 participated in the questionnaire and 1340 in the clinical examination.