

Occupational and Non-Occupational Allergic Contact Dermatitis: A Follow-Up Study

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Key Words

Occupational contact dermatitis · Prognosis · Prevention of occupational skin diseases · Asymptomatic contact sensitization · Patch testing

Abstract

Background/Aims: The aim of this study was to obtain insight into the clinical course and prognosis of allergic contact dermatitis (ACD), including potential effects of genetic and environmental factors. **Methods:** Eighty-two patients with previously defined ACD acquired occupationally (OACD) or non-occupationally (NOACD) were patch retested and evaluated for the presence of persistent eczema, atopy and filaggrin mutations. **Results:** The crude risk for the persistence of a positive patch test (PT) reaction was 6.3 times higher (95% CI 3.63–11.0) for PT reactions assessed as '+++' compared to '++' reactions at the first PT. Among the categories of OACD, NOACD, age, gender, atopy, and the number of positive PT reactions at the first and second PT, only OACD (OR 10.0, 95% CI 1.95–51.2) and number of positive PT reactions at retesting (OR 3.85, 95% CI 1.57–9.44) were found to be predictors of persistent eczema. **Conclusions:** Occupationally acquired contact allergy was emphasized as the most important factor in predicting poor prognosis of ACD.

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Introduction

There are considerations that, once developed, contact sensitization (CS) based on a delayed, cell-mediated immune reaction is highly persistent in humans, even throughout one's life. However, these observations have not yet been unambiguously proven. The course of CS and its clinical expression, allergic contact dermatitis (ACD), is hard to predict, and risk factors related to poor or good prognosis of ACD have not yet been clearly defined [1]. ACD is considered to be a frequent disease, involving up to 20% of the general population, more women than men, with nickel salts as the most prominent contact allergen [2]. It is believed that the development and course of ACD is influenced by environmental and genetic factors, but the impact and interactions of these factors are not fully understood. Some authors put more stress on environmental factors, i.e. the degree of exposure to relevant contact allergens including their concentration and duration of exposure, thus making occupational exposures highly important [3]. On the other hand, recent studies have indicated the potential involvement of certain genetic factors in the development of ACD, such as polymorphisms of genes encoding proinflammatory cytokine TNFA-308, filaggrin (FLG) and claudin-1 [4–6]. However, the influence of these gene polymor-

phisms has not yet been clearly established, and the impact of FLG mutations has been shown for the development of nickel ACD [7, 8]. Atopy, defined as a genetically defined tendency toward the development of IgE-mediated immune reactions to common environmental allergens with allergic rhinitis, allergic asthma or atopic dermatitis as related clinical phenotypes [9], is clearly presented as the most important risk factor in the development of irritant contact dermatitis (ICD) [4, 10]. However, the impact of atopy on the development and course of CS and ACD is still controversial. There are studies that have not found any relation between atopy and CS [4, 11], while other studies pointed out atopy as a predictor of poor ACD prognosis [12]. On the other hand, a certain number of studies indicated that severely expressed atopic diseases protected from the development of CS [13, 14].

The aim of this follow-up study was to improve the understanding of the clinical course and prognosis of CS and ACD, including potential effects of genetic and environmental factors. Patients with previously defined CS or ACD status, both occupationally and non-occupationally acquired, were retested and evaluated for the presence of persistent eczema, atopy and FLG mutations.

Subjects and Study Design

This follow-up study involved patients who visited the outpatient clinic at the Institute for Medical Research and Occupational Health due to the suspicion of having occupational ACD (OACD). A total of 311 patients with a medical record of CS to at least one standard allergen who visited the clinic over a 20-year period (from 1989 to 2008), and for whom valid contact information could be provided (telephone number or postal address) were invited to participate in the study. Among the 93 patients that responded positively (response rate 30%), 82 patients had complete data on patch testing with a standard set of allergens at the time of the first visit to our outpatient clinic and were included in the study. These patients came to the control visit during 2009 and 2010, during which a structured medical interview, standard patch testing with European standard series of contact allergens [15], and a buccal swab collection were obtained. All patients were informed about the study aim and protocol at the control visit, and signed a consent form. The study was designed in accordance with the Helsinki Declaration and approved by an authorized Ethical Committee (Decision from May 25, 2009, Register No. 01-74/2-09).

Methods

Inspection of Earlier Patient Records

The inspection of earlier patient records was focused on the information on the patients' occupation and workplace, patch test-

ing results, and established diagnoses of OACD and non-occupational ACD (NOACD), or asymptomatic CS (positive patch test, PT, without signs and symptoms of contact dermatitis). Additionally, atopy was defined with the diagnosed atopic disease (allergic rhinitis, allergic asthma and/or atopic dermatitis) in the patient records by a physician.

Structured Medical Interview

The structured medical interview was performed in all patients, with an emphasis on the information regarding the occupation and workplace of the patient, and the presence of the skin symptoms (eczema) in the period between the first and the control visit. Persistent eczema was defined as the presence of eczema in the year previous to the control visit and between two visits in a form of relapsing eczema episodes.

Patch Testing

All patch testing at the first and control visits was performed by a standard method [16]. After a 2-day occlusion, skin reactions were read on the 2nd and 3rd days following application of allergens during the first visit, and for the control visit, only on the 3rd day. Erythema, induration and vesicles ('++' or '+++') presented on the 3rd day were considered to be a positive reaction for the first and control visits. Reactions interpreted as '+' on the 3rd day were considered as weak positive PT reactions for the first and control visits. Patch testing during the first visit was performed in two different Croatian clinics for dermatovenereology or in our outpatient clinic using slightly modified European standard series [17] of commercial contact allergens (Institute of Immunology, Zagreb, Croatia) for the period before 1995, and European standard series [15] of commercial contact allergens (Brial, Greven, Germany, Epipharm Allergy Service GmbH, Linz, Austria, or Institute of Immunology, Zagreb, Croatia) after 1995. Patch testing at the control visit was performed in our outpatient clinic using European standard series [15] of commercial contact allergens (Brial) on Cu-ratest (Lohmann, Neuwied, Germany) plaster strips.

DNA Sampling and Isolation

In all subjects, genomic DNA was extracted from buccal swab samples collected during the control visit using proteinase K (Invitrogen, Carlsbad, Calif., USA) digestion and a DNA isolation kit (Puregene® Cell Lysis Solution; Gentra Systems, Minneapolis, Minn., USA), in accordance with the manufacturer's procedures as described previously [18].

Genotyping of FLG Null Mutations

FLG mutations R501X and 2282del4 were genotyped using previously reported methods [18, 19]. Genotyping for R2447X [sequence: caccacAagcaggca(C/T)gagacagctccaggc] and S3247X [sequence: ctgTtcaggagcagt(A/C)aaggcacggctccag] was performed by KBioscience (<http://www.kbioscience.co.uk>) using the KASP SNP genotyping system, a homogeneous fluorescent resonance energy transfer-based system, coupled with competitive allele-specific PCR.

Statistical Analysis

Comparison of continuous data (age, time interval between the first and control visits) between 3 groups (asymptomatic CS, NOACD and OACD) was performed by analysis of variance (ANOVA), followed by the Bonferroni multiple-comparison post

Table 1. General characteristics and prevalence of atopy and eczema in study subjects

	NOACD	OACD	Asymptomatic CS
Number	51	18	13
Men	7 (14) ^a	7 (39) ^b	1 (8) ^{a, b}
Age at the first visit, years	39.0 ± 10.5	38.4 ± 8.3	45.3 ± 10.6
Age at control visit, years	46.3 ± 10.8	50.3 ± 8.1	52.6 ± 12.0
Time interval between the visits, years	7.3 ± 4.0 ^c	11.9 ± 3.7 ^d	7.3 ± 3.4 ^c
Seniority at the first visit	–	16.9 ± 8.1	–
Atopy	11 (22)	1 (6)	3 (23)
Allergic rhinitis	9 (18)	1 (6)	2 (15)
Allergic asthma	5 (10)	1 (6)	0
Atopic dermatitis	1 (2)	0	2 (15)
Persistent eczema	10 (20) ^a	14 (78) ^b	n.a.

Data are presented as number with percentage in parentheses or arithmetic mean ± standard deviation. Asymptomatic CS subjects are those with CS but without eczema at the first visit. Atopy was defined as the presence of physician-diagnosed allergic rhinitis, allergic asthma or atopic dermatitis. Data on atopy were not available for 1 subject with OACD. Seniority = duration of employment at the time of the first visit; persistent eczema = eczema in the last year reported at the control visit. ^{a, b} Significant differences between groups obtained by Pearson's χ^2 test or Fisher's exact test, $p < 0.05$ (different letters designate statistically significantly different groups). ^{c, d} Significant differences between groups obtained by ANOVA followed by Bonferroni multiple-comparison post hoc test, $p < 0.05$. n.a. = Not applicable.

hoc test if the overall ANOVA effect was significant. Comparison of categorical data (e.g. gender, atopy status, atopic diseases, the prevalence of eczema and persistent PT reactions at the control visit) was performed by Pearson's χ^2 test or Fisher's exact test (if any expected value in the contingency table was ≤ 5).

The relationship between the persistence of a positive PT reaction at the control visit and the intensity of PT reaction ('+' vs. '++' vs. '+++') or type of allergen (metals vs. non-metal allergens) was evaluated calculating the crude risk ratio. The predictors of persistent eczema were evaluated by multiple logistic regression, with persistent eczema as the dependent variable and occupational/non-occupational exposure to contact allergens, number of positive PT reactions at the first visit, number of positive PT reactions at the control visit, age at the first visit, gender, atopy, and interval between the first and control visits as predictors.

Statistical analysis was performed using Stata/SE 11.2 for Windows (Stata Corp. LP, USA).

Results

The general characteristics of the study subjects are presented in table 1. According to the presence of eczema at the first visit, subjects were divided into 2 groups: 13 subjects with a positive PT ('++' or '+++') without eczema (subjects with asymptomatic CS) and 69 subjects with a positive PT and eczema (subjects with ACD). Subjects with ACD were further divided into 51 subjects with NOACD and 18 subjects with OACD. The highest pro-

portion of men was observed among subjects with OACD, although the difference was statistically significant only in comparison with subjects with NOACD, probably due to the low number of subjects with asymptomatic CS. The age of the subjects at the first visit was similar for all 3 groups (asymptomatic CS, N OACD and OACD). The mean interval between the first and control visit for all study participants was 8.3 ± 4.3 years (range 2–20 years). Patients with OACD had on average a 4.6-year longer interval between their two visits compared to NOACD patients and subjects with asymptomatic CS.

Out of the 18 subjects with OACD, 12 subjects (67%) were retired after the first visit resulting in a diagnosis of occupational disease, 5 subjects (28%) changed their jobs, and 1 subject (6%) continued working at the same workplace. The median age of retirement was 43.5 years (range 31–58 years), and the mean duration of the cessation of relevant occupational exposure after the first visit was 10.1 ± 4.0 years (range 0–18 years).

Patch Testing

Lists of contact allergens with positive PT reactions during the first visit in subjects with asymptomatic CS, NOACD and OACD are presented in table 2. The most frequent contact allergens in all 3 groups were hard metal salts (chromium, cobalt and nickel salts), contributing

Table 2. List of contact allergens that induced positive reactions at the first and control patch testing

NOACD					OACD					Asymptomatic CS				
allergen	number of positive reactions				allergen	number of positive reactions				allergen	number of positive reactions			
	P1	lost	per-sisted	new		P1	lost	per-sisted	new		P1	lost	per-sisted	new
Nickel	32	9 (28)	23 (72)	1	Nickel	8	4 (50)	4 (50)	2	Cobalt	3	2 (67)	1 (33)	1
Cobalt	17	12 (71)	4 (24)	1	Chromium	6	2 (33)	4 (67)	1	Nickel	3	3 (100)	0	0
Fragrances	12	8 (67)	4 (33)	0	Cobalt	6	4 (67)	2 (33)	3	Fragrances	3	2 (67)	1 (33)	1
Chromium	9	8 (89)	1 (11)	0	Thiurams	3	2 (67)	1 (33)	1	Chromium	2	2 (100)	0	1
Peru balsam	5	3 (60)	2 (40)	0	IPPD	3	1 (33)	2 (67)	0	PPD	2	2 (100)	0	0
Neomycin	4	3 (75)	1 (25)	0	MBT	2	2 (100)	0	0	Neomycin	2	2 (100)	0	0
Benzocaine	3	3 (100)	0	0	PPD	2	1 (50)	1 (50)	0	Peru balsam	2	2 (100)	0	0
Wool alcohols	3	3 (100)	0	0	Mercapto mix	1	1 (100)	0	0	Benzocaine	1	1 (100)	0	0
PPD	2	2 (100)	0	1	Formaldehyde	1	1 (100)	0	0	IPPD	1	1 (100)	0	0
Parabens	2	2 (100)	0	0	Neomycin*	1	1 (100)	0	2	Wool alcohols	1	1 (100)	0	0
Thiurams	1	1 (100)	0	0	Wool alcohols*	1	1 (100)	0	0	Epoxy resins	1	1 (100)	0	0
Colophony	1	1 (100)	0	0	Fragrances*	1	1 (100)	0	0					
IPPD	1	1 (100)	0	0	Colophony*	0	–	–	1					
Epoxy resins	1	1 (100)	0	1	Peru balsam*	0	–	–	1					
Clioquinol	1	1 (100)	0	0										
Kathon CG	0	0	0	1										
Total	94	58 (62)	35 (37) ^a	5	Total	35	21 (60)	14 (40) ^a	11	Total	21	19 (90)	2 (10) ^b	3

P1 = PT results at the first visit; lost = positive PT reaction that became negative at the control testing; persisted = PT reactions that remained positive at the control visit; new = sensitization detected at the control visit, and not present at the first visit. Data for lost and persisted PT positive reactions are expressed as number with percentage in parentheses of positive reactions at the first

patch testing (P1). ^{a, b} Significant differences in the prevalence of persistent PT reactions at the control visit (Pearson's χ^2 test, $p < 0.05$). PPD = *p*-phenylenediamine; MBT = mercaptobenzothiazole; IPPD = N-isopropyl-N'-phenyl-*p*-phenylenediamine. * Contact allergens without occupational relevance.

up to 38% of the positive PT reactions in the asymptomatic group, 62% in the NOACD group, and 57% in the OACD group during the first PT. The proportion of positive PT reactions to hard metal salts was even higher in the OACD group if only occupationally relevant allergens were taken into account (67%). A list of occupations and occupational allergens related to study subjects with OACD is presented in table 3. Mercapto mix, mercapto-benzothiazole and formaldehyde were established as exclusively occupational allergens.

Patch testing during the control visit revealed positive PT reactions in 48 out of the 82 subjects (58.5%). The persistence of positive PT reactions at the control visit was lowest in the asymptomatic CS group (10% of positive PT reactions during the first visit), followed by the NOACD group (38%), and OACD group (40%). In the NOACD group, the most persistent PT reactions were to nickel salt (72%), whereas in the OACD group they were to chromium salt and N-isopropyl-N'-phenyl-*p*-phenylenediamine

(67%) (table 2). The intensity of the PT reaction during the first testing (expressed as '++' or '+++') had a significant impact on the persistence of sensitization. The crude risk for the persistence of a positive PT reaction at the control visit was 6.3 times higher (95% CI 3.63–11.0; $p < 0.001$) for PT reactions assessed as '+++ compared to PT reactions assessed as '++' at the first visit. The risk ratios were similar for metal salts (5.10, 95% CI 2.68–9.83, $p < 0.001$) and other allergens (7.14, 95% CI 2.52–20.3, $p < 0.001$). Nevertheless, the risk that a '+++ PT reaction assessed at the first visit would persist at the control visit was 1.6 times (95% CI 0.88–2.86; $p = 0.045$) higher for hard metal salts than for other contact allergens. A similar result was not found for '++ PT reactions assessed at the first visit.

Weak positive PT reactions ('+') were present in 26 subjects during the first visit (in 15 subjects with NOACD, in 6 subjects with OACD and in 5 asymptomatic subjects), with 32 reactions in total. During the control visit, 84% of these reactions were lost (27 out of 32),

Table 3. List of occupations and occupational allergens related to CS in 18 study subjects with OACD

Occupation	n	Occupationally relevant allergens
Shoemaker	4	chromium (1), cobalt (2), nickel (2), thiurams (1)
Hairdresser	2	PPD (1), IPPD (1)
Machinist, warehouse worker in an ironworks	2	PPD (1), nickel (2), IPPD (1)
Mason	4	chromium (4), cobalt (2)
Worker in the production of light bulbs	1	cobalt, nickel, formaldehyde
Dentist	1	cobalt, nickel, thiurams, MBT
Textile worker	2	nickel (2)
Worker on a polishing machine	1	thiurams, IPPD, mercapto mix, MBT
Epoxy resin founder	1	chromium

Data are presented as the name of an occupationally relevant allergen that induced a positive PT result at the first visit with the number of subjects sensitized to that allergen in parentheses. n = Number of workers in the occupation; PPD = *p*-phenylenediamine; MBT = mercaptobenzothiazole; IPPD = N-isopropyl-N'-phenyl-*p*-phenylenediamine.

with similar patterns in all 3 groups (18 out of 20 reactions in the NOACD group, 4 out of 6 reactions in the OACD group, and 5 out of 6 reactions in the asymptomatic CS group). The risk for the persistence of a weak positive PT reaction at the control visit did not differ from the risk related to '++' PT reactions, but was approximately 5 times lower compared to '+++' PT reactions (risk ratio 0.204, 95% CI 0.09–0.46; $p < 0.001$). The allergen related to the persistence of weak positive PT reactions was cobalt salt, namely all 5 '+' PT reactions that were not lost at the control visit were related to cobalt sensitization. Out of these, 4 reactions became clear-positive ('++') at the control visit.

The prevalence of subjects with new sensitization(s) was higher in the group of subjects with OACD (10 out of 18), compared to subjects with NOACD (5 out of 51; Fisher's exact test, $\chi^2 = 16.4$, $p < 0.001$) and subjects with asymptomatic CS (2 out of 13; Pearson $\chi^2 = 5.13$, $p = 0.023$). Approximately one half of newly occurring sensitizations were related to metal salts, chromium, cobalt and nickel, similarly to the results of the first patch testing (table 2).

Persistent Eczema

Persistent eczema (eczema in the last year, reported at the control visit) was present in 28 out of 82 subjects (34%). The presence of persistent eczema was significantly more frequent in subjects with OACD than in subjects with NOACD or subjects with the asymptomatic CS at the first visit (table 1). The subsequent result was confirmed by logistic regression analysis with persistent ec-

zema as the dependent variable and OACD/NOACD, number of positive PT reactions at the first visit, number of positive PT reactions during the control visit, age at the first visit, gender, atopy, and the interval between the first and control visits as predictors (pseudo- $R^2 = 0.31$, $p_{\text{model}} < 0.001$). The analysis revealed only 2 predictors of persistent eczema: OACD (OR 10.0, 95% CI 1.95–51.2, $p = 0.006$) and the number of positive PT reactions at the control visit (OR 3.85, 95% CI 1.57–9.44, $p = 0.003$). The results were similar when the number of both positive and weak positive PT reactions at the first and control visits was taken into consideration (pseudo- $R^2 = 0.27$, $p_{\text{model}} < 0.001$; OR for OACD 9.33, 95% CI 1.88–46.2, $p = 0.006$; OR for the number of positive PT reactions at the control visit 2.22, 95% CI 1.13–4.33, $p = 0.020$). The prevalence of persistent eczema showed a linear increase with the increase in the number of positive PT reactions during the control visit: the prevalence was 23.5% in subjects with a positive PT reaction to 1 allergen, 64% in subjects with a positive PT reaction to 2 allergens, and 100% in subjects with a positive PT reaction to 3 allergens. In subjects with OACD, persistent eczema was less prevalent in retired subjects than in subjects who continued to work at the same or another workplace (67 vs. 100%, respectively), and more prevalent in subjects in whom new sensitization(s) occurred at the control visit. Specifically, one half of the subjects without new sensitizations (4 out of 8) had eczema at the control visit, while eczema was present in all 10 subjects with 1 or more new sensitizations (Fisher's exact test, $\chi^2 = 6.43$, $p = 0.023$). Such a relationship was not found in subjects with NOACD and asymptomatic

CS. Four out of 13 subjects (31%) with asymptomatic CS at the first visit reported the presence of eczema during the previous year at the control visit.

FLG Mutations and Atopy

In this study, 4 FLG mutations (2282del4, R501X, R2447X and S3247X) were genotyped in 73 study subjects, with a success rate of 95% (69 subjects successfully genotyped for all 4 FLG mutations). Only 1 heterozygous carrier of the FLG null mutation R501X was found, a female subject with NOACD and persistent eczema. Carriers of other analyzed FLG mutations were not found.

Atopy was found in 15 out of 81 (19%) subjects (data on atopy was not available for 1 subject) (table 1). It was found more often in subjects with asymptomatic CS and NOACD than in subjects with OACD, although this difference was not statistically significant. As described earlier, atopy was not confirmed as a predictor of persistent eczema in the logistic regression model.

Discussion

The results of this follow-up study revealed a clearly different clinical course of CS for OACD and NOACD. Occupationally acquired ACD was strongly related to the development of new sensitizations and the persistence of clinical symptoms (eczema) for a period of approximately 10 years from the established positive PT and diagnosis of OACD. New sensitizations and persistent eczema were found in 55 and 78% of subjects with OACD, in comparison with the 10 and 20% of subjects with NOACD, respectively. The results also showed gender differences between OACD and NOACD with significantly more men in subjects with OACD. For all subjects, the persistence of CS was related to the intensity of PT reactions at the first visit, indicating that subjects with strongly positive reactions ('+++') during the first visit can be considered to be at the highest risk of a long-term persistence of CS. Hard metal salts were confirmed as allergens with the most frequent persistence of positive PT reactions, with mostly persistent PT reactions to nickel in NOACD, and to chromium in OACD. Apart from chromium, rubber additives were confirmed as frequent occupational allergens, with mercapto compounds indicated as exclusive occupational allergens in contrast to thiuram compounds and N-isopropyl-N'-phenyl-*p*-phenylenediamine, which also caused positive PT reactions in subjects with NOACD and asymptomatic CS. Retirement, even at an early age (43 years on average), was the most frequent outcome

for workers with an established diagnosis of OACD. If we defined persistent eczema as a marker of poor prognosis for ACD in our subjects, the occupationally acquired contact allergy and number of newly developed CS at the control visit could be determined as the only predictors of poor prognosis, while age at the first PT, gender, atopy, FLG mutations, and the interval between the first and control visits were not indicated as predictors.

Methodologically similar follow-up studies are relatively scarce in the literature, rarely evaluating differences in the clinical course between OACD and NOACD and rarely distinguishing the prognosis of occupational contact dermatitis (eczema) between ACD and ICD. The PT follow-up is additionally compromised with the frequent presence of methodological differences, i.e. variability in applied test allergens and procedure, variability in the interpretation of positive reactions, intra-individual differences in PT reactivity, and moderate reproducibility of PT results [1, 20, 21]. In the present study, PTs at the first and control visits for some subjects were done with test allergens from different suppliers and interpreted by different experts, which implicates possible variations in potency of PT allergens, possible incoordination in interpretation of PT results, and some modifications of criteria for a positive PT through the analyzed 20-year period. To diminish these methodological limitations, we decided to analyze only clearly positive PT reactions 72 h after occlusion, excluding reactions evaluated as '+' and reactions positive only after 48 h from the analysis in order to avoid doubtful and irritative reactions, respectively. Despite the mentioned obstacles, some of our results are congruent with other studies which found the persistence of positive PT reactions, mostly for hard metal salts, in a range from 71 to 96% with periods leading up to the follow-up from 3 to 32 years [1, 20, 22–24], as well as the relation between severity of sensitization at the beginning of the follow-up and the sensitization persistence [20, 22]. Long-term persistence of sensitization, as well as the development of new sensitizations to hard metal salts are expected [25], due to the ubiquitous presence and therefore limited possibilities for avoidance of contact with these allergens, even in non-occupational conditions. Sensitization to chromium and rubber additives (mostly *p*-phenylenediamine), with the addition of epoxy resins, were found as the most frequent and most persistent CS in OACD patients in a study by Rebandel and Rudzki [23].

Occupational skin diseases, mostly present in the form of hand eczema and based on ICD and/or ACD, are considered to be diseases with frequently poor prognoses and a tendency to ultimately result in chronic conditions with

the proposed term 'persistent postoccupational dermatitis' [3, 26, 27]. The persistence or even aggravation of skin symptoms in subjects with diagnosed occupational contact dermatitis after the cessation of relevant occupational exposure is not rare and has a significant impact on one's working ability, quality of life and compensation claims [27]. Studies from Scandinavian countries showed that the majority of workers with diagnosed occupational skin diseases had to change their job, retire or become unemployed [26, 28] and the present study confirmed the high impact of OACD on working ability, namely more than 2/3 of our subjects with OACD were retired after the established OACD diagnosis. It could be speculated that persistence of the eczema after the cessation of occupational exposure could be caused by further non-occupational exposure to the causative allergens which should be expected with ubiquitous allergens like hard metal salts, or by the development of new sensitizations acquired non-occupationally or at the new workplace. However, persistence of the eczema could also be based on the non-specific inflammation due to the exposure to skin irritants at the new workplace or at home.

So far, the most clearly presented markers of poor prognosis for hand eczema were sex (female), atopy, CS (positive PTs) and wet work [26, 29]. Some studies suggested older age and lower socio-economic status as predictors [12, 28]. According to the literature, it could be suggested that sex (female), atopy, and wet work should be considered as markers of poor prognosis primarily for ICD. Wet work is known as a highly important occupational and non-occupational skin irritant and is performed mainly by female workers [3], while atopy in the form of childhood or adult atopic eczema or some other atopic disease is undoubtedly the most important independent risk factor in the development of ICD [4, 10, 30]. It could be stated that predictors of ACD prognosis have not yet been clearly defined, but there is agreement about the influence and interactions of genetic and environmental factors on the development and course of ACD [1, 22], with a thus far more clearly presented influence of environmental factors [3, 31]. According to the results from the present study, sex (female), age, and atopy were not found to be predictors of poor prognosis for ACD, whereas only a strong influence of one's occupationally acquired contact allergy on the clinical course of ACD was confirmed. It seems that the degree and duration of exposure to contact allergens are essential for the development and course of ACD [3], and that occupational exposure implying high concentrations of allergens and skin contact on an everyday and long-term basis is clear-

ly the most hazardous from this aspect. It can be speculated that such exposure leads to an early development of strong skin sensitization which is, according to this and other studies, confirmed as a predictor of persistent [20, 22] and newly developed sensitizations [32], and persistent eczema. For example, in our study group sensitization to chromium was more intensive in the OACD compared to NOACD group. A PT reaction designated as '+++' was present in 4 out of 6 chromium-sensitized subjects with OACD compared to only 1 out of 9 chromium-sensitized subjects with NOACD (data not shown). However, the parallel interaction of other factors can by no means be excluded from the general consideration of factors influencing the prognosis of ACD. Beside the important role of often concomitant contact with skin irritants in occupational and non-occupational conditions, certain genetic factors seem to influence the prognosis of ACD. For example, some studies suggested a possible role for the TNFA-308 genetic polymorphism (G/A and A/A genotypes) as a susceptibility factor for chemically induced ACD [33], particularly ACD caused by *p*-phenylenediamine and chromate [34, 35]. The polymorphisms of N-acetyltransferases, glutathione-S-transferases, manganese superoxide dismutase, angiotensin-converting enzyme, FLG, claudin-1 and interleukin-16 were also associated with a higher risk of CS [5, 6].

In the present study, only atopy and FLG mutations were analyzed as genetic variations with a possible influence on the prognosis of CS and ACD. While atopy and FLG null mutations are clearly defined as independent risk factors in the development of ICD [4, 10, 30], their role in the development of ACD is controversial. Up to now, 3 studies have suggested a risk of developing contact allergy to nickel in subjects with FLG null mutations, indicating that a damaged skin barrier in persons with FLG null mutations can facilitate the penetration and presentation of nickel to antigen-presenting cells in the skin resulting in the development of easier and earlier sensitization [7, 8, 36]. Additionally, a recent study indicated that FLG mutation carriers with self-reported dermatitis have an increased risk of CS to substances other than nickel [37]. However, our previous study revealed a low frequency of common FLG null mutations in the Croatian population, suggesting that these mutations do not have a significant impact on the development and course of skin diseases, including ACD, in the Croatian and other populations with low penetrations of FLG mutations [38]. The data indicate a decreasing north-south gradient of R501X and 2282del4 FLG mutation frequencies in Europe with a lower penetration of FLG mutations in the

Italian and Croatian population when compared to Ireland, the UK and Germany [38–40]. The results of the present study are in line with these suggestions.

For the most part, no study could confirm atopy as a risk factor for the development of CS and ACD [4, 11], while some studies even indicated that severely expressed atopic diseases protect from the development of CS [13, 14]. Atopy was not confirmed as a predictor of poor ACD prognosis in the present study either. It was even less present in subjects with OACD in comparison to other groups, which is in line with the proposed definitions of persistent postoccupational dermatitis [27]. Namely, diagnoses of persistent postoccupational dermatitis are more apparent if atopy is absent as a cause of endogenous inflammation.

The low response rate of subjects in this follow-up study (30%), as well as the generally small number of subjects, should be mentioned as the limitations of this study. These limitations may have resulted in bias due to a potentially high proportion of subjects who were more motivated to participate in the study because of persistent symptoms or some other problem related to their skin disease, as well as in limited statistical approaches and significance.

The present study included a group of subjects with asymptomatic CS at the first visit, but their number was much too small for serious analysis and discussion of the clinical significance of this phenomenon. CS in healthy persons without skin disorders has rarely been studied, and was found in a range between 7 and 14% of patch-tested subjects [17, 41–43]. According to our results, it can be asserted that 19 out of 21 positive PT reactions (90%) in asymptomatic subjects present during the first visit were no longer present at the control patch testing, and that only 3 new sensitizations occurred at the control visit. Four out of 13 persons with asymptomatic CS at the first visit (31%) developed a clinically manifested disease after several years. Therefore, we cannot suggest that positive PTs in asymptomatic persons are clinically relevant in regard to the subsequent development of skin diseases.

In conclusion, the present study emphasizes the importance of occupational exposure to contact allergens as the most important factor in predicting early development of strong CS and poor prognosis of ACD, which possess a high impact on individual working ability and quality of life, as well as on national economies in general [44, 45]. The results strongly support recent actions implemented in the EU with the aim of improving and standardizing measures for the prevention of occupational skin diseases [46, 47]. Regarding the prevention of ACD, efforts should be aimed at decreasing exposure to occupational contact allergens, including early exposures among adolescents during the period of their education. Questions regarding the relevance of preschool or pre-employment patch testing with standard contact allergens in prevention strategies related to OACD remain open for discussion. Namely, hard metal salts and rubber additives as the most common standard contact allergens often have additional occupational relevance, and early patch testing together with the medical history and physical examination can be valuable in view of later recommendations on individual educational and employment patterns, without significantly increasing the risk of sensitization through patch testing [17, 41].

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Disclosure Statement

All authors declare no conflict of interest.

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