

Occupational contact urticaria and protein contact dermatitis: causes and concomitant airway diseases

Eva Helaskoski^{1,2} , Hille Suojalehto¹, Outi Kuuliala¹ and Kristiina Aalto-Korte¹ 

¹Occupational Medicine, Finnish Institute of Occupational Health, 00251, Helsinki, Finland and ²Department of Public Health, University of Helsinki, 00014 Helsinki, Finland

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Summary

Background. Contact urticaria (CU) and protein contact dermatitis (PCD) are mainly induced by an immediate, IgE-mediated immunological mechanism. Immediate sensitization is also linked to asthma and/or allergic rhinitis.

Objectives. To report causes of work-induced CU and PCD, and to evaluate the occurrence of concomitant airway diseases.

Methods. We retrospectively reviewed the patient files of cases diagnosed with CU or PCD at the Finnish Institute of Occupational Health during 1995–2011. We obtained data on occupation, exposures, clinical and immunological test results, and diagnosed occupational skin and respiratory diseases.

Results. Altogether, 291 cases of occupational CU or PCD were diagnosed during the study period. The most common causes were flour, cow dander, natural rubber latex, and acid anhydrides. Concomitant occupational asthma caused by the same agent as the skin disease was detected in 60 patients (21%), and occupational rhinitis was detected in 111 patients (38%).

Conclusions. Almost half of the patients (46%) with occupational CU and PCD had concomitant occupational airway disease. Patients with CU/PCD should always be asked about respiratory symptoms, and preventive measures at the workplace should include protection of both the skin and the airways.

Key words: acid anhydrides; chemicals; cow dander; enzymes; flour; grain; natural rubber latex; occupational asthma; occupational rhinitis; plants.

Contact urticaria (CU) and protein contact dermatitis (PCD) are immediate contact skin reactions that manifest as itching wheals and/or eczema following skin contact with the causative agent (1). The most significant causative agents in an occupational setting are proteins in organic materials, such as foodstuffs and natural rubber

latex (NRL) (2, 3), but CU induced by chemicals has also been described (4). Immunological CU and PCD are usually triggered by an immediate IgE-mediated mechanism. Type I allergic mechanisms are also associated with the development of occupational asthma and occupational allergic rhinitis (5). The mechanisms by which chemicals cause these diseases are mainly unknown, but some low molecular weight agents, such as platinum salts, acid anhydrides, and diisocyanates, are capable of inducing IgE-mediated sensitization (6, 7).

Although immediate sensitization can provoke both cutaneous and respiratory diseases, data on the prevalence of concomitant immediate skin and airway diseases are limited (8). Simultaneous occupational dermal and airway diseases are mainly described in case reports (9).

Correspondence: Dr. Eva Helaskoski, Finnish Institute of Occupational Health, Occupational Medicine PL 40, 00251 Helsinki, Finland. Tel. +358304741. E-mail: eva.helaskoski@ttl.fi

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The aim of this study was to characterize the patients diagnosed with occupational CU or PCD at our clinic. We focused on concurrent occupational asthma and occupational rhinitis caused by the same agent as the CU or PCD.

Patients and Methods

The occupational medicine clinic at the Finnish Institute of Occupational Health (FIOH) is a tertiary referral centre that receives patients with suspected occupational diseases from throughout the country. We retrospectively reviewed the FIOH's patient and test files for the period 1 January 1995 to 31 May 2011 to identify all patients who had been diagnosed with occupational CU or PCD. From their medical records, we obtained data on occupation, work tasks and occupational exposures, types of work-related symptoms (cutaneous, bronchial, and nasal), chronology of manifestation of symptoms, results of clinical examinations and immunological tests, and diagnosed occupational diseases.

The diagnosis of an occupational disease always requires a clear relationship between exposure at work and symptoms. A confirmed diagnosis of occupational allergic (immunological) CU was based on typical immediate symptoms (itchy visible skin changes) after skin contact with a work-related agent, and demonstration of immediate sensitization to the same substance by prick tests and/or specific IgE. A positive result after open application performed on healthy skin further supported the diagnosis, but was not required. The diagnosis of occupational PCD required demonstration of immediate sensitization to a protein-containing material by prick tests or specific IgE, sufficient direct skin exposure to the same agent at work, eczematous changes on exposed skin areas that healed when skin contact with the material was avoided, and, finally, a positive result on open application to the same material (wheals or minute papules). Vesicles are only exceptionally noted during the short test of 40–60 min.

We diagnosed occupational non-immunological CU (NICU) only rarely, when the patient reported immediate skin reactions at work after contact with a substance known to cause NICU (e.g. sorbic acid) and the open application yielded a positive result. A negative open application result after intake of a non-steroidal anti-inflammatory drug further supported the diagnosis of NICU. Regarding chemicals and non-proteinaceous materials, immediate sensitization can rarely be verified. In these cases, for typical immediate symptoms at work and a positive open application result, we used the diagnosis of occupational CU without specifying it as immunological or non-immunological.

The FIOH's assessment of a patient with suspected CU or PCD normally include prick tests with common environmental allergens, supplemented with cow dander and NRL (Stallergenes, Antony, France), and the suspected causative work-related agent(s). We used commercial allergen extracts of work-related agents for prick tests when available. Prick-to-prick testing was primarily used for prick tests with fresh food, vegetables, and plants. Flour, grains, animal feed, spices and other dry substances were diluted in a potassium phosphate buffer, and then used for prick-to-prick testing. We also used several in-house test series for chemicals and enzymes during the study period. Many chemicals (e.g. acid anhydrides, diisocyanates, oxidative hair dyes, and epoxy resin) were tested as hapten conjugates with human serum albumin, as described previously (10). Prick tests with substances supplied from the patients' workplaces were also frequently used. Antihistamine medication was paused 1 week before the prick tests. The prick test reaction was considered to be positive if the wheal caused by the test substance had a minimum diameter of 3 mm and was at least half the size of the positive histamine control wheal (histamine hydrochloride 10 mg/ml) in the absence of a reaction to the negative control.

We used measurement of specific IgE, if available, to confirm sensitization. During the study period, we used several different commercial methods, as well as the in-house radio-allergosorbent test and ImmunoSpot, to measure specific IgE (11).

Open application was performed on some of the patients to confirm the diagnosis of CU or PCD. The test substance was applied thinly to a 5 × 5-cm area of healthy skin on the forearm. Protein substances were usually tested 'as is', minced if needed, and applied to the skin. We tested the chemicals either 'as is' or diluted to the desired concentration in aq., pet., or ethanol. NRL was tested by the use of latex gloves or parts of gloves, for example a finger. A dermatologist inspected the skin after 20 min, and the application was repeated on the same area. After 40 min, the test was read again and the test material was removed. The test result was considered to be positive if a reaction of one or several urticarial wheals appeared in the application area. If the clinical symptoms were typical, and sensitization was established by the use of other test methods, open application was not always considered to be necessary.

Specific inhalation challenge tests constituted the primary method used to confirm the diagnosis of occupational asthma and/or rhinitis in patients with work-related respiratory symptoms. Placebo-controlled challenges were performed in a challenge chamber or with commercial allergen extracts by use of a dosimeter,

in accordance with the methods described by Vanhanen et al. (12). In addition, to confirm an occupational asthma diagnosis, we used peak expiratory flow monitoring at work and off work, combined with positive prick test or specific IgE results (13). Local nasal provocation tests, in accordance with the methods described by Airaksinen et al. (14), were used when the patients had only upper respiratory symptoms, and the causative agent was not considered to be particularly irritating to the mucous membrane.

The patient file and database review was approved by the ethical board of the FIOH (approval TTL/1/2008). According to local legislation, ethics committee approval was not required, as no patient intervention was applied.

Results

We found 291 patients who were diagnosed with CU or PCD during the study period. The majority (62%) of the patients were female, but the sex distribution varied according to exposure group (Table 1). The mean age at the time of diagnosis was 38 years (range 20–62 years). CU was diagnosed in 233 cases (80%) and PCD in 59 cases (20%). Flour, grains and animal feed were the most common causes (21%), followed by cow dander (18%). The most common occupations in the study group and the respective most frequent causative agents are shown in Table 2.

Exposure to chemicals was the cause of CU in 41 patients. Organic acid anhydrides most frequently triggered CU, with 21 cases, which we have previously

Table 2. The most common occupations of patients with immunological contact urticaria and protein contact dermatitis at the Finnish Institute of Occupational Health, 1995–2011 and the most common causes according to occupation

Occupation	Number of	
	cases	Most common causes
Food service (chefs, bakers)	93	Flour (n = 43), vegetables (n = 18), fish and shrimps (n = 10), meat (n = 6), NRL (n = 4), egg (n = 3)
Farmers	60	Cow dander (n = 46), grains and animal feed (n = 12)
Healthcare (nurses, dentistry)	32	NRL (n = 27), chloramine-T (n = 4), chlorhexidine (n = 1)
Gardeners, florists	25	Ornamental plants (n = 19), vegetables (n = 3)
Electrical equipment assemblers	17	Organic acid anhydrides (n = 17)
Researchers, laboratory workers	15	Rats and mice (n = 8)
Hairdressers	8	Persulfates (n = 5), permanent (oxidative) hair dyes (n = 3)
Other	37	NRL (n = 12), animal dander (n = 8), chemicals (n = 6), enzymes (n = 5)
Total	291	–

NRL, natural rubber latex.

reported (15). Other chemicals associated with CU were persulfates (5 cases), oxidative hair dyes (3 cases), chloramine-T (4 cases), diisocyanates (3 cases), and epoxy resins, chlorhexidine, formaldehyde, *o*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU), and tetrachloroisophthalonitrile (1 case each). We observed positive prick test results or specific IgE for the causative chemical in all cases except for 2 cases of CU caused by oxidative hair dyes, as reported earlier (16, 17).

Of the patients diagnosed with CU or PCD, 134 (46%) had a concomitant airway disease caused by the same work-related agent (Table 3). A total of 111 patients (38%) were diagnosed with occupational rhinitis, and 60 patients (21%) were diagnosed with occupational asthma caused by the same agent that triggered the skin reaction. Flour, grains and animal feed caused simultaneous allergic rhinitis in 67% and asthma in 25% of the patients diagnosed with CU or PCD. Other groups with large proportions of concomitant airway diseases were patients exposed to ornamental plants (75%), enzymes (60%), cow dander (45%), and other animals (46%). Vegetables and fruit, fish and shrimps and other foodstuffs, on the other hand, rarely caused simultaneous respiratory disease.

Chemicals caused concomitant airway diseases in 54% of the patients with CU, the most important agents being

Table 1. Patients with immunological contact urticaria (CU) and protein contact dermatitis (PCD) at the Finnish Institute of Occupational Health, 1995–2011

Cause	Number of cases			Males, n (%)
	CU	PCD	Total	
Flour, grains and animal feed	40	21	61	30 (49)
Cow dander	32	19	51	17 (33)
Natural rubber latex	45	0	45	8 (18)
Vegetables and fruits	15	6	21	5 (24)
Ornamental plants	19	1	20	5 (25)
Other animals (rat, mouse, dog, horse, fox)	13	0	13	4 (31)
Fish and shrimps	5	5	10	3 (30)
Other food (meat, egg)	5	4	9	4 (44)
Spices, raw coffee	4	1	5	2 (40)
Enzymes	5	0	5	3 (60)
Chemicals	41	–	41	24 (59)
Others	8	2	10	5 (50)
Total	232	59	291	110 (38)

Table 3. Concomitant airway diseases in patients with occupational contact urticaria (CU) and protein contact dermatitis (PCD) at the Finnish Institute of Occupational Health, 1995–2011

Cause	Number of CU/PCD cases	Occupational asthma, n (%)	Occupational rhinitis, n (%)	Both occupational asthma and rhinitis, n (%)	Occupational asthma and/or rhinitis, n (%)
Flour, grains and animal feed	61	15 (25)	41 (67)	13 (21)	43 (70)
Cow dander	51	16 (31)	18 (35)	11 (25)	23 (45)
Natural rubber latex	45	8 (18)	5 (11)	0	13 (29)
Vegetables and fruits	21	1 (5)	2 (10)	1 (5)	2 (10)
Ornamental plants	20	4 (20)	14 (70)	3 (15)	15 (75)
Other animals (rat, mouse, dog, horse, fox)	13	3 (23)	4 (31)	1 (8)	6 (46)
Fish and shrimps	10	0	0	0	0
Other food (meat, egg)	9	0	0	0	0
Spices, raw coffee	5	1 (20)	1 (20)	1 (20)	1 (20)
Enzymes	5	3 (60)	2 (40)	2 (40)	3 (60)
Chemicals	41	6 (15)	19 (46)	3 (7)	22 (54)
Others	10	3 (30)	5 (50)	2 (20)	6 (60)
Total	291	60 (21)	111 (38)	37 (13)	134 (46)

acid anhydrides (17 of 21 cases; 81%), followed by persulfates (3 of 5 cases; 60%). Occupational asthma was diagnosed in 1 of the patients with CU related to diisocyanates, and 1 of the patients with CU related to chloramine-T also had occupational rhinitis.

Of the 134 patients who were diagnosed with both CU/PCD and occupational airway disease, 71 (53%) reported that the skin and airway symptoms occurred simultaneously. In 37 cases (28%), the skin symptoms appeared before the respiratory symptoms, and in 26 cases (19%), the respiratory symptoms appeared first.

We were not able to clearly classify the patients according to local or systemic reactions. Pure occupational CU without an airway disease is usually limited to the areas of skin contact. When airway diseases coexist, it is difficult to determine whether the possible generalized symptoms are attributable to skin contact, as concomitant exposure to the airways may also cause the systemic effects. Occasionally, we have seen patients who initially had CU limited to the contact area, but later developed generalized urticaria after similar skin exposure. More often, generalized urticaria results from airway exposure or ingestion of the substance in question, and is a manifestation of a generalized immunological reaction that is not induced by CU. In some situations, skin exposure might be strong enough to cause systemic symptoms (e.g. bleaching of the patient's own hair), but these are rarely purely occupational cases, and airway exposure cannot be excluded here either.

Discussion

In the present study, which covered the patients from a 16-year period in a specialized occupational clinic, flour,

grains and animal feed were the most common causes of CU or PCD (21%), followed by cow dander (18%), NRL (15%), and chemicals (14%). Correspondingly, the patients with CU or PCD were most commonly food service workers (32%), farmers (21%), nurses (11%), and gardeners/florists (9%).

In Finland, physicians are obliged to report a diagnosed occupational disease to the Finnish Register of Occupational Diseases. CU was separated from allergic contact dermatitis in the register in 1989, and has since been classified as an entity in its own right (18). According to the national register, 411 cases of CU (including PCD) were recognized between 2005 and 2013 in Finland (19). This corresponds to 9.9% of the total number of 4148 recognized cases of occupational skin diseases during this period. The most common causes of CU/PCD were cow dander (48%), and flour, grain and animal feed (18%). NRL was the causative agent in 35 (8.5%) of all occupational CU/PCD cases during this period. At the FIOH, rare causes of CU and PCD are overrepresented in comparison with these national statistics, owing to its tertiary referral clinic status.

In an earlier study in Finland, based on the Finnish Register of Occupational Diseases, covering the period 1990–1994, the leading cause of CU/PCD was cow dander (44.4%), followed by NRL (23.7%), flour, grains and feed (11.3%), and the handling of foodstuffs (3.1%) (18). These figures show that NRL used to be a more significant cause of CU/PCD in the 1990s, but, otherwise, the top three causes have remained the same in the whole country and at the FIOH.

There are not many countries that provide data on CU or PCD. At a tertiary-level occupational dermatology

clinic in Australia, during the period 1993–2005, 9.9% (143 cases) of patients with work-related dermatosis were diagnosed with CU, the most common cause being NRL (52%), followed by foodstuffs (35%) and ammonium persulfate (20). The patients included many chefs and some bakers, pastry cooks, and cooks, but the number of flour-related cases was not given. According to national surveillance systems in the United Kingdom, in 2002–2005, 75.5% of cases of occupational CU were associated with exposure to NRL, 8.6% with foods or animal products, and 14.4% with gloves (21). In a French study, national surveillance data for the period 2001–2010 showed 251 reported cases of occupational CU. In the same study, NRL was the predominant cause ($n = 124$) of occupational CU, although the number of NRL cases declined significantly during the study period, as in Finland. Plants, grains and vegetables were the cause in only 15 cases (22).

We saw a high proportion of CU/PCD cases caused by flour, grains and animal feed in our study, which reflects the large number of flour-exposed workers who visit our clinic because of work-related airway symptoms. Of the 22 bakers, pastry makers and pizza chefs in the present study, 20 had occupational diseases following immediate type sensitization to flour, most commonly wheat or rye. Commercial prick test solutions for wheat and rye flour have been found to have generally low sensitivities (23). This has been the clinical experience in Finland for a long time, and thus, since the early 1990s, most centres in Finland have stopped using the commercial allergen extracts for flour, and use prick-to-prick testing instead. This has probably led to better identification of the sensitized individuals and has assisted in diagnosing the cases.

The high proportion of allergic occupational diseases caused by cow dander in Finland as compared with other countries has also been recognized in earlier studies, and is at least partially explained by the country's long winters, during which cattle are kept indoors, resulting in greater exposure of farmers (24).

NRL was the third most common cause of CU in our population. However, only 5 of the cases were diagnosed later than 2004. Accordingly, no new cases of occupational asthma or rhinitis caused by NRL were diagnosed in the study group after 2004. Finland's national figures also show a significant decrease over time in CU cases caused by NRL (18, 19). The proportion has been generally higher in other countries, but decreasing trends have been observed in recent years, reflecting the preventive measures and decreasing use of powdered NRL gloves in healthcare (22, 25, 26).

Immunological CU induced by chemicals has been considered to be relatively rare (27). In our study, chemicals

caused 14% of the cases. Organic acid anhydrides were by far the most common causes of CU in 21 (51%) of the total 41 cases linked to chemical exposure. Other agents causing several cases of CU were persulfates, oxidative hair dyes, diisocyanates, and chloramine-T. The CU cases related to chemical exposure in the present study have been described in detail in our previous reports (15–17).

In Finland, for decades, clinical experience has shown that occupational CU/PCD and airway diseases occur in the same patients. As IgE-mediated mechanisms are linked to both immunological CU and allergic airway diseases, the coexistence of immediate allergic skin and respiratory diseases is not surprising (8). Recent studies have suggested that skin exposure increases the risk of developing asthma (28), and that skin protection can effectively reduce this risk (29).

Data on the epidemiology of work-related concurrent CU and airway diseases are limited, and are usually only available for a specific branch or agent. In a study of 156 laboratory animal workers, one-quarter of the respondents reported both respiratory and skin symptoms (30). In a German study of 96 workers with occupational asthma caused by platinum salts, 53% of the participants also had skin complaints (31).

This is, to our knowledge, the largest study investigating the concomitant occurrence of occupational airway diseases in patients with occupational CU and PCD. In our study population, concomitant occupational airway diseases were quite common in patients with CU or PCD (134 cases; 46%). Occupational rhinitis was more common (38%) than occupational asthma (21%). The large proportion of simultaneous skin and airway diseases may partly be explained by the nature of our clinic, where we examine both skin and airway symptoms in the same facilities. Even mild and transient CU symptoms might receive attention during the airway examinations, and the CU diagnosis is established.

The proportion of CU/PCD patients with simultaneous respiratory diseases varied significantly according to exposure. This might be explained by the differences between airborne exposures of the different occupational groups. Dusty exposure agents such as flour, grains, and animal feed, as well as animal dander, ornamental plants, and enzymes, caused rhinitis and/or asthma in 45–75% of the patients. Handling these substances easily leads to exposure of both airways and the skin (32). Vegetables and fruits, fish and shrimps, and other food and spices, on the other hand, rarely caused any concomitant respiratory diseases, which corresponds well with the fact that the occupational exposure in these cases occurs mainly through skin contact.

The sequence of the appearance of the skin and airway symptoms was determined on the basis of the patients' self-reports during their assessment at our clinic, and prior medical records. Most commonly, the skin and respiratory symptoms manifested simultaneously. In cases in which the symptoms were reported as having appeared consecutively, the skin symptoms more often appeared first. However, conclusions on this point should be drawn cautiously, because of the retrospective study setting. Moreover, mild skin symptoms may have remained unnoticed. Nevertheless, it is important in clinical work to ask patients with work-related immediate

skin symptoms about related respiratory symptoms and vice versa.

In conclusion, the present results confirm that concomitant allergic airway diseases are quite common in patients with occupational CU and PCD, and that effective preventive measures should include protection of both airways and the skin.

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