

Marie-Sylvie DOUTRE

Service de dermatologie
Hôpital Haut-Lévêque,
Centre Hospitalier de Bordeaux,
33600 Pessac France

Reprints: M.-S. Doutre
<marie-sylvie.doutre@chu-bordeaux.fr>

Occupational contact urticaria and protein contact dermatitis

Irritant dermatitis and eczema are the most prevalent occupational skin diseases. Less common are immediate contact reactions such as contact urticaria and protein contact dermatitis. Occupational contact urticaria can be subdivided into two categories, immunological and non immunological. However, some agents can induce these two types of reactions. Contact urticaria to natural rubber latex is particularly frequent among health care personnel, but contact urticaria to a wide variety of other substances occurs in many other occupations. Among those at risk are cooks, bakers, butchers, restaurant personnel, veterinarians, hair-dressers, florists, gardeners, and forestry workers. Protein contact dermatitis in some of these occupations is caused principally by proteins of animal or plant origin, especially among individuals with a history of atopic dermatitis. Diagnosis requires careful interrogation, clinical examination and skin tests (open tests and prick tests with immediate lecture) to identify a particular contact allergen.

Key words: contact urticaria, occupational skin diseases, protein contact dermatitis

Article accepted on 12/7/2005

Occupational skin diseases hold the first rank of all occupational diseases in many industrialized countries. Irritant contact dermatitis and allergic eczema are the most often observed. However, contact urticaria and protein contact dermatitis are not unusual in some groups of workers because of their frequent exposure to protein allergens in plant and animal products or to certain low molecular weight substances [1].

Occupational contact urticaria

The term contact urticaria (CU) describes a wheal-and-flare response elicited within 30-60 min after exposure to certain agents, that disappears within 24 hours and usually within a few hours. Sometimes, the symptoms are: itching, burning or tingling, alone or accompanied by erythema.

The whealing reactions can be strictly confined to the area of contact but they can also appear as generalized urticaria, sometimes associated with extra cutaneous symptoms (bronchospasms, rhinoconjunctivitis, swellings of the upper airways, gastro-intestinal manifestations) and anaphylactic reactions. The severity of clinical reactions can be classified according to the system of Von Krogh and Mai-bach [2]. Stage 1 of CU syndrome indicates localized urticaria; stage 2 denotes generalized urticaria with or without angioedema; stage 3 includes urticaria with asthma, rhinoconjunctivitis, orolaryngeal and gastro-intestinal symptoms and stage 4 is severe anaphylactic shock.

When urticaria has been induced by airborne contact, the parts of the body most often affected are the uncovered areas.

Although aquagenic urticaria and perhaps even physical urticaria could be considered as subgroups of CU, they are

conventionally classified separately and are not discussed in this paper.

Physiopathology

The mechanisms underlying CU are divided into two main types [3]:

– Allergic (or immunologic) contact urticaria depends on the presence of specific IgE. The symptoms appear after repeated contact, implying a preceding phase of sensitization. Even very small amounts of allergens can induce a reaction and only selected individuals among the exposed persons are affected. Sometimes, immunologic CU spreads beyond the site of contact, producing generalized U, other systemic symptoms and even anaphylaxis. This type of CU develops preferentially in persons with an atopic predisposition or atopic diseases. The list of substances with proven or probable antigen-specific, IgE mediated CU is long. However, this has few epidemiological consequences since many of the allergens have only been published in case reports. Next to latex, foods are the most frequent eliciting agents. Plants, animal products, drugs, cosmetics, industrial agents are also elicitors of immunologic CU.

– In the non-immunologic (non-allergic) type, the most frequent type of CU, no previous sensitization has occurred and the agents will produce CU in most individuals if contact time and concentration are sufficient. With few exceptions, the skin lesions are restricted to sites of contact and they rarely cause systemic manifestations. Many of the eliciting agents in this category may induce urticarial skin reactions via several mechanisms: direct release of histamine and other mediators from mast cells, direct effect on dermal vessels, without causing mast cell release, by vaso-active amines, acetylcholine, leukotrienes, prostaglandins

and others. Non immunological contact urticants are common: plants, animals, cosmetics, topical medications, food preservatives and food flavouring. The most potent and best studied agents are benzoic acid, sorbic acid, nicotinic acid esters and cinnamic aldehyde. Many industrial and laboratory chemicals can also cause non immunological CU.

There are also substances that cause these types of reactions whose mechanism may not be known.

Some agents can induce CU by immunologic and non-immunologic mechanisms. So, pine processionary caterpillars (*thaumetopoea pityocampa*) are included among the agents that elicit CU by a non-immunologic mechanism, due to urticant hairs that are capable of penetrating the human epidermis and mucous membranes [4]. However, recently published studies have demonstrated that an IgE-mediated reaction is involved in most CU produced by *thaumetopoea pityocampa* [5]. A major caterpillar allergen has recently been isolated and characterized: it corresponds with Tha p1 and shows no homologies to other insect allergens already described [6]. It is the same for ammonium persulfate, a chemical used by hairdressers as a booster for peroxide bleaches. The mechanism is uncertain with features of both immunologic and non immunologic CU. However, specific binding of IgE to ammonium persulfate was found in some patients [7].

Diagnosis

The diagnosis of occupational CU is based on a full medical history and on skin tests with suspected substances. Patients should be asked specifically about:

- The sites of the lesions, which must be linked to contact with the product, even if in some cases, the area of the lesions is much larger than the area of contact.
- The list of products handled at work. Some substances are known to trigger CU, such as natural rubber latex, products of animal or vegetal origin, drugs...
- The relationship between the development of the skin lesions and the work schedule and a recurrence of the disease on re-exposure to the same agents.

Some groups of workers are particularly prone to develop CU: cooks, bakers, butchers, veterinarians, gardeners, florists, health care personals, hairdressers, workers in chemical plants, forestry workers, workers in the leather industry and in the rubber industry... However, this list is not exhaustive.

Skin tests with suspected agents are thus of paramount importance. If the patient has suffered from serious symptoms (stages 2, 3, 4 in the classification of Von Krogh and Maibach), tests should be done with the necessary precautions: very low concentrations of allergens should be used; resuscitation facilities should be immediately available.

Testing should be done in several steps [8, 9]:

- Open application on non affected skin.
- Open application on slightly or previously affected skin.
- Occlusive application on non affected skin.
- Occlusive application on slightly or previously affected skin.
- Prick or scratch tests.

The test substances are applied for 15-30 minutes to the skin and readings are taken immediately after their removal as well as 30 and 60 minutes after.

If positive reactions are obtained, further evaluation is discontinued.

On epicutaneous testing, high molecular weight substances like food or latex proteins will at times give positive reactions only on previously involved or possibly even inflamed skin because of better penetration. Suspected foods often give positive skin reactions only with the native substance since commercial extracts are often unreliable. The choice of vehicle is also important: agents suspended in alcoholic solutions or suspensions cause more rapid and fleeting reactions whereas reactions to agents in vaseline last longer. Equivocal tests results should be repeated, simulating the exposure of the patient with the suspected agent.

However, in practice, it is difficult to carry out all the tests. Many authors favour the prick tests (figure 1). Saline is used as negative control and 1% histamine as a positive control. Dermographism is the chief reason for false positive reactions. To minimize false negative reactions, patients must stop antihistamines and steroids for at least 3 days [10, 11]. Determination of specific IgE is helpful when an allergic CU is suspected. Others tests such as basophil activation tests could be used for biological diagnosis [12].

Etiology

Natural rubber latex allergy

Among occupational contact urticarias, natural rubber latex (NRL) is the commonest cause [13]. A high rate of sensitization and clinical allergy to latex has been reported in health care personnel, with an estimated prevalence varying from 5 to 10% in Europe, up to 17% in some studies in Canada and the United States [14-17]. High prevalence of NRL allergy was also found among hairdressers, house-keeping personnel, latex doll manufacturers, latex glove manufacturers, greenhouse workers, construction workers... [18, 19]. Among all subjects with serologic and/or skin test evidence for latex sensitization, numerous subjects were asymptomatic for type I hypersensitivity. Established risk factors contribute to the development of clinical manifestations: personal atopy and exposure to irritants (for example bleach, disinfectants) which can cause hand dermatitis and skin barrier disruption. So, most of construction workers with NRL allergy had a concurrent type IV hypersensitivity to chromate or rubber chemicals that facilitated sensitization to latex [20]. It is the same for health care workers: some studies showed a frequent combination between irritant contact dermatitis, allergic contact dermatitis and CU to latex [21, 22]. In symptomatic latex allergy patients, localized urticaria, sometimes angioedema and/or



Figure 1. Positive prick test with apple.

generalized reactions are the most frequent reported manifestations. Other manifestations such as rhinoconjunctivitis, asthma and systemic anaphylaxis can be observed [23]. Immediate type reactions are caused by proteins of NRL derived from *hevea brasiliensis* (allergic contact dermatitis is caused by rubber chemicals, mostly accelerators, particularly thiurams). NRL contains several hundred proteins of which 13, Hev (hevein) b1 to Hev b13 have been recognized by the International Union of Immunological Societies as latex allergens [24].

Cornstarch powder, which has traditionally been added during glove manufacture to facilitate donning, appears to increase exposure to latex allergens both through direct skin contact and via the respiratory tract [25, 26]. It is rarely an allergenic agent [27]. As an alternative to cornstarch, cotton fluff has been introduced into glove manufacture. However, cotton fluff can also serve as a vector for latex allergens [28]. Surgical and examination gloves are involved in about 80% of cases of latex intolerance. However, gloves are not the sole source of contact with NRL in sensitized health care personnel. NRL is found in numerous medical devices (catheters, tourniquets, syringes...).

The diagnosis of an NRL allergy is based on clinical history, skin prick tests, estimation of specific IgE antibodies and use tests. Skin prick tests must be performed with a standardized latex allergen extract. If in doubt, skin tests can be carried out with glove eluates prepared by a short extraction in isotonic sodium chloride solution. When there is some discrepancy between clinical history and skin test reactions, use tests with latex gloves can be performed very carefully. The quantitative measurement of serum specific IgE antibodies to NRL can be helpful for diagnosis [29]. For fifteen years, cross reactions between proteins in NRL and several foods have been demonstrated, particularly tropical fruits, banana, kiwi, avocado [30]... In addition, there are many publications containing reports of associations between concomitant sensitivity to NRL and various fruits, vegetables and plants. It is useful to ask for a history of food hypersensitivity in patients with NRL allergy. In the absence of a positive suggestive history, routine skin prick tests with food extracts are not useful. However, the patient must be aware of the possibility of future reactions to the most commonly implicated foods, *i.e.* banana, avocado, kiwi and chestnuts. If the latex-allergic patient's history is positive or strongly suspicious for a food allergy, skin prick testing should be done with the suspected food allergens, fresh foods when possible [31].

Other occupational contact urticarias

Numerous agents are also known to induce occupational CU in various jobs, for example:

- In health care personnel, the most frequent cause of CU is NRL. However, some drugs can also induce CU, particularly antibiotics (penicillin, amoxicillin...) [32-34].
- Laboratory workers can develop sensitivity to furred animals, particularly mice and rats. Urine is a major source of allergen production. Hair, dander and, to a lesser extent saliva, are also important rodent sources. Skin reactions are typically the next most prevalent symptoms, occurring in about 40% of symptomatic individuals [35].
- Veterinarians are at risk with animal blood, amniotic fluid, placenta, seminal fluid [36].
- Food handlers, chefs, bakers, butchers... are in constant contact with meats, fruits and vegetables [37, 38].



Figure 2. Contact urticaria on the neck of a forestry worker induced by pine processionary caterpillar.

– In hairdressers, some products as shampoo, shampoo in hair colour, hair-conditioner containing Crotein q, can induce CU [39, 40].

– In pine-cone or resin collectors, woodcutters, farmers, stockbreeders and other forestry personnel, processionary caterpillars can induce immunologic and/or non immunologic CU. The parts of the body most often affected were the uncovered areas (*figure 2*), although very often covered parts were also affected. The wheals join up around the neck and on the flexor surface of the wrists and forearm, and involve several cutaneous areas. Angioedema, especially of the eyelids, rhinoconjunctivitis and, in rare cases, respiratory symptoms and anaphylactic reactions have also been observed [5].

– In florists, gardeners, horticulturists, different decorative house-plants (*figus benjamina*, *yucca*...) [18-41] and flowers (gerbera, tulips, lilies, christmas cactus...) can induce CU.

Sporadic cases of occupational CU also arise with metal salts, isocyanates, organic solvents, epoxy resins, anhydrides due to airborne contact... [42-45].

In fact, the agents that are responsible for occupational CU vary in different countries. Thus, in Finland, in Kanerva's study, cow dander was the most common cause of CU in farmers [46].

So, the diagnosis of occupational CU should be suspected in any worker. The diagnosis must be confirmed or invalidated by a detailed history and skin tests with suspected substances.

Treatment

In CU, the major principle of treatment must be exclusion of the allergen. Unfortunately, this is not always possible and secondary prevention must be adapted. For NRL allergy, there is some evidence that implementation of simple preventive measures (unpowdered NRL gloves, NRL-free gloves) lowers markers of sensitization and NRL allergy [47, 48]. Currently, NRL specific immunotherapy remains an experimental treatment, in spite of a few randomized double blind placebo controlled studies [49, 50].

Protein contact dermatitis

In 1976, Hjorth and Roed-Petersen reported a serie of 33 food caterers with hand dermatitis. The workers reported



Figure 3. Protein contact dermatitis: hand dermatitis in a butcher.

exacerbation of the itch 10 to 30 minutes after contact with meat, fish and vegetables, followed later by erythema and vesiculation. Application of the relevant foods to the affected skin resulted in either urticaria or vesiculation. They proposed the term of protein contact dermatitis (PCD) [51]. Among patients with hand dermatitis (*figure 3*), acute flares of pruritus, urticaria, edema or vesicular lesions are noted a few minutes after the contact with the causative substance. The hands are the most commonly affected site and are generally diffusely involved. Sometimes, lesions may affect only the tips of the first, second and third fingers. Others sites may also be affected, wrists, forearms, face... Extracutaneous reactions such as angioedema, gastrointestinal symptoms, rhinoconjunctivitis and bronchial asthma may accompany the skin reactions. Data from the literature suggests that an association between atopy and PCD occurred in approximately 50% of the patients.

In food handlers, chronic paronychia can be considered a clinical variety of PCD (*figure 4*). Patients have an immediate erythematous-oedematous or vesicular reaction on the proximal nailfold to one or more of the foods that they handled. This reaction is associated with moderate itching. Clinically, the proximal nail fold showed redness and severe swelling [52]. NRL can also induce chronic paronychia [53].



Figure 4. Chronic paronychia in a chef.

These manifestations are induced by contact with products of animal or vegetal origin. The causative proteins have been classified into four groups [54]:

- group 1: fruits, vegetables, spices, plants [55];
- group 2: animal proteins: meat (beef, pork, horse, lamb, chicken...), fish and crustaceans (cod, herring, salmon, lobster, shrimps...) milk, cheese and also saliva, blood, amniotic fluid of animals;
- group 3: grains, particularly rye and wheat, also barley, oats, corn [56];
- group 4: enzymes (alpha-amylase...) [57].

The list of these allergens explains the affected professions: food-handlers in general (butchers, bakers...) food vendors, abattoir workers, veterinarians, laboratory animal workers, gardeners...

However, others jobs can be affected, such as industrial workers.

Diagnosis requires skin tests (preferably performed with fresh material), particularly open tests, prick tests or scratch tests. Positive reactions are observed after a few minutes. In some cases, specific IgE to the substance could be detected. However, RAST are not as sensitive as skin tests and are not available for every suspected allergen. Although PCD presents clinically as chronic eczema, patch-tests are usually negative.

The reactions are species- and organ-specific: calf's liver may provoke an reaction whereas chicken liver may not; chicken meat may provoke an reaction whereas chicken liver may not. Reports of multiple sensitizations are rare [58].

PCD is a type I allergic reaction to high molecular weight proteins. The penetration of these proteins through the epidermis is facilitated by irritant or eczematous dermatitis, particularly in atopic patients. Indeed, atopic subjects have a less effective skin barrier, through which the high molecular weight proteins can penetrate more readily [59, 60].

Conclusion

The incidence of occupational CU and protein contact dermatitis is not known as yet in the literature. There are usually only descriptions of sporadic cases, except for latex allergy. Because of its increasing importance, NRL allergy has stimulated epidemiological studies, showing an estimated prevalence varying from 5 to 10%.

However, the list of eliciting substances grows from year to year and occupational CU is thus rather frequent. The incidence and severity of these reactions can be decreased by preventive measures including the correct diagnosis based on detailed history and skin tests and adequate information. ■

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