# Protein Contact Dermatitis and Testing

8

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## Contents



## 8.1 Introduction

Since Maibach [1] and also Hjorth with Roed-Petersen [2] defined in 1976 protein contact dermatitis (PCD) as an immediate eczema induced after contact with proteins, the clinical expression of the hypersensitivity types could be redesigned.

Maibach described a patient with chronic hand eczema, presumably as a manifestation of atopy. But the treatment resistance appeared due to handling foods that produced burning and stinging in the chronically eczematous skin and not otherwise normal skin. The application of pertinent foods over chronically inflamed skin of the arm and back produced a wheal and flare response. On intact skin, scratch tests with foods produced positive results being the intradermal tests with commercial antigens negative. And the most important proof of causality was the consequence

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of avoidance to contact with these foods, the dermatitis being healed. This case it remains within the strictest today for many reasons. PCD continues to be reported as isolated cases or short series of cases. The basis of the diagnosis continues to be the in vivo provocation tests, and finally, the treatment is based in the avoidance of the involved responsible agent.

The study reported by Hjorth with Roed-Petersen included 33 food caterers suffering exacerbation of the itch, immediately after contact with meat, fish, and vegetables followed by erythema and vesicles. Application of the relevant foods to the affected skin resulted in either urticaria or eczema. A new type of immediate contact dermatitis characterized by the clinical findings of eczema was described. This work was important because it was a perfect example of the occupational relevance of most of the cases of PCD.

The association between atopy and PCD is frequent and was demonstrated in approximately 50 % of affected patients [3]. Nevertheless, PCD is not considered one of the diseases defining major criteria of atopy.

PCD and contact urticaria (CoU) are both immediate contact skin reactions induced by environmental triggers and belong to a more general syndrome, the contact urticaria syndrome (CUS). This syndrome comprises a heterogeneous group of immediate contact inflammatory reactions that usually appear within minutes after contact with eliciting substances. Occasionally, systemic involvement can be present. It was defined as an entity in 1975 by Maibach and Johnson [4]. Contact urticaria (CoU) refers to a wheal and flare reaction following external contact with a substance, usually appearing within 30 min and clearing completely within hours, without residual signs [5]. The term was introduced by Fisher (1973), but this phenomenon has long been recognized [6].

This book chapter is focused on how PCD can be recognized and studied. Its inclusion in any contact dermatitis text is crucial as still remains underdiagnosed. PCD break with the traditional immunological pathways. Both trinomial "immediate hypersensitivity (IgE mediated) – protein – wheal" and "delayed hypersensitivity (T lymphocyte mediated)-low molecular weight chemical-eczema" are not applicable to the PCD.

Patients suffering CUS can develop immediately after the contact with the trigger substance, CoU, and/or dermatitis/eczema as PCD. These immediate contact reactions appear on normal or eczematous skin. Wheals are the characteristic symptoms in CoU. Eczema appears rapidly on the hands in PCD. Both cutaneous symptoms and entities can be induced by the same trigger factor and can be suffered by the same patient.

## 8.2 PCD as Part of the Contact Urticaria Syndrome: How Frequent Is It? Which Is Its Social Relevance?

The global incidence of CUS is not known, but immediate contact reactions are common in dermatological practice [7–12]. There are no available data considering PCD individually. With the exception of latex allergy showing prevalence of

5–10 %, for the rest of trigger factors, just isolated cases or a short series of patients are described [13]. In the occupational setting, CoU and PCD seem to be common although a precise statistical analyses are difficult to obtain in most of the countries because of underreport [14]. In few countries, CoU has been classified as a separate occupational skin disease. This is the case in Finland since 1989. The "Finnish Register of Occupational Diseases" (1990–1994) showed that CoU was the second most frequent cause of occupational dermatosis (29.5 %), after contact allergic dermatitis (70.5 %) [15, 16]. The trigger agents were cow dander (44.4 %), natural rubber latex (23.7 %), and flour, grains, or feed (11.3 %) [16]. Less proportion of occupational CoU was found in a retrospective study done in a tertiary level clinic specializing in occupational dermatology in Melbourne, Australia, showing an 8.3 % CoU prevalence [17]. Hands, arms, and face were the most frequent body area involved. Atopy was a significant risk factor for natural rubber latex, foodstuffs or ammonium persulfate CoU. Health workers, food handlers, and hairdressers were the most common occupations affected. More recently, a survey conducted in 335 restaurant, catering, and fastfood employees in Singapore showed as more common occupational dermatosis irritant contact dermatitis (10 %) being occupational CoU urticaria sporadically reported just in two patients caused by lobster and prawn [18]. If the differential diagnosis in this study included PCD was not reported.

The professional groups with high risk to develop CoU and PCD are food handlers or people involved in agriculture, farming, floriculture, as well as hunters, veterinarians, or biologists. Atopy favors further sensitization in such occupations if protein allergens are concerned [19].

## 8.3 What Is the Clinical Manifestations of PCD as Part of the Contact Urticaria Syndrome?

Contact dermatitis is an inflammatory skin reaction to direct contact with noxious agents in the environment. Pruritus is the hallmark symptom of contact dermatitis. Spongiosis of the epidermis is the histological hallmark of acute eczematous reactions. Clinically, the confluence of espongiosis leads to vesicles and even bullae. The vesicle is the elemental lesion of eczema. It is preceded by erythema and dermal thickening, and because of scratching, the crusts appear. The vesicular response is associated with acute contact dermatitis. Once contact dermatitis relapses, the skin became acanthotic, and macroscopically, the chronic eczema shows a lichenified skin and characteristic painful fissures. The features of chronic dermatitis are pruritus, lichenification, erythema, scaling, fissures, and excoriation.

The vesicular or bullous reaction may be seen in allergic and irritant contact dermatitis as well as in PCD and cannot be used to distinguish between these types of dermatitis [20]. Protein contact with the skin can induce immunological CoU and PCD. Proteins can be responsible of chronic and recurrent eczema. It may be manifested just as a fingertip dermatitis or extend to hand, wrists, and arms. An urticarial or vesicular exacerbation can be noted in a few minutes after contact of the causal agent, especially on previously affected skin. Some cases of chronic

**Table 8.1** Stages of the contact urticaria syndrome

| | |
|---|---|
| Stage 1 | Localized urticaria (redness and swelling)<br>Immediate contact dermatitis (eczema – protein contact dermatitis)<br>Itching, tingling, or burning sensation |
| Stage 2 | Generalized urticaria |
| Stage 3 | Bronchial asthma (wheezing)<br>Rhinitis, conjunctivitis (runny nose, watery eyes)<br>Orolaryngeal symptoms (lip swelling, hoarseness, difficulty swallowing)<br>Gastrointestinal symptoms (nausea, vomiting, diarrhea, cramps) |
| Stage 4 | Anaphylactic or anaphylactoid reaction (shock) |

paronychia were considered a variety of PCD, with redness and swelling of the proximal nail fold, e.g., after handling food or natural rubber latex. As for CoU in PCD, extracutaneous symptoms can appear, as rhino-conjuntivitis or asthma and even anaphylaxia. Abdominal pain, diarrhea, and "oral allergy syndrome" may occasionally develop when the allergen comes in contact with the oropharyngeal mucosa [21].

The CUS can be classified in four stages of severity (Table 8.1)

## 8.4 What Do We Know About the Mechanisms Involved in PCD?

The mechanisms underlying immediate contact skin reactions are partially understood. Each trigger substance has its own mechanism or mechanisms of action. Non-immunologic CoU (NICoU) is due to vasogenic mediators without involvement of immunological processes. The pathogenesis of immunological CoU (ICoU) reflects a type I hypersensitivity reaction, mediated by allergen-specific immunoglobin E (IgE) in a previously sensitized subjects [22]. Skin challenge involves allergen penetration through the epidermis, IgE binding on mast cells, its degranulation, and subsequent release of histamine and other vasoactive substances as prostaglandins, leukotrienes, and kinins.

A combination of type I and type IV allergic skin reactions, the latter supported by positive delayed patch tests, has been suggested as PCD pathogenesis [23, 24]. It has been speculated that PCD is an eczematous IgE-mediated reaction through proteins. PCD shows a similar reaction pattern to aeroallergen-induced atopic eczema or dermatitis [25].

## 8.5 How to Confirm the Responsible Environmental Agent of PCD

Diagnosis of PCD as of any of the diseases included in the CUS is based on full medical history and skin testing with suspected substances (Fig. 8.1).

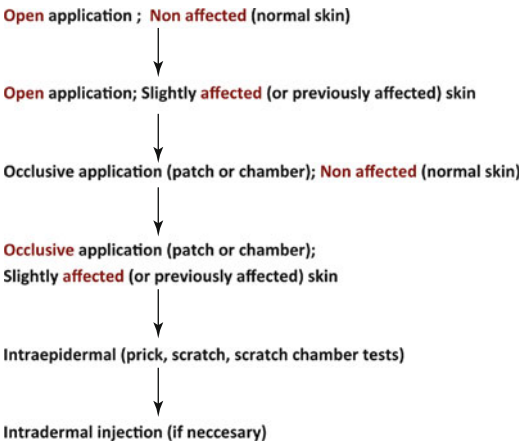


**Fig. 8.1** Diagnostic flowchart to test CoU and PCD from the CUS. Proceed to the following suggested provocation test if the test done is negative

In vitro techniques are available for only a few allergens, including latex. The simplest cutaneous provocation test for ICoU, NICoU, and immediate contact dermatitis as PCD is the "open test." The suspected substance studied is applied and gently rubbed on slightly affected skin or on a normal-looking 3 × 3 cm area of the skin, either on the upper back or the extensor side of the upper arm. Often it is desirable to apply contact urticants to skin sites suggested by the patient's history. The suspected substance, commonly foods, is brought by the patient. A positive result is an edema and/or erythema typical of CoU or tiny intraepidermal spongiotic vesicles typical of acute eczema. An immunological and non-immunological contact reaction usually appears within 15–20 min being the non-immunological one lasting within 45–60 min. ICoU can also show a delayed onset, although this is rare.

When the open test results are negative, "prick testing" of suspected allergens using often "prick by prick is the method of choice for immediate contact reactions (Fig. 8.2).

"Scratch test" and "chamber scratch test" (contact with a small aluminum chamber for 15 min) are less standardized than the prick test but are useful when a nonstandard allergen must be studied. For both prick and scratch tests, histamine hydrochloride serves as the positive control and aqueous sodium hydroxide as negative reference. When other than cutaneous organs are involved, it is important to begin ICoU testing with much diluted allergen concentrations and to use serial dilutions to minimize allergen exposure. When testing with poorly or nonstandardized substances, control tests should be assessed on at least 20 people to avoid false-positive interpretation. Nonsteroidal anti-inflammatory drugs and antihistamines should be avoided because of the risk of false-negative results. Following the recommended protocol is important for minimizing the occurrence of hazardous extracutaneous reactions. Life-threatening reactions have been documented during skin tests; therefore, caution is advised, especially when testing certain occupational substances. Skin tests should be performed only if resuscitation equipment and trained personnel are readily available [26–28].

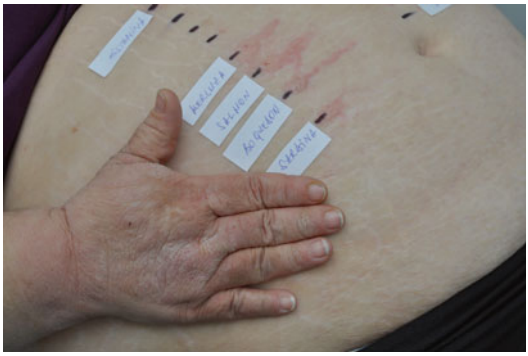

**Fig. 8.2** Eczema at the dorsum of hand induced by proteins habitually touched in the daily work of a fisher woman sailor. Positive wheal induced by prick by prick test with hake, salmon, anchovy, and sardine

## 8.6 Responsible Agents of PCD as Part of the CUS

Proteins (molecular weight 10,000 to several hundred thousands) and also chemicals (molecular weights below 1000) can trigger CUS [29]. Proteins from plants, food, or animals are the main responsible agents of PCD. We know that commonly the same type of protein can be responsible of dermatitis, wheals, or pruritus. Plant or animal proteins, but also chemicals such as drugs and preservatives, or more diverse substances such as metals and industrial chemicals, can induce immunological CoU. Natural rubber latex allergy focused global interest at the end of the twentieth century. Latex sensitization risk factors include atopy and prolonged exposure via damaged epidermis, e.g., glove wearers with hand eczema.

A huge amount of compounds can be responsible of occupational and non-occupational CUS including animal products, plants and plant derivatives, foods, fragrances, cosmetics, flavorings, medications, preservatives, disinfectants, enzymes, metals, and miscellanea of different substances.

## 8.7 Treatment and Prevention of PCD

CUS clinical symptoms are determined by the route, duration, and extent of exposure, the inherent sensitizing properties of the allergen, and an individual's genetic and/or acquired susceptibility. The best way to treat PCD is based in a correct etiological diagnosis. Identifying the responsible agent is required to avoid correctly the cause. Avoidance of further exposure will improve occupational PCD and CoU. Primary and secondary prevention measures are highly recommended being necessary common guidelines in order to prevent well-known occupational risks as, e.g., latex allergy [30].

Hand and wrist dermatitis is the common location of PCD. For hand dermatitis along with emollients, the local treatment of choice is a topical corticosteroid. These agents are very effective in the short term. The disadvantages of topical corticosteroids include cutaneous adverse effects (skin atrophy), tachyphylaxis, and adrenal suppression after systemic absorption; however, this is rare. Anecdotal experience

suggests that intermittent dosing may reduce the risk of adverse effects. Clinical experience suggests that alternating a topical corticosteroid with a topical calcineurin inhibitor may reduce adverse effects, though randomized clinical trials are missing and the long-term safety of this approach is unknown.

The off-label use of topical calcineurin inhibitors tacrolimus and pimecrolimus licensed for the treatment of atopic dermatitis can be considered. The rationale to use them is based in the suggested pathogenic mechanism of the PCD, similar to the immunological pattern involved in atopic dermatitis. Nevertheless any trial can support this clinical practice. Adverse effects include transient stinging and skin infection; despite concerns about the long-term effects of topical immunomodulators, observational data suggest that these agents are not associated with lymphoma.

Severe cases of PCD in the context of the CUS would need systemic inmunomodulator treatment.

## 8.8 Challenges and Further Research in PCD

The knowledge of PCD shows some challenges that need further research. Until now, we assume new cases as exceptional findings adding each year new triggers to lists of substances. Still it is an underreported disease. General population-based epidemiological studies are missing. Proteins are responsible of clinical manifestations, urticaria or eczema, consequence of slightly different pathogenic mechanisms. Sometimes the same substance can induce both clinical patterns. This fact opens the door for new insights into immune system response. It would be useful to replace in vivo tests by effective in vitro testing for diagnostic purposes. After symptoms control, an appropriate etiological diagnosis and the development of concrete preventive measures are required. PCD in the context of the CUS is a worldwide health problem.

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