



Mechanism and diagnosis of protein contact dermatitis

Annick Barbaud

Purpose of review

Protein contact dermatitis (PCD) is a chronic eczema because of immediate hypersensitivity to protein and not related to haptens. As it has to be diagnosed by prick tests, it is probably under-recorded and under-estimated that is why it is important for dermatologists, allergists and occupational physicians to better know this peculiar contact dermatitis.

Recent findings

Some recent series have emphasized that PCD is mainly an occupational dermatosis, mainly observed in food handlers.

Summary

PCD is a chronic eczematous dermatitis, possibly exacerbated by work, suggested if associated with inflammatory perionychia (paronychia inflammation) and immediate erythema with pruritis, to be investigated when the patient resumes work after a period of interruption. Prick tests with the suspected protein-containing material are essential, as patch tests have in most of the cases negative results. Prick-by-prick tests with fresh material are recommended. The product has to be 'pricked', for instance the food, and immediately after the forearm is pricked. In case of multisensitization revealed by prick tests, it is advisable to analyse IgE against recombinant allergens. History of atopy found in 56–68% of the patients has to be checked for. Most of the cases are observed among food-handlers but PCD can also be because of nonedible plants, latex, hydrolyzed proteins or animal proteins.

Keywords

food allergy, food-handlers, prick-by-prick tests, protein contact dermatitis

INTRODUCTION

Protein contact dermatitis (PCD) is a chronic eczema because of immediate hypersensitivity to protein and not related to haptens. As it has to be diagnosed by prick tests, it is probably under-recorded and under-estimated that is why it is important for dermatologists, allergists and occupational physicians to better know this peculiar contact dermatitis. There are only few reports of PCD, and unfortunately some recent reports mixed PCD with contact urticaria, which are two different dermatosis regarding their clinical features and their severity.

CLINICAL FEATURES

PCD was first described in 1976 by Hjorth and Roed-Petersen [1]. The authors reported occupational contact dermatitis mainly observed in food handlers.

Skin lesions, with a chronic and recurring course, are analogous with the clinical picture in allergic contact dermatitis and irritant contact dermatitis; skin patch tests, however, are usually

negative [2]. There is a clear relationship between exposure and symptoms.

The dermatological symptoms usually appear on the skin of hands, wrists and forearms, more rarely they concern only the fingertips. In exceptional cases, they can also appear on the face, as a result of hand contact with sensitizing proteins. A belly's eczema was observed in a cook who used a hand towel tucked into his belt when handling fish [3]. Cheilitis because of food has been reported [3]. Two cases of occupational chronic hand eczema with also foot eczema in one of the two

Sorbonne Université, INSERM, Institut Pierre Louis d'Epidemiologie et de Sante Publique, AP-HP. Sorbonne Université, Tenon Hospital, Department of Dermatology and Allergology, Paris, France

Correspondence to Professor Annick Barbaud, MD, PhD, AP-HP. Sorbonne Université, Tenon Hospital, Department of Dermatology and Allergology, 4 rue de la Chine, Paris, France. Tel: +33 1 56 01 72 25; fax: 33 1 56 01 72 32; e-mail: annick.barbaud@aphp.fr

Curr Opin Allergy Clin Immunol 2020, 20:000–000

DOI:10.1097/ACI.0000000000000621

KEY POINTS

- This review includes an update on the mechanisms involved in PCD and its predisposing factors.
- The most exhaustive published list of causes of PCD is done in this publication.
- Skin test methods, mainly prick-to-prick tests, for diagnosing PCD are detailed.
- To improve future reports on PCD, authors recommend distinguishing PCD from contact urticaria because of protein.
- For a better understanding of the mechanisms involved in PCD, recommendations for studying recombinant allergens are done.

cases, after eating lettuce, developed cheilitis/dermatitis around the mouth and lip swelling respectively, and both had positive patch and prick test reactions to lettuce [4].

Apart from the lesions that are typical for eczema, urticaria or vesicular eruption occurring a few minutes after contact with the inducing factor, may appear on the skin [2[•]]. A paronychia with periungueal erythematous edema would be suggestive of PCD. The skin lesions are accompanied by itching, burning, pricking and pain [2[•],3^{••}]. The immediate urticarial reaction is frequently missing in the patients' history. In the largest series, this immediate reaction was observed in only 12/79 cases [5] and 2/27 cases [6^{••}]. The immediate pruritus just after handling the offending protein material is mainly observed when returning from a long sick leave [3^{••}].

MECHANISMS

The reaction is mainly considered as an immediate hypersensitivity reaction caused by high-molecular-weight proteins penetrating the epidermis. Some authors claim the possibility of co-occurrence of reactions of types I and IV according to Gell et Coombs classification, because of some reports with positive results of patch tests [2[•],3^{••}].

History of atopy varies from 56 to 68% in patients with PCD [3^{••}]. Thus, PCD develops in patients with a history of atopy and it seems to occur in workers repeatedly exposed to protein. The occurrence of PCD could be facilitated by micro-trauma to the skin as it might lead to the penetration of large proteins through the skin. Such skin exposure to proteins might cause IgE-mediated immediate sensitization revealed by prick tests or by

the presence of circulating protein-specific IgE. Sensitization causes immediate mild allergic skin reactions, which might cause the development of the late phase of the skin reaction from protein-containing allergens as it is described in atopic dermatitis [3^{••}]. In a certain way, PCD could be considered as a localized feature of atopic dermatitis exacerbated by contact sensitization to specific proteins. In most of the patients, PCD does not seem to be chemically related to preexisting sensitization to inhalant allergens. Skin sensitization is the first symptom, it can then be complicated by systemic allergic reactions from food. However, in most of the cases, consumption of the food to which the patient is sensitized is well tolerated. The occurrence of PCD and sensitization to inhalant allergens is thought to be the common atopy background of the two diseases, without any causality link between them.

Predisposing factors

The penetration of high-molecular-weight proteins is facilitated by the alteration of the epidermis. It occurs more often in patients with a damaged dermal-epidermal barrier, for example, in previous atopic dermatitis or irritant contact dermatitis [7[•]], physical factors (burns, cuts), chemical factors (detergents), wet work (washing hands frequently), prolonged occlusion by gloves [2[•]]. These conditions are mainly encountered in food-handlers, especially in cooks but also in professionals caring for animals. We could also add skin trauma (cuts and abrasions). In PCD, because of sea products, Loddé *et al.* [7[•]] showed that the population of chefs is more affected than fishermen. Chefs often handle fish bare-handed and liquids from fish, moreover the allergenicity could increase with the postmortem age of the fish.

Risk in case of systemic exposure

Most often, the same-protein containing products eaten by patients do not produce any effects.

Among 22 cases of PCD, only 3 patients had systemic reactions to proteins: 2 in eating food (fish, buckwheat, potato) and 1 cook had asthma when exposed to fish fumes [3^{••}]. A housewife with a PCD to cabbage had a flare up of her hand eczema after she ate Japanese-style savory pancake, okonomiyaki, in which the main ingredient is heat-cooked cabbage [8].

Among 291 cases of protein-induced dermatitis, 233 were contact urticaria (80%) and 59 had PCD (20%). Of the 134/291 patients who were diagnosed with both chronic urticaria or 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 [9[■]]. Unfortunately, it is not possible in this study to distinguish PCD from contact urticaria, and the latter seems to be a more severe disease than PCD. Therefore, it is not possible to compare the systemic risk of exposure to proteins in case of contact urticaria with that of a patient having a PCD. That is why, in order to better understand PCD, in further studies, it is advisable to separate contact urticaria from PCD.

DIAGNOSIS

The diagnosis tools and steps are summarized in Table 1. According to Vester *et al.* [10] PCD is defined as follows: patients having chronic, recurrent eczema that occurs in contact with proteins and have a positive prick test reaction to protein-containing material. However, for some authors, prick test results are not always positive, thus PCD is considered as chronic eczema because of immediate hypersensitivity to proteins with or without positive prick tests. It seems reasonable to consider as PCD, skin conditions with an aspect of chronic eczema associated with immediate hypersensitivity to protein proved by a positive skin test or by the presence of specific IgE assessed *in vitro* [3[■]]. Thus, the most helpful test to investigate PCD is the prick test.

The high incidence of concomitant allergic contact dermatitis to haptens can be misleading and

PCD might be under-diagnosed in patients with hand eczema and relevant positive patch test results [3[■]].

Whenever possible, prick tests are carried out with commercial extracts. When none are available, in order to investigate food or other occupational protein-containing products, prick-by-prick tests are then recommended. The product has to be 'pricked', for instance, the food, and immediately after the forearm is pricked.

Prick-by-prick testing was primarily used for fresh food, vegetables and plants. Flour, grains, animal feed, spices and other dry substances can be diluted in a potassium phosphate buffer, and then used for prick-to-prick testing [9[■]].

As for any other prick test, reading has to be done after 15 or 20 min, using negative (saline) and positive (histamine) controls. Prick test with the protein-containing substance tested is considered positive if at 15 or 20 min the wheal diameter is at least 3 mm larger than the negative control. If prick test results are negative, Hernández-Bel *et al.* [6[■]] suggest performing a rub test by applying the protein-containing substance to the area affected by PCD. The rub-test consists in a gentle rubbing with the material on the damaged skin. In patients with chronic eczema after wearing latex gloves with negative prick tests and specific IgE, a 15-min exposure test to a piece of latex glove can be done [3[■]].

An 'open' patch tests can also be done in posing for a short time the fresh foods on the damaged skin with adhesive plaster. After 20 min, the open patch test is usually positive only on damaged skin. The open patch tests with the same foods are also done

Table 1. Clinical features of occupational protein contact dermatitis and recommended tests for its management

Clinical features	Allergy tests
Aspect of chronic dermatitis, possibly exacerbated by work	Suggestive but inconstant symptoms: Inflammatory perionyxis Immediate erythema with pruritis, to be investigated, for example, when the patient resumes work after a long period of interruption
Patch tests with protein-containing products	Negative (or rarely positive) Warning: co-sensitization with contact allergy to haptens can be found and delay the diagnosis
Prick tests	On normal skin of the forearm with positive (histamin) and negative (saline) controls Essential with the suspected protein-containing material. If no allergen extracts available, perform a prick-by-prick test with the products the patient brought (e.g. native food)
Specific IgE	Useful if available In case of multisensitization revealed by prick tests, in order to study cross reactivities, it is advisable to analyse molecular allergen-specific IgE (recombinant allergens)
Other in-situ skin tests	Open patch test on the lesional skin (20 min under plaster) Rub test: gentle rubbing with the material on the lesional skin
Check for history of atopy	Questioning, prick tests with inhalant allergens

Data from Barbaud *et al.* [3[■]].

Table 2. Causes of protein contact dermatitis reported in literature

Product's family	Sources of responsible proteins
Edible plants: fruits and vegetables	Almonds, apple, asparagus, banana, beans, cabbage, carrots, castor oil, cauliflower, celery, chicory, cucumbers, dill, eggplant, endives, figs, garlic, hazelnut, horseradish, kiwi, lemon, lettuce, maize, mushrooms, onions, peach, peanuts, pineapples, potatoes, shiitake, tomatoes, watercress
Edible plants: spices and condiments	Cardamine, coriander, cumin, curry, caraway, paprika, parsley, parsnips
Inedible plants	Baby's breath (gypsophila), chrysanthemum, cucumber leaf, ficus, lilac, lilies, tulip, Spathiphyllum
Edible animal proteins	Crustaceans (lobster, flounder, clams, scallops, shrimp); fishes (cod, cuttlefish, hake, mackerel, monkfish, pollock, tilapia, salmon, whiting); dairy products: milk, serum milk, cheese, Reblochon cheese; egg, egg yolk; meat: animal offal, beef, horse meat, liver, mutton, pork, poultry, suet
Inedible animal proteins	Amniotic fluid, blood (pig, cow, sheep), serum, organs, placenta, saliva of animals, and mesentery in veterinarians; mucus of amphibians Stomach Wool, animal skin, cow or pig dander Anisakis, worms and maggots (<i>Nereis diversicolor</i> and others) Shellfish fed to aquarium fish, <i>Daphnia</i>
Grain	Buckwheat, rye flour, barley flour, wheat flour, oats,
ENZYMES	alpha-amylase, cellulase, glucoamylase, lactase, papain, protease
Miscellaneous	Latex, hydrolyzed protein hair mask, corn starch glove powder

Data from [2[■],3[■],7[■],8,11].

on the healthy skin of the patient's hands as negative control.

In some cases, the classic patch tests can also be positive [11], but in most of the cases they remain negative.

Whenever possible, skin testing can be completed by specific IgE determination, for example, for food or latex. Specific recombinant IgE would also be done in order to better understand, which epitopes are responsible for PCD, and if cross reactions follow the same rules as described in systemic food allergy. In case of multiple food sensitization, it seems relevant to investigate the presence of molecular allergen-specific IgE (recombinant allergens), which might account for cross reactions. Such reactions have seldom been investigated in case of PCD [3[■]].

Regarding cross reactions, recent case reports showed a bird-egg syndrome in a woman having a palm eczema when handling poultry [12], a possible sensitization to proteins from the pectin methyl-esterase family in a case of PCD to chrysanthemum [13], cross reactions between cabbage and other vegetables belonging to the same species (Japanese mustard spinach and broccoli) in a Japanese patient [8].

CAUSES

Helaskoski *et al.* [9[■]] reported a very large series of patients from the occupational medicine clinic at the Finnish Institute of Occupational Health (FIOH). From 1 January 1995 to 31 May 2011, 291 patients

were diagnosed with contact urticarial or protein contact dermatitis [9[■]]. Food was the main cause of protein-induced dermatosis. Unfortunately, in this very interesting study, it is not possible to select information on the PCD population alone.

In literature, a lot of protein products have been reported as inducers of PCD. According to recent data, the protein inducers are summarized in Table 2. They can be separated in edible plants (fruits, vegetables, spices), inedible plants, edible animal proteins, inedible animal proteins, grains, enzymes, latex, hydrolyzed protein hair mask, corn starch glove powder.

PREVENTION

The main primary protection is wearing gloves and other protective clothing in factories or kitchens, especially in patients with atopic history. A strict medical aptitude selection, which may exclude the more at-risk workers with atopic symptoms has been proposed by Loddé *et al.* [7[■]].

IMPACT OF PROTEIN CONTACT DERMATITIS

In their study, Vester *et al.* [10] showed the very negative impact of PCD on the future of workers in the food industry compared with other occupational skin diseases in this field. Among 175 food-handlers who had occupational hand dermatitis, PCD was

observed in 50 cases (28.6%). All these 50 patients experienced work-related consequences of their skin conditions. Compared with 123 patients with hand contact dermatitis because of other conditions, 31/50 patients with PCD had to change jobs (60 vs. 43%) and 7 patients had to retire (10 vs. 6%, $P = 0.02$). Sick leave more than 3 weeks was more frequent in workers with PCD (10/16, 62.5 vs. 30% in workers with hand eczema of other conditions ($P = 0.02$) and patients with PCD more frequently consulted a physician (55%) than the other patients (31.5%, $P = 0.004$). Loddé *et al.* reported the same negative impact of PCD for fish handlers [7].

TREATMENT

The treatment is a strict avoidance of handling and touching the offender proteins products, for example, by wearing gloves, associated with a topical treatment with corticosteroids.

CONCLUSION

PCD is an eczematous disease, which has to be better known by dermatologists, allergists and occupational physicians as it is probably underdiagnosed. In a patient with chronic hand eczema, especially if professionally, he handles food or nonfood proteins, this diagnosis should be raised and prick tests carried out with the suspect products. The future challenges will be to better understand the epitopes involved in PCD, the links between PCD and atopic dermatitis and to study the differences between two entities, which are too often confused: DCP and protein contact urticaria.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Hjorth N, Roed-Petersen J. Occupational protein contact dermatitis in food handlers. *Contact Dermatitis* 1976; 2:28–42.
2. Obtulowicz A, Pirowska M, Wojas-Pelc A. Contact eczema of hands caused by contact with potato protein. *Ann Agric Environ Med* 2016; 23:377–378. ■
- Review on protein contact dermatitis.
3. Barbaud A, Poreaux C, Penven E, Waton J. Occupational protein contact dermatitis. *Eur J Dermatol* 2015; 25:527–534. ■
- Review on protein contact dermatitis and contact urticaria, and original study with 25 cases of protein contact dermatitis.
4. Paulsen E, Andersen KE. Lettuce contact allergy. *Contact Dermatitis* 2016; 74:67–75.
5. Brancaccio RR, Alvarez MS. Contact allergy to food. *Dermatol Ther* 2004; 17:302–313.
6. Hernández-Bel P, de la Cuadra J, García R, Alegre V. Protein contact dermatitis: review of 27 cases. *Actas Dermosifiliogr* 2011; 102:336–343. ■
- 27 cases of PCD
7. Loddé B, Cros P, Roguedas-Contios AM, *et al.* Occupational contact dermatitis from protein in sea products: who is the most affected, the fisherman or the chef? *J Occup Med Toxicol* 2017; 12:4. ■
- Eight cases of PCD and analysis of predisposing factors explaining why cooks have PCD because of fish more frequently than fishermen.
8. Kishimoto I, Kambe N, Nguyen CTH, *et al.* Protein contact dermatitis induced by cabbage with recurrent symptoms after oral intake. *J Dermatol* 2017; 44:e252–e253.
9. Helaskoski E, Suojalehto H, Kuuliala O, Aalto-Korte K. Occupational contact urticaria and protein contact dermatitis: causes and concomitant airway diseases. *Contact Dermatitis* 2017; 77:390–396. ■
- Two hundred and ninety-one cases of protein-induced dermatitis, with 59 PCD but mixed with cases of contact urticaria.
10. Vester L, Thyssen JP, Menné T, Johansen JD. Occupational food-related hand dermatoses seen over a 10-year period. *Contact Dermatitis* 2012; 66:264–270.
11. Chessa MA, Vincenzi C, Leuzzi M, *et al.* Protein contact dermatitis to suet. *Dermatitis* 2017; 28:288–289.
12. Berbegal L, DeLeon FJ, González I, Silvestre JF. Protein contact dermatitis caused by chicken meat in bird-egg syndrome. *Contact Dermatitis* 2017; 77:253–254.
13. Nahas O, Colomb S, Demoly P, Bourrain JL. Protein contact dermatitis to chrysanthemum. *J Investig Allergol Clin Immunol* 2017; 27:318–319.