

Food-induced cutaneous adverse reactions

Wüthrich B. Food-induced cutaneous adverse reactions.
Allergy 1998; 53 (Suppl 46): 131-135. © Munksgaard 1998.

The skin is the most frequently affected target organ in allergy or intolerance of food and food additives. The most common manifestation is acute urticaria (with or without angioedema), accounting for 40-60% of patients with IgE-mediated food allergy, whereas food additives rather aggravate chronic urticaria (intolerance provocation). The role of food allergy in the pathogenesis of atopic dermatitis is still controversial; however, there is no doubt that, particularly in infants and young children, food allergens can induce atopic dermatitis or aggravate skin lesions. In adults, food allergy as a cause or a trigger of atopic dermatitis is very rare. However, in food-allergic patients with atopic dermatitis, the ingestion of the food item can provoke the whole spectrum of IgE-mediated symptoms, from oral allergy syndrome to severe anaphylaxis. Skin symptoms can also be induced not only after food ingestion in sensitized people, but also after direct skin contact, as lipophilic food allergens can penetrate the skin via the hair follicles or when the skin barrier function is defective. Immediate contact reactions of the skin are a heterogeneous group: they include not only contact urticaria (contact urticaria syndrome) on an immunologic or nonimmunologic basis, but also allergic or nonallergic eczematous reactions caused by food proteins (protein contact dermatitis). A prototype is baker's eczema in a restricted sense with immediate-type sensitization to flour. Atopic eczema provoked by direct contact of the skin with food must also be taken into consideration. Finally, very rarely, allergic contact dermatitis that is due to type IV sensitization to food or food additives (positive delayed type reaction in the patch tests) can occur. The oral ingestion of these foods may provoke in these patients a generalized eczematous rash or dyshidrosiform reactions (vesicles) of the fingers, palms, and soles.

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Key words: atopic dermatitis, baker's eczema, contact urticaria, food allergy, food additives, protein contact dermatitis, skin reactions

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According to the pathogenetic mechanisms involved in food allergy, IgE-mediated reactions are easily recognizable by means of a careful case history; allergy skin prick tests, especially prick-to-prick tests using fresh foods; serum IgE determinations by RAST/CAP and other methods; and oral-challenge procedures (1). Clinical manifestations of food allergy can remain localized at the site of the primary direct contact, i.e., the oropharynx (oral allergy syndrome [OAS]) or the gastrointestinal tract (isolated gastrointestinal food allergy); however, after ingestion, resorption, and hematogenous transport of food allergens to the various target organs, other symptoms can occur. The skin is the most frequently affected organ. Among 402 patients with systemic IgE-mediated allergy to one or more specific foods - OAS and food-induced aggravation of atopic dermatitis were not included - diagnosed over a 10-year period (1978-87) at the Allergy Unit in Zurich,

Switzerland, the skin was affected in 46% of patients, followed by the respiratory tract (25%), the gastrointestinal tract (20%), and the cardiovascular system (10%) (2-4). Twenty percent of food-allergic patients had skin symptoms exclusively. In a second series, 383 predominantly adult patients (66.4% females, 33.6% males) with proved IgE-mediated food allergies, including OAS, seen at the Allergy Unit during the years 1990-4, were evaluated (5). The organ manifesting symptoms of food allergy was most often the skin (60%) with urticaria and angioedema and the orogastrointestinal tract (60%), if OAS was included. Forty percent had respiratory symptoms (rhinitis, asthma) and 7.6% symptoms of the cardiovascular system (anaphylactic shock). Usually, the patients showed involvement of two or more organs, but 44.4% had exclusively skin symptoms, 28.7% isolated OAS, and 9.1% isolated gastrointestinal manifestations.

Allergic skin manifestations following food ingestion

Urticaria and angioedema

Generalized urticaria and/or angioedema (Quincke's edema) may be the only symptoms of an allergic reaction to food. The lesions occur suddenly, usually with intensive pruritus and resolve either spontaneously or after symptomatic therapy within a few hours. Acute urticaria/angioedema may be associated with ocular, respiratory, and gastrointestinal symptoms. A severe, life-threatening symptom is laryngeal edema. Sometimes, in the absence of typical hives, only intensive pruritus, localized or generalized erythema, and a feeling of warmth may be present.

Most cases of chronic urticaria, present for longer than 6 weeks, are not caused by food allergy (6, 7). However, some cases of chronic urticaria/angioedema may be due to IgE-mediated allergy to a hidden food or to different foods (8, 9). Food additives, such as preservatives (antimicrobials and antioxidants), colorants, emulsifiers and stabilizers, fillers such as vegetable gums, flavor enhancers and sweeteners, and enzymes, can also provoke or aggravate chronic urticaria (10–12). We speak of "food additives allergy" if a substance-specific immunologic mechanism can be proved by means of *in vivo* and *in vitro* tests, and of "food additives intolerance" when nonimmunologic mechanisms are involved (1, 13). We do not know the exact mechanism of this intolerance (14, 15).

The diagnosis of allergy to an additive can be done by performing skin prick and epicutaneous patch tests for immediate-type or contact-type allergy, but, in any case, – with the exception of strong anaphylactic reactions – oral challenge tests are needed for diagnosis. Of course, the patient should be tested in a period of stable conditions and after a period of an additive-free diet. Urticaria patients must be challenged in the hospital. In the case of positive results, we should distinguish between intolerance reaction and intolerance provocation.

In an intolerance reaction (13), the ingestion of additives in foods (and drugs) is the cause of the urticaria, and the elimination of these additives from the ingested foods leads to a complete disappearance of symptoms. Relapses occur after the reintroduction of the additives. We can distinguish between the acute or acute recurrent course and the chronic course. In the acute or acute recurrent course, an IgE-mediated mechanism may also be present (16, 17). This situation is, however, quite rare.

More common is intolerance provocation (13), in which the additives exacerbate an existing disease

such as asthma, rhinitis, or urticaria, but the appropriate elimination diet does not lead to complete disappearance of symptoms. Additives are triggers or aggravating factors (10, 13, 18).

Atopic dermatitis

The role of food allergens in the pathogenesis of atopic dermatitis is still controversial (19–21). There is no doubt that food allergens can induce atopic dermatitis lesions or at least a flare-up of pre-existent lesions, particularly in young children (22, 23). Furthermore, many patients with atopic dermatitis, especially with associated respiratory allergies, pollinosis, and asthma, show high levels of IgE antibodies as well as positive prick or intracutaneous tests to various food allergens. The clinical significance of IgE antibodies to food in patients with atopic dermatitis must be clarified by means of a careful history, elimination diets, and oral challenge tests (24–26). The allergic reaction to foodstuffs themselves – when it occurs in these patients after blind or double-blind, placebo-controlled food challenges – usually consists of pruritus, contact or generalized urticaria, morbilliform rashes, angioedema, diarrhea, vomiting, rhinitis, or asthma attacks, and seldom results in anaphylactic shock (type I immediate reactions). On the other hand, some authors insist that food reactions causing atopic dermatitis lesions can be verified only by repeating administration and observation of the patients for some days during the exposure tests (27, 28). In the case of pruritus, erythema, or urticaria, the subsequent scratching can worsen the skin conditions and exacerbate pre-existing atopic dermatitis (dual reaction). Worsening of the eczema occurring 6–48 h after food provocation without an immediate reaction is rarely observed (late reaction). The pathogenesis of such late reactions is unclear – among the mechanisms discussed are a late-phase, IgE-dependent mechanism with formation of leukotrienes and other substances of the arachidonic acid cascade, a type III reaction with circulating IgE or IgG immunocomplexes which activate the complement system, and delayed-type hypersensitivity mediated by T cells and activated eosinophils (29–32). In many cases, no clinical reactions at all occur after food provocation (no clinical sensitization) (33).

Different foods can produce different atopic symptoms, as has been demonstrated in a 43-year-old atopic woman with hay fever to grass pollen, allergic asthma to cat, gastrointestinal symptoms after meat ingestion, and appearance of atopic eczema in the face, neck, and flexurae after cow's milk intake (33).

Allergic food reactions following skin contact

Contact urticaria

Urticaria lesions can be provoked by contact with certain foods (food-elicited contact urticaria), such as fish, shrimp, meat, egg, flour, and potato. The lipophilic allergens may penetrate the skin via the hair follicles and also induce systemic reactions (contact urticaria syndrome [CUS]). This syndrome was defined as a biologic entity in 1975 by Maibach & Johnson (34). Reviews have been published by Lahti & Maibach (35) and by Amin et al. (36). This syndrome is often mediated by an IgE reaction (immunologic contact urticaria [ICU]), but seldom by a nonimmunologic mechanism (NICU). Local wheal and flare is the prototypic reaction of CUS, but generalized urticaria, asthma, and anaphylaxis may also occur after local contact. The diagnosis is made by skin tests, especially rub or open patch tests or prick-to-prick tests with fresh food. If there is risk of anaphylaxis, serum IgE determination by RAST/CAP may be performed before skin testing. The most frequent cause of CUS today is latex protein allergy (37).

Protein contact dermatitis

Immediate contact reactions of the skin are a heterogeneous group. According to Amin et al. (36), they include not only wheal-and-flare reactions (CUS), but also transient erythematous and allergic or nonallergic eczematous reactions caused by proteins or proteinaceous materials.

The term "protein contact dermatitis" (PCD) was introduced in 1975 by Hjorth & Roed-Pedersen (38) to characterize a particular form of contact dermatitis (not urticaria) in food handlers and butchers, showing negative patch tests of the delayed type to haptens and to the offending foods, but very strong positive wheal-and-flare reaction by prick or scratch testing (scratch-chamber tests) to the raw foods, although skin biopsy confirms eczematous changes (39). Studies in baker's eczema had already shown immediate-type sensitization to flour also in the absence of positive patch tests (40–42). For such contact dermatitis of the immediate type in bakers, I proposed the term "baker's eczema in a restricted sense" (41) to distinguish it both from the classic contact eczema due to occupational haptens in the baking industry, such as persulfates, antioxidants, preservatives and dyes, etc. (43), and from irritant dermatitis, which was termed "Zweites Bäckereckzem" by Jordan & Knauer (44). An irritative mechanism and a defective skin barrier function seem to favor the

development of PCD, which is also caused by fruits, vegetables, egg, meat, and spices (45–47). Janssens et al. (47) have divided the causative proteins into four groups:

- 1) fruits, vegetables, spices, and plants
- 2) animal proteins
- 3) grains
- 4) enzymes.

A recent report of the occupational allergic diseases most commonly associated with PCD in Finland has shown that cooks, chefs, and cold-buffet managers are in the fourth position with regard to the frequency of this disease (49). Recently, we described a 47-year-old atopic man working as a cook in his own pizzeria and suffering from work-related dyshidrotic dermatitis on his fingers (48). The skin tests showed positive type I allergies to beef, lamb, horse meat, and pork, to pig and horse blood, and to rye and wheat flour, raw potato, and pasta. The IgE analyses (ImmunoCAP) showed elevated specific IgE values for pork meat (class 1), raw potato (class 3), and rye and wheat flour (classes 4 and 3, respectively). Open oral challenges with raw and cooked potato, rice, lamb, and beef (also in the raw form as tartar) did not show any systemic reaction or aggravation of skin symptoms. Besides a case history of allergic asthma and allergic rhinitis since the age of 25 years, the positive skin prick tests and specific IgE values for different inhalant allergens confirmed the atopy of our patient. Atopic eczema provoked by allergy to food or food ingredients by direct contact of the skin must also be taken into consideration. According to Janssens et al. (47), however, only about 50% of all reported patients with PCD had an atopic predisposition. It is also known that in some cases of PCD no circulating IgE can be detected in the serum by RAST or CAP procedures, despite strong positive skin prick tests of the immediate type. This allows the conclusion that there are other, similar skin-affecting conditions besides atopic dermatitis. In recent studies, Bruijnzeel-Koomen et al. (50) and other authors (39) considered that IgE bound to Langerhans' cells in the epidermis and dermis possibly mediate this type of contact dermatitis.

Allergic contact dermatitis

Allergic contact dermatitis (allergic contact eczema) may be due to type IV sensitization to food or food additives (preservatives, such as benzoic acid, sorbic acid, and its derivatives; flavoring agents, such as vanillin, cinnamic aldehyde, and balsam of Peru; and antioxidants, such as

Wüthrich

butylated hydroxyanisole and butylated hydroxytoluene) (51). The patch test with the responsible food or food additive is positive after 24 or 48 h. In patients sensitized to a contact allergen, oral ingestion may provoke generalized eczematous rash or dyshidrosiform reactions of the fingers, palms, and soles (18, 52). This is also true of nickel allergy and the intake of food containing nickel.

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