

Skin manifestations in food allergy

Skin manifestations represent the most often observed clinical symptoms in food allergy. Immediate symptoms are urticaria, angioedema and sudden erythema (flush). Delayed symptoms which can be observed are exanthema and exacerbation or worsening of eczema (most often atopic dermatitis). Since delayed symptoms are difficult to diagnose, oral provocation tests are often necessary for patients with a suspected late onset of symptoms upon food ingestion. There is evidence that besides specific IgE, specific T cells play a role in the deterioration of eczema in atopic dermatitis. Although urticarial skin lesions are most often observed upon oral provocation with a suspected food, the rate of IgE-mediated food allergy in acute or chronic urticaria is rather low. In some patients suffering from chronic urticaria, intolerance reactions are also suspected. Since no laboratory or skin tests are available yet for the identification of clinically relevant food additives causing urticaria, oral provocation tests are mandatory for these patients.

Thomas Werfel

Dept. Dermatology and Allergology, Hannover Medical University, Hannover, Germany

Key words: food allergy; skin manifestations.

Professor Dr Thomas Werfel.
Dept. Dermatology and Allergology
Hannover Medical University
Ricklinger Straße 5
D-30449 Hannover
Germany
Tel: +49 511 9246 276
Fax: +49 511 9246 440
Email: Thomas_Werfel@t-online.de

The clinical spectrum of food allergy is broad: Both immediate symptoms (urticaria, flush, allergic asthma bronchiale, rhinitis allergica and gastrointestinal symptoms) and delayed symptoms (gastrointestinal, cutaneous, e.g. worsening of atopic dermatitis) can be observed (1–3). Delayed symptoms are difficult to diagnose since an exact attribution of clinical symptoms to the ingestion of a certain foodstuff can be impossible (4, 5). The skin is a major organ which is involved in food allergy. Atopic dermatitis and urticaria/angioedema represent the most often observed skin manifestations triggered by foodstuffs. Since the putative role of foods for the course of atopic dermatitis is a major problem in clinical practice, this short review will focus on this disease. The role of food allergy and pseudoallergy in urticaria will be addressed briefly at the end of this article.

General considerations about the role of food allergy in atopic dermatitis

Proteins from inhalant allergens are well established trigger factors of atopic dermatitis but allergens may also be ingested, and elicit systemic immunological responses and subsequently clinical reactions in atopic dermatitis. Early studies on passively sensitized individuals demonstrated that immunologically active food proteins can enter the circulation and are distributed throughout the body, including on skin sites (6). It is discussed that the intestinal permeability is enhanced in atopic individuals, which may facilitate the resorption of food proteins.

Such resorbed food antigens can directly interact with specific IgE which is bound to Fc receptors on Langerhans cells, mast cells monocytes and basophilic

granulocytes. Eosinophilic granulocytes are activated in food allergic patients suffering from atopic dermatitis as well: a drop in the number of circulating cells can be detected upon oral provocation soon after the onset of the clinical reaction (7, 8) and the eosinophilic cationic protein was found to be increased in serum and in stool samples taken upon oral provocation (7, 9, 10).

The role of food antigens as a trigger factor of atopic dermatitis has been discussed for many years. Grulee & Sanford speculated as early as 1936 that consequent breastfeeding - and thereby elimination of cow's milk - has a protective effect on the manifestation of atopic dermatitis (11). A lower prevalence of atopic dermatitis in the early childhood was indeed described in children from atopic families who had been breastfed or fed with hypoallergenic milk formula (12, 13). After 2 years (or 4 years, respectively); however, there were no differences in the prevalence of atopic diseases between diet and control groups (14, 15).

Clinical observations on elimination diets and oral provocation tests in atopic dermatitis

Many patients with atopic dermatitis (or their parents) suspect certain foods of triggering skin abnormalities. Most patients try diets with uncertain benefit and a risk of malnutrition or additional psychological stress (16). A series of open studies on elimination diets which have been performed since 1918 describes some benefit in a subpopulation of patients (17). A major problem of these studies is their open design, which does not exclude placebo effects and biased investigators' assessments. Atherton et al., however, observed a significant improve-

ment of the dermatitis in children during a period of placebo-controlled diet as well (18). Sampson and co-workers described cutaneous symptoms in a significant percentage of children with atopic dermatitis after some hours of exposure upon placebo controlled oral provocation. Positive provocation tests correlated with skin-prick tests, with specific IgE to the offending food antigen and with a rise of serum histamine in their studies (3, 19, 20). It was postulated that the repeated ingestion of food allergens by patients with atopic dermatitis and food allergy leads to a chronic inflammation and pruritus which provokes frequent scratching and the consequent trauma-induced lichenified lesions (8). Until now, food-induced atopic dermatitis was mainly studied in infants and children, although many adolescent and adult patients with AD attribute worsening of their skin disease to the intake of certain foods.

Diagnostic and immunological aspects in food-responsive atopic dermatitis

In general, oral food challenges represent the "gold standard" for the diagnosis of food allergy (1). Immediate reactions can quite easily be related to the suspected food in most cases but the causes of late eczematous reactions are difficult to identify and repeated provocations of the same food antigens on at least two subsequent days have been proposed by some investigators (21–23).

Since eczematous lesions are triggered by T lymphocytes, new diagnostic approaches may come from the characterization of allergen-specific T cell parameters. The expansion of peripheral blood derived CLA⁺ T cells in response to casein was described for children with milk-induced eczema which directly points to a possible role of food-specific T lymphocytes in a subgroup of children with atopic dermatitis (24). We found significant differences in the proliferative response of blood lymphocytes between patients who reacted to milk with worsening of atopic dermatitis and control groups and were able to generate casein-specific T cell clones from the blood of these patients (25–27). Higher proliferative responses to casein, the major protein fraction in cow milk and thus the main protein source in the alimentation of many human beings, were observed both in atopic children and in adults reacting with worsening of eczema to oral provocation.

Whereas specific IgE to food antigens was detectable in all investigated children with AD who reacted with clinical symptoms (25), we found food-specific IgE in only 41% of adult patients suffering from atopic dermatitis who reacted to oral provocation (27). A type 1 cytokine pattern was detectable in the majority of food-specific T cell clones from these

patients. Moreover, no correlation between specific lymphocyte proliferation and specific IgE was found (27). A lack of correlation between specific IgE and the clinical response to food has been reported for food-responsive atopic dermatitis before (18, 23). This indicates that an IgE-independent mechanism may be involved in the eczematous reaction to food in some patients, stressing the pathophysiological role of allergen-specific T lymphocytes in atopic dermatitis. Interestingly, Schade et al. found a switch from a Th2 to a Th1 cytokine pattern in food specific T cell clones in children with atopic dermatitis who got tolerant to cow's milk. This may indicate different immunological mechanism of specific T-cell-mediated responses in children compared to adult patients with atopic dermatitis (28). Interestingly, Schade et al. found a switch from a Th2 to a Th1 cytokine pattern in food specific T cell clones in children with atopic dermatitis who had become tolerant to cow's milk. This may indicate a different immunological mechanism of specific T cell-mediated responses in children compared to adult patients with atopic dermatitis (28).

The immune responses to casein were further studied with cultured PBMC and dermal lymphocytes from six adult patients reacting to cow's milk with a deterioration of eczema using a limiting dilution protocol. The average frequencies of proliferating T lymphocytes both from peripheral blood and lesional skin were in the same range when casein or an extract of *Der.p.* were added to the cultures. From these limiting dilution cultures, eight food allergen-specific T cell clones have been established so far. These findings point to a direct role of food-specific T cells at the site of inflammation in food-inducible atopic dermatitis.

T cell-mediated cross-reactivity to foods and inhalant allergens in atopic dermatitis

In addition to food antigens, inhalant allergens may provoke flare-ups of the extrinsic variant of atopic dermatitis. In a recent study we investigated adolescents and adults with atopic dermatitis who were highly sensitized to birch pollen antigens (29). In contrast to the majority of birch pollen sensitized individuals (30–32) these patients belonged to the group of one third of all sensitized patients who did not suffer from immediate symptoms to birch pollen related foods. They therefore did not maintain a birch pollen related elimination diet prior to this study. We could show that (i) a subpopulation of the birch pollen sensitized patients react with a marked deterioration of their eczema upon an oral provocation with related foods and (ii) this clinical reaction is associated with a specific T cell-mediated immune response to birch pollen antigens.

The rate of CLA+ blood lymphocytes from food responsive patients, but not from non-responders, increased significantly upon *in vitro* stimulation with birch pollen antigens. In contrast, the proportion of ICAM-1+ cells, which are easily inducible by IFN- γ on T cells, was equally high on cell suspensions from both patient groups. Our LPT results suggest that birch pollen leads to lymphocyte activation in both sensitized patient groups. Food-responsive patients appear, however, to react to birch pollen in a way which enables lymphocytes to "home" into inflamed skin.

Our frequency analysis revealed similar growth rates of lymphocytes in limiting dilution assays in the presence of birch pollen antigens when blood lymphocytes from responders were compared to cells from non-responders. In contrast, a clear difference of proliferating cells in response to birch pollen extract and a mixture of rbet v 1 / rbet v 2 was detectable when cutaneous lymphocytes were compared. T cell lines which had been generated from lesional skin in the presence of bet v 1 and bet v 2 responded to birch pollen extract and bet v 1 but not bet v 2 to a high degree. The majority of T cell lines from reacting patients showed a clear overrepresentation of lymphocyte subpopulations expressing defined TCR-V β elements. This suggests that the presence of birch pollen antigens led to a strong selection of reactive T cells in these cultures. The role of allergen-specific skin-infiltrating T cells was further stressed by our finding that the proportion of specific T cell clones generated from limiting dilution cultures of the skin was significantly higher when we compared cells from reactive to cells from non-reactive patients (29).

A major conclusion from this study is that a clinical relevance of food allergy should be suspected in adolescent and adult patients with AD who are sensitized to pollen antigens even if there is no history of immediate reactions to related foods.

Food allergy and pseudoallergy in urticaria/angioedema

Urticarial skin manifestations are often observed upon oral provocation with foods in sensitized patients. *In vitro* tests (specific IgE) and skin-prick tests are usually positive in these patients (2). However, in chronic urticaria with a clinical cause of longer than 6 weeks, pseudoallergy to food ingredients is often considered as a possible trigger factor of the disease. Pseudoallergic reactions resemble allergic reactions and patients with chronic urticaria, recurring angioedema, polyposis nasi or non-allergic bronchial asthma (intrinsic asthma) suffer from pseudoallergic reactions more frequently. Food ingredients are considered pseudoallergens in addition to non-steroidal antiphlogistica and other drugs that can cause symptoms in sensitive patients (33–35).

There is no clear information about the frequency of pseudoallergic reactions. The published frequency of pseudoallergic reactions to food ingredients ranged from less than 1% to over 50% in chronic urticaria (34–39). A defined pseudoallergen can be identified in only a small subgroup of patients whose symptoms improve during an elimination diet (34, 35, 37).

In contrast to allergic reactions to foods, there are still no *in vitro* or skin tests available for the identification of pseudoallergens that are relevant for a patient. It was possible, however, to detect a hyper-reactivity of basophils and eosinophils in response to unspecific stimuli in pseudoallergic individuals compared to healthy persons (33, 36). It is not possible, however, with the test systems used, to identify a specific cause of a clinical reaction. Elimination diets and oral provocations therefore have to be performed to identify clinically relevant pseudoallergens.

References

1. BRUIJNZEEL-KOOMEN C, ORTOLANI C, AAS K, et al. Allergy adverse reactions to food. Eur Acad Allergol Clin Immunol Subcommittee 1995;**50**:623–635.
2. WÜTHRICH B. Food-induced cutaneous adverse reactions. Allergy 1998;**53**(Suppl):131–135.
3. SAMPSON HA, McCASKILL CC. Food hypersensitivity and atopic dermatitis: Evaluation of 113 patients. J Pediatr 1985;**107**:669–675.
4. WERFEL T. Atopic dermatitis and nutrition. MMW Fortschr Med 1999;**141**:49.
5. WERFEL T, KAPP A. Environmental and other major provocation factors in atopic dermatitis. Allergy 1998;**53**:731.
6. WALZER M. Studies in absorption of undigested proteins in human beings. I. A simple direct method of studying the absorption of undigested protein. J Immunol 1927;**14**:143–174.
7. NIGGEMANN B, BEYER K, WAHN U. The role of eosinophils and their granule protein ECP in monitoring oral food challenge tests in children with food sensitive atopic dermatitis. J Allergy Clin Immunol 1994;**94**:963–971.
8. SAMPSON HA. The immunopathogenic role of food hypersensitivity in atopic dermatitis. Acta Dermatol Venereol 1992;**176**:34–37.
9. KOSA L, KERÉKI E, BORZSONYI L. Copro-eosinophil cationic protein (ECP) in food allergy. Allergy 1996;**51**:964–966.
10. MAJAAMA H, LAINE S, MIETTINEN A. Eosinophil protein X and eosinophil cationic protein as indicators of intestinal inflammation in infants with atopic eczema and food allergy. Clin Exp Allergy 1999;**29**:1502–1506.
11. GRULEE CG, SANFORD HN. The influence of breast and artificial feeding on infantile eczema. J Pediatr 1936;**9**:223–225.
12. HALKEN S, HOST A, HANSEN LG, ØSTERBALLE O. Effect of an allergy prevention programme on the incidence of atopic symptoms in infancy: a prospective study of 159 "high risk" infants. Allergy 1992;**47**:545–553.

13. SAARINEN UM, KAJOSAARI M, BACKMAN A, SIIMES MA. Prolonged breast-feeding as prophylaxis for atopic disease. *Lancet* 1979;ii:163–166.
14. ARSHAD SH, MATTHEWS S, GANT C, HIDE DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493–1497.
15. HIDE DW, MATTHEWS S, MATTHEWS L, et al. Effect of allergen avoidance in infancy on allergic manifestations at age 2 years. *J Allergy Clin Immunol* 1994;93:842–846.
16. WEBBER SA, GRAHAM-BROWN RA, HUTCHINSON PE, BURNS DA. Dietary manipulation in childhood atopic dermatitis. *Br J Dermatol* 1989;121:91–98.
17. ATHERTON DJ. Diet and atopic eczema. *Clin Allergy* 1988;8:215–228.
18. ATHERTON DJ, SEWELL M, SOOTHILL JF, WELLS RS, CHILVERS CED. A double-blind controlled crossover trial of an antigen avoidance diet in atopic eczema. *Lancet* 1978;i:401–403.
19. SAMPSON HA, ALBERGO R. Comparison of results of skin tests, RAST, and double blind, placebo-controlled food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 1984;74:26–33.
20. SAMPSON HA, BROADBENT KR, BERNHISEL-BROADBENT J. Spontaneous release of histamine from basophils and histamine-releasing factor in patients with atopic dermatitis and food hypersensitivity. *N Engl J Med* 1989;321:228–232.
21. HAMMAR H. Provocation with cow's milk and cereals in atopic dermatitis. *Acta Derm Venereol* 1977;57:159–163.
22. SLOPER KS, WADSWORTH J, BROSTOFF J. Children with atopic eczema. I: Clinical response to food elimination and subsequent double-blind food challenge. *Quart J Med, New Series* 1991;80:677–693.
23. HILL DJ, DUKE AM, HOSKING CS, HEDSON IL. Clinical manifestations of cow's milk allergy in childhood. II: The diagnostic value of skin tests and RAST. *Clin Allergy* 1988;18:481–490.
24. ABERNATHY-CARVER KJ, SAMPSON HA, PICKER LJ, LEUNG DYM. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 1995;95:913–918.
25. REEKERS R, BEYER K, NIGGEMANN N, et al. The role of circulating food antigen specific lymphocytes in food allergic children with atopic dermatitis. *Br J Dermatol* 1996;135:935–941.
26. WERFEL T, AHLERS G, SCHMIDT P, BOEKER M, KAPP A. Detection of a κ -casein specific lymphocyte response in milk-responsive atopic dermatitis. *Clin Exp Allergy* 1996;26:1380.
27. WERFEL T, AHLERS G, SCHMIDT P, BOEKER M, KAPP A, NEUMANN C. Milk-responsive atopic dermatitis is associated with a casein-specific lymphocyte response in adolescent and adult patients. *J Allergy Clin Immunol* 1997;99:124–133.
28. SCHADE RP, VAN IEPEREN-VAN DIJK AG, VAN REIJSEN FC, et al. Differences in antigen-specific T-cell responses between infants with atopic dermatitis with and without cow's milk allergy: relevance of TH2 cytokines. *J Allergy Clin Immunol* 2000;106:1155–1162.
29. REEKERS R, BUSCHE M, WITTMANN M, KAPP A, WERFEL T. Birch pollen related food trigger atopic dermatitis with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999;104:466–472.
30. TUFT L, BLUMSTEIN GI. Studies in food allergy. II. Sensitization by fresh fruits: clinical and experimental observations. *J Allergy* 1942;13:574.
31. PASTORELLO EA, INCOVAIA C, PRAVETTONI V, et al. New allergens in fruits and vegetables. *Allergy* 1998;53:48–51.
32. WÜTHRICH B, STAUMANN F. Pollen cross-reactivity. Can we establish a link between the *in vitro* results and the clinical situation? *Allergy* 1997;52:1187.
33. CZECH W, SCHÖPF E, KAPP A. Release of sulfidoleukotrienes *in vitro*: its relevance in the diagnosis of pseudoallergy to acetylsalicylic acid. *Inflamm Res* 1995;44:291–295.
34. METCALFE DD, SAMPSON HA, SIMON RA. Food allergy. Adverse reactions to foods and food additives. Oxford: Blackwell, 1996.
35. SIMON RA, STEVENSON DD. Adverse reactions to food and drug additives. In: MIDDLETON E, REED CE, ELLIS EF, et al., editors. *Allergy, principles and practice*. St. Louis: Mosby, 1993; 1687–1704.
36. DOUGLAS HMG. Reactions to aspirin and food additives in patients with chronic urticaria, including physical urticarias. *Br J Dermatol* 1975;93:135–144.
37. EHLERS I, HENZ BM, ZUBERBIER T. Diagnose und Therapie pseudoallergischer Reaktionen der Haut durch Nahrungsmittel. *Allergologie* 1996;19:270–276.
38. MICHAELSSON G, JUHLIN L. Urticaria induced by preservative and dye additives in food and drugs. *Br J Dermatol* 1973;88:525–532.
39. ZUBERBIER T, CHANTRAINE-HESS S, HARTMANN K, CZARNETZKI BM. Pseudoallergen-free diet in the treatment of chronic urticaria. *Acta Derm Venereol* 1995;75:484–487.