Dermatologic Diseases Secondary to Food Allergy and Pseudoallergy

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Adverse reactions to foods and food constituents represent an increasing problem for the practicing allergist (1–4). The spectrum of clinical symptoms ranges from gastroenteritis, urticaria, bronchial asthma, allergic rhinitis, and anaphylactoid reactions to serum-sickness-type reactions with (a) arthralgia and vasculitis or (b) exacerbations of allergic contact dermatitis or (c) atopic eczema.

Many patients complain that headache, tension fatigue, psychological abnormalities, etc. are not clearly defined and are difficult to assess.

CLASSIFICATION OF ADVERSE FOOD REACTIONS

Undesirable reactions to foods can be elicited by a variety of pathomechanisms. In Table 1, a classification of adverse food reactions according to different pathomechanisms is given (5). Clearly, toxic reactions (such as food intoxication) or increased individual sensitivity toward a specific pharmacologic effect of a food or a food additive (intolerance) have to be differentiated from other kinds of hypersensitivity, which can either be immunologically (i.e., allergic) or nonimmunologically (i.e., idiosyncratic) mediated.

When the symptoms observed mimic symptoms of classic allergic diseases, the term “pseudoallergy” is used (3).

In order to define food allergy, the following diagnostic postulates have to be considered:

1. Reproducible elicitation of symptoms by the specific food.
2. Exclusion of other possible causes of incompatibility.
3. Demonstration of immunologic sensitization.

Table 2 gives the definitions of the most important terms used in this context. Here, we will not talk about genuine intoxications by poisoned food or bacterial contamination, nor will we talk about deficiency states (e.g., of vitamins, trace elements, etc.) by which foods can affect health.
TABLE 1. **Classification of adverse food reactions**

<table>
<thead>
<tr>
<th>Adverse food reaction</th>
<th>Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td>Pharmacological intolerance</td>
</tr>
<tr>
<td>Intoxication</td>
<td>Idiosyncrasy</td>
</tr>
<tr>
<td>Idiosyncrasy</td>
<td>Nonimmunological mechanisms</td>
</tr>
<tr>
<td>Allergy</td>
<td>IgE, IgG/IgM, IgA (?)</td>
</tr>
<tr>
<td>Allergy</td>
<td>Cellular</td>
</tr>
<tr>
<td>Intolerance</td>
<td>Unexpected, sometimes “allergy-like” symptoms</td>
</tr>
<tr>
<td>Pharmacological effect, organ toxicity*</td>
<td>Allergic disease</td>
</tr>
</tbody>
</table>

*If symptoms mimic allergic diseases, the term “pseudo-allergy” is used.

TABLE 2. **Definition of allergological terms**

| Toxicity: | Normal poisonousness |
| Allergy:  | Immunologic hypersensitivity |
| Intolerance: | Hypersensitivity to normal pharmacologic effect |
| Idiosyncrasy: | Nonimmunologic hypersensitivity (unrelated to pharmacologic effect) |
| Pseudoallergy: | Nonimmunologic hypersensitivity with “allergy-like” symptoms |

TABLE 3. **Skin lesions possibly provoked by foods**

<table>
<thead>
<tr>
<th>Erythema</th>
<th>Vesicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheal</td>
<td>Bulla</td>
</tr>
<tr>
<td>Purpura</td>
<td>Pustule</td>
</tr>
<tr>
<td>Papule</td>
<td>Ulcer</td>
</tr>
<tr>
<td>Nodule</td>
<td>Necrosis</td>
</tr>
</tbody>
</table>

There is no specific skin lesion primarily linked to food reactions (6,7), but the whole spectrum of skin lesions can be elicited by allergic food reactions (Table 3). Table 4 gives an overview of dermatologic diseases, which may be evoked by food allergy or pseudoallergy. The most important skin diseases that are possibly evoked by food will be described in detail.
TABLE 4. Skin diseases possibly evoked by foods

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Flush</td>
</tr>
<tr>
<td>Urticaria</td>
</tr>
<tr>
<td>Angioedema</td>
</tr>
<tr>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Swelling of lips and oral mucosa</td>
</tr>
<tr>
<td>Stomatitis</td>
</tr>
<tr>
<td>Glossitis (Papillitis linguae)</td>
</tr>
<tr>
<td>Recurrent aphthae</td>
</tr>
<tr>
<td>Immune-complex vasculitis</td>
</tr>
<tr>
<td>Panniculitis (?)</td>
</tr>
<tr>
<td>Purpura pigmentosa progressiva</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
</tr>
<tr>
<td>Phototoxic and photoallergic reactions</td>
</tr>
<tr>
<td>Exanthematous eruption</td>
</tr>
<tr>
<td>Melkersson-Rosenthal-syndrome (?)</td>
</tr>
<tr>
<td>Bromoderma</td>
</tr>
<tr>
<td>Acne (?)</td>
</tr>
<tr>
<td>Dermatitis herpetiformis</td>
</tr>
</tbody>
</table>

URTICARIA AND ANGIOEDEMA

Foods can elicit urticaria (Fig. 1) or angioedema (Fig. 2) by both allergic and pseudoallergic mechanisms (8–10). Various authors have described positive food provocation tests in urticaria (Table 5). Food additives such as preservatives, antioxidants, etc., which are known to elicit or sustain chronic urticaria (3,4,11,14–19), are particularly important (Table 6).

Certain foods contain considerable amounts of vasoactive amines known to provoke urticaria, asthma, or anaphylactoid reactions (1,5,8,20,21) (Table 7).

In this context, special reference has to be made to the syndrome of contact urticaria (Fig. 3): Urticaria lesions are provoked by contact with certain sub-
stances (22); the diagnosis is done by open patch test (Fig. 4). Many authors have reported food-elicited contact urticaria (1,2,22,23). This syndrome may be mediated by IgE or by nonimmunologic mechanisms.

Most probably, the recently described protein dermatitis or gut eczema or butcher's eczema (24), observed in butchers after contact with the animal gut, does not represent a contact urticaria but, instead, represents an atopic eczema provoked by either irritation or allergy to food ingredients (25).
With regard to genuine allergies, certain cross-reactions between foods and pollens have to be mentioned, as in the case of (a) birch and apple or mugwort and (b) certain spices and celery (1,19,23,26,27). Furthermore, some cases of physical urticaria, especially exercise-induced urticaria or anaphylaxis, may be related or closely connected with food allergy in the
sense of a "summation anaphylaxis"; these patients seem to only develop symptoms after the combination of physical effort and the intake of the specific food, whereas the food or exercise alone is usually well tolerated (3,23). This makes history-taking in these patients extremely difficult. The time interval between food intake and the physical stimulus may be as long as 48 hr.

**ATOPIC ECZEMA**

The role of food allergy in the pathophysiology of atopic eczema (Fig. 5) is not well established, although there is abundant literature about this topic (2,28-43). In Table 8, the most important arguments "for" or "against" the pathophysiological role of food allergy in atopic eczema are listed.

There is no doubt that certain foods can provoke atopic eczema in some patients, but this is surely only one etiologic factor among many others. There is evidence for IgE-mediated sensitization to many food allergens in patients with atopic eczema (28,37). The relevance of these test results (skin test or RAST), however, has to be proven by elimination or provocation procedures. In the literature, the incidence of positive provocation tests with food-induced atopic eczema are controversial and range between 0% and 84% (quoted in refs. 42 and 44). Only a few controlled studies have been performed, especially by the groups of Atherton's group in London (45,46) and Sampson's group in the United States (47,48). Antigen avoidance by an oligoantigenic diet (strict exclusion of milk and egg intake) led to a considerable improvement in 35% of the children under 8 years of age (45). The most striking finding was that among the children who benefited from this elimination diet, some showed no evidence of sensitization to egg or milk in the skin test or RAST. In another study in adults, an antigen-elimination diet failed to demonstrate clinical effects (46).

The placebo-controlled double-blind study by Sampson and McCaskill reported
results of 370 provocations in 113 patients 4 to 24 years old (48). Here, 56% of the patients and 27% of the provocations were positive. Skin symptoms were observed in 84% of cases, beginning within 2 hr as macular erythema and pruritus, sometimes together with wheals; later on, because of the scratch response, excoriations and an exacerbation of eczema were observed.

In 52% of cases, gastrointestinal symptoms were observed; in 32% of cases, respiratory symptoms were observed. The most frequent offending foods were hen's egg (42%), peanut (19%), milk (11%), soy (5%), wheat (5%), chicken (3%), pork (2%), beef (2%), and potato (2%). During positive provocations there was sometimes a rise in plasma histamine levels. It was interesting to note that no child reacted to two different foods from one species. Positive skin-prick tests were more frequent in patients reacting to foods as compared to those who did not react. There was no difference with regard to total serum IgE, history of atopic diseases, or respiratory symptoms. When the identified food was eliminated, significant improvement was observed.

This was a very good study; however, it is still too early to safely state that food allergy plays the decisive role in a rather high percentage of atopic eczema. Another problem that needs to be studied is the influence of pseudoallergic reactions.
### Arguments for and against a role of food allergy in atopic eczema

**FOR**
- IgE-antibodies against foods more frequent in atopic eczema than in other atopic diseases
- Protective effect of breast-feeding
- Increased intestinal absorption of potential allergens in atopic eczema
- Clinical improvement after allergen avoidance
- Positive provocation studies

**AGAINST**
- Only weak correlation between skin test and history of food allergy
- Only weak correlation between RAST results and history
- Lack of effect of elimination diets planned according to skin test or RAST results
- Lack of effect of cow's milk–free nutrition compared to soy in some studies
- In adults, provocation tests are often negative

In the pathogenesis of atopic eczema. While additives are used in provocation tests in urticaria and angioedema, only limited experience is available with these elicitors of pseudoallergic reactions in atopic eczema (40).

We observed the case of a 38-year-old female patient whose eczema flared dramatically after oral provocation with 500 mg of sodium propionate within 1 day (44).

Another very exciting issue is the question of possibly increased intestinal permeability, which is still controversial (20,33,49,50).

In the practical approach for diagnosing food allergy in atopic eczema, there are several major problems. The relevance of *in vitro* and *in vivo* allergy diagnostics has not been established.

Provocation procedures should always be performed in a blind fashion; however, this may be extremely difficult with certain foods. Furthermore, the exacerbation of the eczematous lesions does not necessarily occur within 1 or 2 hr but may, instead, take as long as several days with successive challenges. At the same time, other factors (psychological influences, other allergens, change of topical or systemic treatment, etc.) may elicit an exacerbation of the disease.

In recent years, special interest has focused on the positive influence of breast-feeding in preventing the manifestation of atopic diseases in childhood (31,32, 41,51–61). As Table 9 shows, there are controversial reports on this topic.

There is some evidence that breast-feeding is indeed able to inhibit, or at least delay, the manifestation of atopic diseases in infants with a high risk of atopy (positive family history in two parents or elevated cord blood IgE). It may well be that breast-feeding not only provides a protective effect by allergen avoidance (e.g., elimination of potential allergens as cow’s milk or hen’s egg) but also provides a positive protective effect mediated by specific IgG antibodies to food allergens or by other factors contained in breast milk.

Furthermore, the delayed introduction of solid foods seems to be important in the prophylaxis of food allergy in infants (56).
There is no doubt that small amounts of allergens can be detected in breast milk and can elicit allergic reactions in exclusively breast-fed infants. In these cases, a specific avoidance diet has to be recommended to the mother.

On the basis of these findings, only limited therapeutic recommendations regarding food allergy and atopic eczema can be given. The value of oligoantigenic or other very strict general avoidance diets is largely confined to the short period of allergy diagnosis. For long-term therapy, caution is necessary in order not to induce states of deficiency of essential food ingredients or malnutrition. Every dermatologist has seen the sad cases of totally malnourished children as a result of an extreme diet, not at all based on rational allergy diagnosis but rather on ideological considerations.

There are, however, many foods that are easily avoidable (such as spices, fish, etc.). In these cases, specific allergen avoidance represents the simplest and best therapeutic approach.

Oral hyposensitization with ubiquitous foods represents another therapeutic strategy and may work in some patients (62), although there are no prospective controlled studies available.

The use of oral sodium cromoglycate has been recommended by some authors (23,40,63,64), whereas other authors have found it to be ineffective. In an open study over a six-month period in 19 patients with atopic eczema, we found a significant improvement in seven patients with skin-prick test and RAST results suggestive of food allergy (40). The patients were nonselected and had no history of clear-cut food-induced eczematous lesions.

At present, the role of food allergy in atopic eczema remains controversial and certainly represents only one part of the problem for selected individuals. The core of the treatment of atopic eczema remains the careful dermatologic treatment using the right amount of the right corticosteroid in the right vehicle at the right time and the individually tailored emollient during the phases of remission (3,65).

### TABLE 9. Effect of breast-feeding on the manifestation of atopic diseases (literature)

<table>
<thead>
<tr>
<th>Studies showing an inhibitory effect</th>
<th>Breast-feeding found to enhance atopic disease</th>
<th>No effect of breast-feeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saarinen 1979 (41)</td>
<td>Taylor 1984 (59)</td>
<td>Halpern 1973 (53)</td>
</tr>
<tr>
<td>Kajosaari 1983 (56)</td>
<td></td>
<td>Gruskay (1982 (52)</td>
</tr>
<tr>
<td>Businco 1983 (31)*</td>
<td></td>
<td>Van Asperen 1984 (60)</td>
</tr>
<tr>
<td>Duchateau 1983 (51)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chandra 1985* (32)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Only effective when cord blood-IgE was elevated.
TABLE 10. Nickel content of various foods*

<table>
<thead>
<tr>
<th>Food</th>
<th>μg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentils</td>
<td>3100</td>
</tr>
<tr>
<td>Beans (white)</td>
<td>2850</td>
</tr>
<tr>
<td>Peas</td>
<td>2250</td>
</tr>
<tr>
<td>Chocolate</td>
<td>2200</td>
</tr>
<tr>
<td>Rye (grains)b</td>
<td>2700</td>
</tr>
<tr>
<td>Peanuts</td>
<td>1600</td>
</tr>
<tr>
<td>Milk and milkb products</td>
<td>50</td>
</tr>
<tr>
<td>Potatoesb</td>
<td>250</td>
</tr>
<tr>
<td>Raspberry jam</td>
<td>400</td>
</tr>
<tr>
<td>Herring</td>
<td>300</td>
</tr>
<tr>
<td>Porc</td>
<td>250</td>
</tr>
<tr>
<td>Beer</td>
<td>20</td>
</tr>
<tr>
<td>Wine (white)</td>
<td>100</td>
</tr>
</tbody>
</table>

*Many thanks to Dr. Haeberle from the Department of Dermatology, University of Erlangen, for help in preparing this table.

Photosensitization represents the phenomenon whereby the combination of electromagnetic radiation and the contact with an allergen or another photosensitizing agent provokes skin lesions (68). Among photosensitizing substances are many drugs, but also naturally occurring substances, some of which may be present in foods (Table 11).
DERMATITIS HERPETIFORMIS (DUHRING)

Dermatitis herpetiformis presents clinically as an itchy, sometimes burning, eruption of grouped vesicles on an erythematous base; in most patients the vesicles are scratched so that excoriated papules are seen (6) (Fig. 7).

In the pathogenesis of dermatitis herpetiformis as well as gluten-sensitive enteropathy, the role of specific antigliadin antibodies is discussed (69–71). Gliadin represents the alcohol-soluble fraction of gluten. In patients with dermatitis herpetiformis, antigliadin antibodies (of both the IgG class and the IgA class) have been found and seem to correlate with the existence of enteropathy. The same holds true for antireticulin (or antiendomysium) antibodies (71).

One of the hallmarks of diagnosis is that IgA in the direct immunofluorescence in uninvolved skin remains there over long periods, even under strict gluten-free diet (72).

Immunogenetic studies show an association of dermatitis herpetiformis with HLA-B 8 and DR 3 (71).

Iodides, both topical and systemic, will provoke the exacerbation of blisters by a yet unknown mechanism. The efficacy of a gluten-free diet, which it is undoubtedly in gluten-sensitive enteropathy, is still controversial in the treatment of
dermatitis herpetiformis (6,71,72). Sometimes clinical improvement appears only after 6 months of dietary intervention.

**ALLERGIC VASCULITIS**

Allergic vasculitis (leukocytoclastic vasculitis) represents an immune complex (Type III) reaction leading to perivascular inflammation and extravasation (Fig. 8). Among the common causes of this disease are infectious diseases, drugs, neoplastic conditions, autoimmune diseases, cryoglobulinemia, and others (73).

There are some case reports describing foods as elicitors of allergic vasculitis (74–79) (Table 12). We observed two patients with allergic vasculitis in whom foods were shown to be of clinical relevance by oral provocation tests. Intradermal tests with food allergens had not only produced an immediate wheal-and-flare reaction but also produced marked inflammatory reactions after 8 to 24 hr, which showed histologically and immunopathologically the characteristics of immune-complex vasculitis. The careful avoidance of the most important allergens, together with oral cromoglycate, led to a marked improvement of the condition (75).

Immune complex deposits have also been found in lesions of the oral mucosa in patients with recurrent *aphthae* (80) (Fig. 9).

**PRURITUS**

Pruritus is a very subjective symptom and is often hard to evaluate. Among the patients with "pruritus sine materia," true cases of food allergy (e.g., against hen's egg) can be found and have to be distinguished from pruritus senilis and pruritus, which are induced by dry skin and exsiccation (3,6,23).
FIG. 8. Food-induced allergic vasculitis on the lower leg.

<table>
<thead>
<tr>
<th>Eliciting agent</th>
<th>Authors</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shellfish</td>
<td>Ancona</td>
<td>1951</td>
</tr>
<tr>
<td>Blackberries</td>
<td>Winkelmann</td>
<td>1964</td>
</tr>
<tr>
<td>Tartrazine</td>
<td>Kubba, Champion</td>
<td>1975</td>
</tr>
<tr>
<td>Tartrazine</td>
<td>Wüthrich</td>
<td>1982</td>
</tr>
<tr>
<td>Vitamin B₆</td>
<td>Ruzicka, Ring, Braun-Falco</td>
<td>1984</td>
</tr>
<tr>
<td>Foods, spices, vegetables</td>
<td>Eisenmann et al.</td>
<td>1987</td>
</tr>
</tbody>
</table>

OTHER CONDITIONS POSSIBLY EVOKE BY FOODS

In Table 4, many other skin conditions are listed which may possibly be induced by foods in rare instances.

An increasing problem in the office of the practicing allergist concerns patients' subjective complaints related to foods or chemicals in foods. In many of these patients with what we call clinical ecology syndrome (81), objective investigations failed to demonstrate any causal relationship between food chemicals and complaints (the crucial test is the placebo provocation) (81–85). Psychological factors such as chemophobia or anxiety and depression seem to represent the major problem of these patients. However, a careful allergological examination has to be done in order to truly rule out food allergy or pseudoallergy.
A great deal of research will have to be done to further elucidate the mechanisms and the relevance of these findings. The first step will have to be an improvement in current diagnostic techniques (2,4,13,19,28,40,82,83), possibly by introduction of the intragastral provocation under endoscopic control (IPEC) (86,87).

REFERENCES


286 DERMATOLOGIC DISEASES


DISCUSSION

Dr. Shmerling: When looking for local reactions, is it really necessary to go as far as the stomach? What about the buccal mucosa?

Dr. Ring: There is a lot of controversy about sublingual testing, and the American Academy of Allergy has bluntly stated that this method does not work. I think, however, that you have to differentiate between people whose primary symptoms originate in the mouth, who may be challenged in the mouth, and those with diarrhea or urticaria, in whom you must go to the stomach.

Dr. Guesry: You spoke of reactions to iodine, bromine, and nickel, probably acting through the formation of hapten. Could you enlarge on the mechanism of sensitization by this type of allergen, in contrast to protein allergens? Is there a difference?

Dr. Ring: The mechanism of sensitization is certainly different for these different types of reaction. Iododerma is probably not an allergic response, and there is no obvious immunologic mechanism. Nickel sensitivity is a Type-IV allergic response. It is usually thought, though I do not know on what basis, that nickel is coupled to a protein in the epidermis which acts as carrier protein, transporting it to the Langerhans cells which mediate sensitization to the T-lymphocytes. There are some recent studies which suggest that the nickel molecule coming in contact with the HLA-DR molecule on the surface of the antigen-presenting cell produces a change in the class-II molecule conformation giving the signal for antigen presentation. This is very speculative. What happens when you eat nickel and how it comes to the skin nobody knows.
Dr. Urbanek: We were told by Dr. Frick about increased reactivity in the lungs after food ingestion. Are there any methods for *in vitro* or *in vivo* testing for hyperreactivity of the skin? You said that in some cases there may be a low threshold for reaction to some antigens.

Dr. Ring: This is a matter of current study. It certainly should be possible to test for the postprandial forms of urticaria and anaphylaxis, which show up clearly, using skin-test titrations before and after food challenge. I did not mention urticaria factitia, often thought to have a psychological basis, where striking the skin results in a wheal. Many people with this condition have underlying allergies, suggesting it is not entirely psychological. Perhaps this could form the basis of a test in such patients: dermatographism before and after food challenge!

Dr. Schmitz: You said that eczema might be triggered by itching alone. What, then, provokes the itching in the first place?

Dr. Ring: There are many mediators of itch, including histamine of course, and not all of them are chemical; for example, dry skin per se is a stimulus for itch. In allergy, the release of mediators can be a stimulus.

Dr. Aas: Itch is a very important feature of atopic eczema, and someone once said that eczema is not an eruption with an itch, it is itch with an eruption. It is also a feature of a positive Prausnitz-Küstner test. You can titrate the P-K reaction either with serial dilutions of donor serum or with dilutions of the offending agent and in this way determine, to some extent, the size of the reaction. At the start of any positive reaction you get an itch, up to 5 min before the visible response, though of course the perception of itch is very much determined by the psychological state of the recipient at the time. However, you can also titrate so that you don't get a positive reaction, only an itch. My question touches upon the question of mediators and of whether there are a lot of immunologic and nonimmunologic subthreshold triggers in eczema, among which may be food allergens. It is this: Do you ever try to get an impression of the amount of itch in these patients? I think that the itch is one of the great mysteries in eczema. Some patients with atopic eczema may have a very slight eruption but a tremendous itch, and vice versa.

Dr. Ring: Studies have been done to try to titrate the itch response to different stimuli, and from these it appears that in atopic eczema there is an increased itch response to a particular stimulus, i.e., a reduced itch threshold. However, it is very hard to quantitate itch. We are currently trying out an "itchometer," an itch-watch developed in Newcastle, UK, by Drs. Chadwick and Shuster. This instrument measures the movement of the limbs during the scratch response at night and is at least an attempt at an objective measurement.

Dr. Bellanti: There are observations to suggest that leukocytes in patients with atopic dermatitis have a higher spontaneous release of histamine than normal. We reported a study a few years back in which we injected food antigen into patients and provoked symptoms which were associated with elevated plasma histamine. I have often wondered about this as a possible provocation test. Would it not make sense to bypass the gastrointestinal tract and thus remove one source of variability. One could then titrate a plasma histamine response or a symptom response using carefully selected and quantifiable materials.

Dr. Ring: I agree with you. We also found increased histamine releasability patterns in patients with atopic eczema and sometimes found increased plasma histamine levels. However, one of the big problems we have at the moment is a provocation test for atopic eczema. I was therefore very excited by Mitchell and Platts-Mills' article in which they were able to provoke eczematous lesions on the back by topical contact with extracts of house
dust mite (1). Unfortunately we have not yet been able to reproduce this finding, although it is possible that there are technical and galenic difficulties. This problem has certainly not yet been solved.

DISCUSSION REFERENCE