*Position paper

Controversial aspects of adverse reactions to food

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Contents

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Introduction

Patients are easily given to suspecting a diagnosis of food allergy/intolerance. Furthermore, some doctors believe that this condition may be the cause of many illnesses, even those that do not as a rule depend on allergy.

There are schools of medical thought that hold that the diagnosis of food allergy/intolerance should be based both on the patient's evaluation and on a study of the existing relationship between exposure to a certain food and the onset of symptoms, rather than on laboratory tests, which are deemed to be unreliable for this purpose by these schools of thought. According to these schools of thought, the patient is the focus of diagnosis. However, they fail to provide a validated method to guarantee the validity and the reproducibility of the exposure/symptomatology relationship.

On the other hand, many doctors base their diagnosis on tests and confirm the suspected case history in accordance with these or even formulate the diagnosis of the allergy/intolerance solely on the basis of test results. In reality, no test designed to establish allergy/intolerance carried out on a patient (*in vivo*) or in the laboratory (*in vitro*) will of itself allow one to formulate this diagnosis with certainty. The diagnostic accuracy of currently available tests is low, and for some tests there are no studies on diagnostic sensitivity and specificity.

In recent years, many studies have been done on therapy and prevention of food allergy. However, these studies have not clarified the efficacy of the different preventive and therapeutic measures proposed; thus, theories in this area are much debated.

In 1995, the EAACI Adverse Reactions to Food Subcommittee edited and published a position paper on adverse reactions to food. In this position paper, it was agreed that

the diagnosis of food allergy/intolerance must be based on the observation of the patient's behavior after exposure to the suspected food. This requires a double-blind, placebo-controlled food challenge (DBPCFC) and cannot be based simply on the patient's or doctor's impression. Tests done *in vivo* and *in vitro* serve to explain the pathogenic mechanism which underlies the intolerance. However, the consequent tests must have the scientific guarantee of high reliability.

In this new position paper, the EAACI Adverse Reactions to Food Subcommittee deals both with illnesses which are attributed to food allergy/intolerance and the diagnostic procedures and preventive and therapeutic practices whose validity remains controversial. The available scientific data for each of these topics are presented and discussed.

1. Diseases presumed to be caused by adverse reactions to food

1.1. Chronic fatigue syndrome

Chronic fatigue syndrome (CFS) is a disorder characterized by debilitating fatigue and several nonspecific symptoms, which receive medical attention when they persist in the absence of other known causes. The case definition of CFS was adopted by the Centers for Disease Control in 1987 (1), and was later modified by Fukuda et al. (2) through the identification of inclusion and exclusion criteria.

A common observation in CFS is that it frequently follows certain acute infections with EBV, HHV6, other herpesviruses, etc. Most patients show nonspecific changes in the various immune parameters, and this has led to the hypothesis that an allergic mechanism might be responsible for CFS (3–7).

1.1.1. Diagnosis

The main criterion for CFS diagnosis is the onset of fatigue (activity reduced by >50%) lasting more than 6 months, without evidence of other causes. Other symptoms are persistent or relapsing low-grade fever, pharyngitis, headache, migrant arthralgia, inability to concentrate, depression, sleep disorders, and vision disturbances. Anxiety and depression are prominent in many patients. To date, no diagnostic test for CFS exists.

1.1.2. Pathophysiology

No single cause appears to be responsible for the entire clinical syndrome. Some papers appear to indicate a relationship with the multiple chemical sensitivity syndrome advocated by clinical ecologists and advocates of the multiple chemical sensitivity theory (7, 8). However, this hypothesis is not backed by sufficient data.

Exposure to domestic animals (dogs or cats) negatively correlates with development of CFS, whereas the presence of allergic disease, particularly asthma, seems to predispose to CFS symptoms (9, 10). In several studies, as many as 65–75% of CFS patients reported premorbid allergy to seasonal inhalants, foods, or drugs (10).

1.1.3. Conclusion

No direct relationship between food allergy/intolerance and the development of CFS has been found in either adults or children.

1.2. Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS), which affects up to 25% of the population in Western countries (11, 12), is defined as a functional bowel disorder in which abdominal pain is associated with defecation or changes in bowel habits, and with features of disordered defecation and distention (13). In patients with IBS, the gut seems to be more reactive to various stimuli than in controls. Drugs, hormones, foods, distention, and emotional stress elicit exaggerated motor responses.

A history of adverse reactions to food is common in patients with IBS. In one study of 101 outpatients with IBS, 67% reported that the symptoms of ingestion were aggravated by food, thus making it necessary to follow a selective diet (14). In another study of IBS-like symptoms, patients with staple food-induced gastrointestinal symptoms were investigated. Fifteen out of 36 patients (42%), originally producing an open positive challenge, were positive in DBPCFC (15).

1.2.1. Diagnosis

At present, IBS lacks distinct pathologic or instrumental findings to confirm the diagnosis. Instead, the diagnosis is based on characteristic history and the exclusion of known organic causes.

1.2.2. Scientific evidence of food allergy/intolerance

Food allergy and intolerance as a cause of IBS have been investigated by several studies. In five studies, DBPCFC were done to check the role of food in determining the syndrome (16–20). In one study, none of the IBS patients had adverse reactions to food (19). Only one study confirmed food allergy as a cause of the syndrome in three of the 27

patients studied (16). The three patients showed evidence of associated atopic disease and positive skin prick tests (SPT) to common inhalant allergens. It is worth noting that some studies not using DBPCFC, but only open challenges, carried out in large series of cases with carefully selected diarrheic forms of IBS, reported a high prevalence of adverse reactions to foods, often associated with positive SPT and/or specific IgE to the same foods (21–23). In the three remaining studies, food intolerance was found to provoke symptoms of IBS, respectively, in three of 49 (18), in one of 23 (20), and in six of 27 (16) patients. Lactase deficiency was the mechanism of the intolerance in the food-intolerant patient of one study (20). Alun Jones et al. found an increase in rectal prostaglandins in the food-intolerant patients (16). Interestingly, in one study, nine of 10 patients with negative DBPCFC were found to be strong ''placebo reactors'' (18). Moreover, Bentley et al.'s study revealed minor psychiatric disorders in 12 of 14 patients examined by an independent psychiatrist (17).

Another study considered patients with a history of IBS-like symptoms (abdominal distention, discomfort, nausea, and diarrhea) (24). These patients had shown positive DBPCFC results when challenged with cow's milk, although they all had negative results on SPT and the radioallergosorbent test (RAST). All patients tolerated lactose. Subclinical intestinal challenge with milk induced an increase of inflammatory markers.

1.2.3. Conclusion

A history of adverse reactions to foods is common in patients with IBS. Problems of dietary compliance and blinded challenge procedures are considerable, especially in studies of IBS patients where the placebo response is 30% or more. A very small fraction of patients with IBS may have IgE-mediated food allergy. However, there is evidence of an increase in the inflammatory cells present in the gut of some IBS patients (25). Other mechanisms, such as malabsorption of carbohydrates, should also be considered (26, 27).

1.3. Headache

1.3.1. Scientific evidence of food allergy/intolerance

Some foods and food additives can precipitate an attack of vascular headache, particularly pharmacologic agents present in foods, such as tyramine, phenylethylamine, histamine, ethyl alcohol, nitrates, and monosodium glutamate (28).

A study of 88 children with severe migraine showed that 26/40 of the patients challenged in the test had delayed symptoms (2–7 days) for 55 foods in all (29). These delayed reactions did not correlate with the positivity of the SPT results.

In another study, 19 patients with various symptoms and headache suspected to be caused by food allergy were investigated by three DBPCFC with the suspected food, and twice with placebo, but the diagnosis was not confirmed in any of these (30).

Atkins et al. (31) investigated 36 children with migraine, of whom 16 felt that a specific food would precipitate migraine. However, when DBPCFC were performed with these foods, no migraine headaches were observed.

Another study (32) evaluated adult patients with migraine by SPT, elimination diets, DBPCFC, and plasma histamine dosage. Seven patients with 66% or more reduction in headache frequency during the diet trial underwent DBPCFC. In five of the seven, at least one food provoked migraine. In three subjects, plasma histamine rose during migraine-provoking challenges but did not do so after placebo. All of the five DBPCFC-positive patients were SPT positive for the migraine-provoking food.

1.3.2. Conclusion

It is uncertain whether food allergies can cause headaches, as the results of DBPCFC vary. When dealing with studies that consider subjective symptoms, such as headache, in evaluating challenge results, it is important that the DBPCFC be applied three times. The only study which applied this methodology had negative results (30). Therefore, it is important that well-controlled tests be carried out in order to solve this problem and to establish the relationship between food and migraine.

1.4. Neuropathies and psychological disorders

Some rare, but well-documented case reports with repeated positive DBPCFC, have indicated adverse reaction to food. These included a change in EEG after ingestion of beef (33) and hysteria and crying induced by milk ingestion and prevented by sodium cromoglycate (34).

1.4.1. Scientific evidence of food allergy/intolerance

DBPCFC was performed on 23 adults with various symptoms attributed to food allergy (30). Four patients with clinical manifestations characteristic of food allergy (urticaria) had positive DBPCFC with the provoking food. The four food-allergic patients did not experience neurologic or psychological symptoms during the DBPCFC. None of the 19 patients who reported a wide variety of

nonatopic complaints had positive DBPCFC, and 18/19 had a psychiatric disorder. It was clear that some patients had psychogenic reactions, as symptoms appeared repeatedly during the open challenges, whereas DBPCFC repeatedly gave negative results. Patients who accepted the negative results of the DBPCFC and reintroduced the foods previously suspected had a remission or significant improvement in symptoms, while symptoms tended to persist in patients who refused to accept that they were not allergic to the foods (35).

1.4.2. Conclusion

Social or neuropsychic disorders may be secondary to well-known somatic effects of toxic, pharmacologic, or typically allergic reactions to food. There are, however, no data in the medical literature that prove that multiple atopic symptoms are commonly related to food allergy or intolerance.

1.5. Hyperkinetic syndrome

When children have behavioral problems, an association between ingestion of certain foods or food additives and abnormal behavior is often suspected by parents. More commonly, behavioral problems related to food have other causes such as psychosocial problems (conduct disorder) and food aversion (psychologically conditioned response to food) (36).

1.5.1. Symptoms

In 1975, Feingold reported that at least 30–50% of children with attention deficit syndrome with hyperactivity would improve on a diet free of artificial food flavors and colorings (37). Although these findings have never been published in a peer-reviewed journal, the theory was accepted by many laymen as a fact. However, a scientific review at that time (38) concluded that no controlled studies showed an association of hyperkinesis and food additives, and there was no confirmation that hyperactive behavior improved on a diet devoid of colorings, salicylates, and preservatives.

1.5.2. Scientific evidence of food allergy/intolerance

Since Feingold's original report (37), subsequent trials have not been able to confirm an effect of food colorings and preservatives on behavior. A few controlled studies reported no overall effect of coloring-free and preservative-free diet in school-age children, whereas a small percentage of preschoolchildren showed a benefit from the diet. Overall, effects were small and inconsistent or not apparent. Often, rating scores of behavior by teachers and parents were discordant (39, 40).

The results of double-blind, placebo-controlled studies from the last decade (Table 1) (41–48) do not reveal any further evidence of improved behavior or learning on a Feingold-type diet. Some authors have suggested that atopic children with hyperkinetic syndrome had a significantly more beneficial response to the elimination diet than nonatopic children (41, 46–48), whereas others have been unable to confirm these observations (36, 45).

1.5.3. Conclusion

A large number of studies using proper study dosing, including double-blind, placebo-controlled challenge, have been unable to show a significant effect of coloring- and preservative-free diet on behavior in children with true hyperkinetic syndrome. There is some evidence that an additive-free diet may have a small effect in a small subset of pre-schoolage children. However, the association is much weaker than originally postulated.

1.6. Otitis serosa

Serous otitis media with effusion (OME) is a chronic inflammatory disease of the mucoperiosteal lining of the Eustachian tube, middle ear, and mastoid air cells. The hearing impairment related to this disorder is caused by recurrent accumulation of fluid behind the tympanic membrane. OME is one of the most common causes of acquired hearing loss in children. The disorder is diagnosed by tympanometric abnormalities. Audiometry reveals low-frequency hearing loss, and the disorder is associated with conductive hearing loss in the speech frequencies.

OME has been reported in 23–83% of patients referred for allergy evaluation, especially in patients with allergic rhinitis or allergic asthma (49). This wide range may be due to differences in the definition of allergy and OME, and in study design. In a recent study of children (average age 4.6 years) with refractory OME, a very high frequency of 64% (66/104) was found. However, this result should be interpreted with some caution because of the rather loose diagnostic criteria of food allergy and lack of DBPCFC (55).

In a review of the role of IgE-mediated hypersensitivity in the development of OME, it was concluded that recurrent OME is associated with allergic rhinitis in about 1/3 of the studied population (51). Among patients with allergic

Table 1. Controlled dietary studies of effect of food additives and foods on behavior

Author	Year	Type of elimination and challenge	Allergy evaluation	Outcome measures	Results
Egger (41)	1985	Few limited foods and additives	Yes?	Improved behavior	Positive?*
Gross (42)	1987	Artificial coloring and salicylates	No	Multiple behavior evaluation	Negative
Rowe (43)	1988	Synthetic additives	No	Behavior evaluation	Negative
Kaplan (44)	1989	Artificial colorings chocolate, preservatives, monosodium glutamate, caffeine, foods	No	Behavior evaluation	Positive in 58%
Pollock (45)	1990	Artificial food colorings	Yes	Rating of behavior	Small effect (not detected by parents)
Egger (46)	1992	Food colorings	Yes?	Behavior evaluation	?**
Rowe (47)	1994	Artificial coloring (tartrazine)	Yes	Rating of irritability, restlessness, sleep disturbance	Reduction of symptoms
Boris (48)	1994	Foods, colorings, preservatives	Yes	Rating of behavior	Positive in 62%

*Only minority had double-blind challenges; there was also order effect. **Lack of proof of atopy in children treated with hyposensitization for ""apparent food-induced hyperkinetic syndrome''.

rhinitis and OME, the vast majority suffer from allergy to inhalant allergens. Only a small proportion of patients have OME and food-allergic rhinitis; typically, this will be caused by dairy products and affect children under the age of 2 years (51, 52).

1.6.1. Scientific evidence of food allergy/intolerance

The association between OME and allergic rhinitis has not been clarified, but in the majority of children with OME and allergic rhinitis of the middle-ear mucosa, there is no relationship. It is conceivable, however, that OME may derive from Eustachian tube dysfunction caused by allergic reaction in the nasal mucosa. There is some evidence that inflammatory mediators from the nasal mucosa are transported via the nasal mucociliary system to the nasopharyngeal orifice of the Eustachian tube (51).

In a subgroup of children with OME without diagnosed allergic rhinitis, the effectiveness of elimination diets (especially milk-free diet) has been reported (53, 54). Similarly, it has been claimed that refractory serous otitis media in adults can sometimes be resolved by an appropriate elimination diet (55, 56).

1.6.2. Conclusion

OME is rarely caused by allergy to foods. However, the possibility of food allergy should be considered in very young children with refractory OME (57). The diagnosis of food allergy in OME should be based on proper diagnostic measures, including DBPCFC.

1.7. Collagen/vascular diseases

1.7.1 Vasculitis

Vasculitis of the small blood vessels, most obviously in the skin, is usually considered to be induced by immune complexes. Vasculitis may sometimes appear clinically as itching macules which may develop into purpura, or even arthalgia, myalgia, or joint swelling with malaise, and a slight temperature may follow – lasting from under a week to several months (58–60).

1.7.1.1. Scientific evidence of food allergy/intolerance

Since the 1970s, it has been considered that milk, fish, berries, eggs, peas, azo-dyes (mainly tartrazine), benzoates, or other ingestants such as iodine, large doses of vitamins, and foods containing histamine may aggravate vasculitis (61–63). The

role of sulfites has also been stressed (59, 63). The combination of the symptoms attributed to food intolerance was vasculitis, urticaria, angioedema, asthma or airway hyperactivity, rhinitis, CNS reactions, joint involvement, or contact dermatitis (64). Some clinical observations suggest that histamine and catecholamines present in foods could induce vasculitis under certain conditions (65), but these cases have not been confirmed by DBPCFC.

1.7.2. Joint symptoms

Joint symptoms, i.e., arthalgia, arthritis, swelling, pain, and functional disabilities, may occur in allergic patients (66). This does not necessarily mean that food hypersensitivity contributes to the symptoms. However, recent data seem to show that foods can either aggravate or improve joint symptoms. For example, the amount and ratio of certain polyunsaturated fatty acids modulate the production of pro- and anti-inflammatory mediators (67).

In an early study in a selected group of patients stressing the coexistence of respiratory allergy and arthritis, some symptoms were related to food ingestion (68). Decades ago, Zussman claimed to be able to differentiate between rheumatoid arthritis and food-allergy-induced arthritis, by the anamnestic data of family and individual patient history, the clinical features of non-IgE-mediated mechanisms, and the results of avoidance diet (69). In Felder et al.'s study, although 159 rheumatoid arthritis patients responded to a questionnaire, 52 of them with a positive history of food allergy, none of the 35 evaluated in detail were food allergic (70). It was later considered that food hypersensitivity may affect symptoms of rheumatism only in a subgroup of patients (71).

Other investigators were unable to reduce clinical complaints through avoidance diet in rheumatoid arthritis (72, 73). However, Panush et al. analyzing anecdotal cases, suggested that immune reactions provoked by foods may lead to tissue injury and abnormal immune reactions in the joints, and thus conditions known as ''rheumatic diseases'' may develop (74).

It must also be taken into consideration that vasculitis and joint symptoms are characteristic symptoms of several autoimmune diseases, and recent data support the coexistence and possible etiologic links between food allergies and autoimmune conditions. While gluten-sensitive enteropathy and food-induced eosinophilic proteinopathy seem to be special and rare cases of food allergy, some reports suggest (without the detailed knowledge of the mechanisms) connections between ulcerative colitis, Crohn's disease, or IBS and food allergy (75).

Dermatitis herpetiformis and celiac disease may have a common basis in glutenin–elastin cross-reactivity, and juvenile insulin-dependent diabetes mellitus (IDDM) could be a consequence of cow's milk allergy as well (76, 77). Strand (78) even suggested that the thermal disintegration of bovine serum albumin (BSA) during milk processing could reduce the number of new IDDM cases.

Observations in other autoimmune systemic multiorgan autoimmune diseases (systemic lupus erythematosus, progressive systemic sclerosis) do not in any way support the role of food allergy/intolerance in the induction or conservation of any of the symptoms or mechanisms of systemic autoimmune diseases. On the other hand, the prevalence of autoimmune systemic diseases is by no means increased in food-allergic subjects either (77).

1.7.3. Conclusion

In spite of some data, we have to conclude to date that any probability of an etiologic link between food allergy/intolerance and autoimmune vasculitis and/or arthritis is low. Studies favoring this concept deal mostly with anecdotal single cases and/or were not properly controlled. Only in certain exceptions was the diagnosis of food allergy supported by DBPCFC.

2. Controversies regarding pathogenetic mechanisms

2.1. Food additives

There is a discrepancy between the patient's subjective perception of food-additive intolerance and the results of objective diagnostic tests.

2.1.1. Prevalence

There are two population-based studies on the prevalence of adverse reactions to food additives. In a Danish study in schoolchildren, 6.6% perceived adverse reactions to food additives and 2% developed adverse reactions to a mixture of food colorings, preservatives, and flavors. The main symptom was aggravation of atopic dermatitis or urticaria. One percent reacted to double-blind, placebo-controlled challenge with a mixture of colorings or preservatives in capsules (79, 80).

In a UK population study (81) including both children and adults, 7.4% of subjects reported adverse reactions caused by food additives. Three subjects had a positive challenge to groups of food additives; i.e., colorings, preservatives, and

antioxidants. The symptoms were headache, upper abdominal pain, eczema, and mood swings. The prevalence was calculated to be 0.026%.

The great variation in prevalence estimates of the two studies reflects the difficulty of studying adverse reactions to a large group of substances; in this case, food additives. It also reflects the difference in study populations. From the above, it seems that the highest prevalence of food-additive intolerance is in atopic children with skin symptoms.

2.1.2. Categories of food additives

Chemically and functionally, food additives form a very heterogeneous group of substances consisting of preservatives such as antimicrobials and antioxidants, colorants, emulsifiers and stabilizers, fillers such as vegetable gums, flavor enhancers, sweeteners, and enzymes. By definition, food-additive allergy requires a specific immunologic mechanism that can be proven by *in vivo* and *in vitro* tests. Food-additive intolerance is caused by nonimmunologic or unknown mechanisms. The diagnosis of allergy or intolerance to an additive can be done as described in the EAACI position paper on adverse reactions to foods (82). In case of oral provocation, we should distinguish clinically between an intolerance reaction and an intolerance provocation.

An intolerance reaction (63) means that the ingestion of additives in foods (and drugs) is the cause of the disease and that the elimination of these additives from ingested foods leads to complete disappearance of symptoms. Relapses occur after the reintroduction of the additives. We can distinguish between an acute or an acute recurrent course and a chronic course. An IgE-mediated mechanism could also be present in the acute or acute recurrent course. However, this situation is quite rare, and intolerance provocation is more common. This means that the additives provoke an exacerbation of an existing disease such as asthma, rhinitis, or urticaria, but the appropriate elimination diet does not lead to a complete disappearance of symptoms. Additives are triggers or aggravating factors.

The following paragraphs discuss the single categories of additives regarding symptoms and acting mechanisms.

2.1.2.1. Preservatives

Sulfites can provoke severe attacks of asthma, and urticaria and anaphylactic reactions (84–86). Sulfite sensitivity, as well as intolerance of additives, is not associated in asthmatics with aspirin intolerance (87). In asthmatics, the main mechanism is stimulation of irritant receptors by sulfur dioxide, but an undefined mechanism or sulfite oxidase deficiency is present in urticaria (86). A few cases with positive prick tests, positive Prausnitz-Küstner tests, and positive histamine-release tests from blood basophils suggest IgE-mediated mechanism (84).

Other preservatives such as benzoic acid and its derivatives can produce urticaria, contact urticaria, and also contact dermatitis, but rarely asthma and anaphylactic reactions. The mechanisms appear to be mainly due to pharmacologic histamine release (87, 88). A T-cell-mediated allergy mechanism was present in the case of contact dermatitis and in the few described cases of hematogenous contact eczema after oral challenge with benzoates and parabens (89).

2.1.2.2. Azo-dyes and nonazo-dyes

Tartrazine (E102) is the best-known azo-dye. Azo-dyes can provoke urticaria, aggravation of atopic eczema, purpura, vasculitis, asthma, and possibly severe anaphylactic reactions. Aspirin-sensitive asthma patients do not have a high prevalence of reactions to tartrazine (90). The mechanism of azo-dye intolerance is probably nonimmunologic (91, 92).

The nonazo-dyes are heterogeneous as in the carotinoid dye annatto and carmine, the natural red pigment extracted from the female cochineal insect *Dactylopius coccus*, to which urticaria and anaphylactic reactions are described (93). IgE-mediated allergy to carmine has been recently demonstrated by RAST carmine-specific IgE antibodies (94, 95).

2.1.2.3. Flavor enhancers

Monosodium glutamate (MSG) is thought to cause the ''Chinese restaurant syndrome''. The onset of symptoms occurs about 10–20 min after ingestion. The symptoms include flushing, paresthesia, chest pain, facial pressure and burning, dizziness, sweating, bitemporal constriction, headache, palpitation, weakness, nausea, and vomiting (96). However, in formal double-blind studies (97), these symptoms occurred with both MSG and placebo; therefore, the cause of this syndrome remains in doubt. Severe asthma attacks after MSG challenge with early and late onset were described in a single-blind test (98). The mechanisms are undefined. However, a recent DBPCFC conducted in a group of adults with asthma who believed that they were sensitive to MSG failed to demonstrate the existence of MSG-induced asthma in this group (99). When undergoing oral challenge tests, the patient should be observed overnight, especially in the case of an asthma reaction.

Flavors such as vanillin, cinnamic aldehyde, and balsam of Peru can provoke contact dermatitis or skin rashes and aggravate atopic dermatitis (100–103). In the case of vanillin, bronchospasm has been described in double-blind condi-

tions (104). In the case of skin rashes, contact allergy can often be detected by patch tests; in other cases, the mechanisms are unknown.

2.1.2.4. Antioxidants

Butylated hydroxyanisole and butylated hydroxytoluene can provoke urticaria and flare-up of contact dermatitis (105). Here contact sensitization can be demonstrated by positive patch tests.

2.1.2.5. Enzymes

Enzymes and other food additives that are proteins are very strong inhalant allergens (106, 107). Only a few cases of allergic reactions have been attributed to oral intake: e.g., anaphylactic shock from papain used as a meat tenderizer (108), asthma and rhinitis symptoms from α-amylase in bread (109), and urticaria from castor bean gum (110). In these cases, an IgE-mediated mechanism is responsible.

2.1.3. Conclusion

Food-additive intolerance occurs less often than supposed by patients, and, contrary to the lay and news media perception, food-additive intolerance occurs more often in children and adults with pre-existing disease such as atopic dermatitis or asthma. In such patients, atopic dermatitis, chronic urticaria, rhinitis, and asthma may be aggravated. They rarely provoke gastrointestinal symptoms, headache, or mood change, but occasionally cause life-threatening anaphylactic reactions. In the latter situation, an IgE-mediated mechanism is at work.

2.2. Histamine intolerance

For many years now, clinical, medical, and allergologic practices have been prescribing histamine-free, or so-called histamine-releaser-free diets to patients suffering from chronic urticaria. However, no controlled study has demonstrated that chronic urticaria is due to intolerance of histamine present in food. It is only in recent years that studies have been carried out to evaluate the etiologic role of the exogenous histamine present in food which provokes allergy-like symptoms.

Healthy people may experience severe headache and flushing after ingestion of massive amounts of histamine, as can occur in scombroid (fish) intoxication. Symptoms occur 10–30 min after eating spoiled fish. However, ingestion of strong doses of histidine/histamine is not in itself sufficient to cause the syndrome; histamine enhancement by spoiled fish toxins is required for this to happen.

As the first barrier against orally ingested histamine, enteral diamine oxidase is of main importance for the effective catabolism of histamine (111). In pigs, experimental inhibition of diamine oxidase, followed by food challenge with cheese and wine, induced anaphylactic reactions in each animal and death in 20% of the pigs, thus demonstrating the importance of diamine oxidase. The same experiment under antihistamine pretreatment did not elicit symptoms in the animals (112). In preliminary investigations, serum diamine oxidase levels using the C14 putrescine method (113) revealed decreased activity (mean 0.03 nkat/l) in patients with suspected histamine intolerance, compared to healthy controls (mean 0.07 nkat/l). In pregnancy, diamine oxidase is known to be elevated up to 500-fold as compared to the nonpregnant status, inasmuch as diamine oxidase is produced by the placenta (114). Some drugs can inhibit the degradation of histamine, blocking diamine oxidase (Table 3).

Intraduodenal administration of 120 mg of histamine in patients with chronic urticaria can cause clinical symptoms such as diarrhea, urticaria, headache, accelerated heart rate, and drop in blood pressure, within 1 h of duodenal histamine challenge (115).

Disturbances in the metabolism of histamine (altered intestinal permeability to histamine, deficit or reduced activity of diamine oxidase) could facilitate symptoms of histamine intolerance in some subjects.

Histamine in food may be responsible for some cases of food intolerance such as bronchoconstriction or headache after ingestion of wine (116–119). It must be remembered, however, that the histamine content of foods may vary greatly (Table 2).

2.2.1. Conclusion

It is necessary to carry out controlled clinical studies with a significant number of patients in order to define the clinical role of histamine intolerance in provoking allergy-like symptoms and the threshold concentration for symptom provocation. Although a provocation test with red wine has been proposed to confirm the diagnosis of histamine intolerance, a more specific diagnostic procedure must be defined.

3. Controversies in diagnostic tests

3.1. Diagnostic tests *in vivo*

Methods that have not been shown to be effective and safe by proper clinical trials should be considered ''unproven

Table 2. Histamine content of some foods (119)

Fish	
Tuna	<0.1–13 000 mg/kg
Sardine	110–1500 mg/kg
Anchovy	176 mg/kg
Cheese	
Emmentaler	
Harzer	390 mg/kg
Gouda	29.5–180 mg/kg
Stilton (Roquefort)	158 mg/kg
Camembert	35–55 mg/kg
Cheddar	34 mg/kg
Tilsiter	50–60 mg/kg
Monte Nero	19 mg/kg
Hard-cured sausage	
Osso collo	
Salami	
Westphalian ham	38.2–159 mg/kg
Knappseer	94 mg/kg
Vegetables	
Pickled cabbage	
Spinach	38 mg/kg
Tomato (ketchup)	22 mg/kg
Wine and beer	
Red wine	600–3800 μg/l
White wine	3–120 μg/l
Sparkling wine/champagne	15–78/670 μg/l
Beer	21–305 μg/l

Table 3. Drugs inhibiting histamine degradation by blockade of diamine oxidase (120)

Acetylcysteine
Ambroxol
Aminophylline
Amitriptyline
Chloroquine
Clavulanic acid
Dihydralazine
Isoniazide
Metamizole
Metoclopramide
Pancuronium
Propafenone
Verapamil

methods'' or ''nonvalidated methods''. Such procedures are not recommended in clinical practice, as studies have not shown any difference between the investigated method and the placebo, and harmful effects cannot be excluded.

3.1.1. Subcutaneous and sublingual provocation and neutralization

In this test, food extracts are administered sublingually, subcutaneously, or intradermally to elicit objective or subjective symptoms, after which a weaker or stronger dilution of the same extract is administered which should neutralize the allergic reaction and relieve symptoms. The method is not standardized and different protocols show great variations. In Italy, for example, a test called DRIA (developed by the Associazione di Ricerca Intolleranze Alimentari [ARIA]; hence the name ''DRIA'') has been developed. This sublingual test is based on administration of the allergenic extract and on measurement of muscle strength with an ergometer. The test is considered positive when there is a decrease in muscle strength within 4 s after sublingual contact with the extract. Sublingual and subcutaneous provocation and neutralization has been proposed for the diagnosis of food allergy and a wide variety of illnesses in different medical fields; e.g., thrombophlebitis, vasculitis, arrythmias, etc. (121–126).

No report has shown that provocation-neutralization testing can be useful for the diagnosis of food allergy, nor have any investigations supported the rationale and diagnostic claims of the DRIA test.

The American Academy of Allergy and Immunology has concluded that the provocation-neutralization method is ineffective and without immunologic rationale (127). The National Center for Health-Care Technology reached a similar conclusion (128). Furthermore, the Health-Care Financing Administration concluded that ''sublingual provocation testing and neutralization therapy for food allergy are widely used, but lack scientific evidence of effectiveness'' (129). These procedures have been excluded from Medicare coverage in the USA (131).

3.1.2. Electroacupuncture

Electroacupuncture or electrodermal testing is performed with a device which measures the electric activity of the skin at points considered suitable for detecting food allergy. The patient holds positive and negative electrodes in each hand. Allergy to the food is measured by a drop in electric current when an aluminum plate touches the skin (131). There is no scientific or clinical proof that this method can diagnose food allergy.

3.1.3. Applied kinesiology

This method of diagnosing food allergy is based on the subjective manual measurement of muscle strength (132). The patient holds a glass bottle containing the food in one hand, while the investigator estimates muscle strength in the other hand: a decrease in muscle strength should indicate a positive test result. Alternatively, the bottles may be rested near the chest or even near the patient, but not in contact with the body. There is no documented scientific rationale for or diagnostic efficacy of applied kinesiology.

3.1.4. Bioresonance – diagnosis and treatment

Bioresonance is based on the belief that human beings emit electromagnetic waves which may be either ''good'' or

''bad''. Bioresonance therapy uses an apparatus which is supposed to be capable of filtering the waves and sending the ''rehabilitated'' waves to the patient (133). Pathologic waves may be removed by that process, and the allergic disease should thereby be treated. Unfortunately, it has been demonstrated that the device in use is not capable of measuring the electromagnetic wave presumed to be involved (134). Two recent double-blind, controlled studies failed to demonstrate any diagnostic and therapeutic value of bioresonance in adult patients suffering from hay fever (135) and in children with atopic dermatitis (136).

3.1.5. Conclusion

At present, the data provided by the scientific literature and medical knowledge do not allow the use of the above methods in clinical practice.

3.2. Diagnostic tests *in vitro*

DBPCFC is the reference standard for food hypersensitivity, and any new test must be validated by it (137–139).

3.2.1. Total IgE in serum

Elevated levels of IgE in cord blood are predictive of allergic manifestations in later childhood, although the sensitivity of such determinations is too low to justify their use in clinical routine (140). In other cases, an increased level of total IgE in serum may indicate the atopic status of the patient (provided parasite infestation can be excluded), but cannot be used in specific diagnosis of allergy (141).

3.2.2. Other antibodies (IgA, IgM, IgG including IgG and IgA subclasses)

In the search for suitable clinical food hypersensitivity markers, much attention has been paid to changes in non-IgE immunoglobulins (and their subclasses). Although some papers suggest a possible pathogenic role of IgA-secreting cells, which may increase in number after challenge (142), or IgG4 antibody levels, which have been postulated to correlate with clinical hypersensitivity (143), a pathogenic role of these antibodies has not yet been proved (144–148). In the study by Morgan et al. (143), no correlation was found between the outcome of DBPCFC and the levels of either total IgG or IgG4, nor was any difference found between patients and controls. The levels of other, food-specific immunoglobulins of non-IgE isotype may reflect the intake of food in the individual (149) and may thus be a normal and harmless finding.

3.2.3. T-cell stimulation tests

Fukutomi et al. (150) investigated two groups of patients with atopic dermatitis, one group with immediate reactions and one group with late reactions to DBPCFC. In the latter group, which displayed reactions more than 2 h after challenge, an increase in the proliferative response of peripheral blood mononuclear cells was found *in vitro*. Recently, similar results have been obtained in children with milk-dependent eczema (151). To date, the clinical significance of those findings remains unknown.

3.2.4. Tests related to active disease or applied in a challenge situation

In the case of *in vitro* measurement of histamine release from basophils, or specific IgE or other mediators from the basophils of other leukocytes, there is no need to elicit a systemic reaction in the patient, either under controlled conditions (challenge) or accidentally. Such an *in vitro* test means that it is not necessary to conduct challenges. *In vitro* basophil histamine release has been found to be comparable to measurement of specific IgE (152).

3.2.5. Plasma histamine

It has been demonstrated that basophils from allergic patients show a higher degree of spontaneous release of histamine *in vitro* (153). This is probably due to the increased secretion of a histamine-releasing factor in these patients; however, suggestions that it might prove of value in patients with food allergy have not been sustained (154). Like tryptase, plasma histamine also rises after positive DBPCFC (155), and can be measured with a positive response in DBPCFC (155). However, the test is difficult to perform, mainly due to the short half-life of histamine in the circulation. Furthermore, at least 10% of responses are false-positive, but the major problem with the test is that it requires clinical confirmation, preferably DBPCFC, and will therefore be only an addendum to the clinical evaluation.

3.2.6. Plasma tryptase

Unlike histamine, tryptase is confined to the mast cell. Simultaneous measurement of tryptase together with plasma histamine might, therefore, in theory add to our knowledge of the pathogenic mechanisms underlying the clinical reaction. Unfortunately, however, the only clinical situation in which measurement of serum tryptase has proven valuable is, retrospectively, in cases of anaphylaxis, elicited by food allergy, where a marked rise has been demonstrated (156, 157). Again, the test requires a substantial clinical reaction in the patient in order to be

positive, and is therefore of little diagnostic value in the routine setting.

3.2.7. Complement activation

In the search for involvement of mechanisms other than type 1, several investigations have measured various components or split products. In the period after challenge, either no changes in the complement cascade were found (148, 158), or such markedly heterogeneous changes interindividually were found that the authors concluded that measurement of complement levels was not a useful test for the clinical evaluation of a patient with suspected food hypersensitivity (159).

3.2.8. Immune complexes

Twenty years ago, following observations on complement consumption after milk challenge, and the finding of high-molecular-weight IgE in the sera of atopic patients, the formation of circulating immune complexes was investigated. Both IgE- and IgG-containing immune complexes were detected after food challenge in allergic patients, but not in nonallergic subjects (160, 161). The complexes could bind C1q and therefore activate the complement cascade, and contained immunoreactive protein allergens of the food.

Although it was suggested that the method would be suitable for screening food hypersensitivity, it offered no advantage over other tests, it was not standardized, and it lacked specificity. Therefore, tests based on detection of immune complexes have been confined to the alternative market, and have had limited application. However, the measurement of immune complexes containing food antigens has been used in studies of mucosal permeability, and it offers an advantage over direct antigen detection because high levels of antibodies interfered with food-allergen measurement (162).

3.2.9. Eosinophils

Recently, in a double-blind study, the involvement of circulating eosinophils and an eosinphil activation product, eosinophil cationic protein (ECP), have been demonstrated in food-hypersensitive children (163). The authors demonstrated that a decrease in circulating eosinophils follows immediately after challenge, followed by an increase in serum ECP 8 h after challenge. In previous studies, other authors have also found a decrease in circulating eosinophils after challenge (164, 165). However, the diagnostic efficacy of monitoring of eosinophils and their products is rather low and requires further study.

3.2.10. Permeability tests

In controlled studies, various groups have demonstrated increased permeability to test probes such as polyethylene glycol (PEG) of various sizes or to ratios of sugars such as mannitol, lactulose, or rhamnose in patients with food hypersensitivity (166, 167). However, intestinal permeability varies widely among healthy individuals as well as among food-hypersensitive patients, resulting in an almost total overlap between the groups (163). Nevertheless, changes in intestinal permeability after challenge have repeatedly been demonstrated to distinguish between patients with predominantly gastrointestinal symptoms and others (167, 168), limiting the use of permeability tests in routine clinical work.

3.2.11. Cytokines

Kondo et al. (165) have demonstrated an increased activity of interleukin (IL)-2 and interferon-gamma after challenge. IL-4 has also been demonstrated, *in vitro*, to be involved in the events leading to clinical disease (170). At present, there are no studies of the sensitivity, specificity, or diagnostic efficacy of such determinations as diagnostic tools.

3.2.12. Other tests

All kinds of unproven techniques and tests are abundant in the alternative medicine market, and usually these totally escape official control. Only rarely are results on these tests published in papers covered by the standard databases.

In the cytotoxicity test, a food allergen is added to whole blood or to leukocyte suspensions. The reduction in number or the change in appearance of the cells would indicate a sensitivity to a specific food (171–173). However, controlled studies (174–176) have not shown any efficacy of the test in diagnosing food allergy or intolerance. In contrast, several studies demonstrated that this test cannot distinguish between offending and tolerated foods and between active treatment and placebo (176, 177). Moreover, test results were not reproducible when repeated several times on the same patient with the same food allergen.

A test for non-IgE-mediated food hypersensitivity (ALCAT^{TM}) has been launched; it measures changes in white-cell diameter after challenge with foods *in vitro*. The procedure is not documented, as only a few relevant papers are listed in the databases. Most of these discourage the use of the test due to lack of reproducibility, whereas the other reports do not fulfil the inclusion criteria mentioned earlier (178). Therefore, more investigations need to be published. Since many trials with a negative outcome are never

published, the risk of a tendency to overestimate the efficacy of the test should be borne in mind.

The American Academy of Allergy and Immunology has concluded that no proof is available of the efficacy of the cytotoxicity test in diagnosing food allergy, and that several controlled studies indicate that the test is ineffective (127).

In conclusion, physicians should be alert to protect patients from potentially harmful procedures that may delay appropriate treatment. Approval of these tests awaits controlled studies.

4. Controversies in prevention and treatment

4.1. Prevention

Since cow's milk allergy is most common in infants and young children, alternatives to regular cow's milk substitutes for human milk and infant feeding have been manufactured. Protein hydrolysates possess biologic and immunologic properties which depend largely on the extensiveness of enzyme hydrolysis and ultrafiltration (179). There are extensively hydrolyzed formulations on the market with a very low allergen content, as defined by the American Academy of Pediatrics (180), the European Academy of Allergology and Clinical Immunology (EAACI) (181), and the European Society for Paediatric Allergy and Clinical Immunology (ESPACI) (182). There are also partially hydrolyzed cow's milk products available which do not meet these criteria.

The effectiveness of hydrolyzed cow's milk formulas in prevention of allergic diseases remains uncertain, except possibly for prevention of food allergy in early childhood.

4.2. Treatment

The treatment of food allergy/intolerance is avoidance of the offending food items and additives. Psychological and social support is often necessary in addition.

Cow's milk-allergic infants who are not breast-fed may be given hydrolyzed protein hydrolysates. However, although they have evidenced a high safety profile for more than 50 years, they are not completely nonallergenic, and allergic reactions have been triggered in some situations.

4.2.1. Elimination diets

Elimination diets, particularly if they are extensive, may place a heavy burden on patients and their families. A diet may severely restrict social activities and may cause isolation. Psychological support for the patient and/or the family should therefore be considered in all cases where extensive elimination diets are considered. Therefore, an exclusion diet should be considered only in the case of a positive DBPCFC. In children under the age of 2 years, a positive open challenge is usually accepted as clinical proof of food allergy.

4.2.2. Lactose intolerance

Adverse reactions to lactose are common, as most of the world population is lactase deficient. Treatment involves limiting the intake of fresh milk to the individually tolerated level. Cheese and fermented milk products, e.g. yogurt, are usually well tolerated. Lactase is commercially available and can be used by lactase-deficient individuals who wish to drink milk.

4.2.3. Specific immunotherapy

Avoidance of the responsible food identified by the elimination/challenge procedure is recognized as the best optimal treatment of food allergy (183). However, for some foods, it is extremely difficult to avoid small amounts hidden in food preparations apparently unrelated to the culprit food. Eating even negligible amounts of the culprit allergen in an unsuspected food may expose the allergic patient to life-threatening anaphylactic reactions. Theoretically, in such cases, specific immunotherapy should have the same value as in patients with anaphylaxis from Hymenoptera stings. However, despite encouraging results obtained in some uncontrolled studies in patients allergic to fish (184–186), specific immunotherapy has not been considered as a treatment of food allergy.

4.2.3.1. Subcutaneous immunotherapy

In 1992, the first placebo-controlled study of immunotherapy for food allergy was published (187). Peanut was the food chosen for the study, as it is a frequent cause of anaphylaxis which cannot be safely avoided; moreover, allergy to peanuts, unlike allergy to most other foods, shows no tendency to be outgrown with time (188). Unfortunately, the study was not completed due to a fatal accident caused by inadvertent administration of the active allergen instead of the placebo. However, the three patients who had repeated the DBPCFC did show a marked reduction of symptoms score to the challenge, and no such difference with regard to

the basal challenge was found in the one available placebo-treated patient.

Moreover, the three treated patients had a marked decrease in skin test sensitivity to the peanut extract, as opposed to the three placebo patients, who displayed a slight increase in skin sensitivity. Apart from the fatal accident, the frequency of systemic reactions to immunotherapy was 13.3% (16 out of 120 injections), urticaria being the most common (10 reactions), followed by conjunctivitis and asthma. No cardiovascular reaction occurred.

These preliminary data, as highlighted by Sampson (189) in an accompanying editorial, permit us to consider that specific immunotherapy could be a form of treatment for food-allergic patients at the risk of life-threatening reactions by ingestion of even small amounts of the culprit food. Nevertheless, other controlled studies will have to be performed, analyzing various foods and different protocols of administration, before immunotherapy can be proposed as a practical treatment for food allergy. Furthermore, the US Food and Drug Administration does not recommend injection therapy with food extracts.

4.2.3.2. Alternative immunotherapy

Oral desensitization with cow's milk, diluted in water according to the degree of sensitization of the patient, has been used in an open study on 14 patients, resulting in re-establishment of milk tolerance in nine patients (190). However, further studies should be carried out in a double-blind, placebo-controlled manner.

It has been claimed that food allergies can be relieved by giving successive intracutaneous injections of the extract dilutions of the offending food, until the ''neutralizing'' dose is found. Although a number of studies have not been able to confirm the validity and the reproducibility of this procedure, these studies have been criticized because they did not use the ''correct'' provocation technique (191, 192). Finally, a carefully controlled trial of subcutaneous provocation and neutralization clearly demonstrated the lack of efficacy of this method (193).

In 1992, Egger et al. published a double-blind, placebo-controlled study on hyposensitization with enzyme-potentiated desensitization in children with food-induced hyperkinetic syndrome (194). The major problem in accepting the conclusions of this study is the diagnostic method used to establish the food intolerance. The diagnosis was based on improvement of symptoms after an oligoantigenic diet and their reappearance on reintroduction of the suspected food. No double-blind, placebo-controlled challenges were performed. Therefore, the selection of subjects was inappropriate. The food extract used for hyposensitization was a mixture of more than 40 food antigens and 10 food additives. There is no scientific evidence that such a mixture of food antigens has any clinical efficacy. The demonstration of efficacy of the treatment was based on open food provocation and on patient opinion.

The results of this study cannot be accepted because the treatment was not supported by any conceptual justification or by experimental demonstration; moreover, the selection of patients was not carried out correctly.

4.2.3.3. Acupuncture

The principles of traditional Chinese medicine (TCM) aim to refresh the blood, eliminate humidity, purify the heart, avoid the blockage of blood, and, finally, detoxify the entire organism. In the practice of acupuncture, seven points are located to potentiate immune responses (defensive energy, or wei-qi). Despite the use of acupuncture in the treatment of several allergic diseases, including bronchial asthma and pollenosis, published studies supporting this therapy (195) have been widely criticized for their experimental design. Differences in the clinical trials and in the techniques used make assessment of overall results difficult. In allergic rhinitis, a success rate of up to 84% has been claimed by a few published reports. No reports have ever been published on acupuncture and food allergy/intolerance.

4.2.3.4. Traditional Chinese herbal therapy (TCHT)

A recent study offered a contribution to the potentially beneficial actions of TCHT (freshly made patient-tailored decoctions of mixtures of dried plant materials) in 40 patients with adult atopic dermatitis (196). The study was properly designed, and double-blind, placebo-controlled, crossover assessment was performed, but the patients did not suffer from food allergy. No studies have been performed to evaluate the efficacy of TCHT in patients suffering from food allergy.

Herbal treatment has been known to induce serious side-effects due to the pharmacologic principles contained in variable amounts in different batches of dried herbs. Hepatic damage and interstitial kidney fibrosis have been described, as well as possibly allergic reactions (197–199).

4.2.3.5. Homeopathy in treatment of food allergy

No reports have been published on this matter. No evidence has ever been offered to support such treatment in food-allergic diseases.

4.3. Conclusion

Food allergy is best treated by avoiding the offending foods. It is important that patients and their families be trained properly in this matter to ensure correct avoidance, as well as adequate nutrition. Therefore, treatment of extensive food allergy is based on the work of a team, which should include a physician properly trained in allergology, gastroenterology, and nutrition; a dietician; and a psychologist.

The value of pharmacologic treatment is not clearly documented. At present, there is no evidence that both classical subcutaneous and ''alternative'' immunotherapy are safe and effective in the prevention and treatment of food allergy or food intolerance.

5. Concluding remarks

The diagnosis of food allergy should always be based upon an accurate and comprehensive history, backed up by valid and appropriate diagnostic tests. Properly diagnosed food allergy is best treated by avoidance of the offending foods. To ensure proper avoidance as well as adequate nutrition, proper training of patients and their families is necessary. Therefore, treatment of extensive food allergy is based on teamwork, and the team should include a physician properly trained in allergology, gastroenterology, and nutrition, as well as a dietician. The team should also include a psychologist.

The value of pharmacologic treatment has not been clearly documented. At present, there is no evidence that either classical subcutaneous or ''alternative'' forms of specific immunotherapy are safe and effective in the prevention and treatment of food allergy or food intolerance.

This position paper gives a summary of the controversial aspects of adverse reactions to food. In the field of food allergy, newly developed immunologic and molecular biologic tools have given new insights into antigenic structures of proteins and the type of immunologic reaction involved. Little is yet understood about the mechanisms involved in nonimmune-mediated adverse reactions. Furthermore, the symptoms presented by the patients are often subjective, and the tissues involved are hardly accessible for histologic studies.

The strength of this document is that it points to those controversial areas from which the data reported in presently available literature are not conclusive. Therefore, it emphasizes the need for further research in this field.

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