Best Practice & Research Clinical Gastroenterology
Vol. 20, No. 3, pp. 467–483, 2006
doi:10.1016/j.bpg.2005.11.010
available online at http://www.sciencedirect.com

3

Food allergies and food intolerances

Claudio Ortolani*
Director
Istituto Allergologico Lombardo, Piazza Monsignor Moneta 1, 20090 Cesano Boscone, Milan, Italy

Elide A. Pastorello[1]
Director
S.C. Allergology and Clinical Immunology, Niguarda 'Ca' Granda' Hospital, Piazza Ospedale Maggiore, 3, 20162 Milan, Italy

Adverse reactions to foods, aside from those considered toxic, are caused by a particular individual intolerance towards commonly tolerated foods. Intolerance derived from an immunological mechanism is referred to as *Food Allergy*, the non-immunological form is called *Food Intolerance*. IgE-mediated food allergy is the most common and dangerous type of adverse food reaction. It is initiated by an impairment of normal Oral Tolerance to food in predisposed individuals (atopic). Food allergy produces respiratory, gastrointestinal, cutaneous and cardiovascular symptoms but often generalized, life-threatening symptoms manifest at a rapid rate—anaphylactic shock. Diagnosis is made using medical history and cutaneous and serological tests but to obtain final confirmation a Double Blind Controlled Food Challenge must be performed. Food intolerances are principally caused by enzymatic defects in the digestive system, as is the case with lactose intolerance, but may also result from pharmalogical effects of vasoactive amines present in foods (e.g. Histamine). Prevention and treatment are based on the avoidance of the culprit food.

Key words: adverse reactions to foods; food allergy; food intolerance; oral tolerance; double blind placebo controlled food challenge (DBPCFC); histamine; immunoglobulin E (IgE); mast cells; oral allergy syndrome (OAS); skin prick test (SPT); food patch test (FPT); probiotics; breastfeeding; humanized anti-IgE serum.

BASIC MECHANISMS OF FOOD ALLERGY AND FOOD INTOLERANCE

Oral tolerance (OT) is the state of immunological non-response that is established after the first contact with the food antigens in the gut. It is evident that this is an active

* Corresponding author. Tel.: +39 2 45876607; Fax: +39 2 4500706.
E-mail addresses: all@ambrosianacdc.it (C. Ortolani), elide.pastorello@ospedaleniguarda.it (E.A. Pastorello).
[1] Tel.: +39 2 64444414; fax: +39 2 64442082.

process which is linked to specific T cells since it is possible to transfer the tolerance in mice using spleen cells.[1] Animal studies have highlighted certain mechanisms which lead to the lack of development of OT which could also be operating in man. These consist of:

i. Apoptosis of antigen-specific T cells, with consequent loss of their specific immunological function. This mechanism was observed following contact with high doses of antigen.[2]
ii. Paralysis of the T cells which can occur if the antigen presentation from the epithelial intestinal cells (which function as Antigen presenting cells) is incomplete due to the lack of co-stimulatory molecules.[3]
iii. Defect in the production of the regulatory T cells. The development of these cells is stimulated by external factors such as the intestinal homing of normal bacterial flora after birth. In fact 'germ free' mice are not able to develop normal OT.[4]

The third mechanism is important in man. In the GALT of adult men the IFNγ type cytokine pattern prevails.[5] During foetal life the cytokine pattern of Th2 cells prevails. This profile would limit damage to the placenta by Th1 cells and guarantee the success of pregnancy itself. If the Th2 profile persists after birth it could contribute to the lack of development of OT.[6,7] Microbial homing in the gut immediately after birth, producing inflammatory factors, is a strong stimulus to switch on a Th1 cell-response.[8,9]

The so-called 'hygiene' hypothesis assumes that a great antibacterial prophylaxis would favour an increase in allergies.[10] Some epidemiological studies have provided evidence that allergic children have a major intestinal colonisation of *lactobacillum* and *bifidobacterium*, whilst in non-allergic children *coliform bacteria* and *Staphyloccocus aureus* prevail.[11] Some studies have shown that the *bifidobacterium* homing in the gut of allergic children is delayed.[12] Nevertheless, not everything can be explained by the 'hygiene' hypothesis and the exact role carried out by the intestinal flora in the development of the allergy remains unexplained.

Another important factor to consider is the individual variability of the IgE-mediated immunological response. For instance, a polymorphism in the CD14 gene has been associated with high levels of IgE and food allergy.[13] Moreover, the molecule (TIM-1) encode by Havcr1 gene has shown to be associated with regulation of Th1 and Th2 immune responses. The knowledge of an association in humans of TIM-1 and atopy seems to open a new interpretation of the hygiene hypothesis.[14]

The digestion and absorption of allergenic proteins, could also have a great impact on allergic sensitisation. It has been observed that the transport of food allergens through the epithelial cells of the pre-sensitised gut favours the induction of allergic sensitisation, while on the other hand if the transport of these peptides occurs via the M cells of the Peyer patches the development of OT is favoured.[15] The characteristics of the allergenic proteins of foods in their natural form and after various types of technological food processing could influence digestion and absorption as observed in peanuts.[16]

CLASSIFICATION OF ADVERSE FOOD REACTIONS

In 1995, the EAACI position paper on food allergy established a simple and easy-to-apply classification of adverse reactions to food based on the pathogenetic mechanism (Figure 1).[17]

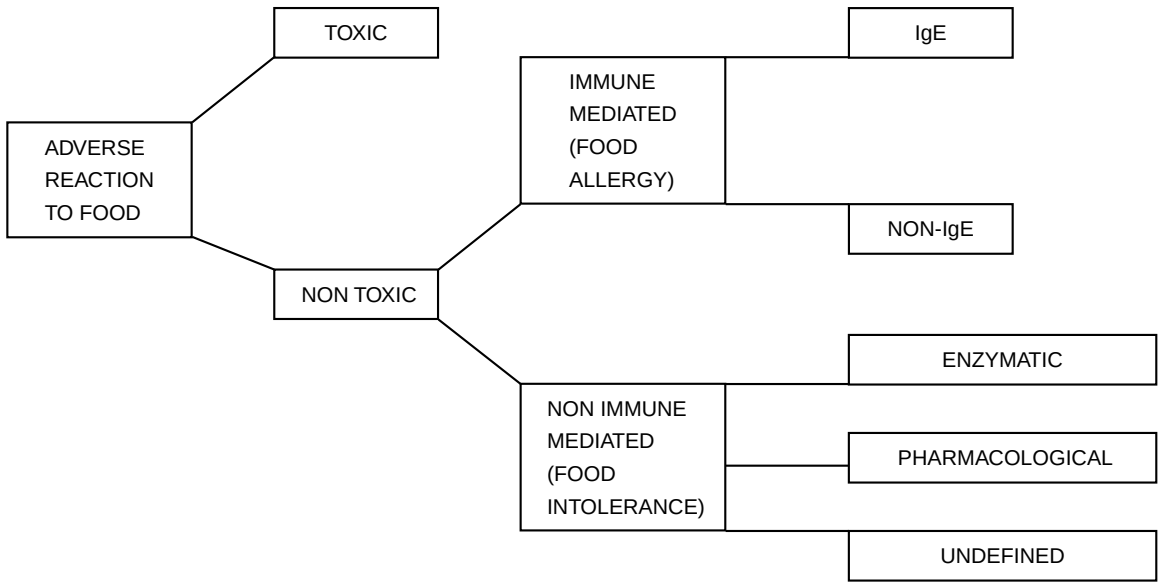

Figure. 1. Adverse reactions to Food EAACI classification.[16]

The first distinction is made between toxic and non-toxic adverse reactions to foods. Toxic reactions result from a primary harmful effect that the food has on all the individuals that eat it. Non-toxic reactions are those that take place in the presence of foods which are not tolerated by a few individuals.

Toxic food reactions

If food toxins are ingested in large quantities or on a frequent basis Toxic food reactions (TFR) can occur but are rather infrequent. In fact modern foods contain small amounts of toxins and dietetic variation does not allow accumulation. Toxins can be naturally present in foods, induced by food processing, or incorporated in food as contaminants or additives. Natural toxins from plants may be both endogenous and exogenous. Some examples of endogenous natural food toxins are glucosinolates in cabbage which have a goitrogenic effect; saxitoxin in shellfish which may cause dyspnoea, paralysis, or haemorrhages; and vaso-active amines, which are described in the subchapter Pharmacological intolerance. Exogenous toxins may result from food processing and storage. These include aflatoxins, found in peanuts and grains contaminated with mould which can cause encephalopathy, hallucinations, and hepatic disease; and nitrites which come from endogenous nitrates in green vegetables causing headaches, hepatic disease and methaemoglobinaemia. Traces of substances used for food production may remain in food, as methionine sulphoximine (bleaching agent),[18] trichloroethylene[19] (used in solvent extraction). TFR symptoms usually involve the Central Nervous System, producing headaches, hallucinations, blood and liver problems.[20]

Non-toxic adverse reactions

Non-toxic food reactions can be sub-divided into immunological (food allergy) and non-immunological (food intolerance); at the present these reactions are referred as: 'non-allergic food hypersensitivity'.[21] food allergy is subdivided into IgE-mediated and non-IgE-mediated.

Food allergy

IgE mediated food allergy. IgE-mediated reactions which constitute the majority of food allergic reactions have been the most well studied. If the OT is not developed there is production of specific IgE for some foods. IgE are linked to high affinity specific FCεRI receptors present on the mast cells, fixed cells present in the mucosa and skin, and basophils circulating in the blood. These cells have numerous cytoplasmic granules in which preformed mediators are stored, principally including histamine. When the allergenic proteins are absorbed in the gut they enter into contact with specific IgEs linked to mast cells/basophils. The conjugation of the IgEs with the allergens triggers a stimulus to these cells, which degranulate, release mediators in the surrounding micro-environment and synthesize new mediators (prostaglandins, leukotriens, cytokines). An immediate reaction follows few minutes after contact with the allergen, due mainly to the histamine. At the base of the reaction there is vasodilation, tissue fluid exudation, smooth muscle contraction and mucous secretion. A late-phase response follows the immediate reaction which begins 4–6 hours after contact with the allergen and continues for several days. This response is caused by chemotactic mediators released at the same time as the immediate reaction which promote selective recruitment of

inflammatory cells, mainly eosinophils and neutrophils, which infiltrate the tissue producing an inflammation lasting a few days.

The two clinical elements required to support an IgE-mediated food allergy are the presence of IgE specific antibodies to the culprit food and a proven relationship between ingestion of the food and the appearance of the symptoms.

Non-IgE-mediated food allergy. Non-IgE-mediated food allergy could consist of immune reactions depending on:

(a) antibodies, of different isotypes from IgE (i.e. IgG, IgM and IgA); (b) immune complexes formed by food and food antibodies; (c) cell-mediated immunity.

It is important to remember that there is no evidence to support the relationship between the culprit food and a reaction to non-IgE antibodies in any allergic disease. However, in normal individuals there is an increase in IgG food antibodies after ingestion of the food.[22] Likewise, there is no hard evidence that cell-mediated immunity is responsible for any allergic disease.

Food intolerance

The cause of intolerance could be an enzymatic defect or the effect of vaso-active pharmacological substances present in food (enzymatic and pharmacological intolerance). The reactions non-classifiable in any known mechanism are referred to as undefined food intolerance.

Enzymatic food intolerance. This is an adverse food reaction resulting from enzymatic defects of the gastrointestinal tract.

The symptoms manifest in the gastrointestinal tract after ingestion of certain foods. The most common one is lactose intolerance. This comes from a β-galactosidase deficiency common in adult populations. It can affect 6–12% of caucasians, but in some ethnic groups the prevalence can exceed 60%.[23] Lactose is a disaccharide composed of glucose and galactose. In the small intestine β-galactosidase facilitates the hydrolysis of lactose in the two monosaccharides which are then absorbed. In β-galactosidase deficiency lactose cannot be completely hydrolysed and the molecules reach the colon where they are degraded by bacteria in H_2O, CO_2 and H_2. The fermentation in the colon causes disturbances such as bloating, abdominal pain and sometimes diarrhoea.

Pharmacological food intolerance. Pharmacological food intolerance is caused by vasoactive amines and other substances present in foods, all of which manifest pharmacological activity. In most cases, there is a dose-effect relationship. Vasoactive amines include dopamine, histamine, norepinephrine, phenylethylamine, serotonin and tyramine.[24]

Histamine is a diamine and it is the chemical mediator of allergies. It is commonly thought that foods which contain high quantities of histamine may provoke symptoms similar to those of an allergic reaction. The histamine in the foods comes from degradation of the histidine by microrganisms and can be found in high quantities in cheese, alcoholic beverages, and fermented foods. Furthermore, intestinal bacteria can also decay histidine in histamine. Histamine is rapidly inactivated by the di-aminoxidase (DAO), largely produced in the gastroenteric tract. Therefore, the ingestion of large quantities of histamine does not produce disturbances in normal subjects. Nevertheless, some drugs or ingestion of other diamines can impair the DAO activity thus producing typical histaminic intoxication symptoms.

Table 1. Vasoactive monoamines which may produce pharmacological effects in intolerant patients.

Monoamine	Foods	Pharmacological effect	Symptoms
Dopamine	Broad beans, legumes	Sympathomimetic Release of noradrenaline endogena	Hypertension
Phenylethylamine	Fermented foods; red wine, cheese	Sympathomimetic Release of noradrenalina endogena	Migraine, hypertensive crisis and anti-MAO
Serotonin	Fruit, vegetables	Muscle vasodilation, vasoconstriction intra- and extra-cranica	Non-Myocardial fibrosis?
Tyramine	Cheese, yeast extract, wine, pickled herring, soya sauce	Sympathomimetic effect releasing norepinephrine	If anti-MAO is consumed: tachycardia, headache, hypertension

Such an example is the scombroid syndrome resulting from the ingestion of spoiled fish. Fish contains a lot of histidine which is transformed into histamine in the gut by bacteria. Additionally, two diamines produced in spoiled fish, putrescein and cadaverin, block the DAO. A histaminic effect then follows in the form of erythema, vasodilation, tachycardia, hypertension, migraine, vomiting and diarrhoea.[25] The symptoms generally resolve within a few hours. Mortality is very rare and generally depends on comorbidity, e.g. patients with coronary artery diseases may risk myocardial infarction.

A similar result can occur from taking DAO-inhibitor drugs. These include isoniazide, aminoguanidine, chloroquine, pentamidine, clavulanic acid, dobutamine, pancuronium, imipenem, and others. Another claim is that some foods have a histamine-releasing effect thus provoking symptoms. However, there is no evidence that histamine releaser foods can provoke any symptom in man.

A monoamine, tyramine is a protein derivative of tyrosine which is inactivated by the enzyme, monoaminoxidase (MAO). In absence of anti-MAO treatment (some anti-depressants), the ingestion of tyramine does not produce any symptoms. However, if ingestion of tyramine, or of other monoamines—(Table 1)—occurs during anti-MAO treatment symptoms such as tachycardia, hypertensive crisis, migraine, fever and hot flushes may be manifested.

Undefined intolerance. Intolerance resulting from non-identified mechanisms, such as food additive reactions, come under this name. The additives employed in food production, at the allowed doses, are Generally Recognised as Safe products (GRAS). However, some predisposed individuals may show intolerance reactions principally to sulphites, nitrites, nitrates, monosodium glutamate and some colourings. Possible symptoms are asthma, rhinitis, urticaria, itchiness, and migraines. The mechanisms of these intolerances are yet to be defined.

Psychosomatic reactions

Psychosomatic reactions to foods depend on a primitive mental disturbance in the individual affected. For this reason they have not been included in the EAACI

classification. In fact, many patients believe that they are allergic or intolerant to certain foods, solely on the basis of self persuasion.

Diseases of uncertain attribution to food allergy

The ascription to food allergy of certain diseases is controversial. In order to clarify the divergent opinions an EAACI PP has been issued which[25] arrives at the following conclusions:

There is not sufficient evidence to attribute chronic fatigue syndrome, neuropathy, mental disturbances, vasculitis, or arthritis to food allergy/intolerance;
There is some evidence that irritable bowel syndrome, serous otitis media, and migraines are rarely due to food allergy/intolerance.

Pseudoallergic reactions

Pseudoallergic reactions are non-immunological reactions that reproduce symptoms of allergic diseases. Only some of the many manifestations that are identified by this term depend on the release of histamine, other manifestations can be due to the release of other mediators.

They are not listed in the EAACI classification which refers to mechanisms. Ultimately, the term does not help in orienting the diagnostic procedure and treatment.

CLINICAL ASPECTS OF FOOD ALLERGY

The clinical manifestations recognised by the scientific community as being attributable to food allergy are basically those demonstrated in IgE-mediated sensitised patients by standardised challenge tests, DBPCFC.[26] IgE-mediated reactions involve the skin, the respiratory apparatus, the gastro-intestinal tract and the cardiovascular system. A very distinctive pattern of food allergy involves the unpredictability of the severity as well as the variability of the reactions. Consequently, a food usually causing a mild reaction can provoke a severe one if consumed after an aspirin, alcohol intake, ACE-inhibitors, or beta blockers or immediately before exercise.[27,28]

Acute urticaria/angioedema is one of the most frequent manifestations of food allergy. In a recent review, it was reported that a total of 710 out of 5622 patients with a positive food challenge reacted to the culprit food with acute urticaria; the foods mostly commonly involved being milk, egg, peanut, additives, mustard and cod.[29] Urticaria is usually linked to other symptoms involving the gastrointestinal or the respiratory apparatus.[30,31] *Chronic urticaria* is usually not associated with food allergy. *Contact urticaria* due to foods may be elicited by mucosal or skin exposure.

In *Atopic Eczema Dermatitis Syndrome* food allergy play an important role. The IgE antibodies bound to Langerhans cells play an important role as receptors, thus it is always important to look for the correlation with any form of sensitisation.[32,33] DBPCFC performed on affected patients demonstrated that food allergy play a pathogenic role in about 35–80% of children with moderate to severe atopic dermatitis. In half of the cases, the cutaneous symptoms were associated with gastrointestinal and

respiratory ones.[34] Milk, eggs, wheat and soy were demonstrated to be the most involved foods.

Gastrointestinal anaphylaxis arises in a sensitised person immediately after ingestion of the culprit food, producing nausea, abdominal pain, cramps, vomiting and diarrhoea. This is the most frequent syndrome of food allergy.[35] The same symptoms, whilst being chronic and possessing a progressive course, are the manifestations of *eosinophilic oesophagytis and gastroenteritis*, characterized by the infiltration of the oesophageal, gastric and/or intestinal wall with eosinophils. These diseases can be associated with food allergy, and in this case an elemental diet seems capable of reducing the infiltration and symptoms.[36]

The *oral allergy syndrome* (OAS) is a very common manifestation of food allergy especially in adults[37] allergic to tree pollen. This syndrome involves oral itching, lip swelling and laryngeal angioedema of the mouth and the pharynx upon contact with an allergenic food. Symptoms can also involve other organs and become more severe. There are four levels of increasing severity: 1, oral mucosal symptoms only; 2, oral mucosal plus gastrointestinal symptoms; 3, oral mucosal plus systemic symptoms (urticaria, rhino-conjunctivitis, or asthma); and 4, oral mucosal symptoms plus life-threatening problems (glottis edema, anaphylactic shock).[38]

Taking into account the symptoms reported in DBPCFC studies, level 1 occurred most commonly (80%), followed by level 3 (16%) and 2 (5%).[37]

Some rare diseases resulting from gastrointestinal food allergy are probably dependent on a cell-mediated mechanism.[39]

Food protein-induced proctocolitis; is a colitis with emission of numerous diarrhoeal discharges containing blood and thus entailing anaemia and loss of body weight; generally caused by allergy to cow's milk.

Food protein-induced enteropathy; it is very common during infancy, it occurs in the form of intestinal inflammation with loss of integrity of the villi and leads to malabsorption syndrome; when triggered by cow's milk it is generally defined as 'intolerance to cow's milk'.

Food protein-induced enterocolitis syndrome; provoking vomiting, diarrhoea, serious dehydration until cardiogenic shock, noted for allergy to soy and cereals.

Heiner's syndrome has been described as a disease which depends on IgG-mediated immunity to cow's milk proteins causing occult gut bleeding, anaemia and pulmonary hemosiderosis.

Asthma, especially poorly controlled asthma, is a risk factor for more severe and fatal food induced anaphylactic reactions.[40] Moreover, airway hyper-reactivity may be induced by food allergy in sensitised subjects. In one study, stable asthma was worsened when small amounts of food allergens were ingested by sensitised subjects.[41] Food allergy was a major risk factor for severe life-threatening asthma, in children, approximately 50% of asthmatic children that required intubation for severe asthma had food allergy compared with about 10% of asthmatics not requiring intubation.[42]

Anaphylaxis is a systemic IgE mediated reaction induced by the massive release of mast cell mediators targeting organs of the cutaneous, respiratory, gastrointestinal and cardiovascular systems. In the 1990's, food allergy was recognized as the most important cause of anaphylaxis outside the hospital.[40,43–46] Currently, there is no agreement on the definition of anaphylaxis. Consequently, the actual prevalence of this severe reaction is unknown even though many epidemiological studies have been conducted. Epinephrine is the medication of choice for treating anaphylaxis yet studies indicate that it is under-utilized.[47]

DIAGNOSIS

Diagnosis of IgE-mediated food allergy is based on history, objective examination, allergy tests, elimination diets and challenge tests.[17,26]

Medical history

Medical history is useful for dealing with reactions which are manifested immediately after the ingestion of a food; but less than 50% of clinical suspects are confirmed by DBPCFC. The following factors must be ascertained from medical history:

- The *latency* between the ingestion of the food and the appearance of the symptoms. The shorter the latency period the more reliable the assumptions made based on medical history.
- The *type of symptoms*. Symptoms of food allergy are OAS, conjunctivitis, rhinitis, asthma, glottis oedema, rash, urticaria/angioedema, vomiting, diarrhoea, anaphylactic shock. Eczema is a delayed symptom. There are contact reactions in skin or eyes and by inhalation. Some reactions appear only after physical exercise (exercise-induced food anaphylaxis).
- The *suspect food*. We can only suspect a culprit food if the reaction occurs a few minutes after ingestion. It is important to know previous food reactions.
- The *duration* of the symptoms. It is improbable that a reaction continuing many hours or days is due to a food allergy.
- The *reoccurrence* of the symptoms after ingestion of a food.

Diagnostic tests

The diagnostic accuracy of Skin Prick tests (SPT) with commercial extracts is extremely variable. In some cases, SPT using the food in its natural form (prick + prick) are more reliable, especially for plant food allergy.[47] The diagnostic accuracy of specific IgE is similar to that of SPT and varies according to the extract used.[48,49] In general, SPT remains the test of first choice since it provides immediate results which allow a direct clinical evaluation and it is cheaper than in vitro methods. Both methods can provide false positive results due to cross-reactivity. For example, subjects allergic to grasses commonly have IgE specifics to cereal flours, but without symptoms.[50] There have been some attempts to correlate IgE antibody levels to DBPCFC outcomes. Children suffering from atopic dermatitis in two studies provided diagnostic decision points (95% PPV) for some allergenic foods. Some confirming studies do not exist for atopic dermatitis whilst no studies exist for other allergic populations and other clinical situations. Additionally, DBPCFC is still the gold standard for diagnosis of certainty for IgE-mediated food allergy.[51,52]

Elimination diets

Elimination diets can be useful in patients with persistent symptoms. Foods testing positive to SPT/RAST and those suspected from history are excluded. Three weeks are usually sufficient to confirm the suspect of a food allergy. The result is considered

positive if a consistent improvement of the symptoms results. If the symptoms reappear when foods are reintroduced a DBPCFC must be performed.

DBPCFC

The Double Blind Placebo Controlled Food Challenge (DBPCFC) is the only validated test for the diagnosis of food allergy.[17] The rules of standardization of the correct procedure for the DBPCFC are described in an EAACI Position Paper.[53] Given that the method is complex and time consuming it is only applied in candidate patients for permanent avoidance of foods essential to diet such as milk, eggs, etc. It is contraindicated in patients with previous severe reactions to food in order to avoid life-threatening reactions. The food to be tested is administered dried or lyophilised in opaque capsules, or alternatively in its natural form masked by an inert base. The placebo consists of a capsule of the same appearance containing dextrose or an inert base consisting of foods, which are certain to be tolerated by the patient and allow an adequate masking of the food to be administered.

Non-IgE-mediated food allergy

Food patch tests (FPT) have been recently introduced for diagnosis of food allergies with delayed symptoms. In children suffering from atopic dermatitis with delayed reactions FPT does improve diagnostic accuracy, but not in the milk allergy of immediate type.[54,55] The method has not yet been validated or standardised for the purpose of routine diagnosis. Even though many studies have been conducted in order to evaluate the usefulness of lymphocytes proliferation and the cytokines increase after exposure in vitro to food allergens, there is no confirmation of their value in the routine diagnostic approach.

Lactose breath test

The diagnosis of lactose intolerance is based on the increase of H_2 in the breath after ingestion of lactose which is determined using a H_2 breath test analyser.

Non-validated methods

Many unproven methods (cytotoxicity tests, provocation and neutralization sublingual or subcutaneous, bioresonance, applied kinesiology, etc.) have been proposed and are used for diagnostic and sometimes therapeutic purposes in food allergy and intolerance. There is no scientific evidence to support the efficacy of any of these methods and in many cases it has been documented that their results do not differ from those obtained using placebo.

CROSS REACTIVITY

Allergen cross-reactivity is the phenomenon that occurs when IgE antibodies originally directed at the epitopes of one allergenic source recognize similar structures in another allergenic source. Cross-reactivity may be only in vitro, serological evidence, but it can also be clinically expressed. Up to now no diagnostic tests have been available to

determine whether an in vitro cross-reactivity will cause a reaction in vivo. Tropomyosin is the main allergenic protein in crustaceans (shrimps, lobster, crab, etc.) and molluscs and it is the principal cause of the wide cross-reactivity between these species.

It has been recently observed that more than 65% of plant food allergens belong to only four structural families, the cereal prolamin superfamily, the cupins, the Bet v 1 homologues and the profilins.[56] This could lead to extensive IgE cross-reactivity even among allergens belonging to taxonomically unrelated plants. Additionally, cross-reactive IgE binding can be retained by up to 35–40% of the amino acid sequence if the conformational structure is preserved. However, the in vitro IgE cross-reactivity is not always clinically expressed and can give rise to many false positive results with diagnostic tests; this implies that the elimination diet should never be based only on allergological tests, but always on the revision of clinical history supported in selected cases by appropriate challenge tests. It is therefore important to avoid predefined lists of foods which are cross-reactive with a give pollen or, even worse, foods containing one of the so-called 'panallergens'. Moreover, it is important not to forget that the majority of allergenic proteins in plants are widespread defensive molecules. To be allergenic a food must present some characteristics that are not related to its protein composition: the frequency of consumption by a given population, the thermal stability upon food preparation, the digestibility in relation to gastric or intestinal fluids.

From a practical point of view, we recognise three main cross-reactivity syndromes: the birch-fruit syndrome (sensitisation to birch pollen and foods such as apple, carrot, hazelnuts etc.), the latex-fruit syndrome (sensitisation to latex and foods such as chestnuts, avocado, banana) and the LTP syndrome (sensitisation to peach and other Prunoideae fruits, walnut, maize). The main elements defining a cross-reactivity syndrome are the presence of different symptoms related to the ingestion of several foods (such as respiratory symptoms to pollen inhalation or cutaneous symptoms due to contact with another substance) and the identification of a molecule that acts as a cross-reactive allergen. The allergens at the base of the symptoms in the three syndromes mentioned above are Bet v 1, Hev b 6.02, and lipid transfer proteins, respectively. In other clinical pictures of reactivity to multiple allergens the lack of identification of a specific cross-reactive allergen does not allow a proper definition of a nosological entity. The definition of a cross-reactivity syndrome also implies an epidemiological criterion as the symptoms due to cross-reactions must be clearly demonstrated in a considerable number of subjects, and not only in single case reports.

TREATMENT AND PREVENTIVE MEASURES

Treatment of food allergy consists of the complete elimination of the allergen from the diet. This may create a problem of nutritional deficiency which can be avoided by using vitamin and mineral supplements. Another problem is the possibility of not detecting the allergen to be avoided in commercial foods. It is therefore important that the patient pay attention to the labels of foods. Recently, the EC approved the Directive 2003/89/ EC with respect to labelling which amends the previous Directive and states that the presence of the 13 allergenic ingredients, listed in the Annex IIIa, in foods must be declared (Table 2).

Table 2. Ingredients referred to in the Directive 2003/89/EC which have to be declared in the labelling of food products.

Directive 2003/89/EC of The European Parliament and of The Council *Annex IIIa* *Ingredients Referred To In Article 6(3a), (10) And (11)*
Cereals containing gluten (i.e. wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and products thereof
Crustaceans and products thereof
Eggs and products thereof
Fish and products thereof
Peanuts and products thereof
Soybeans and products thereof
Milk and products thereof (including lactose)
Nuts, i.e. Almonds (*Amygdalus communis L.*), Hazelnuts (*Corylus avellana*), Walnuts (*Juglans regia*), Cashews (*Anacardium occidentale*), Pecan nuts (*Carya illinoiesis (Wangenh.) K. Koch*), Brazil nuts (*Bertholletia excelsa*), Pistachio nuts (*Pistacia vera*), Macadamia nuts and Queensland nuts (*Macadamia ternifolia*) and products thereof
Celery and products thereof
Mustard and products thereof
Sesame seeds and products thereof
Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre expressed as SO_2.

Specific immune therapy (SIT) for food allergens is not available. An experimental study of SIT using peanuts was suspended due to the level of adverse reaction being too high.[57]

New promising immunological approaches are being applied in the study of mice, one of these is based on the use of recombinant allergens engineered with modification of the epitopes, another employs the allergen mixed with heat killed listeria (HKL) as an adjuvant.[58,59]

An interesting kind of approach to prevent serious food allergic reactions employs humanized monoclonal anti-IgE antibodies. The antibodies connect to the IgE receptors on the mast cells without inducing cell degranulation and temporarily blocking the reaction. Preliminary reports indicate that anti-IgE therapy is able to significantly increase the quantity of peanut protein necessary to provoke allergy symptoms in subjects allergic to peanuts.[60] The use of anti-IgE therapy in conjunction with SIT could be a useful treatment in the future.

Acute food reaction therapy is based on anti-histamine drugs (anti H1), corticosteroids and in the case of life-threatening reactions, 1 M epinephrine. There is not an evident role for sodium chromoglycate.

Various researches have demonstrated that prolonged breastfeeding reduces the incidence of allergic diseases. In particular, a meta-analysis highlighted the reduction of atopic dermatitis in children predisposed to atopy who were breastfed for at least 3 months compared to children predisposed to atopy who were fed cow's milk[61] for the same period. Another study demonstrated the preventive effect of breastfeeding on the development of asthma in children.[62] On the base of this evidence both European and American guidelines[63,64] recommend exclusive breastfeeding for allergy-prone infants for 4–6 months and 6–12 months, respectively. American guidelines also advise mothers to avoid including peanuts and tree nuts from their diet during lactation.

Lactic acid bacteria (LAB) present in the human gut play a beneficial or probiotic role including the improvement of the local immune system. Scientists have attempted to

select strains of LAB with immunostimulatory properties to use against gut diseases (bacterial, cancer) or to improve gastrointestinal mucosal immunity and OT. Some beneficial effects on the prophylaxis of atopic dermatitis and other allergic diseases have been reported.[65,66] The role played by LAB on enhancement of gut and systemic immunity is supported by extensive evidence but the development of an effective and safe mucosal vaccine of LAB requires more basic knowledge on the gut antibody response and on the pharmacokinetic of LAB vaccines.[67] In conclusion, more studies need to be done before considering routine use of probotics in the prevention and therapy of allergic disease.

Practice points

- embracing the EAACI classification based on pathogenesis has improved the comprehension of Adverse Reactions to food
- an adverse food reaction can only be confirmed when the relationship between food ingestion and symptoms has been proven. A confirmed AFR can only be classified as food allergy if SPT/RAST to the culprit food is positive
- ingestion of food rich in histamine generally does not produce disturbances
- gastrointestinal anaphylaxis and oral allergy syndrome are the most common manifestations of food allergy
- epinephrine is the medication of choice for anaphylaxis
- the DBPCFC remains the only test which has been validated for diagnosis of food allergy
- the only treatment of food allergy consists of the complete elimination of the allergen from the diet
- prolonged breast feeding reduces the incidence of allergic diseases

Research agenda

- the role carried out by intestinal flora and regulatory T cells in the development of allergy must be further studied
- an agreement on the definition of anaphylaxis must be reached
- controlled studies need to be done in order to validate an in vitro test which could substitute the DBPCFC
- epidemiological and clinical studies are necessary for identification of the threshold dose of anaphylaxis (Non-Observed Adverse Effects Level) in different enhancing conditions in order to improve the safety of food labelling
- new models of SIT, possibly combined with anti-IgE treatment, must be developed

SUMMARY

The EAACI classification of adverse reactions to food based on pathogenesis allows a clear understanding of these diseases. There is sufficient evidence to support

IgE-mediated food allergy based on many controlled studies, some randomised, that have applied DBPCFC.

Symptoms can be clearly defined for every disease classified as IgE-mediated food allergy from the results of studies based on DBPCFC.

Food intolerance is less clearly defined with the exception of lactose intolerance which can be precisely diagnosed using the Breath Test.

The diagnosis of both food allergy and food intolerance must be based on the demonstration that they are real harmful effects of the suspected food. This demonstration can only be obtained by submitting the patient to DBPCFC. Skin and sierological tests can only confirm that the allergy is IgE-mediated. Studies have been done to establish the cut-off values of specific IgE which may render DBPCFC unnecessary but they have not yet been confirmed.

The only efficient treatment for IgE-mediated food allergy (and intolerance) is the absolute exclusion of the culprit food from the diet, even in ingredient form. The correct application of the new European Directive for labelling will prevent the risk due to hidden allergenic ingredients in commercial foods. The SIT is not currently available. An important norm of primary prevention for newborns prone to allergy is exclusive breastfeeding for at least the first 6 months. There are interesting results regarding the role of probiotics in the promotion of a normal immunological state of the GALT but a validation of these vaccines does not yet exist.

REFERENCES

1. Mowat AM. The role of antigen recognition and suppressor cells in mice with oral tolerance to ovalbumin. *Immunology* 1985; **56:** 253–260.
2. Chen Y, Inobe JI, Marks R et al. Peripheral deletion of antigen-reactive T cells in oral tolerance. *Nature* 1995; **376:** 177–180.
3. Hoyne GF, Le Roux I, Corsin-Jimenez M et al. Serrate1-induced notch signalling regulates the decision between immunity and tolerance made by peripheral CD4 (+) T cells. *Int Immunol* 2000; **12:** 177–185.
4. Sudo N, Sawamura S, Tanaka K et al. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol* 1997; **159:** 1739–1745.
5. Mac Donald TT & Monteleone G. IL-12 and Th1 immune responses in human peyer patches. *Trends Immunol* 2001; **22:** 224–247.
6. Wegmann TG, Lin H, Guilbert L & Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a T_H2 phenomenon? *Immunol Today* 1993; **14:** 353–356.
7. Holt PG, Sly PD & Bjorksten B. Atopic versus infesctious diseases in childhood: a question of balance? *Pediatr Allergy Immunol* 1997; **8:** 53–58.
8. * Romagnani S. The role of lymphocytes in allergic disease. *J Allergy Clin Immunol* 2000; **105:** 399–408.
9. Neurath MF, Finotto S & Glimcher LH. The role of Th1/Th2 polarization in mucosal immunity. *Nat Med* 2002; **8:** 567–573.
10. Strachan DP. Hayfever, hygiene and household size. *BMJ* 1989; **299:** 1259–1260.
11. Björksten B, Naaber P, Sepp E & Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish infants. *Clin Exp Allergy* 1999; **29:** 342–346.
12. Ouwehand AC, Isolauri E, He F et al. Differences in Bifidobacterium flora composition in allergic and healthy infants. *J Allergy Clin Immunol* 2001; **108:** 144–145.
13. Woo JG, Assa'ad A, Heizer AB et al. The -159 C→T polymorphism of CD14 is associated with nonatopic asthma and food allergy. *J Allergy Clin Immunol* 2003; **112**(2)**:** 438–444.
14. Umetsu SE, Lee WL, McIntire JJ et al. TIM-1 induces T cell activation and inhibits the development of peripheral tolerance. *Nat Immunol* 2005; **6:** 447–454.

15. Santos LM, al-Sabbagh A, Londono A & Weiner HL. Oral tolerance to MBP induces regulatory TGBβ secreting T cells in peyer patches of SJL mice. *Cell Immunol* 1994; **157:** 439–447.
16. Chambers SJ, Wickham MS, Regoli M et al. Rapid in vivo transport of proteins from digested allergen across pre-sensitized gut. *Biochem Biophys Res Commun* 2004; **325:** 1258–1263.
*17. Bruijnzeel-Koomen C, Ortolani C, Aas K et al. Position paper of the European academy of allergology and clinical immunology on adverse reactions to food. *Allergy* 1995; **12:** 357–378.
18. Swanson RA, Shiraishi K, Morton MT & Sharp FR. Methionine sulphoximine reduces cortical infarct size in rats after middle cerebral artery occlusion. *Stroke* 1990; **21:** 322–327.
19. Vernon RJ & Ferguson RK. Effect of trichloethlyne on visual motor performance. *Arch Environ Health* 1969; **18:** 894–900.
*20. May CD. Immunologic versus toxic adverse reactions to foodstuffs. *Ann Allergy* 1983; **51:** 267–268.
21. Johansson SG, Hourihane JO, Bousquet J et al. Position paper. A revised nomenclature for allergy. An EAACI position statem from the EAACI nomenclature task force. *Allergy* 2001; **56:** 813–824.
22. Paganelli R, Quinti I, D'Offizi GP et al. Immune-complexes in food allergy, a critical reappraisal. *Ann Allergy* 1987; **59:** 157–161.
23. Suarez FL & Savaiano DA. Diet, genetics, and lactose intolerance. *Food Technol* 1997; **51:** 74–76.
24. Fritz SB & Baldwin JL. Pharmacologic food reactions. In Metcalfe DD, Sampson HA & Simon RA (eds.) *Food Allergy: Adverse Reactions to Foods and Food Additives*, 3rd edn. Malden, MA: Blakwell Science, 2003, pp. 395–407.
25. Maire R, Dreiding K & Wyss PA. Incidence and clinical aspects of scombroid fish poisoning. *Schweiz Med Wochenschr* 1992; **122**(50)**:** 1933–1935.
*26. Ortolani C, Bruijnzeel Koomen CA, Bengtsson B et al. Controversial aspects of adverse reactions to food. European Academy of Allergology and Clinical Immunology (EAACI) reactions to food subcommittee. *Allergy* 1999; **54:** 27–45.
*27. Sampson HA. Food allergy—accurately identyifing clinical reactivity. *Allergy* 2005; **60**(supplement 79)**:** 19–24.
28. Matsuo H, Morimoto K, Akaki T et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2005; **35:** 461–466.
29. Mullins RJ. Anaphylaxis: risk factors for recurrence. *Clin Exp Allergy* 2004; **33:** 1033–1040.
30. Bindslev-Jensen C & Oesterballe M. Food-induced urticaria and angioedema. In Metcalfe DD, Sampson HA & Simon RA (eds.) *Food Allergy: Adverse Reactions to Foods and Food additives*, 3rd edn. Malden, MA: Blakwell Science, 2003, pp. 160–168.
31. Scibilia J, Pastorello EA, Zisa G, et al. Wheat allergy: a double blind, placebo-controlled study in adults. *J Allergy Clin Immunol*; in press.
32. Bieber T, Kraft S, Jugeng M et al. New insights in the structure and biology of the high affinity receptor for IgE (FcεRI) on human epidermal Langerhans cells. *J Dermatol Sci* 1996; **13:** 71–75.
*33. Sampson HA & Sicherer SH. Eczema and food hypersensitivity. *Immunol Allergy Clin North Am* 1999; **19:** 495–518.
34. Niggemann B, Sielaff B, Beyer K et al. Outcome of double blind placebo controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; **29:** 91–96.
35. Sampson HA, Sicherer SH & Birnbaum AH. AGA technical review on the evaluation of food allergy in gastrointestinal disorders. American Gastroenterological Association. *Gastroenterology* 2001; **120:** 1026–1040.
36. Rothenberg ME. Eosinophilic gastrointestinal disorders (EGID). *J Allergy Clin Immunol* 2004; **113:** 11–28.
*37. Pastorello EA & Ortolani C. Oral allergy syndrome. In Metcalfe DD, Sampson HA & Simon RA (eds.) *Food Allergy: Adverse Reactions to Foods and Food Additives*, 3rd edn. Malden, MA: Blakwell Science, 2003, pp. 169–182.
38. Pastorello EA, Farioli L, Pravettoni V et al. The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 1999; **103:** 520–526.
39. Nowak-Wegrzyn A. Food protein-induced enterocolitis, enteropathy, and proctocolitis. In Metcalfe DD, Sampson HA & Simon RA (eds.) *Food Allergy: Adverse Reactions to Foods and Food Additives*, 3rd edn. Malden, MA: Blakwell Science, 2003, pp. 227–241.
40. Pumphrey RS. Fatal anaphylaxis in the UK, 1992–2001. *Novartis Found Symp* 2004; **257:** 116–128.

41. James JM, Bernhisel-Broadbent J & Sampson HA. Respiratory reactions provoked by double-blind placebo controlled food challenges in children. *Am J Respir Crit Care Med* 1994; **149:** 59–64.
42. Roberts G, Patel N, Levi Schaffer F et al. Food allergy as a risk factor for life threatening asthma in childhood: a case controlled study. *J Allergy Clin Immunol* 2003; **112:** 168–174.
43. Yocum MW & Khan DA. Assessment of patients who have experienced anaphylaxis: a 3-year survey. *Mayo Clin Proc* 1994; **69:** 16–23.
44. Kemp SF, Lockey RF, Wolf BL & Lieberman P. Anaphylaxis. A review of 266 cases. *Arch Intern Med* 1995; **155:** 1749–1754.
45. Cianferoni A, Novembre E, Mugnaini L et al. Clinical features of acute anaphylaxis in patients admitted to a university hospital: an 11-year retrospective review (1985–1996). *Ann Allergy Asthma Immunol* 2001; **87:** 27–32.
46. Helbling A, Hurni T, Mueller UR & Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004; **3:** 285–290.
*47. Sampson HA, Munoz-Furlong A, Bock SA et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005; **115:** 584–591.
48. Ortolani C, Ispano M, Pastorello EA et al. Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989; **83:** 683–690.
49. 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.
50. Jones SM, Magnolfi CF, Cooke SK & Sampson HA. Immunologic cross-reactivity among cereals grains and grassesin children with food hypersensitivity. *J Allergy Clin Immunol* 1995; **96:** 341–351.
51. Sampson HA. Utility of food specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; **107:** 891–896.
52. Garcia-Ara C, Boyano-Martinez T, Diaz-Pena JM et al. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk protein in the infant. *J Allergy Clin Immunol* 2001; **107:** 185–190.
*53. Bindslev Jensen C, Ballmer-Weber BK, Bengtsson U et al. Standardization of food challenges in patients with immediate reactions to foods—position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004; **59**(7)**:** 690–697.
54. Isolauri E & Turnjanmaa K. Combined skin prick and patch testingenhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; **97:** 9–15.
55. Roher CC, Reibel S, Ziegert M et al. Atopy patch test, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; **107:** 548–553.
*56. Jenkins JA, Griffiths-Jones S, Shewry PR et al. Structural relatedness of plant food allergens with specific reference to cross reactive allergens: an in silico analysis. *J Allergy Clin Immunol* 2005; **115:** 163–170.
57. Nelson HS, Lahr J, Rule R et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanuts extract. *J Allergy Clin Immunol* 1997; **99:** 744–751.
58. Sampson HA. Immunological approchaes to the treatment of food allergy. *Pediatr Allergy Immunol* 2001; **12**(supplement 14)**:** 91–96.
59. Yeung VP, Gieni RS, Umetsu DT & De Kruyff RH. Heat-killed Listeria monocytogenes as an adjuvant converts established murine TH2-dominated immune responses into TH1-dominated responses. *J Immunol* 1998; **161:** 4146–4152.
*60. Leung DJ, Shanahan Jr. WR & Sampson HA. New approaches for the treatment of anaphylaxis. *Novartis Found Symp* 2004; **257:** 248–260.
61. Gdalevich M, Mimouni D, David M & Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001; **45:** 520–527.
62. Oddy WH, Holt PG & Sly PD. Association between breastfeeding and asthma in 6 year old children: findings of a prospective birth cohort study. *Br Med J* 1999; 815–819.
63. Host A, Koletzko B, Dreborg S et al. Joint statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committe on Hypoallergenic Formulas and the European Society for Peaediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. Dietary products used in infants for treatment and preventionof food allergy. *Arch Dis Child* 1999; **81:** 80–84.

64. American Academy of Pedriatics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000; 106: 346–349.
65. Majamaa H & Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997; **99:** 179–185.
66. Kalliomaki M, Salminen S & Arvilommi H. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001; **357:** 1076–1079.
67. Perdigon G, Fuller R & Raya R. Lactic acid bacteria and their effect on the immune system. *Intest Microbiol* 2001; **2:** 27–42.