Food allergy : a challenge for the clinician

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Abstract

Adverse reactions to food resulting in gastrointestinal symptoms and due to immunologic reactions (allergy) are discussed : their pathogenesis, the prevalence of food allergens and the clinical digestive expressions of food allergy in children and adults are reviewed. In IgE-mediated food allergy, the usefulness of the biological available tests is considered, mainly CAP tests, for proceeding to the diagnosis and the monitoring of the allergic disease. Finally, the best actual diagnostic tools in food allergy are considered (clinical history, skin tests, biological tests and food oral challenges), with their limitations and indications. (Acta gastroenterol. belg., **2006**, 69, **38-42**).

Introduction

Adverse reactions to food resulting in gastrointestinal symptoms are common in the general population but only a minority correspond to immunologic reactions, i.e. truly food allergy (1). These immune reactions are mediated by immunoglobulin E-dependent and –independent mechanisms. It is estimated that in Europe and the USA 2-3.2% of adults and 7.5-8% of children present IgE-mediated food allergies (2,3). It is thus important to know the spectrum of adverse reactions potentially induced by food allergies, to correctly diagnose and manage these patients.

Non-allergic food hypersensitivity can be due to metabolic disorders of the host (eg, lactase deficiency) or to toxic reactions to some compounds present in food such as toxic contaminants (eg, histamine in scromboid fish poisoning) or pharmacologic substances within the food (eg, tyramine or histamine) which can affect most healthy individuals when given in large enough doses.

In the meeting held by the *Société Royale Belge de Gastro-Entérologie* on October 15th 2004 in Brussels, part of the program was devoted to food allergy. During this session*, the clinical digestive manifestations were recalled, the specificity and sensitivity of in vitro diagnostic tests were discussed and finally, the best actual diagnostic tools for food allergy in children and adults were highlighted.

(* Invited speakers : Grand J.L., Liège ; Kochuyt A.M., Brussels ; Moneret-Vautrin D.A., Nancy-France and Pirson F., Brussels).

Pathogenesis of food allergy

Food allergy is due to an abnormal response of the mucosal immune system to antigens delivered through the oral route. The mucosal immune system is in daily contact with enormous quantities of antigens without reacting to harmless foreign antigens. The gastrointestinal mucosal barrier is a very large surface area for processing and absorbing ingested food and discharging waste products. With the innate (natural killer cells, polymorphonuclear leukocytes, macrophages, epithelial cells, digestive enzymes, peristaltic movement, and toll-like receptors) and adaptative (lymphocytes, Peyer's patches, sIgA, cytokines) immune system, the mucosa contributes to provide an active barrier to foreign antigens. The immature state of the mucosal barrier is one cause of increased prevalence of gastrointestinal infections and food allergy in the young children. Even with a normal mucosal barrier, 2% of the ingested food antigens are absorbed and transported throughout the body in an immunologically intact form. Tolerance develops in most individuals (role of regulatory T cells, epithelial cells and dendritic cells). The commensal gut flora is probably also important in the induction of oral tolerance.

Sensitization to food allergens can occur in the gastrointestinal tract (class 1 food allergy) or be a consequence of cross-sensitization between a food antigen and an inhalant allergen that acts as the first sensitizer (class 2 food allergy). In this later option, the food allergic symptoms may nevertheless precede the allergic respiratory manifestations. The distribution of prevalence of food allergens is quite different between children and adults and is modulated by cultural and geographical dietary influences. The recent prevalence of food allergens among children and adults in the United States is presented in *table 1* and among populations of children and adults in France in *figure 1* (2,3). In children, the food allergens are most often from animal origin (milk, egg, fish) with one exception for peanuts whereas vegetal allergens are most often responsible of allergic reactions among the adult population.

Food allergy is partly genetically determined and is often associated with a personal or a family history of atopic disorder. In the epidemiologic study conducted among the French population (less than 61 yrs old)

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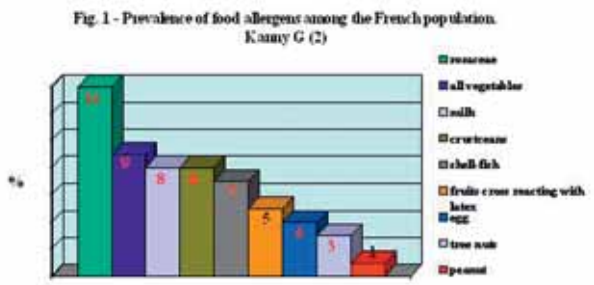

Fig. 1. — In this French epidemiological carried out on 33,110 subjects who answered a questionnaire addressed to 44,000 French subjects aged ≤ 60 years, representative sample of the French population on a scale of 1:1000, the most frequent allergens were of plant origin : Rosaceae fruit, 14% ; all types of vegetables (e.g., umbelliferae and leguminosae), 9% ; milk, 8% ; crustaceans, 8% ; shellfish, 7% ; fruit cross-reacting with latex, 5% ; egg, 4% ; and tree nuts, 3%. Peanut alone represented 1% of food allergens.

Table 1. — **Prevalence of food allergens in the United States (3)**

Food	young children	adults
Milk	2.5%	0.3%
Egg	1.3%	0.2%
Peanut	0.8%	0.6%
Tree nuts	0.2%	0.5%
Fish	0.1%	0.4%
Shellfish	0.1%	2.0%
Overall	6%	3.7%

between 1997 and 1998, 57% of subjects with food allergies presented with a past or active atopic disease versus 17% of the control population (2).

Some children with food allergy will outgrow their hypersensitivity : 80% of children who developed cow's milk allergy in their first year of life become tolerant before their 5th birthday. But the emerging tolerance is not the rule for all the allergens : eg, most of the young patients with peanut IgE-mediated allergy will keep their sensitization in their adult life (2).

Clinical manifestations of food allergy

Allergic reactions mediated by food-specific IgE antibodies usually result in symptoms that occur soon (between minutes to 2 hours) following ingestion while cell-mediated disorders may present with chronic manifestations or with a delayed onset (hours or days).

The effects of food allergy are reported in *table 2* following the end-organ affected, the mechanism involved and the age of the patient (4).

Gastroenterical allergic disease IgE-mediated

The oral allergy syndrome is extremely frequent, affects adults and children and is elicited by plant proteins cross reacting with inhalant allergens, especially birch or grass pollens. Approximately 40-50% of patients sensitized to birch pollens present oro-labial pruritus or lips swelling or itching of tongue or pharyngeal mucosa when eating raw apple, pear, plum, peach, cherry, carrots, celery, potatoes, hazelnuts and kiwi. The symptoms are generally present within 1 to 5 minutes after the ingestion. Patients with grass pollen allergy might have symptoms when eating raw tomatoes. The allergens responsible of these manifestations are generally destroyed by heating or gastric enzymes and the symptoms are generally limited to the oral or pharyngeal mucosa : the risk of gastrointestinal anaphylaxis (nausea, vomiting, colicky abdominal pain, diarrhoea) with these allergens is low, between 5 to 8%, and generally associated to manifestations in other target organs.

Gastroenterological allergic diseases associated with eosinophilic infiltration

First, other diseases associated with eosinophilic infiltrations have to be excluded like parasitosis, drug toxicity, connectivitis, inflammatory bowel diseases, idiopathic hypereosinophilic syndrome.

Three allergic diseases are considered here :

– eosinophilic oesophagitis, essentially in children presenting symptoms of gastro-oesophageal reflux not improved after standard treatment. The Ph-metry is normal but the mucosal biopsies revealed > 20-24 eosinophils (40× power)
– eosinophilic gastroenteritis : is characterized by the infiltration of the oesophagus, stomach and/or the intestinal walls with eosinophils. It may be due to IgE-mediated food allergy, non IgE-dependant food allergy or both. Peripheral hypereosinophilia is not always associated. It can occur at any age with different symptoms following the location of the involvement : diarrhoea, vomiting, abdominal pain, blood loss in the stools, iron-deficiency anaemia, weight loss, and protein-losing enteropathy.
– eosinophilic proctocolitis : disorder due to non IgE-mediated food allergy seen in young infants, generally in the first few months of life. Symptoms are generally induced by cow's milk or soy protein-based formulas but these babies might be sensitized to food proteins passed in the breast milk. The main symptom is the presence of blood in the stools (macro-or microscopically) while the infants appear healthy. The lesions are localized to the distal large bowel with mucosal oedema, eosinophilic infiltration in the epithelium and lamina propria. It could be a particular form of protein-induced proctocolitis.

Protein-induced enterocolitis syndrome

It's a cell-mediated hypersensitivity disorder affecting generally infants before 3 months of age (or later if they are breast-fed). The symptoms are often induced by cow's milk or soy protein-based formulas. Breast-fed babies might be sensitized to food proteins passed in the

Table 2. — **End-organ effects of food allergy (4)**

Organ	Disease/Symptoms	IgE-mediated	Afflicted age group
GI tract	Immediate GI hypersensitivity	+++	all
	Oral allergy syndrome	+++	children, adults
	Eosinophilic gastroenteropathies	+	all
	Eosinophilic oesophagitis	+	infants, children
	Eosinophilic gastritis	+	all
	Eosinophilic enterocolitis	+	all
	Eosinophilic proctitis	+	infants, children
	Dietary protein enterocolitis and proctitis	–	infants
	Chronic constipation	–	children
	Dietary protein enteropathy	–	infants
	Celiac disease	–	children, adults
	Irritable bowel syndrome	?	adults
Respiratory	Rhinitis	++	all
	Asthma	++	all
	Alveolitis	+	all
Skin	Urticaria and angiooedema	++	all
	Atopic eczema	+	infants, children
	Dermatitis herpetiformis	–	children, adults
Cardiovascular-	Vasculitis	+	all
	Systemic anaphylaxis	+++	all

breast milk and present reactions later on the first absorption of the whole food.

Three presentations are considered here :

– food-protein induced enterocolitis : prolonged vomiting beginning between 1 and 3 hours after the allergen ingestion (cow's milk and soy proteins essentially in infants, shellfish in adults). Abdominal distension and diarrhoea may be observed 5-8 hours later. Hypotension may be present among 15% of them. An elimination diet during 2-3 days followed by a challenge test with recurrent symptoms confirms the diagnosis.
– Food protein-induced enteropathy : appears in the first months of life and the symptoms are poor weight gain and diarrhoea. It is induced by cow's milk, rarely by egg, soy or cereals. The ileal biopsy reveals a Th1 Lymphocyte infiltration, villous atrophy or thickening.
– Food protein-induced proctocolitis : affects generally babies before they are 4 months old with symptoms of bloody stools or diarrhoea. The inflammatory infiltration is localized to the rectosigmoid segment of the large bowel with 6-20 eosinophils at power 40× histologic examination. The elimination diet of the suspected food (cow's milk, soy, egg, wheat), clears the symptoms in 2-3 days.

The celiac disease is a more extensive enteropathy leading to malabsorption. It is associated with a non IgE sensitivity to gliadin found in wheat, barley and rye. The HLA-DQ2 is present in more than 90% of the celiac patients (5).

Biological tests for IgE-mediated food allergy

It is well known that the skin prick tests (SPT) with foods and particularly SPT with fresh foods have a higher sensitivity than the determination of specific IgE (sIgE) or CAP tests (Sweden Diagnostics) to foods. Whether the SPT investigate the presence of food sIgE bound to mast cells and the capacity of the allergen to cause cross linking of these sIgE for inducing mast cell degranulation and thus clinical reactivity, the CAP tests only measure circulating food sIgE but are not indicative of the clinical relevance of these sIgE.

Food allergens are a mixture of (glyco)proteins of which some are resistant to heat and digestion (*stable* allergen) and others are not (*unstable*) but all may act as allergens and bind sIgE.

Many of the pollen-related food hypersensitivities with immediate oropharyngeal or oesophageal symptoms are associated with false negative CAP tests (low sensitivity) because these allergens (unstable) may be lost during the extraction procedures. Allergy to stable

allergens like in animal foods or plant foods inducing anaphylaxis, cutaneous, gastrointestinal or respiratory symptoms is generally associated with true positive CAP tests. Thus the sensitivity of the CAP tests depends on the type of food and, for this food, on the type of allergen (unstable or stable) recognized and may also be influenced by geographical factors. So, the sensitivity of CAP tests with birch pollen associated foods is very low. It is quite higher with latex associated food allergens and house dust mite crossed food allergens (snail and shellfish). The sensitivity of the CAP tests with primary food allergens (stable) like nuts, peanut, legumes, milk, egg, meat and cereals is good.

The specificity of the CAP tests with food is influenced by the existence of cross reactivity. These cross reactions between allergens are due to the presence in these allergens of homologous structures that bind the same IgE antibodies. The term "cross sensitization" indicates that the SPT and/or CAP tests are positive for different allergens due to the presence of cross reactive IgE and when this cross sensitization is clinically relevant the term "cross allergy" is used. Cross reactive IgE can be directed to peptides and these IgE may be clinically relevant. But cross reactive IgE can be also directed to carbohydrates and these antibodies are not clinically relevant even if they cause multiple false positive CAP tests. A primary sensitization to peptides in foods often causes cross allergy to phylogenetic related (particularly with animal) foods. For plant foods, the prevalence of secondary pollen associated sensitizations is higher due to the increasing prevalence of inhalant allergies : in this situation, cross sensitization is more frequent than cross allergy with little or no clinical relevance because these allergens are unable to cause mast cell degranulation. A good example is the presence of IgE for "panallergens" such as profilins present in a wide range of plants and vegetable foods but with low or no biological activity. Carbohydrate determinants are presents in pollens, vegetable foods and insect venoms : the presence of IgE to such panallergens results in multiple false positive CAP tests : the specificity of CAP tests with plant foods is low in patient with a pollen or insect venom allergy.

There is a poor correlation between the absolute sIgE level to a particular food and the severity of the reaction observed after ingestion of that food. Moreover, the intensity of the symptoms may be influenced by the intake of drugs like non steroidal anti-inflammatory drugs, ACE inhibitors, b-blockers or by the association with exercise, ingestion of alcohol and by the amount or combination of food allergens ingested.

It is also important to measure sIgE simultaneously with total IgE : low total IgE levels are often associated with borderline positive CAP tests which nevertheless may be clinically relevant ; on the other hand, very high total IgE levels are often associated with high sIgE levels and may cause non specific IgE binding to the CAPs with false positive CAP tests.

Actually, there are no data which prove in a scientific way that food sIgG antibodies are pathogenic or can cause food allergic disease in adults. The presence of IgG to a particular food is indicative for exposure to that food : IgG to common dietary antigens can be detected in healthy and sick people. The determination of food-specific IgG is not clinically relevant.

The best diagnostic tools in food allergy

The clinical history is probably the best useful and sensitive tool to suspect a food allergy in a patient. It is very important to spend enough time to investigate the sequence of clinical digestive manifestations, the eventual associated symptoms, and the relation with the suspected allergens intake, the effect of a dietary eviction test and the evolution of the symptoms after the food reintroduction. It is quite easy to suspect cross allergic disease, in particular with inhalant allergens by looking for signs of rhino-conjunctivitis, asthma. The chronology of the symptoms and the type of clinical manifestation may often suggest the allergic mechanism involved. With all these data, the next step is to perform the skin tests (prick tests with food and inhalant allergens, prick-by-prick tests with fresh foods for IgE-mediated allergy and atopy patch tests for cell-mediated allergy). A positive SPT is just a proof of IgE sensitization to this allergen but doesn't sign the diagnosis of IgE clinical allergy. The gold standard procedure to make a diagnosis of food allergy is to perform a double-blind, placebo- controlled food challenge test (DBPCFCT) that needs first a period of eviction of the suspected allergen, followed by it's blinded oral reintroduction in a hospital with a continuous and specific medical assistance (with a blinded challenge with placebo on a separate day). In this test, the masked suspected food is progressively ingested up to the observation of a clinical objective adverse effect and this is also the best way to establish the critical dose for the patient developing symptoms (6).

For some allergens (peanut, milk, soy, egg, wheat), in population of allergic children ($\leq$ 2 yrs, $\leq$ 14 or $\leq$ 16 yrs following the studies), the measurement of food specific IgE antibodies were useful to establish decision points allowing prediction of clinical relevance (positive predictive value of 95% and 99%) : thus, when the determination of specific IgE concentration in the serum is equal or higher than the corresponding threshold level, the DBPCFCT is unnecessary. This is valid only for the population studied and may be submitted to geographical variations (7,8,9). The threshold levels were also established for SPT to foods (cow's milk, hen's egg, peanut) with a positive predictive value of 90 to 100% in different populations of allergic children (10,11,12).

The atopy patch tests (epicutaneous skin tests performed with immediate type allergens) are also interesting to explore the late food allergic manifestations like atopic dermatitis (13,14) and to identify the causative food in eosinophilic oesophagitis (15).

Finally, more recently, based on the monitoring of food sIgE levels in children allergic to cow's milk and hen's egg, a model was established for predicting the likelihood of developing tolerance based on the decrease in food sIgE over time. Using this model, the clinicians can provide prognosis information and in timing subsequent food challenges, thereby decreasing the number of premature and unnecessary DBPCFCT (16).

Conclusion

The better understanding of pathogenesis, the knowledge of the multiple clinical expressions of food allergy, their evolution over time and the emerging data of the studies performed let us hope that in the next future the clinicians will have a panel of precise and useful diagnostic tests. But this needs a rigorous methodology for evaluating the food allergic manifestations, identifying the culprit foods and establishing by this way the best dietary regimen able to correct the clinical disease. Indeed, up to now, the most effective treatment is the total eviction of the allergenic foods. Once the diagnosis is established, the patient has to be monitored by repeated skin tests, sIgE measurements and limited DBPCFCT over time for predicting the development of food tolerance.

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