

Gastrointestinal allergy in adults

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The prevalence of food allergy reaches 3% in the adult population. Chronic gastrointestinal allergy is a rare entity: 4.2% of food allergies in adults, and represents 3.2% of all intestinal disorders. Non-specific symptoms are the rule but eosinophilic gastrointestinal disorders are the subject of much interest. Endoscopy and biopsies of the gastrointestinal tract help the differential diagnoses. Food allergy is suspected from the patient's history leading to skin tests and laboratory tests identifying a sensitization but allergy is only confirmed by standardized challenges or eviction diets over a sufficiently long period. New types of investigations coupling oral challenges to foods to gastroenterological techniques should be studied further. *Eur J Gastroenterol Hepatol* 17:1293–1297 © 2005 Lippincott Williams & Wilkins.

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Introduction

Food allergy has emerged in a spectacular fashion over the past 20 years. Characterized by a group of signs related to particular food allergens, it now constitutes a problem as important as respiratory allergy. Its prevalence varies, probably in accordance with a country's socio-economic standard, but in developed countries where food processing is highly industrialized, it reaches 8% of children and 3% of adults [1–5].

Clinical signs vary greatly: in adults, urticaria, angio-oedema, possibly fatal anaphylactic shock and asthma are more frequent than eczema and gastrointestinal disorders [1]. Although the route of introduction is ingestion, it is odd that gastrointestinal allergy in adults is not well identified. Up to now gastrointestinal allergy has been poorly defined and without a general diagnostic methodology: even its existence is controversial [6]. In children, gastrointestinal allergy syndromes have been identified. Pathophysiological studies remain experimental [7] or have been mainly concerned with gastrointestinal allergy of infants and young children [8,9]. It appears to depend predominantly on a localized IgE-dependent mechanism associated with activation of type Th2 lymphocytes [10] and a delayed hypersensitivity mechanism related to Th1 lymphocyte activation cannot be ruled out.

This review deals with the current knowledge on gastrointestinal food allergy in adults and, especially, diagnostic methods.

Mechanisms of gastrointestinal allergy

The characteristics of IgE-dependent allergic mucosal inflammation are well documented for nasal and bronchial mucosa. The observation of identical cell populations

(mast cells, eosinophils, T lymphocytes), the presence of Th2 cytokines, such as IL-5, in oesophageal mucosa, together with the mucosal remodelling seen with eosinophilic oesophagitis suggest that the processes are similar in both respiratory and gastrointestinal mucosae [11]. An increase in activated eosinophils, cell populations carrying IgE, and of IL-4 positive cells is seen in the intestinal mucosa of people with food allergy, whilst their IFN- γ + lymphocytes are reduced [10]. Perfusion of an isolated jejunal segment challenged with food extracts revealed the release of tryptase, histamine and PGD₂ which demonstrated the activation of local sensitized mast cells. The presence of eosinophil peroxidase indicated a late phase reaction of the IgE-dependent process, linked to the activation of eosinophils [12].

The common occurrence of cross-reactivity between several airborne allergens and food allergens reinforces the hypothesis of an identical IgE-dependent mechanism [13]. Mishra *et al.* showed experimentally that eosinophilic oesophagitis can be induced in mice by sensitization to airborne allergens [14]. Magnusson *et al.*'s study reported that, in patients with birch pollen allergy and complaining of abdominal pain, MBP + eosinophils and IgE-carrying mast cells were increased in the duodenal mucosa during the birch pollen season, as compared with off-season [15]. In such cases, the gastrointestinal disorder could be due to an inflammatory response in the gastrointestinal tract, linked to the allergy to inhalants in the respiratory mucosa.

It is tempting to postulate that, in man, gastrointestinal allergy might result from eating fruits and vegetables in people sensitized to pollens, due to cross-reactions.

Finally, the effective use of topical corticosteroids in eosinophilic gastrointestinal disease suggests an IgE-dependent process [16].

Also, a disorder of histamine catabolism could be implicated; the activity of diamine oxidase is significantly reduced in all intestinal segments of adults presenting with food allergy and chronic diarrhoea [17,18].

There are many questions concerning the dysfunction of regulatory T cells. In eosinophilic gastroenteritis and food-induced enteropathy of children, a lack of T-regulatory cytokines (TGF- β and IL-10) and a production of Th2 cytokines have been demonstrated [19]. The possible role of specific IgG has not been documented [20].

There are other possible links between auto-immune inflammation and intestinal allergies. Anomalies in regulatory T lymphocytes are indicated in both cases. The pathophysiology of coeliac disease opens interesting perspectives since it provides an example of the association of an auto-immune response with an anti-food-antigen response. Some rare publications in the literature associate coeliac disease with food allergy [21].

Allergens inducing gastrointestinal allergy

Many fruits and vegetables (Prunoideae, Apiaceae) cross-react with birch pollen. If eaten raw, they induce principally buccal or pharyngeal symptoms. Their major allergens, cross-reacting with the birch pollen major allergen, Bet v 1, are fragile and easily destroyed by cooking and pepsin. In the event of cross-allergy with latex, the allergens of peppers and buckwheat appears to be resistant both to cooking and digestion. Allergen resistance to cooking, pepsin and gastric acidity appears to be necessary characteristics to induce gastrointestinal signs. A recent hypothesis postulates that antacid treatments could favour food allergies [22].

The commonest allergens are those most frequently ingested: wheat flour, milk, egg and meats [23]. Prunoideae and Apiaceae are also cited [24]. In our series of 13 adults with gastrointestinal allergy, four reacted to two foods. Allergens were varied: wheat flour, three; milk, two; egg, one; offal (poultry livers, kidneys), two; lettuce, one; avocado and peppers, one; soya, one; sesame, one; sunflower, one; fish, one; mussels, one; and metabisulphites, one.

It is necessary to realize that the allergenicity of digestion by-products, different from native foods, may explain the negative results of tests with native foods. This possibility is often evoked for gluten allergies [25].

Clinical forms of gastrointestinal allergy in adults

The difficulty in characterizing gastrointestinal allergy syndromes is illustrated by a study of the detection of food allergy in 375 adults with abdominal symptoms, because 32% of patients suspected that foods were responsible. It was taken into account by physicians in 14%, but firmly confirmed in only 3.2% [26].

Acute gastrointestinal allergy in the context of systemic allergy occurs quite frequently and can be correctly identified: 13% of 287 adults with food allergy reported periodic vomiting, abdominal pain and acute diarrhoea [1]. The symptoms, triggered by increasing amounts of food allergens, can be carefully observed during standard double-blind placebo-controlled challenges (DBPCFC). Twenty per cent of such trials produce gastrointestinal symptoms: abdominal or epigastric pain (14%), diarrhoea or vomiting (6%) (personal unpublished data on 214 DBPCFC in adults with food allergy).

On the other hand, chronic gastrointestinal allergy is much rarer. It represents only 4.2% of food allergies in adults [1] and 3.2% of all intestinal disorders [26].

The symptoms are variable and non-specific: episodic vomiting, chronic diarrhoea or simple abdominal pain. Unlike the situation with children, chronic constipation is not observed in adults. Such patients had been often diagnosed as suffering from irritable bowel syndrome, a disease that has many causes. At most, food allergy probably represents only 13% of cases [27–29] and the causal allergen is frequently wheat flour.

Eosinophilic gastrointestinal disorders are the subject of much interest [30]. Amongst the various segmental disorders, eosinophilic oesophagitis related to food allergy is best understood. Multiple food allergy has been formally identified as the cause in children [31] and probably the same applies to adults. No allergological enquiries have as yet been conducted concerning eosinophilic oesophagitis in adults, but atopy and/or asthma have been observed in 48% of cases [32]. The studies by Straumann *et al.* demonstrated allergic inflammatory reactions with the presence of mast cells, eosinophils and Th lymphocytes whose increased IL-5 expression indicated a Th2 profile. A history of allergy was recorded for 60% of patients, and 13% reported food allergy. Forty-two per cent had high levels of total IgE [33].

The incidence of food allergy in cases of eosinophilic gastroenteritis in adults, which is much rarer than in children, is poorly documented, although 33–50% have a history indicating allergy [34,35]. The response to corticosteroids suggests an IgE-dependent process [36].

In one series of 15 cases studied over 15 years, food allergy was only certain in two cases [35]. Some cases of eosinophilic gastroenteritis due to food allergy have been published [21,37,38]. The allergens responsible were those most frequently ingested: e.g., wheat flour, meat albumins, milk, eggs.

No link has been found between gastritis due to *Helicobacter pylori* and food allergy [39].

A link between food allergy and Crohn's disease has been suggested. Higher proliferative responses of blood lymphocytes to food antigens have been found in patients with Crohn's disease than in controls, but this was also true for bacterial and yeast antigens [40]. Anti-food specific IgEs could not be detected in the sera of patients with Crohn's disease [41]. The fact that the rectal flow increased after local contact with foods may reflect irritability of the diseased mucosa [42]. In a personal case, specific IgE to wheat and a positive mucosal reaction to the local injection of wheat extract were observed in a young adult. However, the disease resolved without an eviction diet (3 year follow-up), showing that food allergy was not involved in the Crohn's disease. Food allergy appears to be rare in Crohn's disease [43].

Similarly, a link between food allergy and ulcerative colitis has been suggested [44]. Allergological investigations carried out in 50 patients with ulcerative colitis confirmed the significant frequency in allergy (52% vs. 18% in controls) and food allergy (38% vs. 12%), and more pronounced local eosinophilia in patients with food allergy, thus suggesting a link between ulcerative colitis and food allergy [45]. We observed complete recovery after the eviction of food allergens in one case [46].

Certain cases of lymphocytic and collagenous colitis have been attributed to food allergy [47]. However, a strict hypo-allergenic diet did not modify the clinical and biological outcome for 17 patients presenting with collagenous colitis [48].

Natural course in gastrointestinal allergies

There are no precise data concerning natural evolution. Quality of life has been rarely studied. In the absence of a diagnosis, recovery seems to be rare, as seen in patients with eosinophilic oesophagitis: only one of 30 was cured at the follow-up examination [33,49]. However, since we have observed clear improvement after accurate diagnosis and relevant eviction diets in chronically affected patients, we feel that gastrointestinal dysfunction can be cured.

Diagnosis of gastrointestinal allergy

Gastroenterologists faced with chronic gastrointestinal disorders without changes in general health or inflamma-

tory syndromes will make a differential diagnosis. Screening for coeliac disease using specific serology is usually done routinely, given the silent forms of the disease. Other diagnoses are based on the different foods incriminated by the patient: these non-immune adverse reactions to food include lactose intolerance due to low lactase activity acquired in adult life, fermentation colopathy with gas production linked to excessive intake of foods containing starch, dyspepsia induced by high fat diets, irritable bowel syndrome linked to cabbage and foods rich in fibre, pseudo-allergic reactions to biogenic amines, and psychological intolerance. Gastro-allergic anisakiasis should be suspected in patients with persistent gastric symptoms after frequent ingestion of raw or undercooked seafood [50].

Endoscopy to obtain biopsies is of little help in the common forms of gastrointestinal allergy dominated by functional disorders. They show eosinophilic infiltration in the mucosal type of eosinophilic gastroenteritis but give no information when the muscularis or sub-serosa are affected [24]. The diagnosis of gastrointestinal allergy can be completely ruled out with the presence of any villous atrophy indicating coeliac disease.

This is why we have questioned the role of some biochemical markers: the presence of IgE in intestinal secretions or faeces is not specific to allergy since it could indicate parasitosis [51]. Similarly, high levels of eosinophilic cationic protein (ECP) in intestinal secretions demonstrate eosinophilic inflammation but do not explain the cause [52]. Eosinophil activation markers (eosinophil peroxidase/eosinophil derived neurotoxin, ECP and myeloperoxidase) are present in the stools of only 30% of cases [53]. Intestinal permeability tests, even with the introduction of the allergen, show no anomaly, which is not the case in neonates. The concentration of faecal calprotectin is unchanged [8,54]. However, the results of the serum ECP assay are interesting since any marked increase indicates activated eosinophilic lesions and the physician will look for eosinophilic infiltration within a segment of digestive mucosa.

The diagnosis of allergy comprises three steps: suspicion of allergy drawn from the patient's history, identifying a range of allergens using skin or laboratory tests and confirmation by challenge or eviction diets over a sufficiently long period [5,54].

The interview may not reveal any family history suggesting allergy. Personal atopy (asthma and/or sensitization to airborne allergens) is found in only a third of adults with gastrointestinal allergy; 20% according to Bengtsson *et al.* [23]. Allergy to pollen and latex is an excellent indicator of suspected allergy to fruit and vegetables. Concomitant symptoms affecting other

organs – nose (rhinitis), bronchi (asthma), skin (urticaria or atopic dermatitis) – are valuable indicators of gastrointestinal allergy. The onset of signs during effort suggests food allergy, particularly to wheat flour.

It is necessary to establish the presence of a sensitization. Although prick tests are very effective in diagnosing both systemic and respiratory food allergies, they are less sensitive in gastrointestinal allergy. The same applies to circulating specific IgE. They are more effective, however, in eosinophilic forms than for other gastrointestinal disorders with histologically normal digestive mucosae. Atopy patch tests to food allergens have improved the diagnosis of eosinophilic oesophagitis in children [31]. The performance of patch tests has been assessed only briefly in adults with atopic dermatitis [55].

The diagnosis of gastrointestinal allergy must be confirmed by a double-blind, placebo-controlled food challenge (DBPCFC) [1,23], or by an eviction diet, making allowance for a specific cause or, alternatively, a random association. In study of 42 patients with Crohn's disease, 47% incriminated foods, 23% reacted to open challenge, but only 7% were confirmed by DBPCFC [43].

Suspect foods must be eliminated from the diet 3 weeks before challenge. A DBPCFC is carried out first, then an open test at higher doses. Gastrointestinal symptoms usually occur within a few hours but sometimes after 24 h. If results are negative, it is necessary to complete the test with a fixed and sufficient amount of food for 7–15 consecutive days, and to draw up a score for symptoms. The method is difficult because of poor compliance. Challenge with a caecal intra-mucosal injection has been proposed (COLAP) [44]. It is not certain whether positive results to this are clinically relevant. The test may be similar to a skin test and demonstrate only sensitization.

The alternative is the use of an eviction diet for up to several weeks, requiring elemental diets with amino acid formulae and a restricted range of some non-allergenic foods (well cooked potato, rice or corn). This procedure has proved valuable [48]. Serial re-introductions of suspect foods are then made. This method is difficult to implement in active, working adults. But in some cases, only recovery after prolonged eviction confirms the diagnosis [24].

New types of investigations should also be evaluated: intestinal endosonography and small bowel manometry, coupled with allergen challenge [56,57]. Coupling oral challenge to certain foods with wireless-video-capsule endoscopy might be a promising technique.

Conclusion

Gastrointestinal allergy in adults is much rarer than in children. In contrast to well-characterized syndromes

seen in children, functional disorders such as irritable bowel syndrome are commonly observed in adults. Few studies have established an IgE-dependent process localized to the gastrointestinal mucosa. The pathophysiology is probably different to that in children, where the allergic process is a sign of a marked disorder in physiological tolerance. In adults, the frequency of irritable bowel syndrome emphasizes a combination of a low degree of local sensitization and the role of neurokinins. The diagnosis of gastrointestinal allergy following the three steps: suspicion, establishing a sensitization and confirmation, though necessary, still lacks the necessary biochemical and immunological markers to be effective. This is why new gastroenterological techniques applied to diagnosis of gastrointestinal allergy should be studied further.

Annotated references

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