

Gastrointestinal allergy: clinical symptoms and immunological mechanisms

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Introduction

The gastrointestinal tract (GIT) and its associated lymphoid organs (*gut-associated lymphoid tissues*: GALT) is the largest organ of the immune system. This is an evolutionary response to the huge and constant burden of both harmless and dangerous pathogens and antigens that are encountered daily by the GIT.

The mechanisms of dynamic immunological control are complex. Perturbation can result in severe or fatal infection by normally tolerated organisms (such as *Giardia lamblia* or *Cryptosporidium* species) or in development of intolerance of antigens – including food antigens – that were previously tolerated. The role of neuroendocrine control of GIT immune responses is an underdeveloped area of scientific enquiry. Other areas such as IgE associated food allergy and coeliac disease have long been fruitful areas of research and of huge benefits for affected subjects. This short review aims to outline some of the symptom complexes and the mechanisms thought to underlie some of the common and more unusual gastrointestinal presentations of intolerance and allergic diseases.

The aetiology and symptomatology of adverse reactions affecting the gastrointestinal tract are variable. The mechanisms involved and the site of the reaction influence the time taken for symptoms and clinical signs to develop after eating the

food product. Any part of the gastrointestinal tract can be involved. The features may occur alone or together as part of a syndrome.

Vomiting

Vomiting alone or in combination with acute or chronic diarrhoea is a common feature of adverse reactions to food (1–3). It results from inflammation of the mucosa of the stomach and oesophagus. Bleeding may also be caused through repeated writhing through small tears in the mucosa. Vomiting may be a psychological response due to aversion, rather than an immunologically mediated or biochemical intolerance.

Gastro-oesophageal reflux

Gastro-oesophageal reflux can occur as an adverse reaction to food, particularly in infants with allergic gastroenteropathy and a constituent eosinophilic oesophagitis (2). Gastro-oesophageal reflux as measured by oesophageal pH monitoring can be detected soon after a milk feed, although features of an eosinophilic oesophagitis take longer to develop. In adolescents and adults, coffee drinking and smoking may contribute to reflux by relaxing the gastro-oesophageal sphincter (4).

Diarrhoea

Frequent loose stools can result from impaired absorption of nutrients and water or from intestinal secretion of fluid as part of an inflammatory response, or from a combination of both. The inflammatory response may also cause bleeding, so an additional feature would be blood in the stools. Problems such as bacterial overgrowth syndromes and fermentative diarrhoea may arise from gastrointestinal functional disturbances following conditions such as gastroenteritis and surgery.

Constipation

In 65 children (aged 11–72 months) with chronic constipation a double-blind cross-over study showed that 68% of the children improved when their customary intake of cow's milk was replaced by soya milk. Many of those who responded had perianal lesions including fissures and chronic rectal inflammation. It was suggested that the resultant painful defaecation induced stool retention and constipation. Some 25% had other features of atopy, the majority had no such evidence (5). It needs to be established if the beneficial intervention was the reduction of cows' milk intake or the introduction of soya milk or both.

Oral allergy syndrome

Oral allergy syndrome is an IgE-mediated immediate Type 1 allergic reaction characterised by an initial burning sensation and itching at the lip and oral mucosa, including the palate, followed by oedema within several minutes of contact with the food. In some instances the syndrome can extend to the larynx and pharynx: laryngeal oedema may cause tightening of the throat, cough, hoarseness and wheezing. These oral effects are associated with rhinoconjunctivitis in about two-thirds of cases (6). Other systemic reactions can develop and can be delayed until 30–60 minutes after exposure. Patients mostly react to fresh fruits and raw vegetables (apples, cherries, peaches and other fruits, fennel and celery) and they are often allergic to grass, mugwort or birch pollen (7, 8). The syndrome is also associated with consumption of tree nuts, peanut and egg, milk or fish. Oral allergy syndrome is a variable syndrome and different foods can cause different symptoms on different occasions in the same subject.

Enteropathies

The major feature of the enteropathies is a loss of the normal structure of the intestinal mucosa which reduces mucosal digestive and absorptive function (1, 9). Among the food-induced enteropathies, coeliac disease manifested by a life-long gluten intolerance and symptoms affecting the gut and other organs of the body, has been most intensively studied and will not be discussed here. Other enteropathies have been reported in response to cow's milk, soya, eggs, rice, fish and chicken.

Allergic eosinophilic gastroenteropathy

This represents a spectrum of conditions, which predominantly affect infants and young children, and in which there is inflammation of the gastrointestinal mucosa, with eosinophilic infiltration. Involvement of the stomach or oesophagus may present with vomiting. Damage to the small intestine and colon can cause significant loss of endogenous protein and nutrients as well as impaired digestion and absorption. Consequently the range of symptoms include bloody diarrhoea, impaired weight gain and linear growth. In severe cases protein losing enteropathy (with low immunoglobulins, suggesting primary immunodeficiency), enterocolitis, and a colitis which mimics inflammatory bowel diseases may occur.

Sometimes children present only with an anaemia associated with an occult loss of blood in the stools. Some patients have atopic features, but otherwise other organs are not directly involved. Most cases present in the first 3 months of life and resolve spontaneously in early childhood (10).

Infantile colic

Sometimes known as 3-month colic, this is a common problem in babies. A study in babies and older children with challenge proven cow's milk allergy found that 75% reacted with colic during a challenge with capsules containing whey protein (11). Sampson (12) considered that 10–15% of colic is associated with elevated IgE concentrations. It has been suggested that bovine IgG in formulas and in maternal breast milk might be responsible for this relationship. However, possible mechanisms have not been investigated fully and the relationship of infant colic with cow's milk and other foods or food components that might be present in maternal breast milk or formulas needs further study. A

recent systematic review concluded that infantile colic should initially be managed by reducing the stimulation which their carers might be giving the baby. If this is unsuccessful, then a 1 week therapeutic trial of cow's milk exclusion, for example using a "hypoallergenic formula", could be used (13).

Mechanisms

The causes and mechanisms of these conditions are not well understood. Some cases are associated with atopic clinical features, an increase in the number of eosinophils in their blood and with positive allergen-specific IgE and skin prick tests (SPTs) as evidence of a possible involvement of a type I reaction, but others do not have these features (10, 14). These are rare diseases and it is thought that between a third and a half of cases may be caused by food allergy, most frequently to cow's milk or soya (15).

Eosinophilic colitis can occur in an exclusively breast-fed infant (16). In such circumstances the mother should go onto an exclusion diet (17, 18).

Immediate-type immunological reactions (allergy)

Most common food allergies are mediated by IgE antibodies, this being the class of antibody responsible for immediate-type hypersensitivity reactions (19). In susceptible individuals, exposure to the food allergen, in sufficient quantity and by an oral or inhaled route or even on minimal, cutaneous contact, will stimulate the production of allergen-specific IgE. This sensitisation may provoke a hypersensitivity reaction on subsequent encounter with the inducing allergen. The allergen will cross-link mast cell membrane-bound allergen-specific IgE. This in turn signals mast cell degranulation and the release of both preformed and newly synthesised inflammatory mediators, including histamine and leukotrienes that are capable of provoking an acute hypersensitivity reaction.

Cognitive interactions between T- and B-lymphocytes and certain regulatory cytokines influence both the initiation and maintenance of IgE responses. Of particular importance is interleukin 4 (IL-4), a cytokine that has been shown, in mice, to be necessary for normal IgE responses (20). Mice that lack a functional gene for IL-4 fail to display IgE responses (21), whereas mice that have a transgene for this cytokine have increased serum concentrations of IgE and mount more vigorous IgE responses (22). The counter balance to IL-4's effects, provided by interferon- γ (IFN- γ), a

cytokine that antagonises the production of IgE antibody, has been well established (23). The same cytokines serve to reciprocally regulate the stimulation of IgE responses in humans (24). Another cytokine, interleukin 13 (IL-13), which shares some homology with IL-4, also plays a part as a promoter of IgE production and immediate-type hypersensitivity reactions (25). Of particular relevance to the stimulation of qualitatively distinct immune responses are functional sub-populations of T-lymphocytes and their cytokine products. Heterogeneity among CD4 T lymphocytes of a similar, although not necessarily identical, type to that found in mice (26) has been described in humans (27).

One of the major determinants of selective Th cell development appears to be the local cytokine microenvironment, in association with other co-stimulatory factors produced by antigen-presenting cells. Broadly speaking, it is Th1-type cytokines that drive the development of Th1 cells, while IL-4, IL-10 and other products of Th2 cells favour Th2 responses. The same cytokines are reciprocally antagonistic insofar as IL-10 inhibits cytokine synthesis by Th1 cells and IFN- γ inhibits the proliferation of Th2 cells.

Cytotoxic CD8 T-cells (Tc) also show functional heterogeneity. Two populations, that have been designated Tc1 and Tc2, display selective cytokine secretion patterns comparable, respectively, with Th1 and Th2 cells. Tc1-type cells may play a particularly important role in the negative regulation of IgE responses (28). Taken together, the available evidence suggest that an important determinant of allergy is the development with time of discrete functional sub-populations of T-lymphocytes and the production by them of cytokines that direct the quality of specific immune responses (Fig. 1).

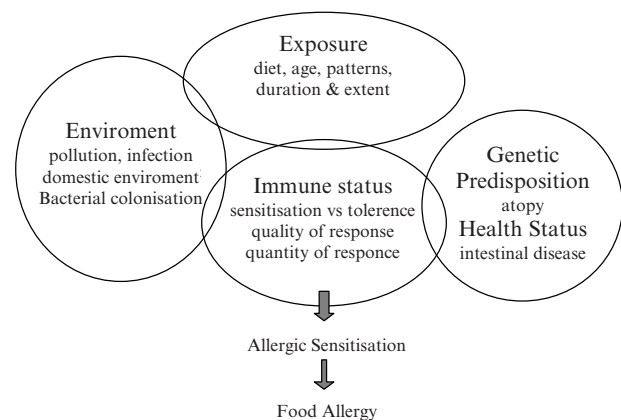


Fig. 1.

The discussion of the broad spectrum of gastrointestinal immunological-mediated reactions highlights the aetiological complexity and diagnostic challenges of these conditions. Our improved understanding of the interrelationship of acute, immediate-onset and late-onset cell-mediated immunological reactions will clearly help in identifying the underlying mechanism of conditions currently being classified as "non-immunological" or "unknown".

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