

Gut Inflammation and Extraintestinal Manifestation of Food Allergy

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Food allergy (FA) is a subgroup of adverse effects of food on the health of an individual, and it is defined as caused by altered immunologic mechanisms. The evidence of IgE mediation in acute FA is well established, its most common manifestations are erythematous and urticarial skin symptoms, but acute gastrointestinal symptoms often associate these and may occur alone. The gastrointestinal symptoms of delayed FA are chronic diarrhoea, more rarely vomiting, and the associating skin symptom is chronic eczema. Immune mechanisms causing delayed FA are not well defined—at least in the chronic enteropathy, T cells play a role. Most studies on the intestinal inflammation of FA have dealt with chronic, slow reactions to foods, but some describe patients with immediate, IgE-mediate reactions, too.

Enteropathy associated with allergy to cows' milk and causing chronic diarrhoea and malabsorption was described 40 years ago (1). This type of food allergy is associated with severe morphologic and inflammatory changes in the intestine. The morphologic findings in the jejunal biopsy specimens are like those in Celiac disease, though often less pronounced: There is a varying degree villous atrophy with crypt hyperplasia and inflammation both intraepithelially and in the lamina propria. The average number of cells in the crypts was 1.8 times the number in controls. The morphology of jejunal damage in soy-protein-induced enteropathy had characteristics similar to those described for cows' milk induced enteropathy. We found that the epithelial cell renewal rate was much increased as the result of increased mitotic rate and larger crypt cell compartment. Both morphology and a monoclonal antibody associating most strongly with mitotic cells have been used to measure mitotic activity in the jejunal crypts. Both methods showed increased mitotic activity in the crypts, though of a moderate degree (1).

In most cases, there was an increase in the number of intraepithelial lymphocytes; we found three times as many lymphocytes intraepithelially as seen in the normal intestine, a value that did not differ from that found in untreated Celiac disease. During cow milk challenge, the

counts did not always rise as much (1). The density of eosinophils in the epithelium has been shown to be increased.

The great majority of intraepithelial lymphocytes are CD3+ α/β T-cell receptor-bearing cells, and as in normal intestines, they were mostly suppressor/cytotoxic, CD8+ cells. The proportion of TIA1 positive cells among intraepithelial lymphocytes (UCHL1+ cells) in specimens from patients with malabsorption in cow's milk allergy (CMA) was increased and decreased with the length of the elimination diet. TIA1 is a specific cytotoxic granule-associated protein expressed only by T lymphocytes and natural killer cells. Thus, the proportion of cytotoxic cells in the epithelium of these patients was high; the same has been shown for specimens from patients with Celiac disease (1).

In patients with severe enteropathy, several studies have shown a moderately increased densities of intraepithelial γ/δ TCR+ cells. The same was seen in school-aged children with slow developing mild gastrointestinal symptoms in cows' milk challenges (1,2).

In the lamina propria the numbers of lymphocytes, plasma cells and eosinophils are increased.

Early studies on immunoglobulins and complement in the intestines of patients with this syndrome showed a strong infiltration of IgA and IgM containing cells at the time of clinical reaction either to cow's milk (CM) or soy, while the role of complement remains uncertain. The presence of increased numbers of IgE-positive cells is disputed (1).

CD4+ T helper cells predominated in the lamina propria, as in normal intestines. Many CD4+ cells were also HLA-DR+, suggesting that they were activated. These cells diminished during CM elimination. The number of lymphocytes positive for homing receptor $\alpha 4/\beta 7$ was increased in the lamina propria of adults with slow food reactions; these patients also showed a higher numbers of ICAM-1+ cells in the lamina propria (3). Hauer et al., using enzyme-linked immunoabsorbant spot technique, showed an elevation in IFN- γ and, to a lesser extent, IL-4 secretion in duodenal biopsies of 14 infants with cow milk sensitive enteropathy (4). Cells secreting IFN- γ were ten times as abundant as cells secreting IL-4, indicating a Th1 dominance. The numbers of cells secreting interleukin-5 and -10 were unchanged (4). In our recent

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study, patients with untreated food allergy had a higher density of IFN- γ -positive cells in the lamina propria than did treated FA patients and controls. Moreover, the untreated FA patients exhibited a significantly higher proportion of crypt cells in mitosis than did treated FA patients and stronger staining of HLA-DR in the crypts and increased density of γ -T cell receptor-positive intraepithelial lymphocytes than did controls. *In situ* hybridisation method showed changes only in specimens from celiac patients: expression of IL-4 mRNA was significantly higher than in the other study groups, and the same was true for IFN- γ mRNA (5).

The study of Perez-Machado et al. included both IgE- (8 patients) and non-IgE mediated reactions (22 patients) (6). They did not find any significant Th1/Th2 skewing by flow cytometry amongst duodenal lymphocytes of 30 children with FA when compared to controls. They found reduced amounts of TGF- β 1 lymphocytes both in the intraepithelial compartment and in the lamina propria. TGF- β 1 reduction was also detected in the biopsies of FA patients by immunohistochemistry and *in situ* hybridisation. The dominant mucosal abnormality was therefore not Th1/Th2 deviation, but impaired generation of Th3 cells in these patients (6).

When intestinal symptom are less severe, the pathology and inflammation in the intestine are less severe. We found that in children predominantly with skin symptoms and having both IgE- and non-IgE-mediated reactions, the most sensitive measure for intestinal pathology was villous height to crypt length ratio (1); this finding is confirmed in a recent study on patients most of whom were allergic to several foods and showed both rapid and slow symptoms (7).

EXTRAINTESTINAL MANIFESTATIONS OF FOOD ALLERGY

Chronic inflammation of the intestine is associated with varying degree of malabsorption and its consequences: growth failure and various nutritional deficiencies. Skin symptoms occur in the minority of patients;

chronic eczema is present in 20 to 30 percent of patients. Respiratory symptoms, rhinitis and wheezy bronchitis, occur in an equal proportion. Several other organ manifestations (e.g., sudden infant death, central nervous system symptoms) have been suggested to associate with food allergy, but the evidence is weak.

Clinically, IgE-mediated food allergy predominantly has skin symptoms; they are mostly either urticarial or erythematous eruptions. Respiratory symptoms may more rarely accompany rapid reactions.

CONCLUSION

Recent studies demonstrate that Th1 cells are more strongly activated in intestinal inflammation associated with FA than Th2 cells. Regulatory Th3 cells may be deficient at the site of antigen entry and allow uncontrolled immune reaction to food antigens to take place.

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