

Food allergy: immunology of the GI mucosa towards classification and understanding of GI hypersensitivities

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Introduction

The gastrointestinal (GI) tract and immune system confront an enormous quantity of foreign proteins and pathogens over the life of an individual. The GI tract must process foreign nutrient proteins for growth and energy needs of the individual while the GI immune system must differentiate between foreign pathogens and nutrients, responding aggressively against the former while “ignoring” the latter. Given the enormity of this task, it is not surprising that a variety of GI hypersensitivity disorders may develop. A recent consensus workshop (*Workshop on the Classification of Gastrointestinal Diseases of Infants and Children*) was held in November 1998 in Washington, DC (1). (summary: *J Pediatr Gastroenterol Nutrition* 2000; 30 (suppl 1): S1–94). Allergist and gastroenterologists from Europe and the United States attempted to classify the GI hypersensitivity disorders in an attempt to provide a common nomenclature for investigators to utilise. Participants readily acknowledged that the consensus classification of these disorders would be a “dynamic”

document, and perhaps deliberations at this symposium in honor of our dear colleague, Dr Luisa Businco, will shed new light on these disorders. GI hypersensitivities may be exclusively IgE-mediated, partially IgE-mediated, or exclusively cell-mediated. Regardless of the immunological mechanism involved, symptoms of GI hypersensitivity are very similar in nature, but generally vary in time of onset, severity and persistence. Only with a precise, universally accepted classification of these disorders can we hope to understand their underlying immunopathology.

IgE-mediated disorders

Immediate gastrointestinal hypersensitivity is an IgE-mediated gastrointestinal reaction that generally accompanies allergic reactions in other target organs (e.g. skin, lungs) and results in a variety of symptoms (495). Symptoms due to immediate gastrointestinal hypersensitivity typically develop within minutes to 2 hours of consuming the responsible food allergen and

Table 1 Gastrointestinal hypersensitivity disorders

IE ←	→ Non-IgE
Immediate GI hypersensitivity	
Oral allergy syndrome	
	Allergic eosinophilic esophagitis Allergic eosinophilic gastritis Allergic eosinophilic gastroenteritis
	Dietary protein enterocolitis Dietary protein proctitis/proctocolitis Dietary protein enteropathy [celiac disease]

consist of nausea, abdominal pain, colic, vomiting and/or diarrhea.

The *oral allergy syndrome [OAS]* affects up to 40% of adolescents and adults suffering from pollen allergy, especially to birch, ragweed and mugwort pollens (2). OAS is a form of contact allergy that is confined almost exclusively to the oropharynx, provoking the rapid onset of pruritus, tingling and angioedema of the lips, tongue, palate and throat, and occasionally a sensation of pruritus in the ears and/or tightness in the throat.

Mixed IgE- and non-IgE-mediated disorders

Allergic eosinophilic esophagitis, gastritis and gastroenteritis are characterised by infiltration of the esophagus, stomach and/or intestinal walls with eosinophils, basal zone hyperplasia, papillary elongation, absence of vasculitis and peripheral eosinophilia in about 50% of patients. Allergic eosinophilic esophagitis is seen most frequently during infancy through to adolescence, and presents with chronic reflux [gastroesophageal reflux (GER)], intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance and failure to respond to conventional reflux medication.

Non-IgE-mediated disorders

Dietary protein enterocolitis syndrome is a disorder seen most frequently in the first several months of life in which infants present with irritability, protracted vomiting and diarrhea, not infrequently resulting in dehydration (3, 4). Vomiting generally occurs 1–3 hours following feeding, and continued exposure may result in bloody diarrhea, anemia, abdominal distention and failure to thrive. Hypotension occurs in about 15% of cases following allergen ingestion (5, 6). In adults, shellfish (e.g. shrimp, crab, lobster) sensitivity may provoke a similar syn-

drome with severe nausea, abdominal cramps and protracted vomiting.

Dietary protein proctitis/proctocolitis presents typically in the first few months of life as blood-streaked stools in otherwise healthy-looking infants. About 60% of cases are seen in breast fed babies (7–9), with the remainder largely in infants fed cow milk or soy protein-based formula. Blood loss is typically modest but occasionally can produce anemia.

Dietary protein enteropathy often present in the first several months of life with diarrhea (not infrequently steatorrhea) and poor weight gain (10). Symptoms include protracted diarrhea, vomiting in up to two-thirds of patients, failure to thrive, abdominal distention, early satiety and malabsorption. Anemia, edema and hypoproteinemia are occasionally seen.

Celiac disease is a dietary protein enteropathy due to gluten sensitivity characterised by a more extensive loss of absorptive villi and hyperplasia of the crypts leading to malabsorption, chronic diarrhea, steatorrhea, abdominal distention, flatulence and weight loss or failure to thrive. Celiac disease is associated with the HLA-DQ2 (and DQ8) haplotype and about 90% of celiac patients ingesting gliadin possess IgA anti-gliadin and anti-endomysium antibodies (11). Endoscopy typically reveals total villous atrophy and extensive cellular infiltrate. It is now believed that generation of unique gliadin epitopes by tTGase enzymatic modification leads to activation of DQ2 (and DQ8)-restricted T cells, a breakdown in tolerance, and initiation of an autoimmune process that generates inflammation in the gut (12).

Other gastrointestinal disorders have been described that are believed to be the result of food-induced inflammatory processes, although the pathogenesis is unclear. Ingestion of pasteurised, whole cow milk by infants, especially less than 6 months of age, frequently leads to *occult gastrointestinal blood loss*, leading occasionally to iron deficiency anemia, has been described in young infants ingesting pasteurised,

whole cow milk (13). In a recent study, *chronic constipation* was found to be associated with cow milk hypersensitivity in 68% of the children studied (14). The role of food hypersensitivity in inflammatory bowel disease (Crohn's disease and ulcerative colitis) remains speculative, although elemental diets have been shown to promote resolution of symptoms. Future studies will undoubtedly lead to further modification of this proposed classification of GI hypersensitivities and provide insight into the underlying immunopathogenic mechanisms. Armed with this new information, physicians will be better equipped to diagnose and manage, and perhaps prevent, these often debilitating disorders.

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