Non–IgE-mediated gastrointestinal food allergy

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Non–IgE-mediated gastrointestinal food-induced allergic disorders (non-IgE-GI-FAs) account for an unknown proportion of food allergies and include food protein–induced enterocolitis syndrome (FPIES), food protein–induced allergic proctocolitis (FPIAP), and food protein–induced enteropathy (FPE). Non-IgE-GI-FAs are separate clinical entities but have many overlapping clinical and histologic features among themselves and with eosinophilic gastroenteropathies. Over the past decade, FPIES has emerged as the most actively studied non-IgE-GI-FA, potentially because of acute and distinct clinical features. FPIAP remains among the common causes of rectal bleeding in infants, while classic infantile FPE is rarely diagnosed. The overall most common allergens are cow's milk and soy; in patients with FPIES, rice and oat are also common. The most prominent clinical features of FPIES are repetitive emesis, pallor, and lethargy; chronic FPIES can lead to failure to thrive. FPIAP manifests with bloody stools in well-appearing young breast-fed or formula-fed infants. Features of FPE are nonbloody diarrhea, malabsorption, protein-losing enteropathy, hypoalbuminemia, and failure to thrive. Non-IgE-GI-FAs have a favorable prognosis; the majority resolve by 1 year in patients with FPIAP, 1 to 3 years in patients with FPE, and 1 to 5 years in patients with FPIES, with significant differences regarding specific foods. There is an urgent need to better define the natural history of FPIES and the pathophysiology of non-IgE-GI-FAs to develop biomarkers and novel therapies. (J Allergy Clin Immunol 2015;135:1114-24.)

Key words: *Food protein–induced enterocolitis syndrome, allergic proctocolitis, food protein–induced enteropathy, food allergy, non–IgE-mediated food allergy*

Allergic reactions to foods affecting the gastrointestinal tract have been known since ancient times. Hippocrates noted that cow's milk (CM) caused gastrointestinal symptoms, as well as urticaria, and that some infants fed CM had diarrhea, vomiting, and failure to thrive (FTT) that resolved only after removal of CM from their diets.[1] At present, non–IgE mediated gastrointestinal reactions to food proteins (non-IgE-GI-FAs) are less well studied than other food allergies. The major reason for the limited understanding of non-IgE-GI-FAs is lack of access to target gastrointestinal tissue; many patients' symptoms improve with empiric food avoidance, and endoscopy and biopsy are not performed. Even if biopsies are performed, they might not capture the myenteric plexus, where the inflammatory response is localized, or in the case of a patchy inflammatory process, the histology might be normal. Furthermore, mast cell staining and careful enumeration of intraepithelial lymphocytes (IELs) is not performed routinely.

CLASSIFICATION

Non–IgE-mediated food allergy encompasses a wide range of disorders affecting the gastrointestinal tract (food protein–induced enterocolitis syndrome [FPIES], food protein–induced allergic proctocolitis [FPIAP], food protein–induced enteropathy [FPE], celiac disease, and CM allergy–induced iron deficiency anemia), skin (contact dermatitis to foods and dermatitis herpetiformis), and lungs (Heiner syndrome, also known as pulmonary hemosiderosis).[2-5] Celiac disease, eosinophilic esophagitis, and extragastrointestinal manifestations of food allergies will not be discussed in this review. We will focus on new developments and areas of controversy, predominantly concerning FPIES. Once considered to be a very rare food allergy, over the past decade, FPIES has emerged as the most actively studied non-IgE-GI-FA. It can be hypothesized that the potential for severe reactions, improved recognition of the symptom pattern, emergence of lay patient organizations raising awareness, and an increase in prevalence are all potential contributing factors.[6-8] Recently, features of FPIES and non-IgE-GI-FAs have been reviewed extensively; Table I summarizes the cardinal features of non-IgE-GI-FAs discussed in this review.[9] It has been demonstrated that isolated gastrointestinal dysmotility (too rapid, too slow, disturbed, or retrograde) is caused by non-IgE-GI-FAs in a subset of patients manifesting as pathologic gastroesophageal reflux, vomiting, delayed gastric

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Abbreviations used

CM: Cow's milk
EC: Eosinophilic colitis
EGID: Eosinophilic gastrointestinal disorder
FPE: Food protein–induced enteropathy
FPIES: Food protein–induced enterocolitis syndrome
FPIAP: Food protein–induced allergic proctocolitis
FTT: Failure to thrive
IEL: Intraepithelial lymphocyte
Non-IgE-GI-FA: Non–IgE-mediated gastrointestinal food-induced allergic disorder
OFC: Oral food challenge

emptying, diarrhea, constipation, or irritable bowel syndrome (Table II).[4,10-26]

MANIFESTATIONS

Recent studies from large, geographically diverse pediatric populations have defined the features of FPIES (Table I).[27-31] FPIES to CM and soy usually starts within the first 3 to 6 months of life; FPIES to solid foods usually starts at 4 to 7 months, reflecting the sequence of introduction of these foods to the diet. In patients with FPIES, the symptom pattern is determined by the frequency and dose of food allergen in the diet. Acute symptoms develop with intermittent exposure or re-exposure after a period of food avoidance and manifest as severe, projectile, and repetitive emesis starting within 1 to 3 hours of food ingestion. Associated features include pallor and lethargy, with or without diarrhea. Hypotension has been reported in up to 15% of reactions. FPIES is a systemic reaction distinct from IgE-mediated anaphylaxis (eg, lacking urticaria/angioedema or respiratory symptoms).[32] Chronic symptoms develop in young infants with regular intake of the food (eg, infant formula) and include intermittent but progressive emesis, diarrhea (with or without blood), and FTT.[33,34] Transition from chronic to acute symptoms in patients with FPIES resembles IgE-mediated food allergy associated with atopic dermatitis, in which avoidance of the offending food results in an anaphylactic reaction on subsequent exposure.[35] In contrast, such acute symptoms on reintroduction of food after a period of avoidance are not a feature of FPIAP and FPE.

FPIAP typically starts in the first 6 months of life, with blood-streaked and mucous stools.[2,36-39] FPIAP is estimated to account for up to 60% of healthy infants with rectal bleeding. Breast-fed infants are often older at the time of initial presentation and have less severe histologic findings.[38,40,41] New-onset FPIAP can also occur in older children and adults.[42,43] Onset is usually insidious, with a prolonged latent period after introduction of the food, although rarely, onset can be acute, within 12 hours after the first feeding. Infants typically appear well; however, increased gas, colicky behavior with pain on defecation, intermittent emesis, or increased frequency of bowel movements can be present. FTT is absent. Even when the offending food remains in the diet and bleeding continues, children grow well, although they can experience anemia despite iron supplementation.[38,40] FPIAP represents an infantile form of eosinophilic colitis (EC). In young adults EC is rare, has a chronic relapsing course, and is typically more severe, with symptoms including diarrhea, abdominal pain, and weight loss. In the majority of cases of adult EC, there is no evidence of food allergy.[44]

FPE presents with protracted diarrhea in the first 9 months of life, typically the first 1 to 2 months, within weeks after the introduction of the food.[45,46] More than 50% of affected infants have FTT, and some present with abdominal distension, early satiety, and malabsorption. In many infants symptom onset is gradual; in others it mimics acute gastroenteritis complicated by protracted diarrhea caused by secondary lactose intolerance with transient emesis and anorexia. It might be difficult to distinguish FPE from postenteritis syndrome, especially because FPE can develop after infectious gastroenteritis.[47]

OFFENDING FOODS

The single most common food allergen in patients with non-IgE-GI-FAs is CM, followed by soy and cereals, including rice and oats. FPIES is caused by a single food in the majority of children (65% to 80%), usually CM or soy. US studies report that about 30% to 50% of infants react to both CM and soy,[28,48,49] whereas most non-US studies report a far smaller percentage.[27,31,50] About 5% to 10% are allergic to more than 3 foods, although very few are allergic to 6 or more foods.[28,29] In addition to CM and soy, different cereals, egg, vegetables, fruit, poultry, and the probiotic yeast *Saccharomyces boulardii* have been reported in young children, whereas fish, shellfish (crustaceans and mollusks), and mushroom have been reported in older children and adults.[31,48,50-63] Fish was a common trigger in infants from Italy and Spain.[50,57] Feeding routines, age of introduction of the specific food into the diet, and genetic predisposition might underpin geographic differences in patients with FPIES.

FPIAP in formula-fed infants is typically caused by CM and soy; extensively hydrolyzed formulas cause FPIAP in about 4% to 10%.[38,40,41] FPIAP in breast-fed infants is usually caused by CM, soy, egg, or corn in the maternal diet.[38,64] In older children and adults CM, egg, and wheat have been reported as FPIAP triggers.[42,43]

Infantile FPE is usually caused by CM formula. Soybean, wheat, and egg have also been confirmed as frequent triggers in children with allergy to multiple foods and coexistent CM-induced FPE.[45,46]

BREAST-FEEDING AND NON–IgE-MEDIATED FOOD ALLERGY

Infants with FPIES and FPE are usually asymptomatic during exclusive breast-feeding without maternal dietary restrictions, whereas up to 60% of FPIAP develops during exclusive breast-feeding.[51] FPIES to the food allergens transmitted through breast milk is rare, and the symptoms of acute FPIES develop on direct feeding with the offending food.[65,66] However, in Japanese infants with challenge-proved FPIES, symptoms are reported during breast-feeding in approximately 10%, highlighting potential ethnic, dietary, and geographic differences.[67,68] It is not clear how exclusive breast-feeding moderates the onset of FPIES; it has been hypothesized that breast milk IgA, either alone or as a complex with secreted antigens, might play a protective role by modulating the local gut mucosal immune responses and limiting the amount of available antigen.[40] In addition, the lower dose of food allergen in breast milk might mitigate the full expression of FPIES by not reaching the threshold of clinical reactivity.