Food protein–induced proctocolitis and enteropathy

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ABSTRACT

Non-IgE (immunoglobulin E) mediated gastrointestinal food allergies include several separate clinical entities, including food protein–induced allergic proctocolitis (FPIAP) and food protein–induced enteropathy (FPE). Although FPIAP and FPE both primarily affect the gastrointestinal tract, their presentations are vastly different. FPIAP presents with bloody stools in otherwise healthy infants, whereas FPE presents with chronic diarrhea, vomiting, malabsorption, and hypoproteinemia. These both typically present in infancy and resolve by early childhood. Although the presenting signs and symptoms may be different, management is similar in that both require avoidance of the suspected causal food.

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In the spectrum of non-IgE (immunoglobulin E) mediated adverse reactions to food, three distinct disorders primarily affect the gastrointestinal tract: food protein–induced enterocolitis syndrome (FPIES), food protein–induced enteropathy (FPE), and food protein–induced allergic proctocolitis (FPIAP). Perhaps because of their lengthy and similar sounding names, they frequently provide an opportunity for confusion. FPIAP, FPE, and FPIES are all diseases of early childhood that present with gastrointestinal symptoms. Although these non–IgE-mediated food allergies are distinct clinical entities, they have common clinical features among each other and with eosinophilic gastroenteropathies.[1] FPIES is discussed separately in its own section.[2] Despite how commonly some of these disorders may be diagnosed, relatively little is known about the pathophysiology of these non–IgE-mediated food allergies. As such, these disorders are defined clinically through expert opinion and consensus.

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NOMENCLATURE, DEFINITIONS, AND CLASSIFICATION

FPIAP and FPE have a long and confusing history of nomenclature throughout the literature. FPIAP and FPE are on the spectrum of non–IgE-mediated food hypersensitivities, with FPIAP being the most benign form. FPIAP was formerly known as allergic or eosinophilic proctocolitis; it is also frequently referred to as "protein intolerance" or, in the setting of reactions to cow's milk, it may be colloquially referred to as "milk protein allergy." FPIAP is typically considered a benign disorder that is characterized by blood and sometimes by mucous in stools of otherwise healthy, normally growing infants.[3] It affects infants <12 months of age and typically appears between 2 and 8 weeks of life.[4] The onset of symptoms may be acute (<12 hours after exposure) but is often more insidious, with a gradual increase in symptoms as the food protein is introduced.

FPE has also been referred to by many names, including allergic enteropathy, cow's milk sensitive enteropathy, and malabsorption syndrome with milk intolerance. FPE is distinct from FPIAP in that the small bowel is affected. It is characterized by chronic gastrointestinal symptoms while the food is being regularly ingested. It typically starts in the first months of life and presents as recurrent vomiting, diarrhea, malabsorption, failure to thrive, abdominal distention, and hypoalbuminemia.[5] FPE can be distinguished from the other non–IgE-mediated gastrointestinal allergies by its malabsorption with steatorrhea, which can be seen in up to 82% of affected patients.[6] FPE can be difficult to differentiate from chronic forms of FPIES, but, importantly, it lacks both the acute symptoms seen in the FPIES (at the start or on reintroduction after a period of avoidance) as well as the severe dehydration and metabolic acidosis of chronic FPIES.

EPIDEMIOLOGY

The exact prevalence of FPIAP among the general population is unknown; it is commonly estimated to affect 1 to 2% of infants. However, a prospective population-based study from Israel ($N > 13{,}000$ children) reported the prevalence of milk-induced proctocolitis at only 0.16%.[7] Conversely, a recent analysis of the Gastrointestinal Microbiome and Allergic Proctocolitis study,[8] which is a large ongoing prospective observational healthy infant cohort study in suburban Massachusetts, 17% of the infants (153 of 903) were diagnosed by their pediatrician with FPIAP. However, although these children had confirmed evidence of gastrointestinal bleeding, they were diagnosed without challenge.[8]

These vast differences are likely related to study methodology, cultural practice patterns, and a lack of clear biomarkers for the disease. But some researchers have questioned whether FPIAP may be an overdiagnosis and thus overestimated as a cause of rectal bleeding in infants. Even among infants with rectal bleeding, the frequency of FPIAP as the cause of this bleeding has been highly variable in studies, ranging from 18 to 64%.[9,10] By strictly using milk elimination, followed by subsequent challenge to make the diagnosis of FPIAP, Arvola *et al.*[10] were able to confirm disease in only 18% of infants who presented with rectal bleeding. Likewise, in a small cohort of 16 neonates with rectal bleeding, 10 of 16 colonic biopsy specimens supported the diagnosis of FPIAP, but only two were confirmed to be food induced by oral food challenge.[11] Those not confirmed by oral food challenge had spontaneous resolution after an average of 4 days and were diagnosed with idiopathic neonatal transient colitis. Taken together, these studies raise the prospect that many infants who present with rectal bleeding may have a benign and self-limited cause other than FPIAP.

FPIAP was first described in infants who were breast-fed and is often considered more common in children who were exclusively breast-fed.[3] However, in a meta-analysis that included 214 patients, only 49% of patients (153) were exclusively breast-fed.[12] The most commonly implicated food triggers for FPIAP are cow's milk protein and soy protein.[14] Infants usually present in the first 4 months of life, usually at 1–4 weeks of age. FPIAP in children who are breast-fed can often present later and is usually caused by cow's milk, soy, egg, or corn in the maternal diet.[3,10]

Even less is known about the prevalence of FPE; the prevalence is thought to be declining over time.[6] This decrease may be due to an increase in breast-feeding rates because, in contradistinction to FPIAP, FPE is associated to the use of formula.[14] In addition, FPE has not been reported in infants who were exclusively breast-fed. The most common trigger for FPE is cow's milk or soy; other foods, *e.g.,* rice, wheat, egg, poultry, beef, fish, and shellfish, have also been reported as triggers but frequently are coincident with cow's milk.[6,14]

PATHOPHYSIOLOGY

The pathophysiology of both FPIAP and FPE are not well understood. Several mechanisms have been suggested in the pathophysiology for the development of FPIAP, including an immature immune system, altered intestinal permeability, and activation of local immune function (eosinophils). FPIAP is specifically associated with eosinophilic inflammation, principally in the rectosigmoid. An endoscopy of patients with FPIAP reveals focal erythema with lymphoid nodular hyperplasia.[10] Biopsy specimens of the affected area reveal prominent eosinophilic infiltrates in colonic and rectal mucosa.[9,10] The eosinophils are frequently degranulated and localized next to the lymphoid nodules. The number of eosinophils varies from 6 to >20 per 40 high-power field.[12]

Intestinal microbiota may also play a role in the pathophysiology of FPIAP. Patients with FPIAP have reported lower levels of *Bifidobacterium* species, *Bacteroides fragilis,* and *Lactobacillus* and/or *Enterococcus* compared with controls.[10] Baldassarre *et al.*[15] showed that the addition of *Lactobacillus rhamnosus* GG probiotics to a diet of extensively hydrolyzed casein formula led to a significantly reduced time of recovery compared with hypoallergenic formula alone. Similarly, Martin *et al.*[16] report a series of four patients with clinically diagnosed FPIAP who had rapid resolution of symptoms when treated with *L. rhamnosus* GG monotherapy.

Multiple T lymphocytes are thought to play a central role in FPE. The highest increase is in the number of intraepithelial lymphocytes. Most of these intraepithelial lymphocytes are suppressor cytotoxic $CD8^+$ T cells.[6] Kokkonen *et al.*[17] also found an increase in the number of intraepithelial $\gamma\delta$ T cells. Activated $CD4^+$ T cells expressing human leukocyte antigen-DR (HLA-DR), however, predominate in the lamina propria in FPE and diminish after food elimination.[6] Endoscopic findings can be similar to those of celiac disease, with diffuse or patchy villous injury with cellular infiltrates in the small bowel.[18] As expected with this villous injury, jejunal biopsy specimens show increased interferon γ and interleukin 4 levels.[19]

DIAGNOSIS

A diagnosis for FPIAP and FPE are primarily clinical. For most patients, a history and physical examination is adequate in establishing a diagnosis of FPIAP. A diagnosis relies on a history of rectal bleeding and a response to an elimination diet; clinical improvement of gross bleeding usually occurs within 72–96 hours but may take weeks to fully resolve. However, given the uncertainty of the prevalence of FPIAP, some have called into question the reliance on a presumptive

diagnosis. As such, considering food challenge 4–8 weeks after resolution of symptoms to confirm the diagnosis may be helpful and reduce unnecessary food restrictions.[10] Furthermore, it is important to exclude other causes of rectal bleeding, such as infection, necrotizing enterocolitis, intussusception, or anal fissure. Alternative diagnoses should also be considered if any atypical features, such as irritability, pain, feeding intolerance, vomiting, weight loss, or failure to thrive, are present.

Testing for FPIAP is generally unnecessary. Tests for IgE-mediated food hypersensitivity are nonillustrative and unlikely to identify the food trigger. Fecal occult blood testing (FOBT) may be helpful if bleeding is not apparent but FPIAP is suspected. However, in a case-control study that looked at the validity of FOBT for the diagnosis of FPIAP, more than a third of healthy control infants had abnormal results that caused the investigators to discourage the regular use of FOBT in the diagnosis of FPIAP.[20] Fecal calprotectin may be elevated in infants with FPIAP,[21] but its clinical utility has not been established. Flexible sigmoidoscopic or endoscopic evaluation with biopsy is a useful tool if the diagnosis is in question. Endoscopy is usually reserved for patients with atypical or recalcitrant symptoms.

A diagnosis of FPE, however, is significantly enhanced with histology. A diagnosis is confirmed in a patient with consistent symptoms and a small bowel biopsy specimen that shows villous injury, inflammation, and crypt hyperplasia.[6] Biopsy specimens may also show lymphonodular hyperplasia, increased intraepithelial lymphocytes, and extracellular deposition of major basic protein. Laboratory studies that look for malabsorption of vitamins, minerals, proteins, and fats may be helpful in making the diagnosis. Increased fecal fat excretion may be found in up to 80% of patients.[6] A D-xylose absorption test may also be abnormal because of poor carbohydrate absorption.

Avoidance of the offending food usually leads to resolution of clinical symptoms within 1–3 weeks. Villous atrophy usually improves within 4 weeks, but complete resolution may take up to 1.5 years.[6] Challenge with the suspected food can be performed at home[22] and is recommended in FPE to confirm the diagnosis as well as avoid unnecessary food restrictions.[23] As with FPIAP, tests for IgE-mediated food hypersensitivity are nonillustrative and should not be performed for FPE only.

MANAGEMENT

Management of FPIAP and of FPE consists of restriction of the offending food protein until the food can be successfully reintroduced at home. A multidisciplinary team, including allergists, gastroenterologists, dietitians, psychologists, speech therapists, and occupational therapists, can be helpful for management of patients from a diagnosis through resolution. If the patient with FPIAP is being breast-fed, then maternal elimination can be instituted first. The majority of infants who are breast-fed and have FPIAP respond to elimination of cow's milk from the mother's diet, and only a few require elimination of multiple foods.[13] If there is no resolution in infants who are breast-fed after starting a maternal elimination diet, further elimination of foods from the maternal diet can be counterproductive and the health of the mother should be considered. The benefits of continued breast-feeding versus an extensively hydrolyzed formula should be discussed. Further, reintroduction of previously eliminated foods should be considered for the mother.

An extensively hydrolyzed formula should be considered for infants who are formula-fed. Because a large proportion of infants with FPIAP may have symptoms with both milk and soy (up to 30%), soy-based formula is often not recommended.[24] An elemental or amino acid formula is rarely needed for FPIAP but may be required in up 10% of children when extensively hydrolyzed formula proves insufficient.[14] The evidence for probiotic supplementation is too limited at this time to make a recommendation.[15,16] For FPIAP, the food protein can generally be successfully reintroduced by 1 year of age. In some circumstances, it may be possible to reintroduce the offending protein into the diet as early as 6 months of age.[13]

Moreover, up to 20% of infants who are breast-fed may have spontaneous resolution without any changes in the maternal diet.[14] Because patients with FPE have malabsorption and may be more chronically ill, they may need a period of prolonged intravenous nutrition.[5] If cow's milk avoidance does not improve the symptoms, other elimination trials (*e.g.*, soy, egg, wheat) may be attempted sequentially. FPE resolves clinically in the majority of children by age 1–2 years, but the proximal jejunal mucosa may be persistently abnormal at that time.[6]

CLINICAL PEARLS

- Food protein-induced proctocolitis and FPE are non–IgE-mediated food allergies, most commonly triggered by cow's milk protein or soy, although other food proteins, *e.g.*, wheat and egg, are also implicated.
- Food protein-induced proctocolitis is a common cause of rectal bleeding in young infants, is a benign disorder of healthy infants, and is characterized by an inflammatory reaction to a food allergen limited to the rectum and distal sigmoid colon; it typically affects infants <12 months of age.

- FPE causes small bowel injury, which leads to malabsorption, intermittent vomiting, diarrhea, failure to thrive, and, rarely, bloody stools; FPE usually presents in the first 1–2 months of life but may start as late as 9 months of age.
- A diagnosis for FPIAP and FPE relies on meticulous medical history taking, physical examination, and response to an elimination diets; due to the risk of nutritional deficiencies associated with food restriction for both FPIAP and FPE, all unnecessary restrictions should be avoided in infants; food challenges or reintroducing foods if they do not seem to affect symptoms is important to optimize nutrition during this critical time for growth and development.

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