IN BRIEF

Food Protein–Induced Enterocolitis Syndrome

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OVERVIEW

Food is essential for growth, nutrition, and good health. Yet at times, food proteins have the potential to be allergens, inducing systemic responses by the body. Allergic reactions to food proteins are typically thought of as IgE-mediated type I hypersensitivity reactions that can cause life-threatening anaphylaxis and require emergency medical treatment. However, food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated allergic reaction to food proteins, primarily in infants, that is much less common, although not rare, with an incidence approaching 0.7%. It has a variable clinical presentation, typically characterized by vomiting and diarrhea associated with allergen ingestion. Presentations range from mild-moderate to severe or even chronic forms. It remains a largely clinical diagnosis.

PATHOPHYSIOLOGY

FPIES is a non–IgE-mediated reaction to food protein. The causative immunologic response implicated in disease formation is activation of the innate immune system. Ingestion of allergens induces activation of monocytes, neutrophils, and eosinophils, which is accompanied by production of inflammatory molecules, namely, interleukin (IL)-2, IL-8, IL-10, and tumor necrosis factor α. Studies that assessed the role of the adaptive immune system in FPIES found that there is no clear implication of T cells or antibodies in the response to allergens in those who have diagnosed FPIES. Biopsy findings of the gastrointestinal tract, although not useful in diagnosis, may show nonspecific inflammatory changes associated with this immune response. Occasionally, marked eosinophilia and inflammation in the esophagus and the stomach, edema and villous injury in the small intestine, or crypt abscesses with diffuse inflammatory cell infiltrate in the colon can be seen.

FPIES is theoretically induced by any food protein; however, the allergens most likely to be implicated in the disease process are cow milk and soy milk, followed by rice and oats. Other foods noted to induce FPIES include meats, fish, fruits, and vegetables. The data suggest that 60% of infants with FPIES have a response to only 1 food, 30% react to 2 or 3 foods, and approximately 10% react to 4 or more foods. Human milk has not been implicated in FPIES, even with maternal consumption of the offending allergen; however, this is not completely understood. Based on review of the literature, the prevalence of FPIES among breastfed infants versus nonbreastfed infants remains unknown.

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PRESENTATION

The first FPIES episode typically occurs in infancy. Among those who react to liquid foods (ie, cow milk or soy milk), the average age at onset is between 2 and 7 months. For those who react to solid foods, the average age at onset is later, between 6 and 12 months. This difference is suspected to be attributable to the timing of the introduction of liquid and solid food into the diet. Most often, FPIES resolves spontaneously, and data suggest that approximately 80% of patients will no longer experience FPIES reactions by 4 years of age. Although much less common, some studies report persistence of FPIES into adolescence or adulthood, with approximately 15% of cases persisting past 5 years of age. There are also reports of FPIES persisting into the teenage years; seafood seems to be the primary offending allergen in these cases.

Clinical diagnoses of FPIES consist of acute, chronic, and atypical phenotypes. Acute FPIES results from intermittent ingestions of allergen. It is characterized by profuse projectile vomiting onset 1 to 4 hours after ingestion of causative allergen. Acute FPIES is often accompanied by diarrhea 6 to 8 hours after onset of vomiting. Hypotonia, hypothermia, lethargy, and pallor may or may not be present. All symptoms resolve within 24 hours after ingesting the offending allergen. Chronic FPIES results from frequent consumption of the allergen. It is characterized by profuse watery diarrhea, intermittent vomiting, and possibly poor weight gain. Symptoms resolve within days to weeks of ceasing consumption of the offending agent. Both acute and chronic FPIES may cause dehydration, hypovolemia (possibly shock), and metabolic acidosis. Notably, FPIES does not present with fever, although isolated reports from Japanese studies acknowledged the presence of fever, suggesting a possible ethnicity-related difference in presentation. Atypical FPIES presents phenotypically similar to typical FPIES but is characterized by IgE production and a positive skin prick test to the FPIES trigger allergen. Although most patients with FPIES present with a typical phenotype, as many as 30% of patients with a reaction to cow milk may present atypically. Patients with atypical FPIES have a higher likelihood that the allergic response will transform into a typical IgE-mediated response (approximately a 25% chance), although that risk is present for all patients with FPIES.

DIAGNOSIS

Diagnosis of FPIES is primarily clinical, although several laboratory findings may support the diagnosis. Patients with FPIES typically experience a transient neutrophilia, with at least a 3,500 cell/mL increase during the symptomatic period. Inflammatory markers are typically not elevated, but some reports note an increase in methemoglobin. Most patients with FPIES do not require specific IgE testing; however, patients with suspected atypical FPIES may benefit from consultation with an allergy specialist to determine the need for testing on a case-by-case basis.

The differential diagnosis of patients presenting with acute FPIES includes but is not limited to infectious gastroenteritis, anaphylaxis, and sepsis. The key differentiating factor of acute FPIES is primarily the unique timing of food consumption followed by vomiting and then by diarrhea in the absence of fever, potentially supported by findings of neutrophilia and normal inflammatory markers.

The differential diagnosis of patients presenting with chronic FPIES includes but is not limited to infectious gastroenteritis, food protein-induced allergic proctocolitis, food protein–induced enteropathy, and celiac disease. The key differentiating factors of chronic FPIES are the absence of fever and hematochezia, the presence of lethargy, and the absence of small-bowel injury on endoscopy.

TREATMENT

Treatment of the acute phase of FPIES requires supportive care. Depending on the degree of hypovolemia, patients may require admission to the hospital for aggressive intravenous fluid resuscitation. Notably, epinephrine or antihistamine therapy has no role in treatment, unlike in IgE-mediated hypersensitivity reactions. In the nonacute phase, the only treatment is avoidance of trigger foods. Specifically, infants who rely on cow milk formula for nutrition benefit from transition to an extensively hydrolyzed formula or amino acid–based formula. Given the 40% cross-reactivity among milk and soy proteins, soy formula is not recommended. Most infants will respond to extensively hydrolyzed formulas, and less often is amino acid–based formula required. Studies suggest that after 12 to 18 months, a physician-supervised oral food challenge with the offending agent may be pursued to determine whether an FPIES reaction is still elicited. During these challenges, patients consume standardized doses of the offending allergen and are observed up to 6 hours for symptoms. If multiple allergens have been implicated, care is taken for a slow, stepwise approach. These challenges can be performed in the inpatient or outpatient setting depending on the severity of the FPIES phenotype. For those with a severe phenotype, challenges must be performed in the inpatient setting given the risk of severe hypovolemia.

CONCLUSIONS

FPIES is a less common allergic reaction to food allergens, with acute, chronic, and atypical phenotypes, that warrants

physicians' attention. Although rare, a subset of patients with FPIES presents with hypovolemic shock, requiring aggressive fluid resuscitation. Diagnosis is largely clinical and requires a high index of suspicion. Avoidance of offending allergens is the only maintenance therapy, with food exposure trials later in life to follow resolution.

COMMENTS: This is an important In Brief because it reminds us as health-care providers of the need to consider FPIES in the differential diagnosis of pediatric patients who present with the more common symptoms of vomiting and diarrhea and the importance of a careful history to determine which food products were ingested before the onset of symptoms. Yet, even fruits and vegetables can be implicated. As mentioned, FPIES is a clinical diagnosis because laboratory features may be present in only approximately 50% of cases. In more severe presentations, a partnership with a pediatric allergist or gastroenterologist might be prudent. The first international guidelines for FPIES were released in 2017, and although a helpful guide, additional research and future study is needed to gain a more complete understanding of the pathophysiology of the disease, identifying additional potential biomarkers, therapies to accelerate resolution of symptoms, and long-term follow-up of patients. Yet, timely diagnosis and avoidance of the appropriate allergens is critical to the health and well-being of our patients.

–Janet Serwint, MD
Associate Editor, In Brief

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