Clinical pearls

Food protein–induced enterocolitis to hen's egg

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Food protein–induced enterocolitis syndrome (FPIES) is potentially severe, non–IgE-mediated food hypersensitivity characterized by profuse emesis and diarrhea[1] that progresses to dehydration and shock in 15% to 20% of patients.[2] The diagnosis is based on clinical criteria and/or an oral food challenge (OFC).[1,3] The pathophysiology of FPIES is not well characterized; the gastrointestinal T-cell response to food protein is a plausible mechanism. FPIES is usually caused by cow's milk or soy in formula-fed infants; solids, such as rice, oat, barley, chicken, turkey, fish, and peanut, can also cause FPIES.[4] We report the case of an infant with FPIES caused by hen's egg and discuss the clinical features and differential diagnosis of FPIES.

CASE PRESENTATION

A 7-month-old boy born full term by means of vaginal delivery and exclusively breast-fed from birth had bloody stools at the age of 3 months. Maternal dietary elimination of dairy did not resolve bloody stools. Elimination of egg, soy, wheat, nuts, fish, corn, and oat led to resolution of the gross blood, although intermittent occult fecal blood persisted until 8 months of age. Stool cultures were negative for *Salmonella* species, *Clostridium difficile*, and *Camphylobacter* species. Allergic proctocolitis was diagnosed, and it was recommended that he avoid milk and soy and that solids be introduced into his diet. At the age of 11 months, he ingested scrambled egg without immediate symptoms, although his stool became positive for occult blood the following day. One month later, a second exposure to scrambled egg resulted in repetitive vomiting with irritability and pallor after 2 hours and diarrhea the following day. He recovered with oral rehydration at home. Two similar reactions occurred after ingestion of products (eg, cake) containing egg.

He was otherwise healthy and growing well and had no eczema or asthma. Skin prick test responses, serum food-specific IgE levels, and atopy patch test results to egg white, milk, and soy were negative. Laboratory tests revealed anemia (9.7 g/dL; normal, 10.3-13.2 g/dL) with a ferritin level of 21 ng/mL (normal, 20-200 ng/mL). The serum albumin level was 4.5 g/dL (normal, 3-5 g/dL).

Eosinophilic gastroenterocolitis was considered in the differential diagnosis. The patient underwent endoscopy at the age of 16 months, 3 months after the last exposure to dietary egg. Biopsies showed the colon to have preserved architecture with intralaminar eosinophil counts of 10 or less per high-powered field, mild gastritis with 5 or fewer eosinophils per high-powered field and no esophageal eosinophilia.

At 22 months, he was hospitalized for physician-supervised OFCs.[3] The challenges to cow's milk and soy were negative. OFC to 50 g of lightly cooked egg ingested over 45 minutes caused repeated emesis after 2 hours, with an increase in neutrophils from an initial count of 2200 to 8000 cells/mm^3 at 6 hours. The eosinophil count decreased from 600 to 100 cells/mm^3 at 6 hours. Directly after the onset of symptoms, intravenous boluses of normal saline (total 20 mL/kg) and a dose of methylprednisolone (1 mg/kg) were administered. Symptoms subsided within 4 hours. Discharge recommendations included strict egg avoidance and follow-up evaluation in 1 year.

DISCUSSION

Egg allergy is one of the most common childhood food allergies and can induce various IgE- and non–IgE-mediated disorders.[5] We describe a case of FPIES to egg confirmed by an OFC. Egg has been reported previously[6] in one series of 10 young infants with milk or soy FPIES; 30% had acute symptoms to egg OFC (intended to be a negative control for milk and soy) at a median age of 5.5 months. Subsequently, to our knowledge, no more cases were published, suggesting that the natural history of FPIES is likely modified by a common practice of delaying introduction of foods of higher allergenic potential or from the same food group (eg, wheat in rice FPIES).[4]

Diagnosis of FPIES, especially when triggered by solids (eg, cereal grains), is often delayed because of a low index of suspicion and clinical features that overlap with other food protein-induced gastrointestinal disorders (Table I).[4] The diagnosis of FPIES is based on clinical criteria and/or a standardized OFC.[1,3] OFC in FPIES is considered a high-risk procedure because 50% of the reactive challenges require intravenous hydration. In our practice an initial diagnosis of FPIES is based on the clinical criteria. OFCs are performed within 12 to 18 months after the most recent FPIES reaction to assess whether tolerance to the offending food has developed. However, recent studies suggest that resolution of milk-induced FPIES might occur sooner.[7,8]

The differential diagnosis includes disorders that cause vomiting, diarrhea, and poor growth, possibly progressing to dehydration, lethargy, and shock in infants.[2] Infection is the most likely and most important nonallergic cause to exclude. Metabolic disorders and necrotizing enterocolitis should be

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TABLE I. Food protein–induced gastrointestinal disorders*

	FPIES†	Proctocolitis	Enteropathy	Eosinophilic gastroenteropathy‡
Disease onset	**Days to 1 y§**	**Days to 6 mo**	**2-24 mo**	**Any age**
Symptoms				
Emesis	Prominent	No	Intermittent	Intermittent
Diarrhea	Severe	No	Moderate	Moderate
Bloody stools	Severe	Moderate	Rare	Moderate
Edema	Acute, severe	No	Moderate	Moderate
Shock	15% to 20%	No	No	No
Failure to thrive	Moderate	No	Moderate	Moderate
Allergy evaluation				
Food skin prick test	Negative	Negative	Negative	Positive in 50%
Serum food-specific IgE	Negative	Negative	Negative	Positive in 50%
Total IgE	Normal	Normal	Normal	Normal to increased
Peripheral blood eosinophilia	No¶	Occasional	No	Present approximately 50%
Biopsy findings				
Villous injury	Patchy, variable	No	Variable	Variable
Colitis	Prominent	Focal	No	Might be present
Mucosal erosions	Occasional	Occasional, linear	No	Might be present
Lymphoid nodular hyperplasia	No	Common	No	Yes
Eosinophils	Prominent	Prominent	Few	Prominent; neutrophilic infiltrates, papillary elongation and basal zone hyperplasia
Food challenge‖	Vomiting approximately 2-4 h; diarrhea approximately 5-8 h	Rectal bleeding approximately 6-72 h	Vomiting, diarrhea, or both approximately 40-72 h	Vomiting and diarrhea in hours to days
Natural history	Cow's milk: 60% resolved by 2 y Soy: 25% resolved by 2 y	Resolved by 9-12 mo	Most cases resolve in 2-3 y	Typically a prolonged, relapsing course
Severity	++++	+	+++	++ (+)

*Modified with permission from Metcalfe DD, Sampson HA, Simon RA, editors. Food allergy: adverse reactions to foods and food additives. 3rd ed. Hoboken (NJ): Wiley-Blackwell; 2003.

†The diagnostic criteria proposed by Powell et al[2] to define FPIES include the onset of symptoms before 2 months of age, a positive response to a challenge performed during the first 9 months of age, cessation of diarrhea with elimination of the suspected protein, and recurrence of symptoms after ingestion of the protein.

‡Eosinophilic gastroenteropathy: esophagitis, gastritis, and gastroenterocolitis.

§Anecdotally, acute FPIES to shellfish (particularly mollusks) can start in adulthood.

¶Not observed in patients with acute FPIES.

‖Criteria for a positive challenge in patients with FPIES[2]: (1) emesis, diarrhea, or both; (2) fecal blood; (3) fecal leukocytes; (4) fecal eosinophils; and (5) increase in peripheral polymorphonuclear leukocyte count of greater than 3500 cells/mm^3. The challenge result is considered positive if 3 or more criteria are met, equivocal if 2 are met, and negative if 0 to 1 are met.

considered, particularly for newborn preterm infants. For infants presenting with bloody stools (gross or occult), the differential diagnosis includes common conditions, such as anal fissures, infectious colitis, and lymphonodular hyperplasia. Less common conditions include necrotizing enterocolitis, intussusception, Henoch-Schonlein purpura, familial Mediterranean fever, Meckel diverticulum, pancreatitis, Hirschsprung enterocolitis, amoebic colitis, and inflammatory bowel diseases. It is challenging to distinguish FPIES from other food protein–induced gastrointestinal disorders, including proctocolitis, enteropathy, and eosinophilic gastroenteropathy. These disorders present with overlapping symptoms; however, they generally differ in severity and persistence (Table I).

Our patient manifested 2 distinct patterns: he initially had intermittent macroscopic bloody stools during exclusive breast-feeding on an unrestricted maternal diet. Removal of egg, soy, wheat, nuts, fish, corn, and oat from the maternal diet led to resolution of bloody stools. He subsequently tolerated wheat, corn, and oat in his diet and passed soy and cow's milk challenges. After resolution of chronic symptoms, he had several acute episodes with typical FPIES symptoms after ingestion of egg.

During exclusive breast-feeding, he was given a diagnosis of allergic proctocolitis. Bloody stools can be the initial manifestation of FPIES. An acute-on-chronic form of FPIES was described[2] in infants with chronic vomiting, diarrhea (sometimes bloody), and failure to thrive when continuously exposed to the offending food, but these patients have acute FPIES if the food is reintroduced after a period of exclusion. Lake[9] hypothesized that in the breast-fed infants proctocolitis might represent an attenuated form of FPIES because in both patients with proctocolitis and those with FPIES, an intense inflammatory response can occur in the rectum. He suggested that the protective effects of breast milk (eg, IgA antibodies and partially processed food proteins) prevent expression of classic FPIES. Alternatively, the threshold dose of allergen might not be reached in breast milk to trigger a classic FPIES. Only 1 case report recently published

described an infant with acute FPIES during exclusive breastfeeding.[10] This is in contrast to IgE-mediated food allergies in which acute reactions have been attributed to food protein passage through breast milk.

Our patient had no eosinophilic gastroenteropathy, although biopsy specimens could be false-negative because of removal of dietary egg 3 months before the examination. Clusters of eosinophils have been found in intestinal biopsy specimens from many patients with FPIES.[2] In our patient peripheral eosinophilia decreased after the positive OFC response to egg, potentially reflecting recruitment of eosinophils from the periphery to the digestive tract or the effect of intravenous steroids. Eosinophilic gastroenteritis and the food protein–induced syndromes (enterocolitis, enteropathy, and proctocolitis) might represent a continuum of eosinophilic gastrointestinal disorders with similar underlying immunopathogenic mechanisms.

Infantile FPIES can be caused by hen's egg, and FPIES induced by solid foods can be challenging to diagnose. Indeed, delayed diagnosis and misdiagnosis is common and can lead to incorrect treatment, invasive treatment, or both. More research is necessary to determine whether food protein–induced disorders (Table I) are pathophysiologically distinct from FPIES or represent a spectrum with a similar cause and clinical expression modified by environmental factors.

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