



CME Review

Chronic food protein–induced enterocolitis syndrome Characterization of clinical phenotype and literature review

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Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the presentation, diagnosis and treatment of chronic FPIES
- Recognize chronic FPIES early in its presentation in order to prevent complications

Release Date: September 1, 2016**Expiration Date:** August 31, 2018**Target Audience**

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Introduction

Food protein–induced enterocolitis syndrome (FPIES) is classified as a non-IgE, cell-mediated, food-induced allergic disorder that usually presents within the first 12 months of life.^{1–3} FPIES can manifest with acute or chronic symptoms.^{4,5} The phenotype of acute FPIES is well documented in the literature and is the dominant phenotype reported in older infants, children, and adults.^{6–12} After an isolated ingestion of the offending food, an acute FPIES reaction manifests as profuse, projectile, and repetitive emesis beginning within 1 to 4 hours.⁶ Emesis is often accompanied by pallor, lethargy, dehydration, and, in the most severe cases, hypovolemic shock. In some patients, bloody or mucoid diarrhea follows within 5 to 10 hours.^{13,14} Although severe acute FPIES reactions may require emergency treatment in the hospital, symptoms usually resolve within several hours with or without treatment upon removal of the offending food. The entity of chronic FPIES, however, remains elusive. Chronic FPIES occurs in infants when the offending food is ingested in the diet on a regular basis, such as feeding with cow's milk formula (CMF) or soy-based infant formula.^{13–15} The phenotype of chronic FPIES is characterized by intermittent but progressive emesis and watery diarrhea with mucus and occasional blood. This often leads to failure to thrive (FTT), hypoalbuminemia, metabolic derangements, and ultimately severe dehydration that may culminate in hypovolemic shock.^{13–16} In chronic FPIES, symptoms resolve within a few days and up to 2 weeks after elimination of the offending food protein from the diet.^{13,14} Subsequent ingestions of the offending food after a period of elimination will result in an acute FPIES episode.⁵ However, if the offending allergens are identified and eliminated from the diet, infants will thrive without chronic symptoms. In both acute and chronic FPIES, laboratory findings include metabolic acidosis, elevated white blood cell count with profound neutrophilia, and thrombocytosis. The goals of this review are to describe the clinical phenotype and to review the current literature on chronic FPIES. To illustrate the features of chronic FPIES, we describe a case series of young infants with a diagnosis of chronic FPIES.

Methods

Patients from birth to 7 months admitted to the pediatric intensive care unit (PICU) at Mount Sinai Children's Hospital from

June 2012 to June 2014 with the diagnosis codes of FTT, metabolic acidosis, hypovolemic shock, dehydration, vomiting, feeding problems in a newborn, and allergy to milk were identified. Medical records were analyzed for age at symptom onset and presentation, sex, birth history, feeding history, presenting signs and symptoms, admission and discharge diagnosis, inpatient workup, and treatment strategy.

Results

Nine patients (5 boys and 4 girls) were identified with suspected FPIES. All of the patients presented with lethargy, 8 presented with dehydration and diarrhea, approximately half of which were grossly bloody and half with mucus, and 5 presented with vomiting. Nine patients presented with hypotension, 2 with pallor, and 1 with fever. Age of symptom onset ranged from 6 days to 2 months and delay to diagnosis from 2 days to 2 months. Five patients had FTT, and all of the patients had presented to a physician or emergency department prior to PICU admission. Eight patients were fed CMF and 1 was exclusively breastfed. Nine patients had an anion gap metabolic acidosis, all required fluid resuscitation, and 7 patients underwent a rule-out sepsis (ROS) workup. Sepsis workup included obtaining a complete blood cell count, blood culture, and urine culture, and broad-spectrum antibiotics were given for 48 hours. The results of blood cultures were negative in all instances. Six patients were switched to amino acid–based formula (AAF), and 3 began taking extensively hydrolyzed casein-based formula (eHCF) with resolution.

Case 1

A 7-week-old boy who was breastfeeding with CMF supplementation since birth presented with 5 weeks of intermittent vomiting, bloody stool with mucus, lethargy, weight loss, and dehydration. This was the patient's third presentation to the hospital; the results of an ROS workup were previously negative. Laboratory tests revealed metabolic acidosis, an elevated lactate level, anemia, and thrombocytopenia (Table 1). Abdominal radiography revealed dilated air-filled loops of bowel. Endoscopy with intestinal biopsy revealed normal architecture. The patient continued to receive parenteral nutrition for 15 days and was then given AAF with gradual resolution of symptoms.

Table 1
Patient Laboratory Data

Patient No.	pH level	Lactate Level, mmol/L	White Blood Cell Count, $\times 10^3/\mu\text{L}$	Neutrophil Count, $\times 10^3/\mu\text{L}$	Band Count, $\times 10^3/\mu\text{L}$	Platelet Count, $\times 10^3/\mu\text{L}$	Sodium Level, mEq/L	Potassium Level, mEq/L	Bicarbonate Level, mEq/L
1	7.13	9.6	6.6	NA	NA	24	131	4	8
2	7.18	2.8	10.3	17	23	14.6	135	4.2	6
3	7.29	0.9	13.3	22	0	526	144	4.4	6
4	7.4	2	7.8	NA	NA	208	137	5.8	27
5	7.17	0.8	26.2	20	25	383	139	3.9	8
6	7.15	2.3	17.8	53	0	622	140	3.2	8
7	6.8	NA	75	NA	25	NA	NA	NA	4
8	7.28	0.5	14.6	28	26	535	150	2.9	15
9	7.18	1.1	18	NA	NA	660	153	3.8	14

Abbreviation: NA, not applicable.

Case 2

A 9-day-old girl feeding CMF presented with 2 days of vomiting, loose stools, pallor, lethargy, dehydration, and weight loss. The patient previously presented to her pediatrician with weight loss. Laboratory evaluation revealed metabolic acidosis, hyponatremia, and leukocytosis with bandemia. The results of an ROS workup were negative. The patient was given nothing by mouth for 3 days and her diet was slowly advanced to eHCF with resolution of symptoms and demonstration of weight gain after 7 days. Before discharge CMF was tried and after 24 hours the patient had increased stools and appeared pale and listless. The patient was discharged home with AAF after a 13-day hospitalization.

Case 3

An 8-week-old girl who was exclusively breastfed presented with 1 week of vomiting, bloody stool, lethargy, fever, and dehydration. The patient had previously presented to her pediatrician with similar symptoms. Laboratory tests revealed metabolic acidosis, anemia, leukocytosis with left shift, and thrombocytosis. Stool specimens tested positive for reducing substances. The results of an ROS workup were negative. She was given AAF with symptom resolution in 10 days.

Case 4

A 1-week-old girl, who was previously breastfed and given CMF 2 days before presentation, presented with vomiting, lethargy, decreased oral intake, and weight loss. Laboratory test results were normal. An upper gastrointestinal tract series revealed reflux. The patient was admitted for ROS workup and continued to be fed CMF. While an inpatient, the patient had an observed cyanotic episode and developed bloody stools. Abdominal radiography revealed a normal bowel gas pattern and was not significant for a surgical pathologic findings. She was given nothing by mouth for 4 days and then transitioned to eHCF with resolution of symptoms within 6 days.

Case 5

A 4-week-old boy breastfed with CMF supplementation since birth presented with 4 days of diarrhea, progressive pallor, and lethargy. The patient had previously presented to the pediatrician with FTT. On admission, the patient was toxic appearing and hypotensive with a blood pressure of 76/39 mmHg. Laboratory evaluation revealed metabolic acidosis and leukocytosis with bandemia. The ROS workup were negative. The patient was given AAF with resolution of symptoms and demonstration of weight gain after 9 days.

Case 6

A 2-month-old girl receiving CMF presented with 3 days of vomiting, loose stools with mucus, and lethargy. The patient appeared dehydrated with dry and cracked lips, prolonged capillary

refill greater than 3 seconds, and cool extremities. Laboratory studies were notable for metabolic acidosis and leukocytosis with neutrophilia. A stool guaiac test result was positive. The results of an ROS workup were negative, and the patient was discharged after stabilization and rehydration with the diagnosis of acute gastroenteritis. The patient was readmitted to the PICU 10 days later with metabolic acidosis and was then given eHCF with symptom resolution within 8 days.

Case 7

A 3-week-old, late preterm boy breastfed with CMF supplementation presented with 1 day of loose and bloody stool, lethargy, and dehydration, as well as significant weight loss from birth. The patient had previously presented to the pediatrician with similar symptoms. He was hypotensive with a distended abdomen and sunken fontanel on presentation. Laboratory findings were notable for metabolic acidosis, leukocytosis with bandemia, and elevated blood urea nitrogen and creatinine levels. The results of ROS workup were negative. Abdominal radiography revealed gaseous distension with air fluid levels significant for small bowel obstruction. An exploratory laparotomy was performed, which revealed no signs of malrotation or obstruction and a healthy bowel. The patient was kept on bowel rest and gradually given eHCF with slow symptom resolution.

Case 8

A 7-week-old boy presented with 1 day of bloody stools, lethargy, and dehydration. He had been receiving eHCF, but it was substituted with CMF 1 day prior to presentation. The patient presented in hypovolemic shock, and laboratory tests revealed metabolic acidosis, leukocytosis with bandemia, and thrombocytopenia. An upper gastrointestinal tract series revealed an abnormally located duodenojejunal junction and was significant for malrotation. The patient underwent a laparotomy during which adhesions were noted and a Ladd procedure was performed to alleviate the intestinal malrotation. His diet was then advanced to AAF and the patient was discharged home. The patient was readmitted to the PICU 5 days later with persistent diarrhea and metabolic derangements attributed to persistent intestinal inflammation. Symptoms resolved with bowel rest and slow reintroduction of AAF.

Case 9

A 6-week-old boy receiving CMF presented with 10 days of vomiting, diarrhea, and lethargy. He had 1 prior presentation to an outside hospital before admission. On examination he appeared dehydrated with sunken eyes. Laboratory test results were notable for metabolic acidosis, leukocytosis, and hypernatremia. The patient was stabilized and switched to AAF with resolution of symptoms within 10 days.

Discussion

Chronic FPIES is a disorder of young infants with an onset within 3 months after birth. In a US study, the median age of onset was 3.5 months.⁶ Chronic FPIES develops when the offending food is introduced early in life and ingested daily, and it has only been reported in young infants fed CMF or soy-based formula.^{13,14} Symptoms usually begin within 1 to 4 weeks after the introduction of CMF or soy-based formula. Patients with chronic FPIES present with intermittent emesis, bloody diarrhea, and dehydration, as well as weight loss, FFT, and metabolic acidosis.^{11,13,14} There is no clear temporal association between symptoms and food ingestion. Diarrhea is a cardinal feature of chronic FPIES in infancy; however, in older children presenting with acute FPIES reactions, diarrhea is less common (30%–50%). In older children, vomiting is the most constant feature, followed by pallor and lethargy. Hypoalbuminemia and weight gain of less than 10 g/d have been identified as independent predictors of chronic cow's milk (CM) FPIES in young infants with chronic gastrointestinal symptoms.¹⁵ Approximately 75% of infants will appear acutely ill on presentation and 15% are hypotensive and require hospitalization and rehydration.¹⁷ Laboratory studies reveal anemia, hypoalbuminemia, and neutrophilic leukocytosis.¹⁵ In the most severe cases, infants develop acidemia and methemoglobinemia, requiring treatment with methylene blue and bicarbonate.¹⁸ When symptoms of chronic FPIES are recognized early, elimination of the offending protein can prevent full expression of FPIES and its potential complications.^{19,20} Infants with chronic FPIES usually improve within 3 to 10 days with removal of the offending agent, intravenous fluid rehydration, and replacement with hypoallergenic or AAF.^{13,14} However, if the food is reintroduced after a period of avoidance, an acute FPIES episode will occur with the classic onset of emesis within 1 to 4 hours.^{13,14} The distinctions between acute and chronic FPIES are outlined in Table 2.

Offending Foods

Most patients react to a single food.^{6,7} The most common inciting foods are CM and soy; in US studies, up to 50% of young infants react to both, whereas soy formula FPIES is much less common in other countries.^{19,21–23} This difference could be attributed to differences in soy formula use in infancy or a different phenotype based on referral populations. Specifically, extensively hydrolyzed formula is the first-choice replacement for CM allergy in Europe, and soy formula is rarely prescribed before 6 months of life.²⁴ The younger the age of an infant, the more likely is the coallergy to CM and soy.⁶ Solid foods can cause acute FPIES as well, including rice, oat, barley, chicken, turkey, egg white, green pea, fish, and peanut.^{10,12,25,26} Solid food FPIES has a later age of onset, usually between 4 and 7 months of age, correlating with the introduction of solid food into the diet.^{6,7,19} There are no published reports of chronic FPIES caused by solid foods. Both acute and chronic FPIES have been rarely described in exclusively breastfed infants, and most breastfed infants with FPIES are asymptomatic when the mother is not ingesting the foods that trigger FPIES reactions on direct ingestion.^{27–30} Although largely thought of as a pediatric disease, there have also been reports of acute FPIES reactions occurring in adults. FPIES in adults most commonly occurs to seafood (fish and shellfish) and egg.^{30,31}

Laboratory Findings

Leukocytosis has been reported in more than 90% of patients and thrombocytosis was reported in 63% of patients with FPIES.^{9,14} Stool examination may reveal occult blood, leukocytes, Charcot-Leyden crystals, and reducing substances.^{13,14,23} However, these tests have a low sensitivity and specificity. In infants with chronic milk FPIES, hypoalbuminemia and weight gain of less than 10 g/d were identified as independent predictors of the diagnosis.¹⁵ Methemoglobinemia has also been reported in severe FPIES, but

Table 2
Comparison of the Clinical Features of Acute and Chronic FPIES

Feature	Acute FPIES	Chronic FPIES
Age of onset	Any; largely a pediatric disease occurring by 12 months of age, although there are case reports in older children and adults	Described exclusively in infancy
Offending foods	Any foods ingested on an intermittent basis; most commonly reported foods include: cow's milk, soy, rice, oat, barley, chicken, turkey, egg white, green pea, and peanut	Foods ingested on a regular basis, most commonly cow's milk or soy-based formulas
Clinical manifestations	Profuse and repetitive emesis within 1–4 hours of ingestion accompanied by lethargy and pallor; diarrhea may follow usually within 5–10 hours	Intermittent emesis without clear temporal association to food ingestion, chronic diarrhea, lethargy, poor weight gain, and failure to thrive
Laboratory findings	Leukocytosis with neutrophilia, thrombocytosis, and metabolic acidosis	Leukocytosis with neutrophilia, thrombocytosis, metabolic acidosis, hypoalbuminemia, methemoglobinemia, and anemia
Fecal studies	Stool test positive for polymorphonuclear neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances	
Management	Trigger food elimination, rapid intravenous hydration, prompt treatment of unintentional reactions	Trigger food elimination, rapid intravenous hydration, replacement of CM- or soy-based infant formula with a hypoallergenic formula such as eHCF or AAF, occasionally bowel rest is required
Resolution of symptoms after trigger food elimination	Complete resolution within 24 hours after elimination of the food from the diet	Complete resolution of symptoms within 3 to 14 days of elimination of the food from the diet
Reaction on reexposure after a period of food elimination	Exposure to the offending food with result in acute FPIES symptoms within 2–4 hours	Subsequent feeding of the offending food after a period of avoidance will result in the acute FPIES symptoms within 2–4 hours
Breastfeeding	Rare reports of acute or chronic FPIES reactions while exclusively breastfeeding	
Growth	Growth is normal	Failure to thrive is common
IgE positivity	Patients with detectable food specific IgE tend to have a more protracted course	
Natural history	Self-limiting; time to resolution varies by population though many cases resolve by 3 years of age	
Prognosis	Favorable; no reported long-term complications	

Abbreviations: AAF, amino acid–based formula; CM, cow's milk; eHCF, extensively hydrolyzed casein-based formula; FPIES, food protein–induced enterocolitis syndrome.

its sensitivity is low.¹⁸ In one study, predominance of leukocytes in gastric aspirate was associated with FPIES diagnosis.³²

Diagnosis

The diagnosis of FPIES is often delayed because of the nonspecific nature and delayed onset of the symptoms in relation to food ingestion, absence of cutaneous and respiratory symptoms characteristic of acute IgE-mediated food allergic reactions, and lack of a definitive biomarker for diagnosis.^{9,33,34} Diagnosis of chronic FPIES can be presumptively made based on a history of classic symptoms that resolve after removal of the offending food from the diet.¹ However, on reintroduction of the food, an acute FPIES reaction will occur; this is the only definitive confirmation of a chronic FPIES diagnosis.^{13,14,16} Physician-supervised oral food challenge (OFC) is the gold standard for diagnosis, but it is not often necessary. OFCs are most often used when the diagnosis is unclear or to determine whether tolerance has developed before reintroduction of the trigger food. All children with physician-diagnosed FPIES to CM should recover completely and remain asymptomatic and thriving on AAF. Children with reported ongoing symptoms while being fed AAF should be offered physician-supervised OFCs to verify the diagnosis of FPIES and should also be evaluated for alternative causes.

Differential Diagnosis

Because FPIES lacks specific biomarkers, the differential diagnosis is extensive (Table 3).³⁵ In its chronic form, FPIES resembles metabolic disorders, primary immunodeficiencies, neurologic conditions, and other types of non-IgE-mediated food allergy, such as food protein–induced enteropathy, allergic proctocolitis, eosinophilic esophagitis, eosinophilic gastroenteritis, or other nonspecific non-IgE-mediated gastrointestinal food allergies.^{35–37} In its acute presentation, FPIES can present similarly to sepsis, acute gastroenteritis, anaphylaxis, and surgical emergencies.³⁵

Pathophysiology

Endoscopy and biopsy are rarely performed in FPIES because diagnosis is based on clinical criteria and symptoms resolve with dietary elimination of the offending food. Limited insight into FPIES pathologic mechanisms comes from rare older reports of endoscopic evaluations and biopsy specimens that were obtained in infants with a clinical phenotype consistent with FPIES. Endoscopy revealed diffuse colitis with variable ileal involvement. Focal erosive gastritis and esophagitis were found and prominent eosinophilia and villus atrophy were observed in the most severe cases.³⁸ Colon mucosa appeared mildly friable to severe spontaneous hemorrhage and minute ulcers were found.^{39,40} Crypt abscesses have also been described in some patients. Jejunal biopsies revealed variable villus atrophy, edema, and increased numbers of lymphocytes, IgM- and IgA-containing plasma cells, eosinophils, and mast cells.⁴¹ Increased expression of tumor necrosis factor α (TNF- α) and decreased expression of transforming growth factor β (TGF- β) receptors have been reported in the intestinal mucosa of patients with FPIES.^{41–44} Additional studies exploring the role of food protein–specific T lymphocytes used peripheral blood and reported a release of TNF- α and interferon γ (IFN- γ) by activated peripheral blood mononuclear cells. Studies found that children with active FPIES to CM have deficient T-cell–mediated TGF- β responses to casein.⁴⁵ In a cohort of Japanese infants with non-IgE-mediated food allergy, TNF- α , interleukin (IL) 6, and T_H2 cytokines (IL-3, IL-5, and IL-13), but not IFN- γ or IL-17, were increased in the supernatant from milk protein–stimulated peripheral blood mononuclear cell cultures compared with nonallergic controls.⁴⁶ Humoral responses in FPIES are characterized by a paucity of

Table 3
Differential Diagnosis of Chronic FPIES

Condition	Features That May Distinguish From FPIES
Infections	
Infectious gastroenteritis (eg, viral, bacterial)	Single episode of illness that self-resolves in several days, fever, sick contacts with similar symptoms, emesis unrelated to specific food ingestion
Sepsis	Fluid resuscitation alone not effective and antibiotics are required for recovery, fever, infectious source
Necrotizing enterocolitis	Apnea, respiratory failure, temperature instability, intramural gas, severe abdominal distention, abdominal tenderness, and gastric retention
Food allergic disorders	
Anaphylaxis	Symptom onset is acute (approximately 2 minutes to 2 hours), positive IgE test result, usually other allergic manifestations (eg, urticaria), epinephrine is helpful
Food protein–induced enteropathy	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe
Eosinophilic gastroenteropathies (eg, eosinophilic esophagitis, eosinophilic gastroenteritis)	Usually not associated with specific food intake, symptoms more chronic than episodic, vomiting less severe, more likely to have positive IgE test results to specific foods
Gastrointestinal disorders	
Gastrointestinal reflux disease	Chronic and less profuse emesis (ie, does not lead to dehydration), only upper gastrointestinal tract symptoms present
Hirschsprung disease	Delay in passage of the first meconium, marked abdominal distention
Obstructive problems (eg, malrotation, Ladd bands, volvulus)	Not related to specific food intake, evidence of obstruction on radiologic studies
Other	
Inborn errors of metabolism	Developmental delay, neurologic manifestations, organomegaly
Neurologic disorders (eg, cyclic vomiting)	No relation to specific food intake, only upper gastrointestinal tract symptoms present
Immune enteropathies (eg, inflammatory bowel disease, autoimmune enteropathy, immunodeficiency)	Rare in infancy, not related to specific food intake
Celiac disease	No temporal association between symptoms and specific food intake; progressive malabsorption; celiac serologic test result is positive
Severe lactose deficiency	Gas, bloating, cramps, diarrhea, borborygmi, and vomiting after ingestion of liquid milk and large doses of dairy products
Primary immunodeficiency	Frequent infections, no association with specific food ingestion

Abbreviation: FPIES, food protein–induced enterocolitis syndrome.

specific antibody production across all immunoglobulin classes.^{45,47} At this time, the pathophysiology of FPIES requires further study.

Positive Food Specific IgE

Allergy tests are often not helpful because most patients have a negative skin prick test result and nondetectable food specific IgE levels. However, in a subset of patients, food specific IgE can be detected to the offending food, which is referred to as atypical FPIES.²² In a series of young infants with CM FPIES in Japan, CM-specific serum IgE was detected in 37% of the patients.⁴⁸ In a US

study, approximately 25% of patients with FPIES developed IgE positivity with a negative skin prick test result.⁶ IgE positivity in FPIES is associated with a more protracted course.^{6,22} Most of these patients retain the FPIES phenotype, although in 1 US study up to 41% of those with CM FPIES and positive IgE test results developed symptoms of immediate IgE-mediated allergy on subsequent ingestion of milk.⁶

Patch Testing

In a study of 19 infants aged 5 to 30 months with challenge-confirmed FPIES, atopy patch tests (APTs) predicted the outcomes in 28 of 33 OFCs and all patients with positive OFC results had positive APT results.⁴⁹ In another study, however, APTs performed in 25 children before follow-up OFC found a positive predictive value of 40%, revealing poor utility of APT in predicting tolerance development in FPIES.⁵⁰ At this time, APT is not recommended for routine diagnosis of FPIES.¹

Treatment

The long-term management of chronic FPIES is strict avoidance of the offending food.^{1,51} It is difficult to assess the amount of protein that a patient can tolerate because of the late onset of the symptoms and the threshold dose may get smaller with repeated episodes. Formula is initially replaced with eHCF. AAF is needed for persistent symptoms to eHCF in approximately 10% to 15% of the infants.⁶ In severe cases, and as demonstrated in our case series, bowel rest, correction of the metabolic derangements, and intravenous fluids are required with slow reintroduction of hypoallergenic infant formula (eHCF or AAF). It is generally not recommended that patients ingest cooked forms of the food; however, in one report, patients with CM FPIES tolerated cooked forms of CM.⁵² Rarely, FPIES can occur in breastfeeding infants, as noted in case 3.^{27,51,53} Current recommendations are that the offending food should only be removed from the maternal diet if acute reactions occur, chronic symptoms are present, or the infant has FTT.³⁶

Solid foods in infants with CM or soy formula FPIES should be introduced at home between 4 and 6 months of age, preferably starting from fruits and vegetables and then followed by grains and other foods as tolerated. Although delayed introduction of solid foods beyond 6 months of age has been previously recommended, more recent evidence supports not delaying food introductions unless FPIES symptoms to multiple foods have occurred. On the basis of our experience, even with timely introduction of solid foods, many infants with FPIES have abnormal feeding behaviors likely attributable to prior unpleasant experiences associated with FPIES reactions. Delaying introduction of solid foods may increase this risk of food refusal and feeding difficulties in infancy.⁵⁴

In acute FPIES with moderate-severe symptoms, in addition to vigorous intravenous rehydration, a single dose of 1 mg/kg of intravenous methylprednisolone is given empirically based on the presumed pathophysiologic mechanisms that involve cell-mediated immune responses to food proteins.³⁷ Recently, intravenous or intramuscular ondansetron has been reported to stop vomiting during an acute FPIES episode.^{55,56} Ondansetron is not expected to have efficacy in chronic FPIES.⁵⁶ Although intravenous vasopressors may be required for treating severe hypotension, epinephrine has no effect on emesis during an FPIES reaction. Self-injectable epinephrine is not routinely prescribed for FPIES unless the patient has risk factors for anaphylaxis, such as a detectable food specific IgE, asthma, or other IgE-mediated food allergy.

Natural History

The natural history of infantile FPIES is favorable with children acquiring tolerance to FPIES trigger foods throughout childhood.⁵⁷

No fatalities from FPIES have been reported. The data on time to FPIES resolution vary greatly between populations and phenotypes.⁵⁷ Children with a mild phenotype outgrow FPIES by 2 to 3 years of age, whereas those with a more severe phenotype, characterized by more severe reactions and/or reactions to multiple food triggers, or those with detectable food specific IgE may have a more protracted course.²¹ Individual patients may have persistent FPIES into adolescence or young adulthood.⁵⁷ In a study conducted in Israel, 90% of the 44 children had outgrown CM FPIES by 3 years of age.²¹ In a retrospective US study, lower rates of resolution of FPIES were found, with 35% outgrowing FPIES by 2 years of age, 70% by 3 years of age, and 80% by 4 years of age.⁷ They did not find a significant difference among CM, soy formula, and solid food FPIES. FPIES due to solid foods tends to resolve by 5 to 6 years of age.^{6,19} Interval physician-supervised OFC should be performed to assess for resolution. Current US consensus is that an OFC be performed every 18 to 24 months to assess for resolution of symptoms.¹ These challenges should be performed with physician supervision; it is prudent to secure an intravenous access before starting the OFC. In addition, testing for specific IgE may be done before the OFC because some patients develop IgE-mediated immediate hypersensitivity.¹ Data from Korea suggest that more frequent challenges may be indicated, especially in the infantile soy formula FPIES. In 1 study, challenges were undergone at the age of 6 months and repeated in 2-month intervals. In that study, tolerance rates to soy were 75.0% at 6 months of age, 90.9% at 8 months of age, and 91.7% at 10 months of age.⁸

Conclusion

Chronic FPIES is a non-IgE, presumably cell-mediated food allergy that affects infants. Presenting symptoms are chronic diarrhea, intermittent emesis, bloody stools, dehydration, FTT, and feeding difficulties. Diagnosis is based on the history and symptoms that resolve with removal of the offending food, exclusion of other causes and, if necessary, a physician-supervised OFC. The only conclusive diagnostic test that confirms chronic FPIES is resolution of chronic symptoms with the removal of the offending food from the diet and redevelopment of acute symptoms within hours on repeated food ingestion. FPIES is frequently misdiagnosed and patients undergo extensive diagnostic evaluations. Early recognition is required to prevent progression to FTT, anemia, dehydration, and hypovolemic shock. CM and soy formula FPIES usually resolves by the age of 3 years and physician-supervised OFCs can be done to assess tolerance. Patients with detectable food specific IgE levels may have a more protracted course, with FPIES persisting into older childhood or adolescence. Further research is required to understand the pathophysiologic mechanisms, to identify diagnostic biomarkers, and to develop treatments that enhance resolution of FPIES.

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