Food Protein-Induced Enterocolitis Syndrome (FPIES): Current Management Strategies and Review of the Literature

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Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic. FPIES is elicited most commonly by milk and soy proteins; however, rice, oat, and other solid foods may also elicit FPIES. Certain FPIES features overlap with food protein-induced enteropathy and proctocolitis, whereas others overlap with anaphylaxis. FPIES is not well recognized among pediatricians and emergency department physicians; the affected children are often mismanaged as having acute viral gastrointestinal illness, sepsis, or surgical disease, delaying diagnosis of FPIES for many months. The aim of this review is to provide case-driven presentation of the features of FPIES. Although randomized clinical trials on management options are missing, the relevant current literature and authors' experience are reviewed in detail. © 2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:317-22)

Key words: *Food protein-induced enterocolitis; Enterocolitis; Food-induced; Food allergy; Cow's milk; Soy; Solid food; Multiple foods; Gastrointestinal*

Food protein-induced enterocolitis syndrome (FPIES) is a non−IgE-mediated gastrointestinal food hypersensitivity that manifests as profuse, repetitive vomiting, often with diarrhea, leading to acute dehydration and lethargy or weight loss and failure to thrive if chronic[1] (Box 1; see also Table E1 in this article's Online Repository at www.jaci-inpractice.org). Here, we present the clinical features according to the age of onset and trigger food [cow's milk (CM) and soy FPIES versus solid food FPIES versus multiple foods FPIES] as well as according to acute or chronic presentation.

CLINICAL FEATURES

Age of onset and trigger foods

CM/soy FPIES. A common presentation of FPIES is profuse, repetitive emesis and diarrhea in a young infant fed with CM or soy formula[2-4] (Box 1; see also Table E2 in this article's Online Repository at www.jaci-inpractice.org). Classic FPIES begins in early infancy within the 3 months of life (but up to 1 year of age), usually 1 to 4 weeks after introduction of formula. In the Israeli population-based birth cohort, the median age of FPIES onset was 30 days; all infants presented younger than 6 months of age.[5] Delayed introduction of CM or soy in breast-fed infants may result in a later onset. FPIES to CM and soy present in the breast milk in exclusively breast-fed infants is extremely rare, although reported in two case studies (see "Breast-feeding").[6,7]

Solid foods FPIES. FPIES may be induced by solid foods, with age at onset later than that of CM and soy FPIES, because solid foods are usually introduced between 4 and 7 months of age.[2,8] Rice is the most common solid food that induces FPIES,[9] followed by oat, barley, chicken, turkey, egg white, green pea, peanut, sweet potato, white potato, corn, fruit protein, fish, and mollusks.[10-15] The common triggers in FPIES, rice and oat and vegetables, are considered to be hypoallergenic for IgE-mediated food allergy and are usually the first solids introduced into an infant's diet.

Natural history of FPIES appears to be modified by delaying introduction of foods with higher allergenic potential (eg, egg) or from the same food group (eg, wheat in rice FPIES). Egg is rarely reported as an FPIES trigger. However, in an Australian cohort of 38 patients, egg FPIES occurred in 10%.[16] In addition, among 10 infants with CM or soy FPIES, 3 (30%) developed egg FPIES when exposed to egg at a median age of 5.5 months.[17] Wheat FPIES has been reported only twice,[18,19] presumably because of significantly delayed introduction of wheat to the diet of infants with FPIES.[10,20] FPIES onset after 1 year of age is rare, although FPIES to fish and shellfish (including mollusks and crustaceans) has been observed in older children and adults.[8,21]

Multiple food FPIES: CM and soy FPIES. Up to 50% of the patients react to both CM and soy in the US studies.[10,22-24] Studies from Australia and Israel reported no patients reacting to both CM and soy.[2,5] These differences may reflect selection bias with more severe cases reported from the allergy referral

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Supported by National Institutes of Health/National Institute of Allergy and Infectious Diseases grant K08-AI091655 (K.M.J.).
Conflicts of interest: K. M. Järvinen has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases; receives royalties from UpToDate; and has received travel support from the NIH/US Department of Agriculture Bethesda. A. Nowak-Węgrzyn declares she has no relevant conflicts of interest.
Received for publication January 11, 2013; revised April 16, 2013; accepted for publication April 18, 2013.
Available online June 3, 2013.
Cite this article as: Järvinen KM, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome (FPIES): Current management strategies and review of the literature. J Allergy Clin Immunol: In Practice 2013;1:317-22. http://dx.doi.org/10.1016/j.jaip.2013.04.004.
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2213-2198/$36.00

http://dx.doi.org/10.1016/j.jaip.2013.04.004

Abbreviations used
APT- Atopy patch test
CM- Cow's milk
FPIES- Food protein-induced enterocolitis
OFC- Oral food challenge
SPT- Skin prick test

populations in the US studies, different feeding practices, genetic factors, or lack of exposure to both CM and soy because of feeding with a hypoallergenic formula after a diagnosis of FPIES to CM or soy.

Multiple food FPIES: CM/soy FPIES and solid foods FPIES. Approximately one-third of infants with CM or soy FPIES develop solid foods FPIES, commonly caused by rice and oat, the grains typically introduced at weaning.[10,20] In the US study, 50% of infants reacted to more than one grain: rice, oat, or barley.[10] In contrast, 1 of 14 Australian infants with rice FPIES reacted to oat.[9] There is a variably high rate of multiple foods in solid FPIES. Eighty percent of infants with solid foods FPIES reacted to more than one food, and 65% were previously diagnosed with CM and/or soy FPIES.[10] However, in an Australian study, only 17% of infants with solid foods FPIES reacted to multiple foods.[2]

Acute symptoms

FPIES may present acutely, after the food has been removed from the diet and then re-introduced, or if it is ingested intermittently (Box 1, Case 1). Severe, projectile, repetitive (up to 15-20 episodes) emesis starts within 1 to 3 hours after food ingestion, accompanied by lethargy with pallor and ashen appearance. Diarrhea may follow within 2 to 10 hours (mean onset, 5 hours), especially in severe reactions. Stool may contain blood, mucous, sheets of leukocytes and eosinophils, and have increased carbohydrate content.[25] Peripheral blood neutrophil counts are usually elevated, peaking at 6 hours. In 63% of those with a recorded white blood cell count, thrombocytosis ($>500 \times 10^9$/L) was seen.[2]

Chronic symptoms

FPIES may be chronic while the food is a staple of the diet, such as with CM or soy formula in infants[25] (Box 1, Case 1). Chronic FPIES applies to situations when the culprit food is introduced early in life and every day. This can present as intermittent emesis, bloody diarrhea, lethargy, dehydration requiring intravenous hydration, abdominal distension, weight loss/failure to thrive, and metabolic acidosis that may begin within the first days of life.[25-28] Laboratory studies show anemia, hypoalbuminemia, and an elevated white blood cell count with a left shift and eosinophilia. Methemoglobulinemia was reported in approximately one-third of infants with severe reactions and acidemia; some required methylene blue and bicarbonate treatment.[26] Intramural gas was seen on abdominal x-rays, prompting a diagnosis of necrotizing enterocolitis. Overall, approximately 75% of infants with FPIES appear seriously ill; 15% develop hypotension and require hospitalization.[5] Symptoms improve with food elimination and bowel rest within several days and recur acutely on food reintroduction.

EPIDEMIOLOGY

Approximately 40% of CM-protein hypersensitivity in young children are due to non-IgE, T-cell–mediated gastrointestinal immune reactions to CM proteins.[20] The prevalence of FPIES is unknown. The only population-based birth cohort study in Israel reported CM FPIES in 0.34% of 13,019 infants, compared with 0.5% of IgE-mediated CM allergy diagnosed in the first year of life.[5] FPIES is slightly more common in boys (52%-60%).[2,5,10] Approximately 30% of infants with FPIES have atopic diseases, such as atopic dermatitis (25%-65%), asthma (3%-20%), or allergic rhinitis (20%).[2,9,11] Family history of atopy is present in 40% to 80% of patients, including food allergy in approximately 20%.[11] However, no familial cases of FPIES have been reported.[10,23]

PATHOPHYSIOLOGY

The pathophysiology of FPIES remains obscure. Antigen-specific T cells and proinflammatory cytokines that modify intestinal barrier permeability may play a role. Ingestion of food allergens may cause local inflammation, leading to increased intestinal permeability and fluid shift.[29] Systemic food-specific IgE antibodies are typically absent in FPIES. Intestinal mucosal IgE antibody may facilitate antigen uptake and intestinal inflammation, but this requires further study.[29]

DIAGNOSIS

Diagnosis is based on the history, symptoms, exclusion of other causes, and an oral food challenge (OFC). It is harder to make the correct diagnosis with the chronic form of FPIES. In infants with chronic symptoms, hypoalbuminemia and weight gain of <10 g/day were identified as independent predictors of CM FPIES.[30] In chronic FPIES, food elimination for 2 weeks, followed by a supervised OFC may be necessary for a conclusive diagnosis because of the nonspecific nature of the FPIES symptoms. Infants often present with multiple reactions and extensive evaluations before the diagnosis of FPIES is considered, especially when FPIES is caused by solid foods.[2,11] The nonspecific symptoms and lack of definitive diagnostic tests contribute to a delay in diagnosis.

Allergy tests

Most patients have negative skin prick tests (SPTs) and undetectable serum food-specific IgE. In total, approximately 21% with solid FPIES and 18% to 30% with CM or soy FPIES have detectable food-specific IgE.[5,10,23] Atopy patch test (APT) was evaluated in 19 infants aged 5 to 30 months with challenge-confirmed FPIES.[24] APTs predicted the outcomes in 28 of 33 OFCs; all positive OFCs had a positive APT. These results have not been confirmed by other studies; thus, further evaluation of APT in the diagnosis of FPIES is needed. We performed APTs in 25 children before 38 follow-up OFCs and found sensitivity of 12%, specificity of 86%, positive predictive value of 40%, and negative predictive value of 55%. These results indicate that APT had poor utility in predicting tolerance development in FPIES.[31]

Fecal tests

In chronic diarrhea, stool examination may show nonspecific findings, such as occult blood, neutrophils, eosinophils, Charcot-Leyden crystals, and reducing substances.[30]