Clinical features and resolution of food protein–induced enterocolitis syndrome: 10-year experience

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Background: Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy. FPIES diagnosis is frequently delayed because of the absence of classic allergic symptoms and lack of biomarkers.
Objective: We sought to characterize the clinical features and resolution of FPIES in patients evaluated in our practice.
Methods: Subjects 6 months to 45 years of age with FPIES were prospectively recruited for oral food challenges (OFCs). Medical records were searched to identify the subjects who did not participate in OFCs.
Results: Among 160 subjects, 54% were male; median age at diagnosis was 15 months. We performed 180 OFCs to 15 foods in 82 subjects; 30% of the study population had FPIES confirmed based on OFC results. The most common foods were cow's milk (44%), soy (41%), rice (22.5%), and oat (16%). The majority (65%) reacted to 1 food, 26% reacted to 2 foods, and 9% reacted to 3 or more foods. The majority were atopic, and 39% had IgE sensitization to another food. Thirty-nine (24%) subjects had positive specific IgE levels to the food inducing FPIES. Among children with specific IgE to cow's milk, 41% changed from a milk FPIES to an IgE-mediated phenotype over time. The median age when tolerance was established was 4.7 years for rice, 4 years for oat, and 6.7 years for soy. Median age when milk tolerance was established for subjects with undetectable milk-specific IgE levels was 5.1 years, whereas none of the subjects with detectable milk-specific IgE became tolerant to milk during the study ($P = .003$).
Conclusion: FPIES typically resolves by age 5 years. Milk FPIES, especially with detectable food-specific IgE, can have a protracted course and eventually transition to acute reactions.
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Key words: *Food protein–induced enterocolitis syndrome, allergic enterocolitis, food protein–induced enterocolitis, food allergy, milk allergy, soy allergy, rice allergy, oat allergy, natural history*

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy that usually presents in young infants and manifests as profuse repetitive vomiting and lethargy, typically occurring 2 to 4 hours after ingestion of the offending allergen and occasionally followed by diarrhea 5 to 10 hours later.[1-3] Chronic exposure manifests as intermittent emesis and chronic diarrhea with blood, mucus, or both and can result in failure to thrive and hypoalbuminemia.[4] Cow's milk and soy, followed by rice and oat, are the most common causes of FPIES in the United States, although there are reports of reactions to many other foods, including egg, poultry, beans, vegetables, and seafood.[5-11] FPIES has been described in adults, usually related to shellfish ingestion.[12,13] Prevalence estimates of FPIES are limited to a single report from Israel that found 0.34% of infants with FPIES attributable to cow's milk; the same population included 0.5% with IgE- mediated cow's milk allergy.[14]

FPIES is underrecognized, and the diagnosis is not straightforward. Skin prick test (SPT) responses or serum allergen-specific IgE antibody results are typically negative.[2,13] Considering that FPIES pathophysiology is presumably T cell mediated,[15] patch tests have been proposed for diagnosing FPIES.[16] However, we and others have shown that atopy patch tests to common food allergens had poor utility in the follow-up management of FPIES.[6,12,17] US food allergy guidelines[18] recommend using the medical history and oral food challenge (OFC) results to establish a diagnosis of FPIES. A confirmatory OFC is considered unnecessary when the typical symptoms occur within 2 to 4 hours after food ingestion (particularly more than once), there is no alternative explanation for the symptoms, and the child remains well if the food is eliminated from the diet.[2] Data on the resolution of FPIES are lacking, particularly for solid foods.

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Abbreviations used
ANC: Absolute neutrophil count
FPIES: Food protein–induced enterocolitis syndrome
IQR: Interquartile range
OFC: Oral food challenge
SPT: Skin prick test

The aim of our study was to characterize the clinical features and resolution of FPIES to improve the management of subjects with this condition.

METHODS

Study population

The research protocol was approved by the Mount Sinai Institutional Review Board. Written informed consent was obtained before enrollment. This study includes a mixed prospective and retrospective method of patient ascertainment. Subjects aged from 6 months to 45 years with FPIES were prospectively recruited for OFCs under the natural history of the FPIES protocol from the Mount Sinai Allergy and Immunology Clinic patient population (New York, NY) between 2001 and 2011. All subjects with suspected FPIES were offered participation; for those who declined OFCs, the medical records database at the Mount Sinai Allergy and Immunology Clinic was searched. The terms FPIES, food protein–induced enterocolitis syndrome, and enterocolitis were used to identify the subjects who chose not to participate in OFCs. These patients were followed clinically to assess the natural history of FPIES. The diagnosis of FPIES was based on Powell's clinical criteria[2,19]: (1) exposure to the incriminated food elicits repetitive vomiting, diarrhea, or both within 4 hours without any other cause for the symptoms; (2) symptoms are limited to the gastrointestinal tract; (3) avoidance of the offending protein from the diet results in resolution of symptoms; and (4) a standardized OFC or isolated re-exposure elicits the typical symptoms. Age of diagnosis was defined as the age at which the physician suspected a diagnosis of FPIES, which could have been before presenting at Mount Sinai. The age of resolution was determined with either OFCs or parental report of food introduction at home. Exclusion criteria included a history of immediate (<2 hours) allergic reactions with cutaneous symptoms, respiratory symptoms, or both to the suspect food and a biopsy-confirmed diagnosis of allergic eosinophilic gastroenteritis or allergic eosinophilic esophagitis.

Study procedures

During the study visits, subjects underwent SPTs with bifurcated needles (Allergy Labs of Ohio, Columbus, Ohio) with commercial food extracts (Greer Laboratories, Lenoir, NC), saline (negative control), and histamine (positive control); results were read between 10 and 15 minutes after the prick.[20] Serum food-specific IgE antibody levels were measured with UniCAP (Thermo Fisher, Portage, Mich), with a lower limit of detection of 0.35 kU_A/L and an upper limit of detection of 100 kU_A/L.

OFCs were performed after a minimum of 12 months after the most recent FPIES reaction to a specific food. A subset of subjects underwent periodic OFCs to the same food to evaluate possible resolution. In children with multiple food–induced FPIES, history of severe reactions to 1 food, or both, OFCs were sometimes done to foods that had never been ingested previously but were avoided as a precaution. OFCs were undertaken in the Mount Sinai Clinical Research Unit according to the guidelines of Powell,[19] as modified by Sicherer and colleagues.[2,4] A peripheral intravenous line was placed before the OFC. Subjects were given from 0.06 g up to 0.6 g of food protein per kilogram of body weight (usually 0.3 g of protein/kg body weight; maximum, 3 g of protein) in 3 equal doses over a 45-minute period and remained under observation for 4 to 8 hours after the ingestion of the challenge food. In the case of grains with low protein content, such as rice and oat, an age-appropriate food portion was served. We used modified Powell criteria to determine the positivity of an OFC result: (1) emesis, diarrhea, or both and (2) increase in peripheral polymorphonuclear leukocyte count of 3500 cells/mm^3 or greater. The OFC result was considered positive if both criteria were met, equivocal if 1 criterion was met, and negative if both were negative.[19] If symptoms of a reaction developed, subjects were treated and kept under observation for approximately 6 hours. A CBC with differential was obtained immediately before the OFC and before discharge (ie, at 6 hours if the OFC result was positive). The treatment was administered at the attending physician's discretion and included intravenous normal saline bolus, intravenous corticosteroids, or both. In the subjects who had specific IgE to the incriminated food during follow-up, the OFC protocol was adapted by administering incrementally increasing doses of the food protein every 15 minutes, as per the protocol for IgE-mediated food allergy.[21]

Statistical analysis

Analyses were performed with SAS/STAT Version 9.2 software (SAS Institute, Cary, NC). Comparisons of risk factors and between-group data for continuous variables were assessed with a *t* test for independent variables or a Mann-Whitney *U* test. A *P* value of less than .05 was considered significant. Cumulative survival curves were drawn by using the Kaplan-Meier method to investigate the natural course of FPIES.

RESULTS

Subjects' characteristics

Subjects' characteristics and the offending foods are summarized in Table I and Fig 1. One hundred sixty subjects were enrolled. Eighty-six 86 (54%) were male, and the median age at diagnosis was 15 months (25% to 75% interquartile range [IQR], 9-24 months). Among those 160 patients, 82 (51%) were enrolled prospectively, and 78 were identified through the retrospective chart review. Thirteen (8%) subject received a diagnosis after 5 years of age; 5 of them had FPIES to fish or shellfish with late onset. Six subjects with FPIES to milk and 2 with FPIES to soy or egg were given diagnoses after 5 years of age, although symptoms appeared earlier in life (median age of 9 months; IQR, 8-12 months). Forty-eight (30%) children had at least 1 positive OFC result confirming the diagnosis of FPIES; the other 112 (70%) subjects presented with a history of typical symptoms after ingestion of the food less than 12 months before the initial visit, and a confirmatory OFC was not performed.[2] The median delay between first reaction and diagnosis was 7 months (range, 0-143 months).

The majority of subjects had an allergic background, and 39% were sensitized to another food(s) (ie, detectable specific IgE, positive SPT response, or both). Thirty-nine (24%) subjects with FPIES had positive specific IgE to the FPIES food, and 82% of those children had FPIES to milk, soy, or both. Comparison of characteristics of children with milk FPIES and a positive specific IgE to milk with those with milk FPIES but who were not sensitized to milk is shown in Table II. None of the children with IgE sensitization to milk resolved their milk allergy while in the study. Among those who had no IgE sensitization to milk, the median age of milk FPIES resolution was 61 months ($P = .003$, Fig 2). Detailed information regarding the individual subject's course of IgE positivity is presented in Table E1 in this article's Online Repository at www.jacionline.org.

Causative foods

Cow's milk and soy were the most commonly reported individual foods (n = 70 [44%] and n = 66 [41%], respectively), followed by grains (n = 70 [44%], including rice [n = 36], oat [n = 26], barley [n = 6], and wheat [n = 2]; Fig 1). The majority of subjects reacted to 1 food (n = 104 [65%]), 42 (26%) children reacted to 2 foods, and 14 (9%) children reacted to 3 or more foods (median, 3 foods, range, 3-10 foods). Comparison between