

Clinical features of food protein–induced enterocolitis syndrome

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Objective: To describe the clinical characteristics of food protein–induced enterocolitis syndrome (FPIES), a symptom complex of severe vomiting and diarrhea occurring several hours after the ingestion of particular food proteins in infants.

Study design: Retrospective review of a referral population.

Results: Sixteen patients had typical FPIES; 11 reacted to milk, 11 to soy, and 7 to both. Mean age at diagnosis was 7 weeks for milk reactivity and 8 weeks for soy reactivity. Two patients also had rice- and pea-induced FPIES. Among 14 patients who were followed up for a median period of 25 months, loss of sensitivity to milk occurred in 6 of 10 patients and loss of sensitivity to soy occurred in 2 of 8. Six additional cases of FPIES were considered atypical: 1 patient had late-onset disease caused by poultry, and in 5 patients IgE antibody to milk or soy developed. During supervised food challenges with milk and soy, the peripheral blood neutrophil count rose over 3500 cells/mm³ in 9 of 10 positive challenges and did not rise above this value in the 7 negative challenges. Emergency treatment was required in 62% of challenges.

Conclusions: Although most patients with FPIES are infants reactive to milk and/or soy, this diagnosis should be considered in older children and for other foods. Food-specific IgE sensitivity may develop in some patients. Standardized food challenges are helpful for diagnosis and follow-up. (*J Pediatr* 1998; 133:214-9)

Food allergies are most prevalent in the first 2 years of life, affecting 6% to 8% of infants.¹ About half of these reactions are due to IgE-mediated hypersensitivity; the skin and gastrointestinal tract are the most common targets of these reac-

tions. There are a number of food-related gastrointestinal hypersensitivity disorders with an immunologic basis but without evidence of IgE-mediated sensitivity; these include food protein–induced enterocolitis, celiac disease, food-

induced proctocolitis, food-induced enteropathy, and allergic eosinophilic gastroenteritis in a subset of patients.²

See editorial, p. 175.

Food protein–induced enterocolitis syndrome describes a symptom complex of profuse vomiting and diarrhea with or without microscopic blood in the stool, which is diagnosed in infancy. When severe, these symptoms may lead to lethargy, dehydration, and hypotension and may be complicated by acidosis.³⁻⁶ Approximately half of the infants diagnosed with cow's milk allergy are first seen with enterocolitis symptoms.⁷ In an early report Powell³ described a series of 9 newborns with projectile vomiting and protracted diarrhea leading to dehydration after ingestion of cow's milk or soy-based formula. The patients rapidly recovered with milk- and soy-free diets. During confirmatory oral challenges, symptoms recurred 1 to 10 hours after ingestion and were accompanied by an increase in the peripheral blood absolute neutrophil count. On the basis of this early report, clinical criteria were proposed to establish the diagnosis in infants. Although initially substantiated with biopsy findings, the diagnosis of FPIES is now most often made on the basis of clinical criteria.

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ANC	Absolute neutrophil count
DBPCFC	Double-blind, placebo-controlled food challenge
FPIES	Food protein–induced enterocolitis syndrome
TNF- α	Tumor necrosis factor- α

Although cow's milk and soy proteins are most often responsible for FPIES,

Table. Characteristics of patients

Patient No.	Sex	Food sensitivities	Age at diagnosis	Symptoms	Time of symptom onset (hr)	Status of sensitivity	Duration of sensitivity (method shown)
Typical FPIES							
1	F	Milk	4 wk	V	Immediate	Sensitive	12 mo (presumed)
		Soy	6 wk	V, D	Immediate	Sensitive	12 mo (presumed)
2	M	Soy	3 mo	V, D, H	1	Lost	36 mo (accident)
3	M	Milk	2 wk	V, L, H, A	12	Lost	24 mo (challenge)
4	F	Milk	3 mo	V, L	1.5	Sensitive	4 yr (challenge)
5	M	Milk	6 wk	V, D	2	Sensitive	7 yr (challenge)
		Soy	7 mo	V	2	Sensitive	3 yr (challenge)
6	M	Milk	5 mo	V, D	ND	Lost	6 mo (challenge)
7	M	Soy	2 mo	D	4	Lost	24 mo (challenge)
		Milk	2 mo	V, D	Immediate	Lost	24 mo (challenge)
8	F	Milk	1 wk	V, D	1	Sensitive	5 yr (challenge)
		Soy	1 wk	V, D	2	Sensitive	1 yr (accident)
9	F	Soy	1 wk	V, D	1	Sensitive	2 yr (accident)
		Milk	2 mo	V, D	2	Lost	22 mo (challenge)
10	M	Milk	2 wk	V, D	2	Lost	30 mo (challenge)
		Soy	3 wk	V, D	2	Sensitive	6 yr (challenge)
11	F	Soy	3 mo	V, D	1	Sensitive	21 mo (accident)
12	F	rice	6 mo	V, L	1.5	Sensitive	16 mo (accident)
13	M	Milk	2 wk	V, D	ND	Sensitive	45 mo (accident)
		Soy	3 wk	V, D	ND	Not tested	
14	F	Soy	1 mo	V	1.5	Sensitive	33 mo (challenge)
		Pea	5 mo	V	0.75	Not tested	
15	F	Milk	3 mo	V, D, L	3	Lost	25 mo (challenge)
16	M	Soy	3 mo	V, D, L	1.5	Not tested	
Atypical FPIES							
17	F	Turkey	2 yr	D, L	2	Lost	9 yr (challenge)
		Chicken	2 yr	D, L	2	Lost	9 yr (challenge)
18	F	Soy	9 yr	V, D	3	No follow-up	
19	M	Soy	1 yr	V	3.5	Sensitive	2 yr (challenge)
20	F	Milk	1 wk	V, L	1.25	Sensitive	2 yr (challenge)
6	M	Soy	7 mo	V, D, L	0.25	Sensitive	1 yr (accident)
11	F	Milk	1 mo	V, D	1	Sensitive	40 mo (accident)

V, Vomiting; D, Diarrhea; L, lethargy; A, acidosis; H, hypotension; ND, no data.

typical symptoms have also been induced by egg, wheat, rice, oat, peanut, tree nuts, chicken, turkey, and fish in older individuals.^{3,8-10} IgE antibodies to the responsible food protein are characteristically negative. Thus there are patients with clinical characteristics similar to those seen in infants with milk- or soy-induced enterocolitis who would not fulfill Powell's criteria of infantile FPIES, either because they are sensitive to proteins other than milk or soy or because they are beyond the infant age group. In this article we describe the characteris-

tics of children with clinical symptoms of FPIES, regardless of the incriminated food protein or age of the patient. Diagnostic features, laboratory evaluation, results of controlled challenges, and clinical course are discussed.

METHODS

Subjects

All patients referred to the Johns Hopkins Pediatric Food Allergy Clinic between 1990 and 1996 because of recurrent vomiting and/or diarrhea attributable

to non-IgE-mediated food hypersensitivity were evaluated for the diagnosis of FPIES. Subjects were diagnosed with "typical" FPIES if: (1) they were younger than 9 months of age at initial diagnosis; (2) repeated exposure to the incriminated food elicited diarrhea and/or repetitive vomiting within 24 hours without any other cause for the symptoms; (3) there were no symptoms other than gastrointestinal symptoms elicited by the incriminated food; (4) removal of the offending protein from the diet resulted in resolution of the symp-

toms, and/or a standardized food challenge elicited diarrhea and/or vomiting within 24 hours after administration of the food. If monitored during a challenge, an increase in the ANC by over 3500/mm³ at 5 to 8 hours after the challenge^{3,4} was additional presumptive evidence of a positive challenge response. Subjects fulfilling the clinical criteria of FPIES who were older than 9 months of age at diagnosis or who had IgE antibodies to the incriminated food were considered to have "atypical" FPIES.

Laboratory Evaluation

Skin prick tests with glycerinated food extracts (Greer Laboratories, Lenoir, NC) and determination of food-specific IgE levels by the FEIA CAP-RAST system (limit of the assay <0.35 KU_A/L; Pharmacia, Uppsala, Sweden) were routinely performed in all patients at the time of the initial evaluation.

Food Challenges

After informed consent was obtained, challenges were performed according to the guidelines suggested by Powell⁵ and McDonald et al.¹¹ Before the challenge, an intravenous line was inserted, and patients were then given an open challenge consisting of a total of 0.6 g of protein per kilogram of body weight in increasing doses over a 45- to 60-minute period. However, the total amount of protein given during the challenge was lower (0.15 to 0.3 g protein/kg body weight) if the patient had a history of a severe reaction after a small ingestion. Emergency medications were immediately available. The patients remained under direct physician supervision for 6 to 8 hours, regardless of the outcome of the challenge.

Double-blind placebo-controlled food challenges were performed in selected patients with previously described methods.^{12,13} Briefly, patients suspected of having IgE-mediated food allergy (ie, atopic dermatitis) to the incriminated food received the challenge substance or placebo in a graded fashion until a total of 8 to 10 g of dry food or 60 to 100 g of wet food had been ingested. Negative DBPCFC responses were followed by open ingestion of the food under observation.

RESULTS

Patient Characteristics and Food Sensitivities and Reactions

The characteristics of the patients, food hypersensitivities, reactions, and status of the reactivity over time are shown in the Table. Sixteen subjects demonstrated reactions typical of infantile FPIES. Eight patients were male, and the median age at diagnosis was 7 weeks (range, 1 week to 7 months). Eight were breast fed for a period of 1 day to 12 weeks (median, 4 weeks). Nine subjects were from families with a history of atopy (2 patients were adopted and the family history was unknown). Atopic disease was diagnosed in 7 patients: 5 had atopic dermatitis, 3 had allergic rhinitis, and 2 had drug hypersensitivity. Reactions to milk occurred in 11 patients and to soy in 11, and 7 reacted to both. Additional foods responsible included rice and pea, each in 1 patient. The median age of initial reaction was 6 weeks to both milk (range, 1 to 20 weeks) and soy (range, 1 to 28 weeks). Although symptoms occurred immediately after ingestion in 3 patients, most reactions occurred after an initial symptom-free period of 45 minutes to 12 hours (median, 2 hours). In 12 of 16 patients, symptom severity required hospitalization, and patient 5 experienced acidosis and methemoglobinemia. Hydrolyzed formula was used successfully in the treatment of all of these patients except for patient 1. This patient experienced repetitive vomiting 2 hours after receiving this formula during challenge but tolerated an amino acid-based formula (Neocate).

In 6 patients the reactions were considered "atypical." Patient 17 experienced reactions to turkey and chicken, which were not IgE-mediated and occurred at age 2, beyond the typical age for development of FPIES. The remaining 5 patients, 2 of whom had typical non-IgE-mediated FPIES reactions to another protein, demonstrated positive IgE reactivity to the proteins that elicited typical FPIES.

IgE Sensitivities

Among the 16 patients with "typical" FPIES reactions, none exhibited positive

RAST or skin prick test responses to the responsible protein. Among these patients, screening skin test results were positive in response to egg and peanut in patient 12 and in response to egg in patient 14. Five patients with atypical FPIES had IgE antibody to the incriminated food. Patient 18, with a specific IgE value of 4.5 kU_A/L to soy, had a history of facial swelling and throat tightness after soy exposure and was challenged with soy in a DBPCFC that resulted only in symptoms of FPIES. Patient 19, with a specific IgE level to soy of 7.7 kU_A/L, had asthma and atopic dermatitis with multiple IgE-mediated food sensitivities (soy, milk, wheat, egg, apple, pear), and similar to patient 18, had only symptoms of FPIES on DBPCFC. It is likely that this positive RAST response to soy (7.7 IU/ml) represents cross-reactivity with peanut (16.9 KU_A/L).¹⁴ Patient 20 fulfilled the criteria for typical FPIES and at age 2 had a negative skin test response to milk. This patient, however, had a positive skin test result and a low level of milk-specific IgE antibody (0.7 kU_A/L) at age 5. Similarly, patient 11, who had typical FPIES in response to milk and soy and no detectable IgE to milk at the age of 1 year, had a low positive level of milk-specific IgE (3.6 kU_A/L) and a positive skin test response to milk at age 2 years. Patient 6 who had typical FPIES in response to milk had a small positive skin prick test response and low positive level of IgE (0.5 KU_A/L) to soy. The low positive CAP-RAST values in patients 6, 11, and 20 are not usually associated with acute IgE-mediated clinical reactions.¹⁵

Challenge Results

A total of 26 oral food challenges were performed in 15 patients. Among the patients with symptoms of typical FPIES, 12 were challenged with milk (patients 1, 3-9, and 14), 7 with soy (patients 4, 5, 7, 10, and 14), and 1 with corn. Challenges were performed with foods not causing FPIES to ascertain their safety for administration for patient 4 (soy), patient 12 (corn), and patient 14 (milk); and the results were all negative. The remaining challenges were performed to monitor reactivity or to confirm the diagnosis. Re-

sults of 11 of the 16 challenges with relevant foods were positive, and 7 subjects required aggressive treatment (intravenous fluids in 7 and steroids in 3). Positive challenges typically elicited symptoms (primarily vomiting) 1 to 4 hours after ingestion of the challenge substance. Late-onset diarrhea (6 to 24 hours) was reported in approximately half of patients who had positive challenge results, after discharge from the hospital. Although the stool was not analyzed for blood at home, 1 patient who had diarrhea at 3 ½ hours had heme-positive stools.

The ANC measured before and then 5 to 8 hours after the challenge showed a rise of greater than 3500 cells/mm³ in 9 of 10 positive challenges with an average rise of 7774 cells/mm³ (range, 2449 to 13,538 cells/mm³). Among the 8 negative challenges, the ANC rose an average of 467 cells/mm³ (range, -458 to 1376 cells/mm³). Patient 5 had an equivocal challenge response to soy because he experienced only diarrhea, and family members had gastroenteritis symptoms. This patient's response to the third milk challenge was judged to be positive on the basis of the rise in ANC and the previous symptoms, although only mild abdominal discomfort occurred during that challenge.

Challenges performed in 4 patients with atypical FPIES included 3 with soy (patients 18, 19, and 20 [confirmation of nonreactivity in patient 20]) and 1 each with milk (patient 20) and chicken and turkey (patient 17). The initial diagnosis of FPIES was made during challenges for patients 18 and 19 who, although they had a low level of IgE antibody to soy protein, experienced delayed gastrointestinal symptoms (accompanied by a rise in ANC of 6061 cells/mm³ in patient 19). Although the results of challenges with 0.6 g/kg of turkey and chicken in patient 17 were negative, this patient had severe vomiting that required treatment in the emergency department 2 hours after turkey was eaten 1 month after the challenge.

Follow-up Data

Over a median follow-up period of 25 months (range, 6 months to 7 years), loss of sensitivity in patients with *typical*

FPIES occurred for 19 foods in 14 patients. Loss of sensitivity to milk among 6 of 10 milk-sensitive patients occurred after a median time of 24 months (range, 6 to 30 months), whereas sensitivity to soy was lost in 2 of 8 patients after 24 and 36 months. Among the patients with *atypical* FPIES, patient 17 lost sensitivity to chicken and turkey, and the 4 patients with specific IgE antibodies to the incriminated food (milk or soy) also remained reactive. These patients experienced solely gastrointestinal symptoms on exposure to the offending foods.

DISCUSSION

In 1967 Gryboski¹⁶ described a series of 21 children diagnosed with gastrointestinal symptoms of cow's milk allergy. Most children began to experience symptoms during the first 6 weeks of life; they were first seen with emesis, diarrhea, and occasionally dehydration. Half of the patients became milk tolerant by 1 year of age, and almost all patients could ingest milk at 3 years of age. Ten years later, Powell⁴ reported 2 low-birth-weight infants who were first seen early in life with bloody diarrhea, profuse emesis leading to dehydration, and marked leukocytosis while fed with milk-based formula. In a subsequent study the same author described a group of 9 infants with cow's milk- or soy-induced enterocolitis with symptoms starting in early infancy after only a short period of milk-based formula feeding.⁵ The symptoms first resolved when infants were switched to a soy-based formula, but patients often experienced sensitivity to soy only a few weeks later. Infants who continue to ingest the causal protein or proteins may have diarrhea with polymorphonuclear leukocytes, anemia, lactose malabsorption, and hypoproteinemia, implicating the involvement of both the small and large intestine (enterocolitis).^{3,17-20}

FPIES is a clinical diagnosis.⁵ It is not unusual for infants with FPIES to present with lethargy, vomiting, diarrhea, and an elevated polymorphonuclear leukocyte count leading to an evaluation for sepsis. When the causal food protein is re-introduced to the diet, symptoms

recur and the diagnosis becomes evident. Oral challenge has been suggested by Powell⁵ for confirmation of the diagnosis.

The findings from endoscopy and biopsy in FPIES are nonspecific. Colonic biopsy specimens obtained from patients with symptoms reveal crypt abscesses and a diffuse inflammatory cell infiltrate with prominent plasma cells; small-bowel biopsy specimens reveal edema, acute inflammation, and mild villus injury.¹⁶⁻²⁰ In some cases focal erosive gastritis and esophagitis are found with prominent eosinophilia and villus atrophy.^{17,21,22} Because most patients become completely free of symptoms with the removal of the causal protein from the diet, endoscopy and biopsy are usually not indicated. Because no biopsies were performed to confirm inflammation in our patients, we have elected to describe these patients as having a "syndrome" of food protein-induced enterocolitis as outlined by Powell.⁵

The diagnostic criteria proposed by Powell et al³⁻⁵ to define infantile enterocolitis include the onset of symptoms before 2 months of age, a positive response to 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. Powell challenged infants who had enterocolitis with milk and/or soy, which resulted in emesis 1 to 2 ½ hours after the challenge, followed 2 to 10 hours later by diarrhea. In patients with a positive challenge response, there was a significant elevation of the ANC, peaking approximately 6 hours after the challenge. On the basis of these observations, suggested guidelines for challenges with milk or soy recommended a dose of 0.6 g protein/kg body weight. Diarrhea containing blood or leukocytes occurring within 24 hours of the challenge accompanied by a rise in the ANC greater than 3500/mm³ were proposed as criteria for a positive challenge response.^{3,11} These rigid criteria were considered important for studies of pathophysiology but were expected to exclude older patients or patients with milder symptoms.

We reviewed the history and follow-up of patients referred with gastrointestinal symptoms consistent with FPIES to

characterize the clinical spectrum of this illness. We broadened the criteria initially set forth by Powell⁵ to include patients who were older than 2 months of age at the time of diagnosis. We included 6 patients who were considered to have atypical FPIES because diagnosis was made outside of infancy or because specific IgE antibody was found. However, we excluded other patients with gastrointestinal manifestations of non-IgE-mediated food hypersensitivity.

Patients with symptoms typical of FPIES in our series were very young at the time of diagnosis for either milk (mean, 7 weeks of age) or soy (mean, 8 weeks of age) sensitivity. Although FPIES is not accompanied by anaphylactic reactions as seen in IgE-mediated food hypersensitivity, ingestion of the incriminated food resulted in profuse vomiting and diarrhea with dehydration and subsequent hospitalization in 75% of the patients. One of the patients in our series who experienced dehydration also had transient methemoglobinemia, a complication described in 6 of 17 infants with soy or milk intolerance who required hospitalization for treatment of dehydration.⁶

FPIES in our patients was elicited most often by milk and soy protein, with 7 of 16 patients having sensitivity to both. This co-sensitization to milk and soy has been observed by others. Half of the patients with soy-induced enterocolitis in the series reported by Halpin et al¹⁸ were found to be sensitive to cow's milk. Similarly, Burks et al²³ reported that 6 of 10 patients with FPIES reacted to both milk and soy.

Several of our patients reacted to antigens other than milk or soy (pea, rice, turkey, and chicken). FPIES elicited by foods other than milk and soy is, however, rarely reported. A patient who had typical symptoms of food-induced enterocolitis in response to chicken at 6 months of age has been described.⁸ In contrast to the typical patients with initial symptoms of FPIES in the first 9 months, our patient with chicken and turkey sensitivity had initial symptoms at 2 years of age. Rice has also been reported to induce symptoms of enterocolitis,¹⁰ and enterocolitis associated with rice was seen in 1 of our patients at age 6 months.

Most studies evaluating FPIES either

do not monitor specific IgE levels or exclude subjects with evidence of IgE-mediated food hypersensitivity.^{3,23} When we considered patients with symptoms of FPIES who had food-specific IgE antibodies to the causal food protein, we identified 1 patient with symptoms of FPIES induced by soy diagnosed at age 1 year and another at age 9 years. Interestingly, an additional 3 patients had specific IgE antibodies to the responsible food in low titer (2 with milk and 1 with soy). All of our patients with specific IgE to the causal food remained sensitive, suggesting that the presence of food-specific IgE is a poor prognostic sign for "outgrowing" the hypersensitivity. Interestingly, in another study of patients with cow's milk sensitivity, 27% of 24 subjects (mean age, 22 months) with active hypersensitivity manifested solely by intestinal symptoms had specific IgE to cow's milk protein, whereas none of 12 subjects (mean age, 24 months) with intestinal reactions, who had outgrown their sensitivity, had IgE to cow's milk.²⁴ Thus the development of specific IgE in patients with FPIES may indicate a reduced likelihood of outgrowing the sensitivity.

Our patients with typical FPIES lost their reactivity more readily to milk (6 of 10 patients) than to soy (2 of 8 patients). The high rate of co-sensitization to milk and soy and the poorer prognosis for rapid resolution of the soy sensitivity emphasize the need for treatment with a hydrolyzed formula after an initial diagnosis of milk-induced FPIES.

Several patients with a history of *severe* reactions were challenged with smaller doses (0.15 to 0.3 g) of protein per kilogram of body weight, which proved sufficient to induce symptoms in all cases.

The pathophysiology of FPIES is incompletely understood. Morphologic studies of the intestine show an increase of IgG- and IgM-containing plasmacytes, as well as an increase of intraepithelial lymphocytes.²⁵ However, the presence of plasmacytes may be the result of a non-specific immune response caused by an increased passage of antigen through the gut mucosa. The immune response to antigen in the gastrointestinal tract may primarily involve T cells. Evidence for activation of antigen-specific T cells was

demonstrated by van Sickle et al²⁶ who showed increased proliferation of antigen-specific peripheral blood mononuclear cells in patients with milk and soy enterocolitis; however, this response is nonspecific and seen in many normal individuals.²⁷ Cytokines secreted by activated T cells significantly influence the integrity of the mucosal barrier of the gut on exposure to the antigen. Heyman et al²⁸ demonstrated that tumor necrosis factor- α secreted by circulating milk protein-specific T cells increased intestinal permeability, thus contributing to the influx of antigen into the submucosa with further activation of antigen-specific lymphocytes. Fecal TNF- α was also found in increased concentrations after positive milk challenge responses in patients with enterocolitis.²⁹ Benlounes et al²⁴ showed that significantly lower doses of intact cow's milk protein stimulated TNF- α secretion from peripheral blood mononuclear cells of patients with active intestinal cow's milk allergy as compared with either patients whose sensitivity resolved or with those with skin, rather than intestinal, manifestations of cow's milk hypersensitivity. Interferon- γ significantly enhances the action of TNF- α on intestinal epithelial cells, and IL-4 was determined to have a similar effect on the gut mucosa.³⁰ Conversely, transforming growth factor- β 1 protects the epithelial barrier of the gut from the penetration of foreign antigens by preventing the detrimental action of interferon- α .³¹

The role of assays for TNF- α secretion in vitro from food protein-stimulated peripheral blood mononuclear cells in the prediction of recovery from FPIES is under active investigation. An evaluation for specific IgE to the involved antigen may be helpful in predicting prolonged sensitivity to the protein in question, but more research in this area needs to be undertaken.

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