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Food Protein-Induced Enterocolitis Syndrome Caused by Solid Food Proteins

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ABSTRACT. *Background.* Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe, cell-mediated gastrointestinal food hypersensitivity typically provoked by cow's milk or soy. Solid foods are rarely considered a cause.

Objective. To describe the clinical characteristics and natural history of FPIES provoked by solid foods.

Methods. Patients with FPIES induced by solid foods were identified and their clinical course compared with a control group with FPIES caused by cow's milk and/or soy evaluated over the same time period.

Results. Fourteen infants with FPIES caused by grains (rice, oat, and barley), vegetables (sweet potato, squash, string beans, peas), or poultry (chicken and turkey) were identified. Symptoms were typical of classical FPIES with delayed (median: 2 hours) onset of vomiting, diarrhea, and lethargy/dehydration. Eleven infants (78%) reacted to >1 food protein, including 7 (50%) that reacted to >1 grain. Nine (64%) of all patients with solid food-FPIES also had cow's milk and/or soy-FPIES. Initial presentation was severe in 79% of the patients, prompting sepsis evaluations (57%) and hospitalization (64%) for dehydration or shock. The diagnosis of FPIES was delayed, after a median of 2 reactions (range: 2–5). Thirty patients with typical cow's milk- and/or soy-FPIES were identified for comparison. Overall, 48% of the 44 infants with FPIES were reactive to >1 food protein, and the risk for multiple food hypersensitivity approached 80% in the infants with solid food or soy-induced FPIES. None of the patients developed FPIES to maternally ingested foods while breastfeeding unless the causal food was fed directly to the infant.

Conclusions. Cereals, vegetables, and poultry meats, typically regarded as of low allergenic potential, must be considered in the evaluation of FPIES, particularly in infants previously diagnosed with FPIES to cow's milk or soy, and as an initial cause in patients who have been exclusively breastfed. Infants with FPIES are at risk for multiple dietary protein hypersensitivities during an apparent period of immunologic susceptibility. Pediatricians should consider FPIES in the differential diagnosis of shock and sepsis. *Pediatrics* 2003;111:829–835; *food protein-induced enterocolitis syndrome, milk-induced enterocolitis syndrome, soy-induced enterocolitis syndrome, oat-induced enterocolitis syndrome, rice-induced entero-*

colitis syndrome, food allergy, non-immunoglobulin E-mediated food hypersensitivity, rice allergy, oat allergy.

ABBREVIATIONS. FPIES, food protein-induced enterocolitis syndrome; IgE, immunoglobulin E; TNF- α , tumor necrosis factor α ; IFN- γ , interferon γ ; TGF- β , transforming growth factor- β .

Food protein-induced enterocolitis syndrome (FPIES) is a severe infantile form of cell-mediated, non-immunoglobulin E (IgE) antibody-associated food hypersensitivity caused typically by cow's milk and/or soy.^{1–6} FPIES is characterized by profuse vomiting and diarrhea, with progression to dehydration and shock in 20% of patients. Initial reports described young infants with these symptoms after ingestion of cow's milk or soy-based formula.^{1,3,4} Patients rapidly recover with milk and soy-free diets, but ingestion of these proteins after a period of dietary elimination triggers subacute symptoms, median onset 2 hours with an associated elevation of the peripheral blood polymorphonuclear leukocyte count. Biopsies show crypt abscesses, diffuse inflammatory cell infiltrates with plasma cells in the colon, and edema with mild villous injury in the small intestine. The diagnosis is now made on the basis of clinical criteria and a standardized oral challenge protocol.⁷ Recent studies suggest that T cells' secretion of tumor necrosis factor α (TNF- α) on milk stimulation is involved in the pathophysiology of FPIES.⁸ A relative lack of expression of transforming growth factor- β (TGF- β) may also be involved.⁹

Although there are case reports of rice^{5,10,11} and other foods (poultry, egg, pea, peanut)^{5,12} causing FPIES, solid food proteins are not well-recognized as potential triggers of FPIES. Over the past 5 years, our group observed 14 infants with FPIES due to dietary food proteins other than cow's milk and/or soy, including several foods (oat, barley, squash, sweet potato) never before reported to cause this disorder. In this study we report the clinical characteristics of these patients and, for comparison, we include data on 30 patients with FPIES triggered by the more typical foods, cow's milk and/or soy, observed over the same time period.

METHODS

Patients presenting by referral for diagnosis and evaluation of food hypersensitivity over a 5-year span to the Mount Sinai Pediatric Allergy and Immunology Clinic (New York, NY), and to the Allergy Clinics of the Johns Hopkins Children's Center (Baltimore, MD), (patients 2 and 7) who were diagnosed with FPIES provoked by solid foods were included. Comparisons were made to patients

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who presented over the same time period who also fulfilled the diagnostic criteria for FPIES, but only reacted to cow's milk, soy, or both and were followed long enough to be sure that solid foods were tolerated; this group represents patients with "typical FPIES". Parents of children whose most recent follow-up visit took place >6 months before study completion were contacted by telephone to update the information on the status of their child's food tolerance.

The diagnosis of FPIES was based on clinical criteria:⁷ 1) age younger than 9 months at initial presentation (reaction); 2) exposure to the incriminated food elicited repetitive vomiting and/or diarrhea within 4 hours without any other cause for the symptoms; 3) symptoms limited to the gastrointestinal tract; 4) avoidance of the offending protein from the diet resulted in resolution of symptoms; and 5) a standardized food challenge or isolated reexposure elicited the typical symptoms.^{2,5,13} Patients underwent physician-supervised oral food challenges according to the guidelines by Powell et al⁷ with an intravenous line in place. Patients were given up to 0.6 g of protein per kilogram of body weight (eg, for whole cow's milk, 18 mL/kg) in increasing doses over a 45- to 60-minute period, and remained under observation for 6 to 8 hours.

Prick skin tests were performed with a bifurcated needle (Allergy Labs of Ohio, Columbus, OH) and commercial food extracts (Greer Laboratories, Inc, Lenoir, NC) with positive (histamine) and negative (glycerol-saline) controls. Prick skin tests were considered positive if the mean wheal diameter was at least 3 mm greater than the saline control. Serum food-specific IgE antibodies were measured by the CAP System FEIA (Pharmacia Diagnostics, Uppsala, Sweden; lower limit of detection, 0.35 kIU/L).

Statistical analysis was performed with the SPSS for Windows, 10.0.5 (SPSS, Chicago, IL), nonparametric variables were analyzed using Mann-Whitney *U* test, and GraphPad Prism 2.01 (χ^2 test; GraphPad, San Diego, CA). Informed consent was obtained and the study was approved by the Institutional Review Board of the Mount Sinai School of Medicine.

RESULTS

Features of Patients with FPIES Induced by Solid Food

Detailed clinical data for 14 patients with FPIES caused by solid foods are shown in Table 1, and a summary with comparison to clinical features of patients with FPIES caused by cow's milk and/or soy is shown in Table 2. Five patients (36%) had FPIES provoked exclusively by solid food protein(s), whereas 9 (64%) had concomitant cow's milk and/or soy-induced enterocolitis syndrome. Interestingly, all 5 infants with exclusive solid food-induced enterocolitis syndrome were breastfed. Two of these 5 patients reacted to the first solid food protein introduced directly to their diet while they were being breastfed, and 3 others tolerated at least 1 solid food protein before introduction of the offending food. Breastfeeding mothers were ingesting the offending foods without any apparent symptoms in their infants. All 9 formula-fed infants developed FPIES to the first whole food protein introduced into their diet. Eleven patients reacted to >1 food, including the 9 who had symptoms induced by cow's milk and/or soy-based infant formula that required treatment with an extensively hydrolyzed casein or an amino acid-based formula.

The diagnosis of solid food-induced FPIES was delayed and established after a median of 2 reactions (range: 2–5) to the offending foods. The presenting symptoms included profuse vomiting, diarrhea, melena, hypotension, lethargy, and/or cyanosis typically commencing 1 to 3 hours after ingestion of solid food, (median: 2 hours). Symptoms were particularly severe in 10 patients (71%), necessitating emergency

department evaluations and/or hospitalizations. Eight patients (57%) developed shock with dehydration, hypotension, or cyanosis, and required emergency medications and intravenous fluids in the emergency room or in the intensive care unit. An extreme example is patient 1 with FPIES caused by oat. He was breastfed exclusively for 2 months when rice cereal was added without a reaction. Subsequently, other cereals were introduced and he experienced recurrent episodes of profuse, repetitive vomiting and lethargy that resulted in hospitalization in the intensive care unit on 5 occasions. He underwent extensive evaluations for infectious, metabolic, and neurologic etiologies of recurrent shock with negative results. His mother then realized that each episode started ~2 hours after the feeding of cereal mixed with the infant's formula. The patient was admitted for diagnostic oral food challenges. He tolerated cow's milk and soy; however, oat given at 0.6 g/kg body weight resulted 2 hours later in repetitive vomiting and hypotension that required fluid resuscitation in the intensive care unit. He again failed an oral oat challenge at 34 months of age.

During follow-up, 4 patients outgrew all of their food hypersensitivities, 5 continued to avoid all the offending foods, and 5 patients outgrew allergies to some foods. Eight patients developed mild atopic dermatitis, and patient 8 had multiple allergic diseases including IgE-mediated hypersensitivity to milk and peanut, allergic eosinophilic gastroenteritis, allergic eosinophilic esophagitis, atopic dermatitis, asthma and allergic rhinitis, along with multiple environmental sensitivities.

Laboratory Features/Oral Food Challenges

Skin tests were negative to the foods implicated in FPIES in all patients; however, 3 patients eventually developed detectable serum food-specific IgE antibodies to the responsible foods (Table 1). Patient 4 had a rice-specific IgE antibody concentration 1.6 kIU/L at 38 months. Patient 8, who was reactive to soy and oat, had a soy-specific IgE concentration 3.5 kIU/L, first documented at 30 months. This patient also had detectable serum IgE antibodies to a variety of foods, including milk, egg, peanut, beef, barley, pea, and carrot, but not to oat. Patient 9 had a low serum concentration of cow's milk-specific IgE antibody. All 3 patients had persistent FPIES at 3 years of age. In addition, patient 1 had positive skin tests to egg and milk, and detectable serum egg-specific IgE (1.2 kIU/L), but tolerated both foods.

Oral food challenges were performed either to confirm the causal food when clinical criteria were not definitive, or to monitor for the development of tolerance. Five patients with solid food-induced FPIES underwent a total of 8 diagnostic food challenges. Patient 1 had a positive challenge to oat at 10 months and again at 34 months. Patient 5 failed chicken challenge at 4 years and patient 7 failed milk challenge at 25 months. Patient 9 had positive challenges to rice at 30 months and soy at 63 months. Patient 12 had positive rice challenges at 5 and 13 months of age. The 8 positive challenges elicited typical symptoms starting at a median of 2 hours

TABLE 1. Characteristics of Patients With Solid Food-FPIES

Patient No.	Sex	Food Causing FPIES	Age at First Reaction (Months)	Diet at First Reaction	Symptoms Onset (Hours)	Symptoms	Hospitalization	Prick Skin Test/Food-IgE	Number of Reactions	Age at Last Reaction (Months)	Clinical Course
1	M	O	6	BF, R, W, Co	1	V, D, L, H	PICU × 5	+ M, E/-	5	10	Persistent (challenge at 34 mo)
2	M	O	6	BF	3	V, D, L	No	-/-	2	7	Resolved by 21 mo (accident)
3	M	R	6	BF	3	V, D, L	No	-/-	3	7	Persistent (unchallenged as of 21 mo)
4	F	R	6	BF	2-3	V, D, M	ER × 1	-/-	3	28	Resolved by 45 mo (challenge)
5	M	Ch	6	BF, O	1-1.5	V, L	No	-1.6	>4	32	Persistent (accident at 32 mo)
6	M	O	7	BF, R, Ch	3	V	No	ND	1	48	Persistent as of 12 y (challenge at 4 y)
7	F	O	6	BF	3	V	No	ND	1	7	Persistent (unchallenged as of 12 y)
8	F	S	3	CH	1	V, L	ER × 1	-/-	2	3	Resolved by 18 mo (accident)
9	M	S	3	CH	1	V, L	No	-/-	2	13	Resolved by 34 mo (accident)
10	F	O	6	BF	2	V, L	No	-/-	3	13	Persistent (unchallenged as of 46 mo)
11	F	S	6	CH	2	V, D	No	-/-	2	13	Resolved by 34 mo (accident)
12	M	O	6	BF	1	V, L	ER × 1	-/-	1	36	Persistent (unchallenged as of 46 mo)
13	M	O	6	BF	2-3	V, L	ER × 1	-/-	3	8	Persistent (unchallenged as of 21 mo)
14	F	S	6.5	BF	2	V, L	No	-/+	1	6.5	Persistent (challenge at 25 mo)
15	F	S	3	BF	2.5	V, L, C	ER × 1	-/-	1	7.5	Resolved by 31 mo (accident)
16	M	S	5	BF	1.5	V, D, L, C	ER × 2	-/-	2	4	Resolved by 31 mo (accident)
17	M	S	1	BF	3	V	ER × 1	-/-	1	5	Resolved by 31 mo (accident)
18	F	O	4.5	CH	2	V, D, L, H	PICU × 1	-/-	1	63	Persistent at 63 mo (challenge)
19	F	S	5.5	CH	1.5	V, D, L	No	-/-	2	30	Persistent (unchallenged as of 63 mo)
20	F	S	<1	BF	<10 min	V	PICU × 1	-/-	1	5.5	Persistent (unchallenged as of 63 mo)
21	F	O	4	CH	1-2	V	No	-3.5#	>4	1	Persistent (unchallenged as of 42 mo)
22	F	CM	<1	CM	chronic	V, D, C, L	Yes	-/ND	*	14	Persistent (accident at 16 mo)
23	F	S	<1	CM	chronic	V, D, C, L	Yes	-/ND	*	1	Persistent (unchallenged as of 16 mo)
24	M	R	6	AA	2	V	No	-/ND	2	12	Persistent (unchallenged as of 16 mo)
25	M	CM	0.1	BF	0.3	V, D	No	-/-	*	6	Persistent (challenge at 12 mo)
26	S	O	0.2	CM	0.3	V, D	No	-/-	*	2	Resolved by 28 mo (accident)
27	O	R	4	CH	2	V, D	No	-/-	3	2	Resolved by 24 mo (accident)
28	R	B	4	CH	2	V	No	-/-	3	29	Resolved by 36 mo (accident)
29	SB	Peas	6	CH	2	V	No	-/-	1	13	Resolved by 24 mo (accident)
30	CM	S	<1	CM	2	V	No	-/-	1	6	Resolved by 24 mo (accident)
31	S	O	<1	CM	1	V, M	No	-/-	*	<1	Resolved by 24 mo (accident)
32	R	CH, B	4	CH, B	1	V, M	No	-/-	*	<1	Persistent (unchallenged as of 19 mo)
33	O	CM	5.5	CH, B	1.5	V, I, C, H	PICU × 1	-/-	1	4	Persistent (unchallenged as of 19 mo)
34	F	CM	2d	BF	chronic	Colic	No	-/-	*	5.5	Persistent (unchallenged as of 19 mo)
35	S	O	1.5	CM	chronic	D, I	No	-/-	*	4	Resolved by 15 mo (accident)
36	R	O	4	CH	<10 min	V, D, M	Yes	-/-	1	20	Persistent (unchallenged as of 21 mo)
37	O	R	4.3	CH	<10 min	V, D, L, C	No	-/-	1	12†	Persistent (unchallenged as of 21 mo)
38	O	Squash	4.5	CH	<10 min	V, D	No	-/-	1	3	Persistent (unchallenged as of 21 mo)
39	Peas	Peas	4.5	CH	<10 min	V, D	No	-/-	1	4.5	Resolved by 14 mo (accident)
40	Peas	Peas	4.5	CH	<10 min	V, D	No	-/-	1	4.5	Resolved by 14 mo (accident)

M indicates male; F, female; O, oat; R, rice; CM, cow's milk; S, soy; B, barley; SP, sweet potato; SB, string bean; W, wheat; Co, corn; Ch, chicken; T, turkey; BF, breastfeeding; CH, casein hydrolysate; AA, amino-acid based formula; V, vomiting; D, diarrhea; L, Lethargy; C, cyanosis; H, hypotension; I, Irritability; M, melena; ER, emergency room; PICU, pediatric intensive care unit; ND, not determined.

* Chronic symptoms of vomiting and diarrhea.
 # This patient also had detectable serum IgE antibodies to a variety of foods, including milk, egg, peanut, beef, barley, pea, and carrot, but not to oat.
 † This patient developed projectile vomiting within 2 hours and heme positive diarrhea within 3 hours after the ingestion of rice at 12 months of age. Patient 6 was breastfed for 1 week, then weaned to CM, finally was switched to Alimentum at 2 weeks because of constipation. CM was introduced at 12 months of age without any difficulties.

TABLE 2. Solid Food-FPIES and Cows' Milk and/or Soy-FPIES Patients-Comparison

	Solid Food-FPIES N = 14 (%)	Cow's Milk and/or Soy-FPIES N = 30 (%)
Sex, N (%)		
Male	8 (57)	18 (60)
Female	6 (43)	12 (40)
Offending foods, N (%) [§]		
Cow's milk	5 (36)	24 (80)
Soy	8 (57)	16 (53)
Cow's milk and soy	5 (36)	10 (33)
Solid food and cow's milk and/or soy	9 (64)	
Solid food(s) only	5 (36)	
Rice	10 (71)	
Oat	9 (64)	
Barley	2 (14)	
Peas	2 (14)	
String beans	2 (14)	
Squash	1 (7)	
Sweet potato	1 (7)	
Chicken and turkey	1 (7)	
More than 1 grain	7 (50)	
Severe initial presentation*		
Hospitalization	9 (64)	13 (43)
Intensive care unit	3 (21)	2 (6)
Sepsis evaluation	8 (57)	14 (47)
Emergency room evaluation	4 (29)	4 (13)
Age at onset, median (range)	5.5 mo (3–7)	1 mo (2 d–12 mo)
Age at resolution, median (range)	24 mo (14–44)	28 mo (14 mo–21 y) [†]
Patients tolerant by 3 y [‡]		
Cow's milk	3 of 4 (75)	15 out of 24 (63)
Soy	3 of 8 (38)	6 out of 22 (25)
Oat	4 of 6 (66)	
Rice	4 of 10 (40)	
Barley	2 of 2 (100)	
Poultry	1 of 1 (0)	
Other [#]	2 of 3 (67)	
Personal atopic disease	8 (57)	11 (37)
Atopic dermatitis	8 (57)	7 (23)
Asthma and/or allergic rhinitis	1 (7)	5 (17)
Family history of atopy	10 (71)	24 (80)
Family history of food allergy ⁺	3 (21)	6 (20)

* Hypotension, shock, lethargy

[†] One patient with cow's milk and soy-FPIES outgrew cow's milk-FPIES by 21 years of age but failed soy challenge at the age of 21 years. This patient had a positive cow's milk challenge at 16 years. Another patient with cow's milk and soy-FPIES failed both cow's milk and soy challenges at the age of 11.5 years.

[‡] Only patients 3 years or older were analyzed.

[#] String bean, squash, sweet potato, and pea.

⁺ Including 1 set of fraternal twins, both boys with soy-FPIES.

after ingestion and required intravenous therapy (fluids, corticosteroids) in 5 cases. In addition, 12 patients with cow's milk and/or soy-FPIES underwent oral food challenges. The median increase in the peripheral polymorphonuclear leukocyte number was 4500/mm³ (range: 700–15 000) after a positive challenge.

Comparison of FPIES to Milk/Soy to FPIES Caused by Solid Food(s)

We compared the 14 patients with FPIES caused by solid foods to 30 with typical cow's milk and/or soy-induced disease observed over the same time period (Tables 2 and 3). Of 30 control patients, 80% had FPIES provoked by cow's milk and 53% to soy. Allergy to multiple foods was common; overall, 21 patients (48%) were reactive to at least 2 food proteins. Nearly 80% of patients with solid food-FPIES or soy-FPIES were reactive to multiple food proteins. In addition, those reactive to 1 cereal grain had a 50% chance of being hypersensitive to another cereal

grain. Patients with solid food-induced FPIES showed a trend toward more severe reactions (hospitalizations, episodes of shock, sepsis evaluations) compared with the control group (χ^2 , $P = .2$). A higher proportion of patients with FPIES caused by solids (57%) compared with controls (23%) had atopic dermatitis (χ^2 , $P = .03$). However, both patient groups were not different with respect to family history of atopy (>70%) or family history of food allergy ($\geq 20\%$).

The time course of disease differed somewhat according to the food trigger(s) (Table 4). The median age at the onset of FPIES caused by solid food was 5.5 months, compared with a median of 1 month for cow's milk or soy-induced enterocolitis syndrome, reflecting the usual sequence of introduction of foods. The median age of achieving tolerance was 24 months for solid food-induced FPIES and 28 months for cow's milk or soy. A majority of patients became clinically tolerant to the offending foods by the age of

TABLE 3. Comparison of Breastfeeding Duration and Age of Introduction of Food Proteins in the Infants With M/S-FPIES Versus Exclusive Solid Food-FPIES Versus M/S and Solid Food-FPIES*

Median (Range)	Solid Food-FPIES (N = 5)	M/S and Solid Food-FPIES (N = 9)	P Value‡	M/S-FPIES (N = 50)	P Value#
Breastfeeding duration	11 mo (0–19)	0.1 mo (0–6)	.026	0.35 mo (0–9.5)	.08
Age at introduction of cow's milk	11 mo (6–18)	0.3 mo (.01–6)	.002	0.8 mo (.01–10)	.001
Age at introduction of soy	12 mo (6–18)	0.5 mo (.01–6)	.002	1 mo (.01–12)	.002
Age at introduction of solids	5.5 mo (2–6)	4.3 mo (2–6)	.968	5 mo (4.5–9)	.414

M/S indicates cow's milk and/or soy.

‡ P value for comparison between solid food-FPIES and M/S and solid food-FPIES.

* M/S-FPIES and M/S and solid food-FPIES were not significantly different in any of the categories. P values calculated with nonparametric Mann-Whitney U test.

P value for comparison between solid food-FPIES and M/S-FPIES.

TABLE 4. Natural History of FPIES

Median (Range)	Solid Food-FPIES	Cow's Milk-FPIES	Soy-FPIES
Age at onset median (range)§	5.5 mo (3–7 mo)	0.5 mo (2 d–10 mo)	1.5 mo (2 d–12 mo)
Age at resolution, median (range)	24 mo (14–44 mo)	28 mo (14 mo–21 y)	28.5 mo* (16–35 mo)
Patients tolerant by 3 y	Oat 66% (4/6) Rice 40% (4/10) Barley 100% (2/2) Poultry 0% (0/1) Other 67% (2/3)#	60% (15/25)	27% (6/22)

§ None of the patients developed FPIES while being exclusively breast-fed; however, 1 patient who was diagnosed with "classic" cow's milk and soy-FPIES at the age of 8 months had intermittent gross blood in her stools during exclusive breastfeeding on unrestricted maternal diet.

* One patient with cow's milk and soy-FPIES outgrew cow's milk-FPIES by the age of 21 years but failed soy challenge at the age of 21 years. This patient had a positive cow's milk challenge at 16 years old. Another patient with cow's milk and soy-FPIES failed both cow's milk and soy challenges at the age of 11.5 years.

String bean, squash, sweet potato, and pea.

3 years, with the exception of soy, where only 30% of children achieved tolerance by that time.

None of the patients developed FPIES during breastfeeding until there was direct feeding of the offending food protein to the infant. The infants with solid food-induced enterocolitis syndrome were breastfed significantly longer than those who had cow's milk and/or soy-FPIES with or without coexisting solid food-FPIES (Table 3). Although the age of solid food introduction was not different among these patient groups, in 11 of 14 infants with solid food-FPIES, subsequent introduction of wheat was delayed until 9 to 30 months of age, perhaps avoiding sensitization/reactions during a possible period of susceptibility.

DISCUSSION

FPIES is a severe syndrome of vomiting and diarrhea typically caused by cow's milk or soy protein in infants younger than 9 months.¹ Approximately half of affected infants react to both milk and soy proteins. Some patients present with dramatic symptoms of profuse vomiting, with or without diarrhea, which may progress to acidemia and shock. Associated methemoglobinemia is thought to result from increased heme oxidation caused by an elevation of nitrates in the intestine.¹⁴ The disorder is cell-mediated and occurs typically without positive allergy prick skin tests or serum allergen-specific IgE antibodies.⁵ Within 2 years, 60% of milk and 20% of soy-induced FPIES resolves.⁵

We report the first series of infants with FPIES caused by solid food proteins. Among the triggers,

oat was a prominent (64%), but heretofore unrecognized cause. Our study shows that proteins other than cow's milk and soy have the potential to cause this hypersensitivity reaction, that reactions are often severe and the diagnosis is delayed, that infants with FPIES are at high risk for multiple food hypersensitivities, and that breastfeeding may have a role in protecting against or delaying the onset of reactions in infants predisposed to FPIES.

There appeared to be a delay in diagnosis of FPIES to solid foods. Indeed, patients in this cohort were not identified until after a median of 2 reactions (range: 2–5) despite a high rate of severe reactions (emergency department evaluations in 10 patients, 8 patients presenting in shock). Most illustrative is the child with FPIES caused by oat who underwent 5 intensive care unit admissions and extensive evaluations before the diagnosis was established. Delayed diagnosis can be attributed to the low incidence of this disorder and to a presentation that mimics sepsis. Moreover, the diagnosis can be particularly elusive when physicians follow the concept that solid foods such as grains, vegetables, and poultry meats are of low allergenic potential. The study was not designed to determine the prevalence of FPIES induced by solids; however, the disorder appears to be reasonably common because in our referral population at Mount Sinai Hospital, 12 of a total of 42 patients (29%) evaluated for FPIES over the same time period reacted to solids. The prevalence of FPIES in the general pediatric population is unknown but it is considered to be a rare form of gastrointestinal food hypersensitivity.

The time course of reactions can also confound the diagnosis. Young infants with FPIES to cow's milk or soy exposed to these proteins on a daily basis typically manifest chronic symptoms of vomiting, diarrhea, melena, and failure to thrive that resolve with substitution to a casein hydrolysate- or amino acid-based formula. It is the subsequent feeding with these proteins after a period of avoidance that results in the classic sequence of repetitive vomiting at a mean of 2 hours after ingestion, diarrhea, and lethargy or shock. For FPIES caused by solids, the presentations tended to be more dramatic (mimicking sepsis), a finding that is not surprising in the context of intermittent exposures to the dietary food proteins in slightly older infants. Perhaps more confusing, patient 14 had immediate reactions of repetitive vomiting after the feeding with rice, oat, squash, and peas when she was <5 months of age. However, accidental ingestion of rice at the age of 12 months resulted in the classic, delayed (2 hours) reaction. The observation indicates that introduction of solids to very young infants with FPIES may result in atypically rapid reactions.

Another roadblock to diagnosis is the lack of a confirmatory laboratory diagnostic test for this cell-mediated disorder. Our report confirmed previous observations that measurements of food allergen-specific IgE antibodies (prick skin test or serum levels) are typically negative.^{2,5} Similar to a previous report, we observed that the subsequent development of detectable IgE to the causal food may represent a poor prognostic sign for tolerance, and it may be important to repeat the tests before diagnostic oral challenges. However, only 3 of our patients subsequently developed detectable IgE, so a direct relationship remains to be proven.⁵

Several interesting observations emerged regarding the sequence of feeding when we compared infants with FPIES caused exclusively by solids to those with additional reactions to milk and/or soy, and to controls with typical FPIES. All of the patients who were not being breastfed at time of the development of the solid food-FPIES already had been given a casein hydrolysate formula by their pediatricians because of intolerance to cow's milk or soy-based formula in the first month of life. We hypothesize that these infants manifested their predisposition for food hypersensitivity in the first months of life and remained at high risk for similar reactions to whole food proteins introduced during an apparent window of immunologic susceptibility. This concept is further supported by observations regarding the frequency of patients with multiple triggers of FPIES. Overall, we found multiple foods-FPIES in >48% of the patients with FPIES from any cause. In particular, 11 of 14 patients reactive to solids reacted to >1 food protein, and those already on a casein hydrolysate formula were sensitive to a median of 4 (range: 1–5) solid food proteins. We also hypothesize that the same predisposition was present but obscured in the breastfed infants, who were not exposed to foreign food protein (infant formula) before the introduction of solid foods. Still, similar to other forms of food allergy, there are in-

fant who react to just 1 particular food protein (eg, patients 1, 3, and 4).

Strikingly, none of the infants developed FPIES during exclusive breastfeeding, although 1 patient who was diagnosed with milk and soy-induced enterocolitis syndrome at 8 months of age had intermittent grossly bloody stools (proctocolitis) while being breastfed on an unrestricted maternal diet that included large amounts of dairy products. We are unaware of any reports of FPIES during breastfeeding in the absence of direct oral feeding of the offending food to the infant. In contrast, food allergic reactions such as acute skin reactions (atopic dermatitis) and colitis (proctocolitis) have been attributed to food proteins passed via maternal breast milk.^{15,16} Therefore, we hypothesize that breastfeeding has an important protective effect against FPIES, the mechanism which requires further investigation.

Infancy may constitute a sensitive window for the development of atopic disease in those with a genetic predisposition.¹⁷ Several factors are proposed to account for the increased risk for food allergy, a breakdown in oral tolerance, observed in infancy. Among these are digestive factors including decreased gastric acidity, decreased activity of intestinal proteolytic enzymes, and immaturity of the intestinal barrier.¹⁸ For example, intact, rather than intestinally processed, cow's milk proteins stimulate peripheral blood mononuclear cells to release proinflammatory cytokines in patients with cow's milk allergy.¹⁹ The immaturity of the immune system is another important factor. After birth, the numbers of B cells and plasma cells increase rapidly and IgG, and more slowly IgA and IgM-producing cells begin to appear over the first weeks of life. Gradually, secretory IgA becomes the dominant Ig at the mucosal surface. T cell reactivity toward food antigens peaks in infancy and then gradually declines.^{17,20} FPIES may result from defects in both barrier and immunologic function. The disorder may result partly from elaboration of the cytokine TNF- α , a proinflammatory cytokine, from food-sensitized T lymphocytes.⁸ Mucosal biopsies from children with challenge-proven cow's milk-induced FPIES show not only an increased expression of TNF- α , but also decreased expression of TGF- β , a cytokine that induces T cell suppression, promotes B cell switching to IgA production, and preserves epithelial barrier function.⁹ Gut maturation occurring in the first years of life may explain why a majority of cow's milk-allergic children outgrow their allergy by the age of 2 to 3 years.²¹

The length of physiologic susceptibility for allergy to food proteins has not been established. In our patient series, none developed FPIES to cow's milk and/or soy after the age of 1 year, and the oldest age for the onset of solid food-induced FPIES was 7 months. However, our data are confounded by the fact that after the onset of solid food-FPIES, subsequent introduction of food proteins was delayed (eg, wheat was not introduced until after the age of 1 year). We also could not identify factors to predict which infants with FPIES induced by cow's milk and/or soy would develop reactions to solid foods. In fact, the median age of introduction of solid

food(s) was not different compared with controls. The only statistically significant difference was that atopic dermatitis was more common among the infants with FPIES due to solids (57%) compared with controls (23%, $P = .03$).

CONCLUSIONS

Solid food proteins traditionally considered of low allergenicity such as cereals (oat, rice, and barley), vegetables (squash, sweet potato, peas, and string beans), and poultry meats (chicken and turkey) have the potential to cause FPIES. Infants with FPIES are at risk for multiple food hypersensitivities and introduction of additional food proteins should be approached with caution. Prospective studies on the natural history of FPIES are needed to better define the length of the period of immunologic susceptibility to foreign whole food protein. However, in view of our report it seems prudent to delay the introduction of solid food proteins to infants with FPIES caused by cow's milk or soy until beyond first 6 to 7 months old. In breastfed infants who develop FPIES to rice or oat, the increased risk for subsequent reactions to proteins from the same food group should be recognized. Finally, breastfeeding appears to have an important protective effect against cow's milk and soy-induced FPIES.

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GROUP POLARIZATION

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Sunstein CR. *On a Danger of Deliberative Democracy*. *Daedalus*; 2002;131:120-124

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