The prevalence and natural course of food protein–induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study

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Background: The prevalence and natural history for food protein–induced enterocolitis syndrome (FPIES) have not been determined.
Objective: We sought to determine the prevalence, clinical manifestations, and rate of recovery for FPIES in a large-scale, population-based prospective study.
Methods: In a prospective study the feeding history of 13,019 infants was obtained. Infants with probable adverse reactions to cow's milk protein (CMP) were clinically examined, skin prick tested, and challenged orally. Diagnostic criteria for CMP-induced FPIES included age less than 9 months, delayed recurrent vomiting (usually with nausea), and lethargy after exposure to CMP in the absence of other IgE-mediated symptoms, such as rash, urticaria, and respiratory symptoms. In addition, a positive challenge response to milk resulted in the above-mentioned gastrointestinal symptoms, removal of milk from the diet resulted in the resolution of those symptoms, or both.
Results: Ninety-eight percent of the cohort participated in the study. The cumulative incidence for FPIES was 0.34% (44/13,019 patients). The most common symptoms were recurrent vomiting (100%), lethargy (77%) diarrhea (25%), pallor (14%), and bloody diarrhea (4.5%). All patients had FPIES within the first 6 months of life. By the age of 3 years, 90% of the patients had recovered. We did not detect any concomitant reaction to soy. Eight patients with FPIES had IgE-mediated cow's milk allergy (IgE-CMA).
Conclusions: The prevalence of FPIES is significant, and its clinical presentation is distinct from that of IgE-CMA. Most patients with FPIES recover, although a proportion might convert to IgE-CMA. The likelihood for a cross-reactivity to soy in this population was less than previously estimated. (J Allergy Clin Immunol 2011;127:647-53.)

Key words: *Food protein–induced enterocolitis syndrome, oral challenge, soy allergy, skin prick test*

Abbreviations used
CMP: Cow's milk protein
FPIES: Food protein–induced enterocolitis syndrome
IgE-CMA: IgE-mediated cow's milk allergy
OFC: Oral food challenge
SPT: Skin prick test

The original description of the food protein–induced enterocolitis syndrome (FPIES) likely dates back to 1967 when Gryboski[1] described a set of 21 children with a gastrointestinal food allergy after chronic ingestion to milk manifested primarily by diarrhea (n = 15/21), vomiting (n = 5/21), both vomiting and diarrhea (n = 1/21), and colic (n = 2/21). Their symptoms improved rapidly after the removal of bovine milk proteins from the patient's diet and recurred with its introduction. More than 20 years later, Sicherer et al[2] described another 22 patients. In their group 11 reacted to milk, 11 reacted to soy, and 7 reacted to both. Their diagnostic criteria were age less than 9 months at initial diagnosis; repetitive vomiting, diarrhea, or both within 24 hours of ingestion; a lack of other symptoms related to the offending food; and a resolution of symptoms after its removal from the diet.

Laboratory evidence during an acute FPIES reaction might include an increase in the absolute neutrophil count of greater than 3,500/mm^3 5 to 8 hours after the start of an oral challenge[2] but is not necessary to establish the diagnosis.[3] The pathophysiologic mechanism underlying FPIES is still not completely elucidated. However, an increased TNF-α response and a decreased TGF-β response might play an important role (as reviewed by Sicherer and Sampson[4]). Furthermore, it is generally accepted that FPIES is IgE independent, and skin prick test (SPT) responses to the inciting food are negative, although low levels of food-specific IgE might develop in some patients.[2,5]

Further studies revealed that FPIES can be triggered by many foods other than milk and soy. These include rice, oats, barley, peas, sweet potato, chicken, and turkey.[6-8] Specifically, in the largest report to date, in which 35 cases of FPIES were evaluated, cow's milk was only the third most common offending food.[8] A distinguishing feature of FPIES is that reintroduction of the offending food, either inadvertently or by an oral food challenge (OFC), leads to characteristic symptoms delayed approximately 2 hours after the ingestion of the offending food.[2,9] In a large retrospective case study of children who presented with acute FPIES from a variety of foods, vomiting was the most common clinical characteristic feature (100%) followed by lethargy (85%), pallor (67%), and diarrhea (24%).[8]

Scientific studies in the literature on FPIES are either retrospective or used selective populations from referral centers. Thus a true incidence and natural history of this disease entity have been difficult to determine. Our article presents a large, prospective, noninterventional population–based study in which several

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fundamental questions regarding milk-induced FPIES were evaluated. Our recruitment of greater than 98% of the 13,234-member newborn cohort[10] allows for definitive answers regarding the true incidence, natural history, and rates of resolution for milk-induced FPIES.

METHODS

Study population

The research protocol was approved by the Helsinki Review Board of the Assaf Harofeh Medical Center. As previously described,[10] 13,234 newborns born over a 2-year period (June 10, 2004, to June 30, 2006) at the Assaf-Harofeh Hospital (Zerifin, Israel) were enrolled. Briefly, breast-feeding was encouraged at the routine anticipatory guidance session, but other alternative cow's milk protein (CMP)–based feeding regimens were also discussed. Parents were asked to fill out a questionnaire or to contact the allergy clinic immediately after any adverse reaction suspected to be related to the initiation of CMP-based feeding or, in the absence of any unusual event, 14 to 30 days after the initiation of CMP-based feeding. Any parent noting a possible adverse event related to CMP (n = 381) was interviewed by one of the investigators (N. R.), and their infants were invited for an examination. In the clinic the patient was examined, and an SPT and an open challenge[10] were offered unless clinically contraindicated.

Criteria for diagnosis of CMP-induced FPIES

Diagnostic criteria previously established for FPIES[2] were used for this study. These included age less than 9 months at the initial diagnosis; gastrointestinal symptoms, such as repetitive vomiting, diarrhea, or both, within 24 hours after the ingestion of milk in the absence of other IgE-mediated symptoms, such as rash, urticaria, and respiratory symptoms; and a positive challenge response to milk resulting in the above-mentioned gastrointestinal symptoms or removal of milk from the diet resulting in the resolution of symptoms.

SPTs

SPTs were done to CMP, soy, negative control, and histamine (1 mg/mL; ALK-Abelló, Port Washington, NY) by using the volar arm and reading the reaction after 20 minutes. A 3-mm or larger wheal response was considered positive.[11]

Oral challenge

A detailed challenge protocol can be found in Table E1 (available in this article's Online Repository at www.jacionline.org). Briefly, the challenge to cow's milk formula was carried out with Materna (Maabarot, Israel) infant formula by using the following consecutive doses: 5 mL (150 mg of CMP), 20 mL (600 mg of CMP), 30 mL (900 mg of CMP), 60 mL (1.8 g of CMP), 120 mL (3.6 g of CMP), and finally a maximum dose of up to 150 mL (4.50 g of CMP) depending on the tolerance of the infant to drink such a volume. After the 60-mL dose and thereafter, the time interval between the doses was 45 minutes. In case of a negative challenge result, the infants were observed for 3 hours, and a subsequent contact was made the next day and 2 weeks later inquiring about the infants' status. The challenge was terminated if a cutaneous, respiratory, gastrointestinal, or systemic response was observed. During the oral challenge, intravenous access, oxygen delivery, vital-sign monitoring equipment, and other resuscitation equipment were readily available in the event a severe reaction were to occur.

Statistical analysis

Statistical analyses were performed with SPSS software (version 16; SPSS, Inc, Chicago, Ill) and MATLAB (Mathworks, Inc, Natick, Mass). As previously described,[10] risk factors that were extracted from the maternity files were entered into the hospital database, NAMER, an SAP-based system, and subsequently transferred to Microsoft Access and Excel for analysis.

TABLE I. Demographics and risk factors of infants with FPIES and healthy infants

	Infants with FPIES (n = 44)	Healthy infants (n = 12,638)	*P* value
Sex: male	23/44 (52.3%)	6,409/12,638 (50.7%)	.836
Sex: female	21/44 (47.7%)	6,229/12,638 (49.3%)	
Gestational age (wk)	39.2 ± 1.6	39.2 ± 1.9	.801
Birth weight (kg)	3,246.1 ± 0.42	3,196 ± 0.55	.555
Maternal age (y)	30.34 ± 3.79	29.69 ± 5.23	.264
Type of delivery: PS	32/44 (72.7%)	10,696/12,638 (84.6%)	.003
Type of delivery: CS	14/66 (27.2%)	1,942/12,638 (15.4%)	
No. of siblings	2.32 ± 1.55	2.35 ± 1.53	.879
Dairy product consumption by mother	44/44 (100%)	12,531/12,638 (99.15%)	
Religion*: Jewish	43/44 (97.7%)	9,789/12,267 (78.9%)	.03
Religion: non-Jewish	1/44 (2.3%)	2,478/12,267 (20.2%)	
Age of CMP introduction (d)	57.68 ± 53.0	61.63 ± 92.45	.626

CS, Cesarean section; *PS*, partus spontaneous.
*In Israel the patient's religion is written down in the national identity card unless the citizen specifies "no religion." The non-Jewish population consists mostly of Arab Muslim mothers (62.6%) and Arab Christian mothers (5.5%), and for the rest, "no religion" was specified. Those for whom no data were recorded (n = 371) were excluded.

Comparisons of risk factors and between-group data for continuous variables were assessed with the use of a *t* test for independent variables or a Mann-Whitney *U* test, as appropriate (Table I). The cumulative probability of recovery from FPIES was calculated by using the 'ecdf' function in MATLAB. Briefly, the ecdf function of MATLAB, [f,x] = ecdf(y), calculates the Kaplan-Meier estimate of the cumulative distribution function (cdf), also known as the empiric cdf, where y is a vector of data values and f is a vector of values of the empiric cdf evaluated at x. In addition, [f,x,flo,fup] = ecdf(y) also returns lower and upper confidence bounds for the cdf. These bounds are calculated by using the Greenwood formula and are not simultaneous confidence bounds.

RESULTS

Study population

As previously reported,[10] recruitment into the study reached 98.4% (13,019) of our cohort (Fig 1). The demographic details of the patients with FPIES are listed in Table I. In 381 (2.9% of the sample) cases the parents either complained about adverse effects that they considered being CMP related or these parents avoided CMP exposure despite having discontinued exclusive or almost exclusive breast-feeding. A causal relationship between the complaint and CMP was ruled out in 244 cases among these infants. In 66 (0.5%) cases, which were described earlier,[10] a diagnosis of IgE-mediated cow's milk allergy (IgE-CMA) was made. There were 71 (0.5% of sample) cases of non–IgE-mediated adverse events. In 35 of these cases, FPIES was excluded: 21 were classified as proctocolitis (isolated blood in stool without vomiting), and 14 included other symptoms in which a causative relationship to CMP could not be excluded (Fig 1).

FPIES

Forty-four infants (0.34% of those studied) were given diagnoses of FPIES (Fig 1). These include 8 patients with FPIES who subsequently had IgE-CMA (Fig 1). On exposure to milk, the most common symptoms for these 44 patients were recurrent vomiting (100%), lethargy (77%), diarrhea (25%), pallor (14%), and bloody diarrhea (4.5%), symptoms typical of an FPIES-related adverse

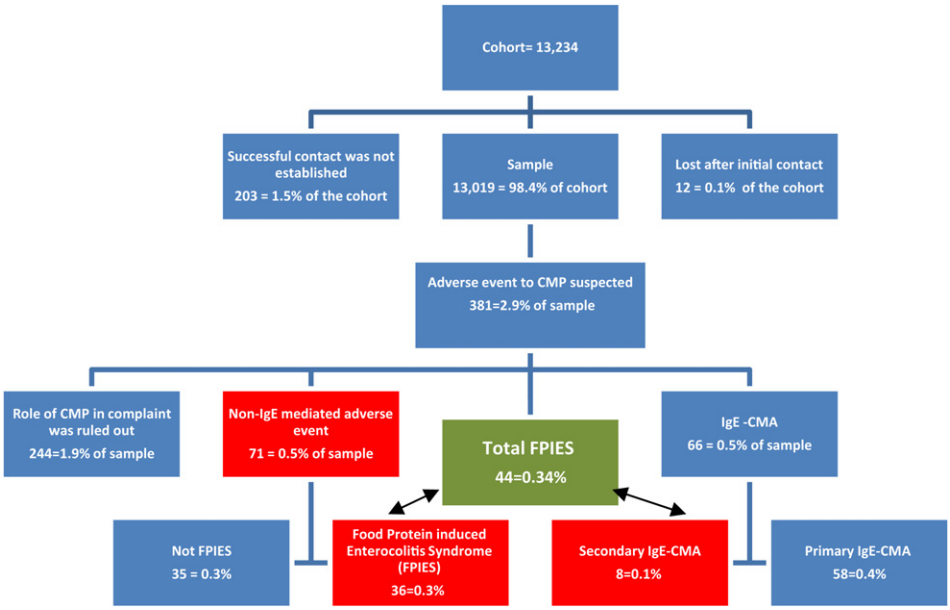

FIG 1. Cohort description. Any patient in whom an adverse reaction to CMP was suspected (n = 381) was interviewed by one of the investigators (N. R.) and invited for an examination. A total of 44 patients with FPIES were given diagnoses, including 8 patients who converted to cases of secondary IgE-CMA.

event (see Fig E1 in this article's Online Repository at www.jacionline.org).[2] Twenty-eight (63.6%) patients fulfilled all clinical criteria, including a suggestive history of a delayed response and recurrent vomiting and in addition had a positive challenge response to CMP. The other 16 patients did not have an OFC. Of these 16 patients, 4 experienced very severe episodes, including 2 hospitalizations before the actual diagnosis was established, and therefore a challenge was not offered. In 8 patients an oral challenge was not performed because of parental refusal; 6 of them had 3 prior reactions to milk, and 2 had 2 episodes. In 4 patients the diagnosis of cow's milk allergy was made by another allergist, and on examination in our institution, they already tolerated milk. For these patients, 2 had only 1 episode, 1 had 2 episodes, and 1 described 3 episodes. These 4 patients had repeated vomiting (4/4), lethargy (2/4), diarrhea (1/4), and a negative SPT response to CMP. In 13 (30%) patients the onset of FPIES was during the first 2 weeks of life, and in another 11 (25%) patients it was before the age of 30 days. The full age distribution for the age of onset of FPIES is shown in Fig 2. The mean age of onset of FPIES was 57.8 ± 53.1 days, and the median age of onset was 30 days. Twenty-eight (63.6%) of the infants experienced symptoms within 1 day of regular exposure to CMP. However, 7 (15.9%) patients tolerated repeated doses of CMP-containing formula for more than 4 days and 5 of them for 14 to 30 days until the development of symptoms (see Fig E2 in this article's Online Repository at www.jacionline.org). None of the patients with milk-induced FPIES had FPIES to any other foods.

Characteristics of the OFCs in patients with FPIES

In the 28 patients who underwent OFCs, the last dose of milk evoking the response and the time from ingestion of the last dose to response was determined. Most of the infants (15/28 [53.6%]) tolerated 121 mL or more of milk before having symptoms (Fig 3). Five (17.9%) of 28 patients started to vomit after 30 to 50 mL, and 6 (21.4%) of 28 patients started to vomit after 51 to 100 mL. Although in more than 60% (17/28) of patients the symptoms started 121 minutes or more after the last dose, 5 (17.9%) of 28 experienced symptoms after 30 to 60 minutes, and 6 (21.4%) of 8 experienced symptoms after 61 to 120 minutes (Fig 4). Detailed characteristics and the symptoms observed during the OFC are presented in Table II. Detailed are the results for 24 patients because in 4 patients the challenge procedure was not performed at our institution and the protocol differed from ours. The cumulative doses received by each infant during the OFC ranged from 55 mL to a maximum of 385 mL, with the latter number depending on the tolerance of the infant to drink completely the last dose of 150 mL (Table II). The time from the administration of the first dose to a reaction ranged from 60 to 315 minutes (Table II). The symptoms during challenge (Table II) did not differ significantly from the historical information derived from those without an OFC (data not shown). Only 2 of 24 of the patients had a positive SPT response to CMP at the time of presentation (Table II). All reactions during the OFC were treated successfully with oral rehydration without the need for hospitalization, and there was no case of clinically significant hypotension.

Coexisting allergy to soy

At the time the formal diagnosis of FPIES was established in our clinic, 35 infants ingested a soy-based formula as a substitute for a CMP-based formula, and 9 were fed with extensively hydrolyzed milk formula (Nutramigen; Mead Johnson & Company, Evansville, Ind). None of these 9 infants had a positive SPT or challenge response to soy. After the negative challenge response, 5 of 9 of these mothers decided to continue to feed with a soy-based formula, whereas 4 preferred to continue with an extensively hydrolyzed milk formula.

Rate of recovery

For the analysis of the rate of recovery from milk-induced FPIES, we excluded the 8 patients who had secondary IgE-CMA.

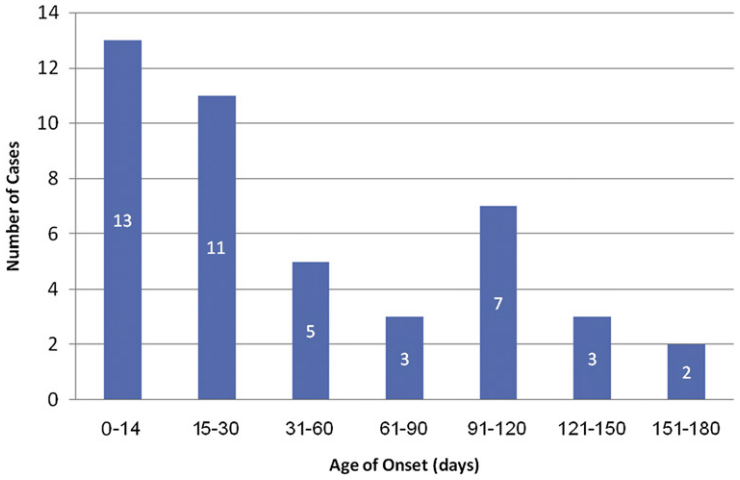

FIG 2. Age distribution for the onset of FPIES. All patients had FPIES before the age of 180 days.

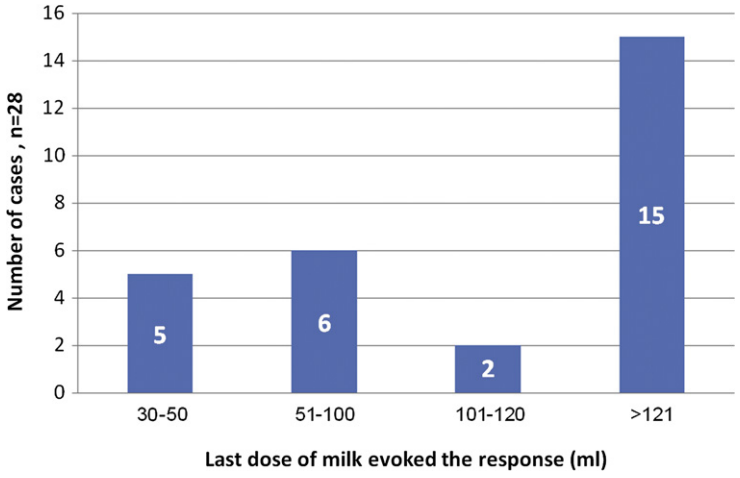

FIG 3. Dose of milk eliciting a response during oral challenge.

They are described separately below. The cumulative probability of recovery is described in Fig 5. Fifty percent (18/36) of patients with FPIES recovered by the age of 1 year, 75% (27/36) by 18 months, 88.9% (32/36) by 2 years, and 34 of 36 by 30 months. Of the remaining 2 patients, 1 had a positive challenge response at the age of 42 months, whereas the parents of the last patient refused a challenge and preferred to avoid milk. Among the patients undergoing an OFC, there was a tendency for them to have a later recovery age compared with those for whom the parents refused a challenge (18.0 vs 12.5 months, respectively). However, the differences did not reach statistical significance ($P = .1$).

Secondary IgE-CMA

Eight patients with FPIES had IgE-CMA. As described previously,[10] these patients were given initial diagnoses of FPIES because of the delayed clinical response of vomiting and lethargy, the lack of any other symptoms suggestive of an immediate-type reaction, and a negative SPT response in all but 1 patient. However, after a prolonged period of withdrawal from CMP, their SPT responses converted to positive, and in 7 of these cases, an immediate response (<10 minutes) to small amounts of CMP was demonstrated.[10] In a single case an IgE type of reaction appeared after 30 minutes. Comparison of these 8 patients with the other 36 patients with FPIES did not reveal any statistical differences in the average age of onset (66.4 ± 68.5 vs 55.95 ± 50 days, respectively), the mean doses evoking the response (125 vs 100 mL, respectively; $P = .23$), the median time to response after the administration of milk (90 vs 120 minutes, respectively), or the SPT results at the time of FPIES presentation (data not shown).

Risk factors for the development of FPIES

Healthy infants from the cohort (n = 12,638) were compared with those given diagnoses of FPIES (n = 44) to determine the risk factors leading to the development of FPIES. All infants whose parents raised concerns about adverse effects but were not proved to have FPIES were excluded from this analysis (n = 315). Table I presents the risk factors that were extracted from the medical chart and from the primary questionnaire obtained from the parent during the first interview or the first visit. The only statistically significant differences between the FPIES and control groups were the type of delivery ($P < .003$, Table I) and the religion of the parents ($P < .03$, Table I).

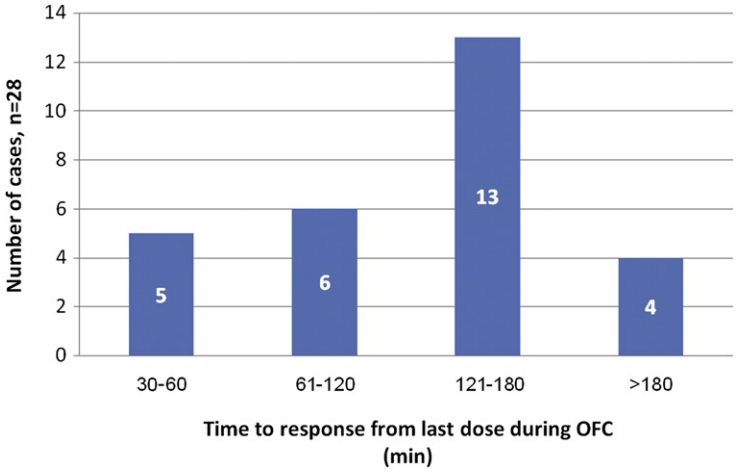

FIG 4. Response time from last dose to clinical symptoms during OFC.

TABLE II. Characterization of the OFC in patients with FPIES

Patient no.	Age (mo)		Dose of milk (mL)		Time (min)		Symptoms during challenge	SPT to CMP	Mode of recovery
	Initial reaction	Evaluation	Last	Cumulative dose	From last dose	From first dose			
1	2	5.6	150*	385*	≥180	315	V, L, P	−	C
2	0.25	5.2	30	55	120	150	V, L	+	C
3	1	4.2	120	235	120	215	V, L, D	−	C
4	0.03	3.5	30	55	30	60	V, L	−	C
5	1	5.4	150*	385*	120	250	V	−	SR
6	3	5	150*	385*	90	220	V	−	SR
7	2	6.8	150*	385*	120	250	V, L	−	SR
8	3	3.7	30	55	30	60	V, L, P	−	SR
9	1.5	5.6	60	115	120	170	V, L, P	−†	SR
10	1	2.6	150*	385*	30	160	V, L, D	−	SR
11	1.5	3.6	150*	385*	120	250	V, L, D_B	−	NR
12	1	3.7	150*	385*	120	250	V, L, D_B	−	SR
13	0.5	3.7	150*	385*	60	190	V, L, P	−	SR
14	1	3.8	120	235	≥180	275	V, L	+	SR
15	1	5.8	150*	385*	≥180	310	V, L	−‡	SR
16	0.25	12.1	100	215	60	155	V, L	−	C
17	0.25	7.6	150*	385*	≥180	310	V	−	SR
18	3.5	18.9	120	235	150	245	V, L, P	−	NR
19	4	5	60	115	≥180	230	V, L	−§	C
20	0.5	4	150*	385*	≥180	310	V, L	−	SR
21	0.25	4.5	60	115	≥180	230	V, L, D, P	−‡	IgE*
22	1	3.9	120	235	120	215	V	−	IgE*
23	4	4	150*	385*	30	180	V	−	IgE*
24	1.5	4.9	150*	385*	≥180	310	V, L	−	IgE*

Twenty-four patients who initially underwent an OFC at our medical center are described.
C, Challenge; *D*, diarrhea; D_B, bloody diarrhea; *IgE**, patients with FPIES who converted to IgE-CMA; *L*, lethargy; *NR*, no recovery; *P*, pallor (change in color); *SR*, self-report; *V*, persistent vomiting.
*Up to a maximum dose of 150 mL or a maximum cumulative dose of 385 mL depending on whether the infant was able to finish the administered dose.
†Negative to CMP but positive to house dust mite.
‡Negative to CMP but positive to egg.
§Negative to CMP but positive to sesame.

DISCUSSION

To our knowledge, this is the first large, prospective, noninterventional population–based study in which several fundamental questions regarding FPIES were evaluated. To minimize bias, we aimed to reach the highest possible percentage of the target population and were able to reach the recruitment rate of 98.4%.[10] From our data, we estimate that the prevalence of FPIES in this population is 0.34%. Sixty-four percent of the cases had an OFC, and in another 9% the reactions were so severe that we declined to offer an OFC based on our clinical judgment. This is the highest rate of OFC performed in any large (>10 cases) published series of FPIES. Included in our estimate are 12 cases in which an OFC was not performed either because of parental refusal (n = 8) or because the diagnosis was previously made by another allergist

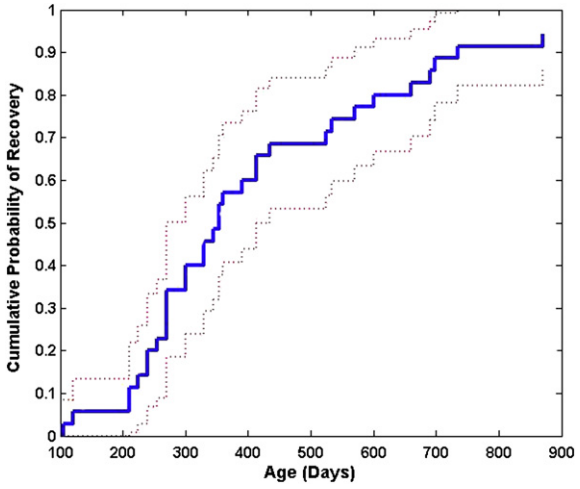

FIG 5. Kaplan-Meier plot for the cumulative probability of recovery from CMP-induced FPIES. More than 90% of patients recovered from FPIES after 900 days.

without an OFC. Of import, 10 of 12 of these patients experienced 2 or more reactions to CMP that fulfilled all other criteria for FPIES, and thus we justify their inclusion to reach the highest reasonable estimate for the prevalence of FPIES in our population.

All of our patients experienced repetitive vomiting after exposure to CMP, but in only a quarter of these cases was diarrhea observed. These results are similar to other descriptions of FPIES-related reactions in which diarrhea was not as prevalent,[2,7] as originally described by Gryboski.[1] For example, in the 66 FPIES episodes experienced by 35 children described by Meher et al,[8] only 16 (24%) of 66 had diarrhea. Our experience is that diarrhea, if present, appears later in the course of the response. It is likely that the prevalence is higher in the report by Grybosky[1] because of the description, for the most part, of more chronically exposed children.

The challenge protocol study design is a suboptimal one for drawing any firm conclusions regarding the amount of milk that can induce a reaction. Because all doses were given within 4 hours or less, it is not possible to know which dose was responsible for the reaction. The same is true for the time to reaction. An optimal study design would be to administer a single dose and increase it every 2 or more days. This would obviously be a very difficult protocol for a large-scale study.

It is interesting to note that having a cesarean section and ethnicity were risk factors for the development of FPIES. Although it is unclear why these associations exist, it is possible that even a greater sample size might be necessary to sort out these potential risk factors.

The lack of proved coexisting allergy to soy in our patients with FPIES is somewhat surprising and deserves a thorough evaluation. The most comprehensive study describing a concomitant allergy in patients with FPIES to CMP and soy is that of Sicherer et al.[2] Of the 11 patients with CMP-induced FPIES followed at that tertiary care referral center, 7 (64%) had a coexisting allergy to soy. In 2 of these patients, the symptoms occurred immediately after ingestion, one to both milk and soy and the other to soy only. In 2 other patients the sensitivity to soy developed months after the sensitivity to milk. In 6 of 7 of these patients, diarrhea was an accompanying symptom of their FPIES reaction. Finally, 5 of 7 patients were still sensitive to both or at least 1 food at the time of their report. Thus the clinical characteristics of these 7 patients differ widely from those reported here, and it is possible that these 7 cases represent a more severe and unique subgroup of FPIES. In fact, in a subsequent article from that same group in which FPIES caused by solid food was compared with CMP-induced FPIES,[6] only a third (33%) of the now 24 patients with CMP-induced FPIES responded to soy, suggesting that the additional patients with CMP-induced FPIES included in the later report had a lower cross-reactivity rate to soy. In support of our findings is the series by Meher et al,[8] in which not a single patient with sensitivity to both milk and soy is described. In our group at least 4 infants continued to consume extensively hydrolyzed milk, and therefore a subsequent development of cross-reactivity to soy cannot be ruled out.[9,12] Given the above, we believe that the automatic exclusion of soy as an alternative in CMP-induced FPIES is unjustified. Nevertheless, the substitution of CMP-based formula with soy-based formula requires follow-up because there is solid evidence that soy-induced FPIES can develop later.[9,12]

The development of FPIES into secondary IgE-CMA has been previously described,[5,6] although the extent to which it can occur is now demonstrated. In a study performing serial follow-up challenges in a group of 23 infants with FPIES, no secondary IgE-CMA cases were noted.[13] It is possible that we were able to classify patients as having FPIES before their conversion to an IgE-CMA phenotype because we followed the patients prospectively in contrast to a tertiary referral center, where an evaluation might occur after a more prolonged lag period from the initial event. Assuming this to be true, the rechallenge of patients with FPIES should be carried out under conditions in which an anaphylactic reaction can be properly treated.

In the series described here, none of the infants required the placement of an intravenous line or exhibited clinically significant hypotension during the OFC. Oral rehydration and observation were sufficient treatment for their adverse events, although we did not challenge 4 patients because of a history of a severe reaction. Others describe the challenge procedure as more dangerous, and in many institutions an intravenous line placement might be the common practice.[3] This could be due to a more selected population at other institutions in contrast to the patients identified from this prospective study, or alternatively, it represents a different clinical approach to the administration of an OFC to patients with FPIES. Although the infants appear very sick during the episode, this is likely because of their lethargy and pallor, which are an integral part of their reaction. As far as we know, unlike cases of IgE-CMA, there is not a single case of mortality or residual disease among infants with FPIES. Thus although the lack of familiarity with this condition among physicians might result in a sepsis workup and initiation of antibiotic therapy,[5,7,8,14] we believe that this is not necessary.

In summary, the prevalence of FPIES is relatively high, and thus pediatricians should be aware of this condition to avoid unnecessary hospitalizations and overtreatment. We suggest its diagnostic criteria should include repetitive vomiting instead of vomiting or diarrhea. Furthermore, the challenge procedure is safe and in the common case usually does not require an intravenous line. Finally, in cases of CMP-induced FPIES, with proper follow-up, soy might be a reasonable feeding alternative.

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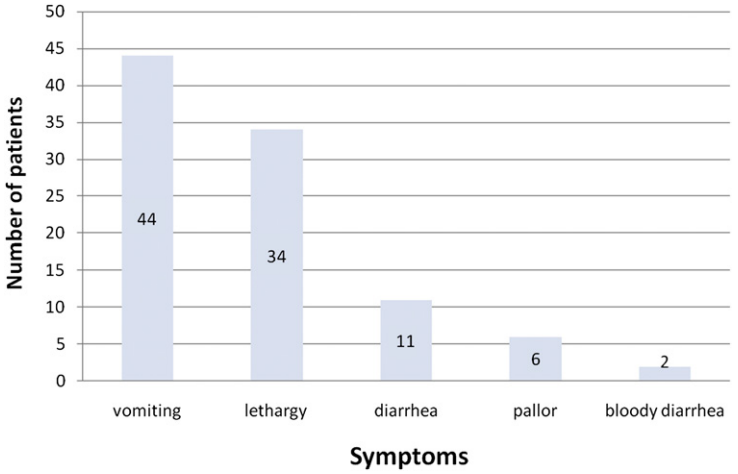

FIG E1. Clinical characteristic of patients with FPIES. The number of patients exhibiting each clinical symptom is depicted within the *bar*. The data are based on historical information from the parents or when available from the OFC.

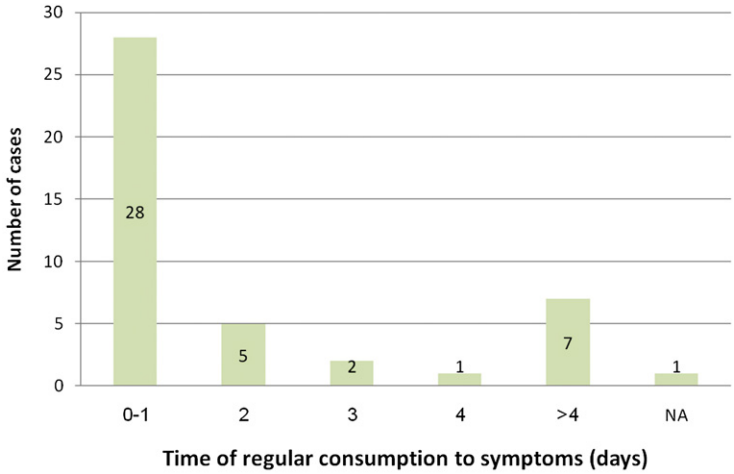

FIG E2. Days of consumption of CMP before the development of symptoms.

TABLE E1. Challenge protocol for patients with milk-related FPIES

Time interval	Cumulative time (min)	Dose (mL)	Cumulative dose (mL)	Dose (mg)	Cumulative dose (mg)
0	0	5	5	150	150
10	10	20	25	600	750
20	30	30	55	900	1,650
20	50	60	115	1,800	3,450
45	95	120	235	3,600	7,050
45	140	150*	385*	4,500*	11,550*
180	320	Observation	385		

*Patients reached a maximum dose of 150 mL and a maximum cumulative dose of 385 mL depending on the ability of the infant to drink the last dose completely.