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Clinical presentation of FPIES in 113 Swedish children

Clinical presentation and management of foodprotein-induced enterocolitis syndrome in 113 Swedish children

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AUTHOR'S CONTRIBUTION STATEMENT

Ulrika L. Fagerberg: conceptualization (supporting); methodology (equal); supervision; writing – review and editing (equal). **Mareike Fech-Bormann:** conceptualization (lead); methodology (equal); writing – review and editing (equal). **Josefin Ullberg:** investigation; formal analysis; writing – original draft; writing – review and editing (equal).

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Conflicts of interest

The authors have no conflicts of interest to declare.

ABBREVIATIONS USED

FPIES: foodprotein-induced enterocolitis syndrome

SPT: skin prick test

OFC: oral food challenge

IgE: immunoglobulin E

ABSTRACT

Background: Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated food allergy causing severe acute gastrointestinal symptoms and lethargy, mainly affecting infants and young children. There are geographic variations in its clinical features. This study aimed to describe the clinical characteristics and management of FPIES in Swedish children.

Methods: The study included children who presented with acute FPIES during 2008–2017.

All Swedish pediatric departments ($n = 32$) were invited to report their known patients. Data were collected through chart reviews and interviews with parents.

Results: Eighteen pediatric departments contributed and 113 patients were included. Most had a family history of atopy (74%) and 51% had an atopic disease. Common trigger foods were cow's milk (26%), fish (25%), oat (22%) and rice (8%). Most patients (85%) reacted to a single food. The median age at first reaction was 3.9 months for cow's milk and 6.0 months for other foods ($P < 0.001$, range 1.0 month to 9 years). Repetitive vomiting (100%), lethargy (86%) and pallor (61%) were common symptoms; 40% had diarrhea. Sixty percent visited the emergency department and 27% of all patients were hospitalized. Most patients were diagnosed clinically (81%). Specific IgE for the trigger food was positive in 4/89 tested patients (4%) and skin prick test for the trigger food was positive in 1/53 tested patients (2%).

Conclusions: In our Swedish study of 113 children, cow's milk, fish and oat were the commonest trigger foods. Most patients reacted to a single food and IgE sensitization was rare.

Keywords: *Food allergy, Food protein-induced enterocolitis syndrome, FPIES, Milk allergy, Non-IgE-mediated food allergy*

INTRODUCTION

Foodprotein-induced enterocolitis syndrome(FPIES) is a non-immunoglobulin E (IgE) cell-mediated foodprotein allergy occurring predominantly in infants and young children.¹ The reaction is delayed, starting one to four hours after ingestion of the trigger food. The primary symptoms are gastrointestinal with repetitive vomiting, sometimes followed by diarrhea. Pallor and lethargy are also frequent symptoms. In the most severe cases, dehydration can lead to hypovolemic shock. The severe, but nonspecific symptoms may be misinterpreted as gastroenteritis, intussusception, sepsis or anaphylaxis.²

The connection between symptoms and previous food-intake is often not understood until several reactions have occurred.³FPIES can be caused by any food⁴and the commonest triggers differ among populations. Cow's milk was thefirst FPIES trigger food to be described and has been recognized as the most common in several countries.⁵⁻⁸ Soy, fish and rice are otherfrequent trigger foods.⁹⁻¹¹

Most patients have a negative skin prick test (SPT) and undetectable specific IgE for the trigger food. However, a subgroup has positive SPT and/or elevated specific IgE. This is called *atypical FPIES* and has been associated with a prolonged course and development of IgE-mediated symptoms.¹¹

In *chronic FPIES*, regular ingestion of the trigger food causes symptoms such as diarrhea, vomiting and failure to thrive.¹² The symptoms resolve when the trigger food is excluded and, when ingested again, causes acute FPIES symptoms.² Chronic FPIES has mainly been reported in patients younger than four months of age with reactions to cow's milk or soy.⁴

Over time, many patients with FPIES develop tolerance, but the age of resolution varies based on trigger food and population.^{2,13} Previous studies have been performed in a limited number of countries, while no large FPIES studies have been conducted in Scandinavia. This study aims to describe the clinical characteristics and management of FPIES in Swedish children.

MATERIALS AND METHODS

Study sample

The sample was patients presenting with acute FPIES during 2008–2017. All Swedish pediatric departments ($n = 32$) were invited to report their known cases of acute FPIES. In two departments, the medical record database was searched to identify patients, using the code for allergic and dietetic gastroenteritis and colitis (K52.2) in the 10th revision of the International Statistical Classification of Diseases and Related Health Problems. However, this code is not used exclusively for FPIES and it was, therefore, unfeasible to perform a large-scale database search.

Patient histories were reviewed retrospectively to assess whether they met the FPIES criteria, defined by the diagnostic criteria described by Feuille and Nowak-Węgrzyn,¹⁴ based on the works of Sicherer and co-workers^{15,16} and Powell¹⁷: (1) exposure to the incriminated food elicits repetitive vomiting and/or diarrhea within four hours without any other cause for the symptoms, (2) symptoms are limited to the gastrointestinal tract, (3) removal of the offending protein from the diet results in resolution of symptoms and (4) a standardized oral food challenge (OFC) or isolated re-exposure elicits typical symptoms. Patients who did not fulfill the criteria were excluded, as were patients who presented before 2008.

Data were collected through chart review. In cases with missing data, supplemental interviews were performed with the parents. A structured questionnaire was used to record information on birth date, gender, family history of atopy and food allergies, comorbidity, trigger food(s), acute and chronic symptoms, number of episodes with acute symptoms, emergency department visits, hospitalization, medical treatment, laboratory data, whether a food challenge was performed and age of resolution.

A specific IgE >0.35 kU/L was considered positive. SPT was considered positive when the wheal diameter was the same size or larger than the positive control.

Ethics

The research project was approved by the Regional Ethical Review Board in Uppsala (2014/507). Written informed consent was obtained from parents before enrolment.

Statistical analysis

Analyses were performed with IBM SPSS Statistics for Windows Version 25.0 (IBM Corp., Armonk, NY). Continuous data are reported as median and range or interquartile range. For comparisons between skewed variables, the Mann–Whitney *U* test was used. A *P*-value <0.05 was considered statistically significant.

RESULTS

Materials

Eighteen pediatric departments reported 118 patients. The parents of eight patients from seven other pediatric departments volunteered to participate. One hundred thirteen patients with acute FPIES were included. Thirteen patients were excluded, ten did not meet the diagnostic criteria (eight had a single acute reaction and two had only chronic symptoms) and three had presented before the start of the study period. In 56 cases, data from medical charts was sufficient; in 57 other cases, parents were interviewed.

Patient characteristics

Characteristics of the 113 patients are presented in Table I. Family history of atopy (defined as asthma, eczema, IgE-mediated food allergy or allergic rhinitis reported in parents or siblings) was reported in 74%. Thirty-three percent had parents or siblings with any kind of food allergy. Three included patients were siblings, all of whom reacted to corn. Four patients had parents with food allergies causing gastrointestinal symptoms exclusively and one patient had a sibling with suspected FPIES. Atopic disease (asthma, eczema, IgE-mediated food allergy or allergic rhinitis) was reported in 51% of the patients.

Onset

The median age at first reaction was 6.0 months (range 1.0 month to 9 years with interquartile range 4.8 to 7.9 months). Patients with cow's milk-induced FPIES had their first episode at median age 3.9 months (range 1.0 to 44.1 months), while patients reacting to other foods had their first episode at median age 6.0 months (range 3.6 months to 9 years) ($P < 0.001$). Patients with fish-induced FPIES had their first episode at median age 8.0 months (range 5.0 to 25.7 months) and those with oat-induced FPIES at median age 5.3 months (range 4.0 to 17.9 months). Forty-five patients reacted upon their first ingestion of the trigger food and 56 had ingested the food at least once previously, without reacting. This status was unclear among the remaining 12 patients.

Diagnosis

Eighty-one percent were diagnosed clinically from symptoms and/or patient history. Twelve percent had undergone a hospital-based diagnostic OFC, and 7% performed a food challenge at home at the request of a physician before diagnosis. The median age at diagnosis was 9.6 months (range 1.8 months to 9 years). The median age at diagnosis of cow's milk-induced FPIES was 5.9 months and the median age at diagnosis of FPIES caused by other foods was 12 months ($P<0.001$). Median time from the first acute reaction to diagnosis was 3.7 months (range 1 day to 6.7 years) and the median number of reactions before diagnosis was 2 (range 1 to 8), excluding reactions during diagnostic food challenges.

Trigger foods

Cow's milk was the most common trigger food, followed by fish and oat (Table II). Reactions to rice, egg, chicken and soy were less common. In two patients, the trigger protein was unclear due to the ingestion of more than one food at the same time; both patients already had FPIES to other food proteins. The majority reacted to a single food. Seventeen patients (15%) reacted to two or more food proteins (range 2 to 4) (Figure 1, Table III). Four of 29 patients (14%) with cow's milk-induced FPIES had multiple FPIES. Two of them reacted to soy (7%). One patient with cow's milk-induced FPIES had an acute FPIES reaction to milk-free baby porridge containing guar gum at five months of age and a hospital-based diagnostic OFC confirmed that the reaction was caused by guar gum. Five of seven patients (71%) with soy-induced FPIES had multiple FPIES. Nine of 25 patients (36%) with oat-induced FPIES had multiple FPIES, among whom seven also reacted to other grains. Six of them reacted to rice (24%) and one to wheat (4%). Among the 28 patients with fish-induced FPIES, two (7%) reacted to other food groups. Five patients with fish-induced FPIES tolerated other fish species. Among the seven patients with chicken-induced FPIES, three reported reactions to turkey.

Symptoms and emergency treatment

The 113 study patients had at least 437 cumulative episodes of acute FPIES. The median number of episodes per patient was three (range two to more than 15). The median time from ingestion to reaction was 120 minutes (range 0 min to 12 hours). Although a delay of up to 12 hours was reported, all patients had at least one reaction within 4 hours. In three patients, immediate reactions were reported, but they also had delayed reactions after 1.5 to 2 hours. All

patients reacted with vomiting and 40% also had diarrhea (Table IV). Lethargy (including unresponsiveness and unconsciousness) and/or paleness was reported in 94%. Other reported symptoms were floppiness, abdominal pain, cyanosis, bloody stools, fever, hypothermia and hypotonia.

Forty-three (38%) patients presented at the emergency department during the first episode of acute FPIES. Sixty-eight (60%) visited the emergency department upon any reaction and 31 (27%) visited the emergency department more than once (range 2 to 6 times). Thirty-one (27%) were hospitalized because of acute FPIES (range 1 to 5 times). Forty-one (36%) were given pharmacologic treatment and/or fluids during acute FPIES. Twenty-six (23%) received intravenous fluids, 17 (15%) received cortisone, 11 (10%) received antihistamine and 8 (7%) received adrenaline injections. Two (2%) received antibiotics and four (4%) received oxygen.

Chronic FPIES

In 15 patients, acute reactions were preceded by chronic symptoms (Table V). Nine of these had chronic symptoms during breastfeeding (cow's milk $n = 7$, rice and oat $n = 2$) and six patients had chronic symptoms from regular direct ingestion of the trigger food (cow's milk $n = 4$, soy $n = 2$). Fourteen of 15 had gastrointestinal symptoms and one patient's parents reported that their general condition was impaired. One patient had an acute FPIES episode from breastfeeding when their mother accidentally ingested cow's milk after having excluded it from her diet for some time.

Allergen sensitization to trigger foods

An SPT ($n = 53$) and/or measurement of specific IgE ($n = 89$) for the trigger food was performed in 105 of the 113 patients (93%) close to diagnosis (SPT median 0 days from diagnosis, specific IgE median 15 days before diagnosis). Most were negative (96%) and sensitization was only seen to cow's milk. Of the patients with cow's milk-induced FPIES, 28 of 29 were tested (SPT $n = 22$, specific IgE $n = 20$) with four (14%) positive. Characteristics of the four patients with atypical FPIES are presented in Table VI. An atopy patch test was performed for the trigger food in two patients, one of which was positive (cow's milk positive, oat negative).

Laboratory tests from acute episodes

Laboratory tests were taken during acute episodes in 38 patients (34%). A complete blood count was performed in 17 patients. Nine had leukocytosis (LPK range 18.9 to 33 $\times 10^9/L$) and three had thrombocytosis (TPK range 586 to 881 $\times 10^9/L$). Absolute neutrophil count was performed in eight patients, among whom six had neutrophilia (range 9.4 to 23.3 $\times 10^9/L$). Blood gas analysis was performed in 25 patients (22%). Two patients had metabolic acidosis and one had acidosis with normal base excess and pCO_2 (pH <7.35). Five had decreased base excess (-3.4 to -7), but normal pH. Two had respiratory alkalosis (pH 7.51 and 7.55). One had elevated CO-Hb (1.4%) and one had low oxy-Hb (69.6%). In two patients, tryptase was tested and was lightly elevated in one (17 $\mu g/L$, reference <14 $\mu g/L$).

Oral food challenges

Forty-nine OFCs to monitor the development of tolerance were performed in 34 patients. Median time from latest episode of acute FPIES to OFC was 21.0 months (range 6.3 months to 5.7 years). Fifteen OFCs in 13 patients were positive (31%), causing symptoms of acute FPIES. All reactions included vomiting and nine patients were lethargic or had impaired general condition. Paleness (n = 4), abdominal pain (n = 4) and diarrhea (n = 2) were also reported. Five patients were treated with intravenous fluid, three with cortisone and one with antihistamine.

Follow-up

The median age at last follow-up was 40.3 months (range 5.4 months to 12.5 years). During follow-up 48 (42%) patients became tolerant to the first food to which they had reacted. Of 86 patients with first reactions to solid foods, 30 became tolerant (35%) at median age 32.3 months (range 7.8 months to 8 years). Eighteen of 29 patients (62%) with cow's milk-induced FPIES became tolerant to cow's milk at median age 22.3 months (range 6.3 to 58 months). Median age at last follow-up for patients without resolution was 37.7 months.

DISCUSSION

This, the first large Scandinavian study of acute FPIES, included 113 Swedish pediatric patients. Cow's milk, fish and oat were the most common food triggers among this sample, with most patients reacting to a single food. Atopic disease and heredity for atopy were common, confirming the relationship between FPIES and atopy. However, IgE sensitization to the trigger food was rare.

Although there are geographic variations in trigger foods, cow's milk has generally been described as the most common. Herein, cow's milk was the most common trigger food (26%), closely followed by fish (25%) and oat (22%). In other European studies from Spain, Italy and Great Britain, fish (12 to 33%) was also described as the second most common trigger food after cow's milk.^{8,18,19} In Greece, fish (54%) was even more common than cow's milk (35%).¹⁰ The high frequency of oat-induced FPIES in this study is unique among European studies, though it is similar to US frequencies (16 to 35%).^{6,11,20} Rice was reported as the most common trigger food in Australia⁹ and in a recent US study.²⁰ In this study, the frequency of rice-induced FPIES was similar to other European cohorts (4 to 10%).^{8,10,18,19} There seems to be a European trigger food pattern, in which cow's milk and fish are common while rice and soy are less common.

There are several possible reasons for geographic variations in trigger foods. Breastfeeding is believed to protect against cow's milk- and soy-induced FPIES⁴ and differences in rate and duration of breastfeeding may play a role.² There are also differences when it comes to which formulas are used and the order in which foods are introduced. Soy-based infant formula is not recommended in Sweden and hence has not been sold since 2009. According to Swedish dietary guidelines, solid foods should be introduced from six months of age. Very small samples of solid foods may be given from four months of age at the earliest. All kinds of food should be introduced during the first year. Oats commonly introduced early, being the main ingredient in commercial baby porridge with recommended use from four months of age. Median age at first reaction to fish was 8 months in this study, in comparison to 10 months in a Spanish study²¹ and 14 months in an Italian study.²² In both studies, the age at first reaction was reported to match the age of introduction of fish to the diet. This implies that fish may be introduced even earlier into the diet in Sweden, than in the Mediterranean countries. Other possible causes for geographic variations are differences in intestinal microbiota and genetics.^{6,23}

Reactions to multiple foods were uncommon. Less than one in six patients reacted to more than one food. Patients with FPIES to grain seem to have a higher risk for reactions to other foods,

particularly other grain types. Concomitant FPIES to oat and rice, seen in six patients, was the most frequent combination in this study. This combination was also seen in previous Australian and US studies.^{9,11,20} Concomitant FPIES to cow's milk and soy was rare in our study, in contrast to US studies where 16 to 29% of patients reacted to both cow's milk and soy.^{6,11}

In our study, the frequency of atypical FPIES was relatively low. A high proportion of patients were tested and 96% had no IgE sensitization to their trigger food. This is consistent with US, Australian and Italian studies (94 to 97%),^{6,8,9} although recent European studies have reported higher rates of IgE sensitization (13 to 16%).^{10,18} The four patients with IgE sensitization in this study all reacted to cow's milk. Caubet et al. described a higher risk of persistent cow's milk-induced FPIES in patients with sensitization to cow's milk because none of their sensitized patients (n = 17) became tolerant during their study.¹¹ In three of our four patients with sensitization to cow's milk, FPIES resolved early and hence we saw no association between sensitization and prolonged time to resolution.

After this study was initiated, international consensus guidelines for the diagnosis and management of FPIES were published, including revised clinical diagnostic criteria.² Following these criteria, vomiting within one to four hours after ingestion of the suspect food and absence of classic IgE-mediated skin or respiratory symptoms are required, along with at least three of nine minor criteria. Although vomiting was not required for diagnosis in our inclusion criteria, all patients reacted with vomiting. Furthermore, 86% of the patients had lethargy, 61% had pallor and 60% visited an emergency department. This can be compared with the study by Díaz et al., performed using the revised criteria, in which lethargy was seen in 88% and pallor in 89%.¹⁸ In the largest study to date (n = 462), 5% had severe symptoms including lethargy, pallor/cyanosis or hypotension.⁶

This study's large cohort is a marked strength, especially in relation to the relatively small Swedish population (approximately 10 million) that it represents. The results provide knowledge about FPIES in a specific geographic region, in which FPIES has not been previously characterized. Thorough data were collected, with few missing data in each case because supplemental parent interviews were performed. There was also a high proportion of relatively severe cases of FPIES in this sample.

The study's limitations include that it was performed retrospectively. The use of retrospective parent interviews may introduce recall biases. Because of the relatively limited coverage of the study, it is unable to provide FPIES incidence in Sweden; not all pediatric departments responded,

as participation was voluntary. Although all included patients met the stated diagnostic criteria for acute FPIES, there is a potential diagnostic bias, as diagnoses first were made in several different pediatric departments. Finally, the follow-up period was too short to determine the age of resolution.

In conclusion, FPIES is a non-IgE-mediated food allergy with severe nonspecific symptoms, mainly affecting infants and young children. We have described the clinical features and management of acute FPIES in 113 Swedish children in the first large Scandinavian study of this disorder. Understanding its clinical characteristics increases our opportunity to reduce the consequences of FPIES. With knowledge about symptoms, correct diagnoses can be made earlier and further reactions avoided. Given that multiple FPIES is rare, most patients can introduce new foods safely following the common guidelines for food introduction. Further studies will be needed to determine the age of resolution, improve our understanding of the pathophysiology involved and identify biomarkers for diagnosis and resolution.

REFERENCES

1. Berin MC. Immunopathophysiology of food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol* 2015;135:1108-13.
2. Nowak-Węgrzyn A, Chehade M, Groetch ME, Spergel JM, Wood RA, Allen K et al. International consensus guidelines for the diagnosis and management of food protein-induced enterocolitis syndrome: Executive summary-workgroup report of the Adverse Reactions to Foods Committee, American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2017;139:1111-26.
3. Leonard SA, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome. *Pediatr Clin North Am* 2015;62:1463-77.
4. Agyemang A, Nowak-Węgrzyn A. Food protein-induced enterocolitis syndrome: A comprehensive review. *Clin Rev Allergy Immunol* 2019;57:261-71.
5. Powell GK. Enterocolitis in low-birth-weight infants associated with milk and soy protein intolerance. *J Pediatr* 1976;88:840-4.
6. Ruffner MA, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel JM. Food protein-induced enterocolitis syndrome: Insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013;1:343-9.
7. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: A large-scale, prospective population-based study. *J Allergy Clin Immunol* 2011;127:647-53.
8. Sopo SM, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicentre retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy* 2012;42:1257-65.
9. Mehr S, Frith K, Barnes EH, Campbell DE. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. *J Allergy Clin Immunol* 2017;140:1323-30.
10. Douros K, Tsabouri S, Feketea G, Grammeniatis V, Koliofoti EG, Papadopoulos M et al. Retrospective study identified fish and milk as the main culprits in cases of food protein-induced enterocolitis syndrome. *Acta Paediatr* 2019;108:1901-4.
11. Caubet JC, Ford LS, Sickles L, Järvinen KM, Sicherer SH, Sampson HA et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 2014;134:382-9.

12. Mane SK, Bahna SL. Clinical manifestations of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;14:217-21.
13. Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. *Curr Allergy Asthma Rep* 2012;12:297-303.
14. Feuille E, Nowak-Węgrzyn A. Definition, etiology, and diagnosis of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;14:222-8.
15. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr* 1998;133:214-9.
16. Nowak-Węgrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003;111:829-35.
17. Powell GK. Foodprotein-inducedenterocolitisof infancy: Differential diagnosis and management. *Compr Ther* 1986;12:28-37.
18. Díaz JJ, Espín B, Segarra O, Domínguez-Ortega G, Blasco-Alonso J, Cano B et al. Food protein-induced enterocolitis syndrome: Data from a multicenter retrospective study in Spain. Gastrointestinal Allergy Working Group of the Spanish Society of Pediatric Gastroenterology, Hepatology and Nutrition (SEGHP). *J Pediatr Gastroenterol Nutr* 2019;68:232-6.
19. Ludman S, Harmon M, Whiting D, du Toit G. Clinical presentation and referral characteristics of food protein-induced enterocolitis syndrome in the United Kingdom. *Ann Allergy Asthma Immunol* 2014;113:290-4.
20. Blackman AC, Anvari S, Davis CM, Anagnostou A. Emerging triggers of food protein-induced enterocolitis syndrome: Lessons from a pediatric cohort of 74 children in the United States. *Ann Allergy Asthma Immunol* 2019;122:407-11.
21. Infante S, Marco-Martín G, Sánchez-Domínguez M, Rodríguez-Fernández A, Fuentes-Aparicio V, Alvarez-Perea et al. Food protein-induced enterocolitis syndrome by fish: Not necessarily a restricted diet. *Allergy*. 2018 Mar;73(3):728-732.
22. Miceli Sopo S, Monaco S, Badina L, Barni S, Longo G, Novembre E et al. Food protein-induced enterocolitis syndrome caused by fish and/or shellfish in Italy. *Pediatr Allergy Immunol*. 2015 Dec;26(8):731-6.
23. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol* 2014;14:208-16.

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TABLES

TABLE I. Sample characteristics

No. of patients	113
Male patients, no. (%)	60 (53)
Family history of atopy* (n = 111), no. (%)	82 (74)
Atopic disease, no. (%)	
Eczema	46 (41)
Asthma	21 (19)
IgE-mediated food allergy	14 (12)
Allergic rhinitis	2 (2)
No. of episodes in total	437
No. of episodes before diagnosis, median (range)	2 (1–8)
Skin prick test positive at diagnosis (n = 53), no.	1
Specific IgE positive at diagnosis (n = 89), no.	2
Diagnosis based on clinical history, no. (%)	91 (81)
Diagnosis based on positive OFC, no. (%)	22 (19)

* Defined as asthma, eczema, IgE-mediated food allergy or allergic rhinitis reported in parent or sibling
OFC = oral food challenge

TABLE II. Trigger foods in 113 children with FPIES

Trigger food	No.	%
Cow's milk	29	26
Grain	33	29
Oat	25	22
Rice	9	8
Corn	4	4
Wheat	1	1
Mixed grains	1	1
Fish	28	25
Soy	7	6
Egg	7	6
Poultry	7	6
Chicken	7	6
Turkey	3	3
Vegetable	7	6
Potato	3	3
Sweet potato	3	3
Green pea	1	1
Bean	1	1
Fruit	2	2
Banana	1	1
Kiwi	1	1
Shellfish	2	2
Meat	1	1
Beef	1	1
Pork	1	1
Quorn	1	1
Guar gum	1	1
Unclear allergen	2	2

TABLE III. Trigger foods in 17 children with multiple FPIES

No.*	Food 1	Food 2	Food 3	Food 4
1	Cow's milk	Egg		
1	Cow's milk	Guar gum		
1	Cow's milk	Soy		
1	Cow's milk	Soy	Green pea	
1	Kiwifruit	Unclear allergen		
1	Oat	Potato		
3	Oat	Rice		
1	Oat	Rice	Egg	
1	Oat	Rice	Soy	
1	Oat	Rice	Fish	Unclear allergen
1	Oat	Soy		
1	Oat	Wheat		
1	Potato	Sweet potato		
1	Pork	Beef	Chicken	
1	Soy	Fish		
17				

*Number of patients

TABLE IV. Acute symptoms in 113 children with FPIES

Acute symptoms	No.	%
Vomiting	113	100%
Lethargy	97	86%
Pallor	69	61%
Diarrhea	45	40%
Floppiness	24	21%
Abdominal pain	16	14%
Cyanosis	9	8%
Bloody stools	3	3%
Fever	3	3%
Hypothermia	2	2%
Hypotonia	2	2%

TABLE V.Reported chronic symptom(s) from regular ingestion of trigger food (n = 15)

Food	Reaction through breast milk	Reported symptom(s)	Hospitalization for acute FPIES episode
Cow's milk	No	Infantile colic	No
Cow's milk	No	Abdominal pain	Yes
Cow's milk	No	Flatulence, crying, bad sleep	No
Cow's milk	No	Diarrhea, abdominal pain, failure to thrive, crying	Yes
Cow's milk	Yes	Vomiting, diarrhea	No
Cow's milk	Yes	Vomiting, abdominal pain	Yes
Cow's milk	Yes	Vomiting, diarrhea, crying	No
Cow's milk	Yes	Vomiting, diarrhea, flatulence, eczema, runny nose	No
Cow's milk	Yes	Infantile colic	Yes
Cow's milk	Yes	Bloody stools	Yes
Cow's milk	Yes	Impaired general condition	No
Oat and rice	Yes	Vomiting, diarrhea	No
Oat and rice	Yes	Bloody stools, Vomiting, diarrhea, abdominal pain	No
Soy	No	Vomiting	No
Soy	No	Abdominal pain, eczema	Yes

FIGURE LEGENDS

FIGURE 1.Number of trigger foods per patient reported as a percentage of patients.

TABLE VI. Characteristics of patients with atypical FPIES (n = 4)

Patient	1	2	3	4
Age at initial reaction	2.0 months	3.7 years	2.6 months	4.0 months
Initial cow's milk S-IgE (kU/L)	<0.35	1.13	0.36	<0.35
Cow's milk S-IgE at follow-up (kU/L)	0.61	<0.35	<0.35	1.5
Initial cow's milk SPT	Negative	Negative	Negative	Positive
Cow's milk SPT at follow up			Positive, but negative 6 months later	Negative
IgE-mediated symptoms from cow's milk	None	None	None	Rash and pruritus after reintroduction of cow's milk, resolved by age 3 years
Concomittant atopic disease	Asthma, allergic rhinoconjunctivitis, eczema	IgE-mediated egg allergy, allergic rhinoconjunctivitis, eczema	Asthma	None
Age of tolerance to cow's milk	23.3 months	Not tolerant at last follow-up 2 years after initial reaction	23.7 months	15.3 months

FPIES = food protein-induced enterocolitis syndrome, IgE = immunoglobulin E, SPT = skin prick test.

