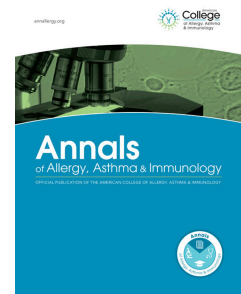


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PII: S1081-1206(21)00100-9

DOI: <https://doi.org/10.1016/j.anai.2021.02.002>

Reference: ANAI 3494

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 1 December 2020

Revised Date: 14 January 2021

Accepted Date: 2 February 2021

Please cite this article as: Moya F, Cid B, Borzutzky A, Hoyos-Bachiloglu R, Clinical Characterization of Chilean Patients with Food Protein-Induced Enterocolitis Syndrome, *Annals of Allergy, Asthma and Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.02.002>.

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Clinical Characterization of Chilean Patients with Food Protein-Induced Enterocolitis Syndrome

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Conflict of interest: none

Funding Source: none

Clinical Trial Registration: does not apply

Keywords: *Food allergy; Food protein-induced enterocolitis syndrome; FPIES; Non-IgE mediated food allergy, Cow's milk allergy.*

Abbreviations: FPIES: Food Protein-Induced Enterocolitis Syndrome, aFPIES: acute

FPIES, cFPIES: chronic FPIES, ED: Emergency department.

Word count: 995

Figures: none

Tables: 1

Food Protein-Induced Enterocolitis Syndrome (FPIES) is a non-IgE-mediated food allergy (FA) with heterogeneous gastrointestinal features which mainly affects young children.¹ Geographical variability in features and trigger foods of FPIES have been reported. Multiple factors could explain these differences, including dietary practices and possibly genetic factors still to be determined.^{1,2} Although clinical series have been reported in Europe, USA, Australia and Asia,³⁻⁸ there are no series of FPIES from Latin America.

We performed a retrospective chart review of pediatric patients with FPIES seen at the allergy and immunology clinics of the UC-Christus Health Network (Santiago, Chile) between 2012-2020. The diagnosis of FPIES and its phenotyping as acute, chronic and atypical was made based on features proposed by the AAAAI.² Data are shown as median (range) and percentages.

Thirty-three patients with acute FPIES (aFPIES) and 29 with chronic FPIES (cFPIES) were studied, two of them had an overlapping phenotype. The median age at aFPIES onset was 6 months (0-36), age at first outpatient visit for aFPIES was 7 months (0-48) and age at diagnosis was 11 months (0-108). Thirteen patients with aFPIES had allergic comorbidities: atopic dermatitis (27%), allergic rhinitis (15%), and asthma (12%). A family history of allergies was reported by 48% of aFPIES patients, IgE and non-IgE mediated FA were described in 18% and 15% of their first-degree relatives, respectively. One of the 5 patients with a family history of non-IgE mediated FA had a relative affected by FPIES. All aFPIES patients had repetitive vomiting within the first 4 hours after ingesting the trigger food. Additional features of aFPIES episodes included: diarrhea (61%), lethargy (42%), abdominal pain (27%) and pallor (18%). Out of twelve patients who visited the emergency department (ED) due to aFPIES, 66% required intravenous fluids, 17% received corticosteroids and 50% required hospitalization. Ondansetron was prescribed to 36% of

aFPIES patients during an episode. The reported triggers of aFPIES are shown in Table 1, 30% of patients reacted to a single food and 6% had symptoms during exclusive breastfeeding. Although no patient with aFPIES had a history of IgE-mediated reactions to foods, allergic sensitization was demonstrated in 9% of them.

For cFPIES median age at onset was 2 months (0-17), age at first outpatient visit for cFPIES was 6 months (0-81) and age at diagnosis was 8 months (0-81). Forty-eight percent of patients with cFPIES had additional allergic diseases: atopic dermatitis (31%), asthma (21%) and allergic rhinitis (17%). Fifty-five percent of cFPIES patients had family history of allergies, while 17% had a family history of IgE and non-IgE-mediated food allergy. In 4/5 patients with a family history of non-IgE mediated FA an FPIES affected relative was reported. Clinical features of cFPIES patients included: recurrent diarrhea (85%), bloody stools (52%), intermittent vomiting (69%), abdominal pain (55%) and failure to thrive (38%). Lethargy and pallor were reported in 2 and 1 patients, respectively. Ondansetron was prescribed to 14% of cFPIES patients. Five patients visited the ED due to cFPIES, 2 received corticosteroids and 1 required intravenous fluids; 75% of those who visited the ED were hospitalized. The triggers of cFPIES are shown in Table 1, 17% of cFPIES patients reacted to one food, 59% of them reacted to more than three trigger foods and 31% had symptoms during exclusive breastfeeding. Allergic sensitization was demonstrated in 17% of cFPIES patients.

Our results align with previous reports of geographical variations in FPIES triggers. As previously reported by others, cow's milk was the most common trigger of both aFPIES and cFPIES in our study (Table 1);³⁻⁷ however, our cohort behaved differently from other reports when additional foods were analyzed. Vegetables were the second most common trigger of aFPIES in our series, while these results are similar to data from the US,³ they

differ from other studies where vegetables are rare triggers.^{4,6} As previously reported in North American studies,⁹ we found that grains and soy follow cow's milk in frequency as triggers of cFPIES. These findings might be explained by similar patterns of solid food introduction between Chile and the US. Although our cohort behaved similarly to reports from the US regarding trigger foods, they differed significantly in the frequency of symptoms during exclusive breastfeeding. In our study, 31% of patients cFPIES had symptoms during exclusive breastfeeding, a finding previously described in Japan⁸, but rarely reported in other studies.¹ This could be explained by the high adherence of Chilean mothers to exclusive breastfeeding during the first six months of life and might explain the earlier onset of cFPIES vs. aFPIES in our series.

Although FPIES is a non-IgE mediated FA, some patients develop IgE-mediated allergic sensitization and are classified as atypical FPIES. The reported frequency of atypical FPIES ranges from 5-30%.¹ Allergic sensitization was demonstrated in 9% and 17% of patients with aFPIES and cFPIES in our study, these rates are significantly lower than those reported in series from the US¹⁰ and may be explained by a lagged raise in the prevalence of allergic sensitization and IgE-mediated FA in Chile compared to developed countries. Due to the low number of FPIES patients with allergic sensitization, further studies are needed to accurately determine the foods involved in atypical FPIES in our population.

As previously reported by others¹⁰, allergic comorbidities, a family history of allergic diseases and IgE-mediated FA in first degree relatives were frequent amongst patients with FPIES in our study. Interestingly, a family history of FPIES was more frequently reported in patients with cFPIES than aFPIES, suggesting a differential role of genetics in the pathophysiology of these conditions.

This is the first clinical series of FPIES in Latin American children. A high prevalence of vegetables as common trigger food was found in our cohort. In contrast with data from other authors, a significant number of patients presented symptoms during breastfeeding. Considering the variability of ethnic backgrounds throughout Latin America, which is not necessarily represented by the population of Santiago, additional clinical and epidemiological studies are needed to better characterize this disease in Latin America as a whole.

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Table 1. Trigger foods of Acute FPIES and Chronic FPIES of 62 Chilean patients and trigger foods reported in other countries

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Trigger food	aFPIES (n=33)	cFPIES (n=29)	USA [‡] (n=74) [†]	UK [‡] (n=44) [†]	Australia [‡] (n=230) [†]	Spain [§] (n=120) [†]	Italy [§] (n=66) [†]
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Cow's milk	15 (45)	21 (72)*	36 (49)	25 (46)	75 (33)	44 (36.7)	44 (67)
Grains	9 (27)	12 (41)	65 (88)	-	119 (52)	-	-
Rice	8 (24)	6 (21)	39 (53)	2 (4)	102 (45)	12 (10)	3 (4)
Wheat	2 (6)	5 (17)	4 (5)	6 (11)	8 (3)	-	-
Oat	2 (6)	3 (10)	26 (35)	3 (6)	21 (9)	-	-
Quinoa	1 (3)	2 (7)	3 (4)	-	1	-	-
Corn	0 (0)	1 (3)	- [§]	1 (2)	2 (1)	-	1 (2)
Soy	4 (12)	11 (38)*	23 (31)	6 (11)	16 (5)	1 (0.8)	-
Vegetables	13 (39)	10 (34)	32 (43)	-	18 (8)	-	-
Carrot	4 (12)	5 (17)	5 (7)	2 (4)	2 (1)	-	-
Squash	5 (15)	4 (14)	9 (12)	-	-	-	-
Potato	3 (9)	3 (10)	6 (8)	1 (2)	5 (2)	1 (0.8)	-
Tomato	2 (6)	3 (10)	-	-	-	-	-
Zucchini	3 (9)	2 (7)	-	-	-	-	-
Chard	3 (9)	2 (7)	-	-	-	-	-
Spinach	3 (9)	1 (3)	-	-	-	-	-
Lettuce	0 (0)	1 (3)	-	-	-	-	-
Broccoli	1 (3)	0 (0)	-	-	-	-	-
Cauliflower	1 (3)	0 (0)	-	-	-	-	-
Legumes	8 (24)	9 (31)	-	-	-	-	-
Lentil	1 (3)	7 (24)*	-	-	2	3 (2.5)	-
Bean	2 (6)	4 (14)	-	-	-	-	-
Chickpea	2 (6)	2 (7)	-	-	-	-	-
Peas	4 (12)	1 (3)	- [§]	-	-	-	-
Green bean	4 (12)	1 (3)	- [§]	-	- [§]	-	-
Poultry	7 (21)	10 (34)	- [§]	- [§]	- [§]	2 (1.7)	2 (3)
Chicken	7 (21)	10 (34)	5 (7)	4 (7)	19 (8)	-	-
Turkey	1 (3)	0 (0)	2 (3)	-	-	-	-
Red meat	7 (21)	4 (14)	3 (4)	-	- [§]	-	-
Beef	6 (18)	3 (10)	1 (1)	2 (4)	6 (3)	1 (0.8)	-
Pork	1 (3)	2 (7)	1 (1)	-	-	-	-
Fish	8 (24)	4 (14)	1 (1)	8 (15)	12 (5)	39 (32.5)	8 (12)
Shellfish	0 (0)	1 (3)	-	-	-	-	-
Fruits	7 (21)	8 (28)	30 (40)	-	22 (10)	-	-
Orange	2 (6)	3 (10)	-	-	-	-	-
Peach	0 (0)	2 (7)	1 (1)	1 (2)	-	-	-
Banana	1 (3)	2 (7)	18 (24)	3 (6)	9 (4)	1 (0.8)	-
Apple	2 (6)	2 (7)	8 (11)	1 (2)	4 (2)	-	-
Pear	1 (3)	2 (7)	7 (9)	-	6 (3)	-	-
Strawberry	0 (0)	2 (7)	1 (1)	1 (2)	-	-	-
Avocado	1 (3)	1 (3)	12 (16)	-	5 (2)	-	-
Kiwi	1 (3)	1 (3)	-	-	-	-	-
Egg	3 (9)	6 (21)	-	7 (13)	27 (12)	13 (10.8)	4 (6)
Tree nuts	1 (3)	3 (10)	-	-	-	-	-
Almond	0 (0)	3 (10)	-	-	-	-	-
Nut	1 (3)	2 (7)	2 (3)	-	-	-	-
Peanut	0 (0)	2 (7)	-	-	1	-	-
Other food	2 (6)	0 (0)	-	-	-	-	-
Sesame	1 (3)	0 (0)	-	-	-	-	-
Coconut	1 (3)	0 (0)	-	-	-	-	-
No. of trigger foods							
1	10 (30)	5 (17)	23 (31)	-	-	101 (84.2)	-
2	7 (21)	2 (7)	13 (18)	-	-	-	-
3	4 (12)	6 (21)	12 (16)	-	-	-	-
≥4	11 (33)	17 (59)*	-	-	-	-	-

* Statistically significant differences between aFPIES and cFPIES in our series (P < 0.05)

† Series did not differentiate between food triggers for aFPIES and cFPIES..

‡ This series reported data for aFPIES and cFPIES separately, 100% of cFPIES patients reacted to cow's milk.

§ Food triggers classified in different food groups from our series. Data was omitted to prevent confounding factors.