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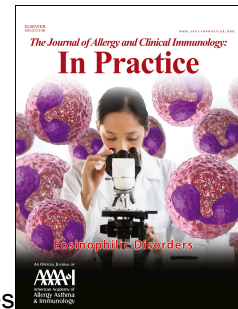
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RELEVANT FEATURES OF ADULT-ONSET FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME

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Clinical implications box: Food protein–induced enterocolitis syndrome differs between adult and pediatric patients in terms of the offending food and symptom profile. Current diagnostic criteria may not be appropriate for adults, making oral food challenge an essential diagnostic tool.

Key words: Adult-onset; Food allergy; Food protein–induced enterocolitis syndrome; FPIES; Gastrointestinal allergy; Non–IgE–mediated allergy; Oral food challenge.

Food protein–induced enterocolitis syndrome (FPIES) is a type of non–IgE–mediated food allergy characterized by delayed gastrointestinal symptoms after the ingestion of a food¹. Given the lack of specific biomarkers of FPIES, diagnosis relies on a detailed history. Oral food challenge (OFC) is indicated to confirm the diagnosis when the history is unclear and to evaluate resolution¹. Adult-onset FPIES has been reported in small case series and is poorly characterized due to its relative infrequency and low index of suspicion^{2,3}.

We performed an ambispective and descriptive study of adults diagnosed with FPIES between January 2016 and December 2019 in our Allergy Department. The diagnosis was made by a compatible clinical history: at least 2 reproducible episodes of gastrointestinal symptoms triggered by a specific food within 1-12 hours, absence of symptoms suggesting an IgE–mediated reaction, resolution of symptoms after elimination of the culprit food, and no other explanation for the symptoms identified⁴.

A skin prick test (SPT), prick-prick test, and determination of serum specific IgE (ImmunoCAP System) were performed. Patients were offered an open OFC with the suspected culprit food to confirm the diagnosis or to identify tolerance. Procedures were performed in a hospital setting and according to the protocol of Infante et al.⁵, which involves giving a single dose per day on 2 non-consecutive days⁵ (Figure E1, available in the Online Repository at www.jaci-inpractice.org). We obtained a baseline blood count and, if the OFC was positive, we drew another sample after the symptoms had developed and 4 hours later. We considered the OFC to be positive when symptoms were reproduced.

The local ethics committee approved the study, and patients provided their written informed consent before inclusion.

The study population comprised 24 patients, whose characteristics are summarized in Tables 1 and E1 (available in the Online Repository at www.jaci-inpractice.org). The median age at onset of symptoms was 37 years (IQR 5.5), and 71% were women. The median delay from the onset of symptoms to diagnosis of FPIES was 2 years (IQR 3.5). The mean number of episodes before diagnosis was 5.8 (range, 2-15).

Most of the cases were caused by seafood (66.7%). Mollusks were the most implicated food (58.3%), followed by crustaceans (29.2%) and fish (29.2%). *Merluccius merluccius* and *Salmon salar* were the most frequently involved fish species. Ten patients developed symptoms with more than 1 group of foods (41.6%). All of the patients reported past tolerance to the offending food.

The latency between ingestion and onset of symptoms was 212.5 minutes (range, 60-720). The initial symptoms (Figure 1) were mainly diarrhea (91.7%), followed by crampy abdominal pain (87.5%) and protracted vomiting (75%). Before diagnosis, one-third of the study population required emergency care. Symptoms lasted 4-48 hours (median 12 hours).

SPT and specific IgE were performed in 15 and 20 patients, respectively. They were only positive in vegetable-induced FPIES, although symptoms suggesting an IgE-mediated reaction were absent.

Most patients refused to undergo an OFC because of severe symptoms with prior exposures. Only 2 patients underwent OFC. Patient 1 reported 4 episodes of intense symptoms after ingestion of crustaceans over a 4-year period and a single milder reaction related to the intake of mussels 3 months previously. OFC was positive 3 hours after ingestion of 2 canned mussels (25% of the portion), and the reaction took the form of abdominal pain and diarrhea. Leukocytosis and neutrophilia reached a peak 7 hours

after intake (20,700 leukocytes/ μ L, 17,900 neutrophils/ μ L), with normalization of the blood count in the following 24 hours. Patient 2 reported 3 reactions after ingestion of clams over a 2-year period, with the most recent reaction occurring 3 months previously. The result of the OFC was negative, and the patient tolerated a whole portion of clams. Since then, she has eaten bivalves on several occasions without developing symptoms.

FPIES begins in infancy after the first or second time that the offending food is introduced into the infant's diet⁶. Unlike children, adults acquire FPIES after years of tolerance of the food trigger⁶.

The frequency with which certain foods trigger FPIES in children varies depending on the geographical location and, therefore, feeding practices¹. Shellfish is the most frequent trigger in all case series of practices¹. In all adult-onset FPIES around the world^{2,6-9}.

Gleich et al⁸ reported 3 patients with prawn-induced FPIES who also reacted to mollusks and 1 to avocado. In the studies published by Tan and Smith⁶, Du et al⁷, and Gonzalez-Delgado et al⁹, 16%, 30%, and 40%, respectively, of patients reacted to multiple foods. In our series, symptoms were triggered by more than 1 food group in 10 patients (41.7%). The most common association was crustacean-mollusk, which was recorded in 5 patients. FPIES by fish-shellfish is also frequent^{6,9} (3 patients in our series).

As there is no specific biological marker of the disease, the diagnosis of FPIES is based on clinical criteria¹. Those outlined in international consensus guidelines are the most widely accepted¹. If we had applied these criteria in our population, half of the patients would have gone undiagnosed owing to differences in symptom profile between adults

and children. Crampy abdominal pain is the most frequent symptom in case series published in adults to date (more than 75% of patients)⁶⁻⁹. In our study, it was exceeded by diarrhea (91.7%). Repetitive vomiting, defined as the major criterion in children, was not observed in all cases in adult-onset FPIES series^{3, 6-9}.

Infant-onset FPIES is considered to have a favorable course, with most children tolerating the offending food over time¹. Adult-onset FPIES might be more persistent, although there are no clear findings predicting when and if clinical symptoms will resolve⁶. In the case published by Fernandes et al², the patient reacted to scallop after 20 years of avoidance². Gonzalez-Delgado et al⁹ described 25 adult FPIES patients, of whom 8 underwent OFC with the offending food and 4 acquired tolerance (3 after an average of 3 years, another after 21 years)⁹. We performed OFC with the offending food in 2 patients who had reacted to ingestion of bivalves. Interestingly, OFC was positive in the patient who had only 1 reaction to mussels (although several to prawns) and negative in the patient who reported 3 previous reactions following ingestion of clams (the most recent, 3 months previously). This could mean either the patient had acquired tolerance within 3 months, although this seems unlikely, or that the initial diagnosis was not correct.

Since the clinical profile of adult-onset FPIES seems to differ from that of children and the appropriate diagnostic criteria may not be entirely applicable, we propose updated criteria for the diagnosis of FPIES in adults and suggest the removal of the major criterion of vomiting. In addition, OFC should be offered to patients to confirm the diagnosis or assess tolerance. Unfortunately, most of the patients in our study refused the OFC because of the severity of their previous reactions and preferred to avoid the offending food. Further studies are needed to understand the natural history of this disorder in adult patients.

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195 Figure 1. Symptoms reported in adult-onset food protein–induced enterocolitis

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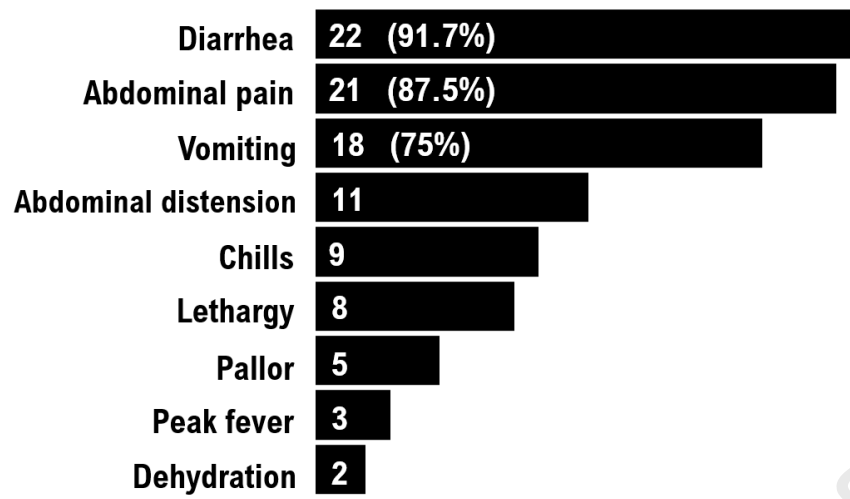
198 Table 1. Clinical characteristics of the study population.

Characteristic		
Sex [no., %]		
Male	7	29
Female	17	71
Age [median, IQR] (years)		
At first reaction	37	5.5
Time to diagnosis	2	3.5
Comorbidities [no., %]		
Rhinoconjunctivitis	12	50
Asthma	7	29.2
IgE-mediated food allergy	7	29.2
Sensitization to <i>Anisakis simplex</i>	7	29.2
Atopic dermatitis	2	8.3
Gastrointestinal conditions	5	20.8
Eradicated <i>H. pylori</i> infection	4	16.7
Diverticulosis	1	4.2
Hiatal hernia	1	4.2
Food implicated [no., %]		
One food group	14	58.3
More than one food group	10	41.7
Latency period [mean, range] (min)	212.5	60-720
Duration of symptoms [mean, range] (hours)	17.6	4-48
Number of episodes per patient [mean, range]	5.8	2-15
Emergency care [no., %]	8	33
Treatment administered [no., %]		
Metoclopramide	4	50
Fluids	3	37.5
Analgesics	3	37.5
Antibiotics	2	25

No	Sex	Age at onset	Age at diagnosis	Offending food	Number of episodes	Latency (min)	Symptoms	Emergency care	Treatment administered	Duration of symptoms (h)	SPT/IgE
1	M	51	55	Crustacean Mollusk	3 1	180	D, V, AP, C	No	-	48	Neg. Neg.
2	F	48	50	Mollusk	3	360	D, V, AP, C	Yes	Metoclopramide, analgesic	48	Neg.
3	F	76	76	Crustacean	2	60	D, V, AP, AD, C, F	Yes	Analgesic, antibiotic	24	Neg.
4	F	27	29	Mollusk	2	60	D, V, AP	Yes	Metoclopramide, fluid	4	Neg.
5	F	64	64	Fish	3	120	D, V, C, L	No	-	4	Neg.
6	F	53	53	Fish	14	60	D, V, AP, L, P	Yes	Metoclopramide, fluid	24	Neg.
7	F	36	46	Crustacean Mollusk	1 3	360	D, V, AP, AD, C, P	Yes	Metoclopramide, fluid, analgesic	4	Neg. Neg.
8	F	29	39	Crustacean	4	120	D, AP, C, P	No	-	8	Neg.
9	F	38	50	Fish Mollusk	5 2	600	D, V, AP, C, L	No	-	24	Neg. Neg.
10	F	19	21	Fish Mollusk	12 3	360	D, V, AP, AD	No	-	12	Neg. Neg.
11	F	54	64	Oat	5	60	D, V, AP, AD, L, Fe	No	-	6	Neg.
12	M	52	58	Mollusk Bean	2 2	120	D, V, AP, C, L, Fe	No	-	24	Neg. Pos.
13	M	66	68	Mollusk	5	120	D, AP	No	-	12	Neg.
14	F	35	37	Fish Crustacean	3 3	60	D, AP, AD	No	-	6	Neg. Neg.
15	F	26	28	Sunflower seed Pepper	3 10	180	D, AP, D AD, C, P, De	Yes	-	24	Pos. Pos.
16	F	57	59	Crustacean Mollusk	4 8	60	D, AP, AD	No	-	12	Neg.
17	F	22	25	Fish	5	180	D, V, L, P, De	Yes	-	48	Neg.
18	M	31	39	Crustacean Mollusk	2 3	240	D, V, AP, AD, L	No	-	6	Neg. Neg.
19	F	37	41	Mollusk	5	720	D, V, AP	Yes	Antibiotic	12	Neg.
20	F	30	32	Fish	4	120	V, AP	No	-	6	Neg.
21	F	18	19	Mushroom	4	120	D, V, AD	No	-	12	Neg.
22	M	52	54	Mollusk	2	120	D, AP, AD	No	-	6	Neg.
23	M	27	28	Peanut	3	240	V, AP, L	No	-	24	Neg.
24	M	19	20	Crustacean Mollusk	2 6	480	D, V, AP, AD	No	-	24	Neg. Neg.

AD, Abdominal distension; AP, Abdominal pain; C, Chills; De, Dehydration; D, Diarrhea; F, Female; Fe, Fever peak; L, Lethargy; M, Male; P, Pallor; V, vomiting.

SPT/sIgE: skin prick test and/or specific IgE to the offending food.



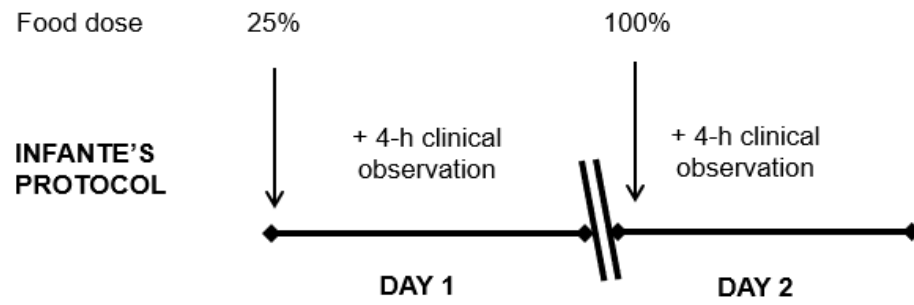


Figure E1. Protocol used in Oral Food Challenges. Source: adapted from Infante et al⁵.