Original Article

Food Protein–Induced Enterocolitis Syndrome in Adulthood: Clinical Characteristics, Prognosis, and Risk Factors

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What is already known about this topic? Food protein–induced enterocolitis syndrome (FPIES) is increasingly recognized in adults, with a predominance in women. Differences in clinical manifestations, trigger foods, and prognosis compared with pediatric FPIES have been reported.

What does this article add to our knowledge? Abdominal pain is the most common symptom, whereas vomiting is absent in some cases. Remission may be observed in some patients. A higher prevalence of comorbid gastrointestinal pathologies was observed compared with the general population.

How does this study impact current management guidelines? Clinical differences compared with pediatric FPIES would support a revision of diagnostic criteria in adults. Oral food challenges are essential in the multiple-food FPIES phenotype to rule out other gastrointestinal entities such as irritable bowel disease and to evaluate for tolerance.

BACKGROUND: Food protein–induced enterocolitis syndrome (FPIES) in adults is being increasingly recognized; however, little is known about its characteristics.
OBJECTIVE: To describe the clinical characteristics, prognosis, and associated factors in adult FPIES.
METHODS: A 10-year prospective study was conducted in the Allergy Section of Alicante General Hospital in adults diagnosed with FPIES. Detailed interviews with patients and oral food challenges (OFCs) were performed to confirm diagnosis or evaluate for tolerance. Comorbidities and possible risk factors were analyzed retrospectively through electronic medical records to assess their association with the disease.
RESULTS: One hundred and seven adults with FPIES (93.5% female) were followed for a median of 6.2 years. Abdominal pain was the most common manifestation (96.3%), followed by diarrhea (72%) and vomiting (60.7%). Seafood (59.8%), egg (14%), and milk (10.3%) were the most common triggers, whereas 43.9% reacted to more than 1 food group. We performed 49 OFCs: 9 to confirm diagnosis and 40 to evaluate for tolerance. After a median 3.5 years, 16.8% achieved tolerance. Resolution was correlated inversely with duration of the disease ($P = .04$) and seafood ($P = .023$) but not with age of onset. The prevalence of gastrointestinal pathologies such as irritable bowel syndrome (IBS), eosinophilic esophagitis, inflammatory bowel disease, and celiac disease was higher than in the general population. A higher number of FPIES triggers were correlated with also having a diagnosis of IBS ($P = .02$).
CONCLUSIONS: Although adult FPIES normally persists, some patients achieve tolerance. Adults with FPIES have a relatively high prevalence of gastrointestinal pathologies. The predominance of women may be related to hormonal factors. The clinical differences with pediatric FPIES warrant a revision of diagnostic criteria in adults. © 2022 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;■:■-■)

Key words: *Food protein–induced enterocolitis syndrome; FPIES; Adult FPIES; Natural history; Contraceptives; Pregnancy; Irritable bowel syndrome*

Food protein–induced enterocolitis syndrome (FPIES) is a non–IgE-mediated food allergy characterized by repetitive vomiting, which can be followed by diarrhea and may be accompanied by lethargy, hypotonia, hypothermia, hypotension, and metabolic derangements. It usually appears 1 to 4 hours after food intake.[1] FPIES is classically described in the pediatric population, but it is increasingly recognized in adults.[2] In a recent cross-sectional survey in the United States, the estimated prevalence in the adult population was 0.22%,[3] whereas in other geographical areas, it is unknown. A predominance in women is reported, although the reason for this has not been elucidated.[4-8]

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Abbreviations used
EMR- Electronic medical records
FPIES- Food protein–induced enterocolitis syndrome
IBS- Irritable bowel syndrome
IQR- Interquartile range
OFC- Oral food challenge
SD- Standard deviation
sIgE- Specific IgE

Diagnosing FPIES is challenging in general, but in the adult population, it is even more complex because numerous other conditions must be excluded, including irritable bowel syndrome (IBS) or enzymatic deficiencies such as lactose or fructose intolerance.[4] In some cases, FPIES may coexist with these conditions. In contrast with the pediatric population, data on the evolution of the disease in adults are lacking, although a persistent course is suspected.[5] The international consensus criteria proposed for diagnosing FPIES may not be suitable for adults.[1]

The aim of this study was to describe the clinical and demographic characteristics and the prognosis of an adult FPIES population. We also studied the association with other gastrointestinal pathologies and explored different factors that may play a role in the higher prevalence observed in women.

METHODS

Study design

We conducted a 10-year prospective longitudinal case series (2010-2020) in adults with a diagnosis of acute FPIES admitted to the Allergy Section of the Alicante General University Hospital. Other factors, such as atopic comorbidities, risk factors for the development of the disease, and episodes before diagnosis, were studied retrospectively.

Patients were enrolled based on compatible clinical history, with the following selection criteria:

- Intake of the eliciting food triggered exclusively gastrointestinal symptoms (vomiting, acute abdominal pain, and/or diarrhea) within 1 to 6 hours.
- Avoidance of the offending food prevented recurrence of the reaction.
- Patients reported at least 2 episodes with the same or related foods.
- Patients reported past tolerance to the offending food.
- Other conditions such as food poisoning and anisakiasis were ruled out by the Gastroenterology Service, which also used a breath test to rule out lactose, fructose, sorbitol, and galactose intolerance.

Inclusion criteria were determined considering previously published case series of adult FPIES and based on the international consensus guidelines,[1] but taking into account that vomiting is sometimes absent in adults.[4-8] An open oral food challenge (OFC) was performed to confirm diagnosis or to evaluate for tolerance every 2 to 3 years, except in patients who had experienced episodes with the incriminated food or other related foods in the previous 2 years and those who refused it. IBS was distinguished from FPIES based on clinical history and OFC. If the patient developed symptoms during an OFC, the trigger food was excluded from the diet; if this resulted in long-term remission of digestive symptoms, we considered that the patient had FPIES and not IBS. Patients who reacted to 3 or more unrelated foods were considered to have multiple-food FPIES. Food groups were fish, crustaceans, bivalves, cephalopods, egg, milk, nuts, meats (pork and beef), mushroom, fruits, and vegetables. Fruits and vegetables were individualized as the number of patients was very low, and the cross-reactivity pattern is not well known.

Electronic medical records (EMR) were reviewed to identify encounters in emergency services that may have arisen from acute FPIES episodes. Patients were asked about the intake of oral hormonal contraceptives and/or pregnancies in the year before the debut of FPIES, and this information was cross-checked in the EMR. Patients were also interviewed for self-reported comorbidities such as inflammatory bowel disease, IBS, eosinophilic esophagitis, celiac disease, and other gastrointestinal pathologies; the data were confirmed with the EMR.

The Ethics Committee of Alicante General Hospital approved the study, and patients provided their informed consent before inclusion.

Study procedures

We performed skin prick tests with commercial extracts (Leti, Barcelona, Spain) and if negative in some cases, prick-prick with fresh food.[9] Serum specific IgE (sIgE) was measured by the ImmunoCAP immunoassay (ThermoFisher Scientific, Phadia, Uppsala, Sweden). Both tests were performed at the first visit to assess the presence of an atypical form of adult FPIES and in follow-up visits before OFCs.

In patients with more than 5 repeated reactions with foods consumed intermittently, such as seafood, fruits, or mushrooms, in which diagnosis was clear with clinical history, an OFC was performed to evaluate for tolerance. If the diagnosis was unclear, as occurred in cases implicating milk or egg (frequent consumption), an OFC was performed as a diagnostic procedure.

OFCs were performed according to Sicherer guidelines,[10] but the total serving size was divided into 2 doses: the first was 25% of the total amount and the rest was administered 2 hours later followed by a 4-hour observation period. The total dose was calculated according to the proposal by the Work Group report on OFC testing.[11] An intravenous line was inserted before the OFC. An OFC was considered positive when symptoms were reproduced.

A complete blood count with differential was obtained before the OFC and 6 hours later if it was positive. In positive OFCs, treatment was administered following the physician's criteria with intravenous normal saline. In case of repetitive vomiting, intravenous ondansetron was also prescribed.

Patients who passed the OFC were contacted 24 hours and 90 days later to determine if they had delayed manifestations after the OFC and to know if they were consuming the offending food regularly.

Disease resolution was defined as passing an OFC and introducing the offending food at home without symptoms of FPIES.

Statistics

Absolute and relative frequencies were used to describe the qualitative variables. Quantitative variables were described using means and standard deviations for normal variables and medians and interquartile ranges (IQR) for nonparametric variables (Kolmogorov-Smirnov test). The χ^2, Student's *t*-test, and median tests were performed to assess associations between outcomes and explanatory variables. The type I error was set at 5%, and the statistical software used was IBM SPSS Statistics 26 (Armonk, NY).

TABLE I. Clinical data from included patients with acute FPIES

Characteristic	Value
Sex, n (%)	
Men	7 (6.5)
Women	100 (93.5)
Age at first reaction (y), median (IQ_{25-75})	30 (23-42)
Age at diagnosis (y), median (IQ_{25-75})	39 (29-48)
Delay to diagnosis (y), median (IQ_{25-75})	4 (2-10)
N episodes, median (IQ_{25-75})	8 (5-10)
Latency period (min), median (IQ_{25-75})	60 (45-120)
Manifestations, n (%)	
Abdominal pain	103 (96.3)
Diarrhea	77 (72)
Vomiting	65 (60.7)
Weakness	54 (50.5)
Lethargy	29 (27.1)
Shivering	41 (38.3)
Hypotension	16 (14.9)
Emergency department, n (%)	15 (14)
Referred to allergy section, n (%)	
By FPIES symptoms	44 (41.1)
By other allergy conditions	63 (58.9)
Atopy, n (%)	70 (65.4)
Rhinitis	69 (64.5)
Asthma	32 (29.9)
IgE-mediated food allergy	20 (18.7)
Positive skin test to aeroallergens, n (%)	
Pollens	53 (50)
Mites	52 (48.6)
Dander (dog/cat)	29 (27.1)
Alternaria	9 (8.4)
IgE-mediated food allergy to other than FPIES, n (%)	20 (18.7)
Associated conditions, n (%)	
Irritable bowel syndrome	13 (12.1)
Eosinophilic esophagitis	5 (4.7)
Inflammatory bowel disease	4 (3.7)
Celiac disease	3 (2.8)

FPIES, Food protein–induced enterocolitis syndrome; *IQ*, interquartile range.

RESULTS

A total of 107 patients with acute FPIES were included. Table I presents a summary of their clinical and demographic data. The vast majority (93.5%) of the sample were female. The median age of onset was 30 years (IQR: 23-42 years), and the median time to diagnosis was 4 years (IQR: 2-10 years). Participants experienced a median of 8 episodes (IQR: 5-10 episodes) before diagnosis.

Abdominal pain was the most common symptom (96.3%), followed by diarrhea (72%) and vomiting (60.7%); 44.4% of patients had all 3 manifestations. Other reported symptoms included transient weakness (50.5%), shivering (38.3%), and lethargy (27.1%). One patient lost consciousness in addition to suffering digestive symptoms.

In total, 14% (n = 15) of patients sought emergency care at the hospital due to symptoms of a possible FPIES episode. EMR revealed neutrophilia in 6 of the 12 patients in whom this was measured, whereas only 1 patient presented with elevated creatinine levels after an acute episode. All patients were discharged home with a diagnosis of gastroenteritis.

FPIES symptoms prompted referrals to our allergy services in 41.1% of the participants, half of whom were referred from the gastroenterology service due to a suspected food allergy after ruling out other pathologies. The remaining 58.9% attended our service due to other allergic conditions, and FPIES was suspected after taking a careful history.

Offending foods

Seafood was implicated in 59.8% of the patients, particularly crustaceans (36.4%) and fish (32.7%), followed by bivalves (18.7%) and cephalopods (17.8%). Eggs were implicated in 14% and milk in 10.3% of the patients. Other triggers are reported in Figure 1.

All patients had negative skin prick tests to the offending foods, and 4 had detectable sIgE to avocado (n = 1), crustaceans (n = 2), and egg (n = 1) (range: 0.42-0.79 kU/L). No changes in the skin tests were detected at the follow-up visits. Specific IgE also remained at similar levels during follow-up. Most patients reacted to 1 food or food group (56.1%), whereas 29% reacted to 2 foods or food groups, and 14.9% to 3 or more foods or food groups (Figure 2).

During the follow-up period, only 5% of the patients developed symptoms with new triggers: 3% with foods in the same group and 2% with foods in a different group.

A strong statistical association was observed between different seafood groups: bivalves and crustaceans ($P = .003$), crustaceans and cephalopods ($P = .008$), and fish and cephalopods ($P = .01$). FPIES to milk and eggs also had a positive correlation ($P = .046$), but no other correlations between foods/food groups were observed (Figure 3).

Oral food challenges

We carried out 49 OFCs in 44 patients with the implicated food (Table II). Eight participants refused an OFC, which was proposed to evaluate for tolerance. An OFC was not considered necessary in 55 others, who had recent and repetitive reactions with the same or related foods. Only 9 OFCs were performed to confirm the diagnosis because the clinical history was inconclusive. Forty OFCs were performed to evaluate for tolerance to the implicated food in patients who followed an exclusion diet and had been asymptomatic for the 2 previous years.

Thirty-one OFCs were positive. Eighteen were negative during the procedure in the hospital, but 2 patients who passed the OFC in the hospital presented with late symptoms of vomiting and diarrhea at home, 5 and 6 hours later, respectively. Four cases who tolerated OFCs at the hospital developed subsequent FPIES reactions on exposure to the trigger food prepared in a similar manner. However, none of these patients required medical care to recover. Symptoms included abdominal pain and vomiting or diarrhea, which resolved in approximately 8 to 12 hours. Triggering foods were fish and crustaceans.

Of the patients with positive OFCs, most reactions (n = 22) were mild and resolved spontaneously without treatment; only 7 required treatment with intravenous normal saline (5 with fish and 2 with eggs), and 4 were also treated with intravenous ondansetron. Colicky abdominal pain was the most common manifestation (100%), followed by diarrhea (69.7%) and vomiting (51.5%). Four patients also showed hypotension, weakness, and lethargy during reactions to fish and egg.

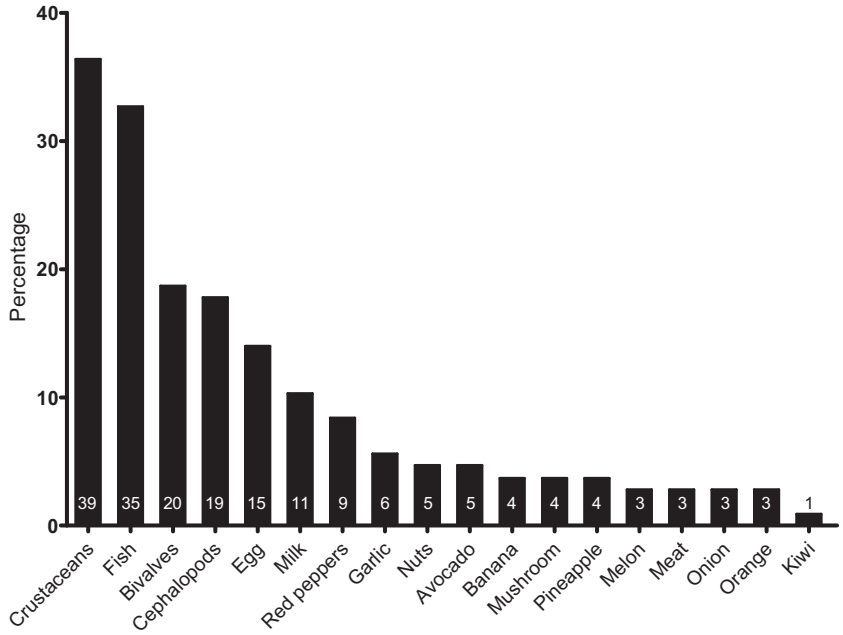

FIGURE 1. Foods causing FPIES, expressed as a percentage and number of patients with FPIES reaction to the trigger food. *FPIES*, Food protein–induced enterocolitis syndrome.

The absolute neutrophil count measured from 31 positive OFCs showed a mean increase of 632.84 cells/mm^3 (IQR: 300-1300 cells/mm^3). Blood tests were not performed in patients with delayed symptoms.

Resolution

Patients were followed for a median of 6.2 years (IQR: 1-10 years). In that time, 18 (16.8%) achieved tolerance to the implicated food and ate it on a regular basis. Ten patients presented tolerance to small amounts of the triggering food (4 tolerated small amounts of egg, 3 milk, and 3 fish).

Of the 18 patients who achieved tolerance, it was confirmed by OFC in 12 patients (66.7%) and by accidental or deliberate intake at home in 6 (33.3%). Some patients had not overcome FPIES after more than 40 years, whereas it affected others for short periods. In patients who overcame FPIES, the median duration was 3.5 years (IQR: 1-6 years). We observed an inverse correlation between disease duration and resolution ($P = .04$), but not with age of onset. Fish and crustacean FPIES tended to resolve more than FPIES induced by other foods ($P = .023$).

Risk factors for developing FPIES

Female sex was clearly associated with FPIES. The prevalence of oral contraception use in female patients in the year before onset of FPIES was 14% (prevalence in female population in our country, 17.3%). A similar proportion (15%) had a pregnancy in the year before onset, and 2 patients developed FPIES during pregnancy.

Associated conditions

Nearly two-thirds (65.4%) of patients were atopic; the most common manifestation was rhinitis (64.5%), followed by asthma (29.9%). Concomitant IgE-mediated food allergy to foods other than those producing FPIES manifestations was present in 18.7%. Other diagnoses included IBS (12.1% vs 4.6% in general population),[12] eosinophilic esophagitis (4.7% vs 0.1% in the general population),[13] inflammatory bowel disease (3.7% vs 0.3% in the general population),[14] and celiac disease (2.8% vs 0.7% in the general population).[15] We observed a correlation between a high number of foods implicated in FPIES and the presence of IBS ($P = .02$).

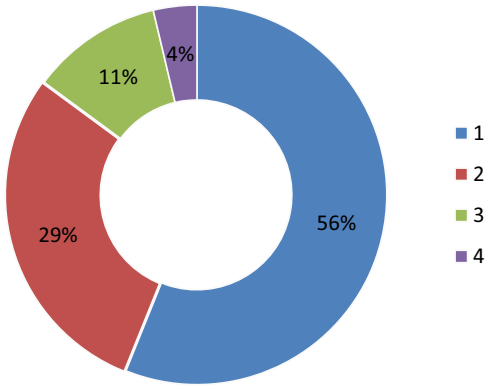

FIGURE 2. Percentage of patients who reacted to 1, 2, 3, or 4 foods or food groups.

DISCUSSION

Since Fernandes et al[16] made the first references to adult FPIES in the literature in 2012, several short series have been published.[4-8,17] However, large gaps in knowledge of this disease, especially in the adult population, remain. This 10-year prospective, longitudinal study set in an allergy service of a tertiary hospital included 107 patients, the largest series of adults with FPIES published until now.

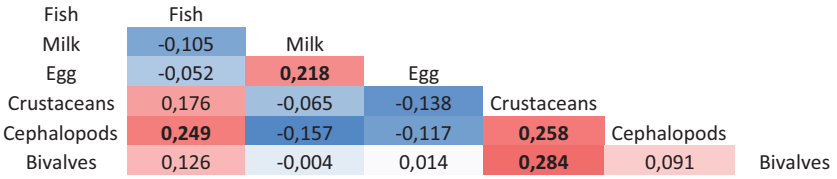

FIGURE 3. The heatmap represents the correlation between different foods. Positive correlations are displayed in red, and negative correlations in blue. The color intensity is proportional to the correlation coefficients ($P < .05$ in bold type).

Our results indicate that virtually all adults with FPIES experience abdominal pain, and diarrhea is present in approximately 72%. By contrast, vomiting, the major criterion for FPIES according to the international consensus guidelines,[1] was present in 60.7%. These findings are concordant with other previous adult series[4-7] and reveal some clinical differences with pediatric FPIES where vomiting is present in almost all cases, and diarrhea is relatively infrequent.[18-20] In some of our patients, we observed remission of vomiting over time, but abdominal pain and diarrhea persisted.

A remarkable percentage of adults reported transient weakness and shivering (temperature was not registered at home in most cases, but it could represent hypothermia). However, only 15.9% sought medical care, and none required intensive care. Only 1 patient attended in the emergency department presented metabolic acidosis. These findings suggest that acute episodes in adults are less dramatic compared with children, who often present with severe clinical manifestations.[21-23,26]

Although seafood was the most commonly offending food in our study, as in previous adult series,[4,6,7] we also identified new triggers, like onion, avocado, orange, and kiwi. These findings could reflect the implication of new emerging foods or a higher index of suspicion in recent years.

After seafood, egg is the second most common trigger, a finding also reported in countries like Australia and Canada.[4,6] In most cases, patients presented with recurrent and frequent episodes of acute FPIES. Some had tolerance to certain presentations, like baked egg, probably due to different conformational modifications of proteins after the cooking process.

In the case of milk FPIES, patients were initially suspected of having lactose intolerance. The normal hydrogen breath test, frequent presence of vomiting in 81.8% of positive OFCs, and neutrophilia observed in half of positive OFCs supported the diagnosis of FPIES. In clinical practice, the differential diagnoses between these entities are challenging, as they share common clinical features.

We observed a strong, positive association between fish and crustaceans and between cephalopods and bivalves. Milk and egg were also significantly correlated ($P = .046$). The literature has also noted such clustering patterns in the pediatric population, between milk and soy and between grains, rice, and oats.[20,24-25] Su et al[26] also noted a moderate association between shellfish and fish, speculating that the association may be related to close taxonomic relationships, even though this would not explain the association between milk and egg. However, the number of patients in our series is not enough to establish a robust association between milk and egg.

TABLE II. Characteristic of the oral food challenges performed

OFC characteristic	n (%)
OFC performed	49
Reason to perform OFC, n (%)	
Confirm FPIES diagnosis	9 (18.4)
Determine tolerance	40 (81.6)
OFC in which total serving was administered, n (%)	46 (93.8)
Positive OFC, n (%)	33 (67.3)
At hospital	31
At home (delayed)	2
Foods implicated, n (%)	
Fish	14 (42.4)
Cephalopods	4 (12.1)
Crustaceans	4 (12.1)
Eggs	4 (12.1)
Milk	4 (12.1)
Onion	2 (6)
Red pepper	1 (3)
Reactions, n (%)	
Mild and resolved spontaneously without treatment	22 (66.7)
Required treatment with saline	7 (21.2)
Required treatment with ondansetron	4 (12.1)
Manifestations, n (%)	
Abdominal pain	33 (100)
Diarrhea	23 (69.7)
Emesis	17 (51.5)
Hypotension	4 (12.1)
Weakness	4 (12.1)
Lethargy	4 (12.1)
Time for recovery (h), mean (range)	8 (4-24)

FPIES, Food protein–induced enterocolitis syndrome; *OFC*, oral food challenge.

Unlike the pediatric population, in which up to one-third show positive IgE to the offending food,[20] particularly in milk FPIES, skin tests were negative in all of the patients in our series. sIgE was detected in a small percentage of patients. Likewise, Crespo et al[7] reported only 1 patient in a series of 24 adults with positive IgE to vegetables, so with the scarce information we have, it seems that atypical FPIES in adults is uncommon.

OFCs were usually performed to test for the development of tolerance because in most patients the diagnosis was based on a convincing clinical history and recent episodes. The regimen for OFCs has not been systematically studied.[1] In children, Infante et al[27] proposed a protocol over 2 to 3 nonconsecutive days to increase the safety of the procedure. Despite the shorter regimen in our study (2 doses on a single day), which had the advantage

of shortening the exploration time, most reactions were mild. Given the characteristics of the disease in adults, this protocol may be the most feasible, reserving longer protocols for patients with a history of severe reactions, as previously recommended.[10]

We consider that 4 hours of observation is an adequate period of follow-up, albeit 2 patients did present mild, more delayed reactions, suggesting that a subsequent phone follow-up at 24 hours would be advisable to detect false negatives after OFC. Otherwise, after passing the OFC, a small group of patients experienced symptoms after reintroducing the food at home. A previous study in children also reported this outcome,[28] so clinicians should warn patients of this possibility.

OFCs were performed openly, as proposed previously.[1,16] However, we postulate that in multiple-food FPIES or in patients with severe or repetitive reactions, the procedure should be double-blinded and placebo-controlled. OFCs could generate anxiety in some patients that mimics symptoms of FPIES, leading to a misinterpretation of the test.

Although FPIES in adults is assumed to have a poor prognosis,[4,5,20] some of our patients overcame the disease and tolerated regular intake of the offending food. Others developed partial tolerance, experiencing symptoms only if they had large servings. There was an inverse correlation between the disease duration and tendency to resolution, meaning that the patients who had had the disease for the shortest time were more likely to overcome it.

Like other authors, we noted a clear female predominance in our sample.[4-7] The fact that around 60% of the patients were recruited from our atopic patients, referred for other allergic conditions, could be a factor influencing the female prevalence. Evidence suggests that estrogens act as enhancers of humoral responses, mast cell reactivity, and delayed type IV allergic reactions.[29] Hormonal changes, brought on by pregnancy or oral contraception, were evaluated as factors favoring the development of symptoms in our population; however, we did not observe a high intake of oral contraceptives or a high pregnancy rate in our series.

There was a significant delay between symptoms onset and diagnosis, probably due to a low index of suspicion and patients' own tendency to avoid consuming the culprit food and forgoing medical care. However, a different profile was observed in a small group of cases of multiple-food FPIES (5 patients), in which regularly consumed foods such as milk, egg, or meat were implicated. These patients were usually referred from the Gastroenterology Service to rule out the implication of foods. IBS or another intestinal pathology was suspected, and different exploratory procedures had already been carried out, including colonoscopy or biopsy. A detailed clinical interview and OFC were then performed, and if the latter was positive, an exclusion diet was followed, with long-term remission of symptoms. Thus, some patients were finally diagnosed with FPIES. The observed correlation between a high number of foods implicated in FPIES and the diagnosis of IBS suggests that some patients diagnosed with this gastrointestinal disorder could actually have multiple-food FPIES. The number of patients in our series with these characteristics, however, was too small to establish conclusions.

Our patients often had gastrointestinal pathologies in addition to FPIES. Like Cianferoni et al,[30] we observed a high prevalence of eosinophilic esophagitis, but our patients were also frequently diagnosed with inflammatory bowel disease and celiac disease. These findings raise the possibility that an underlying intestinal pathology could favor the development of FPIES.

As in other published adult series[4-7] and in the pediatric population, our patients showed a propensity for presenting allergic manifestations such as rhinitis, asthma, and IgE-mediated food allergy. This association is suggestive of shared mechanisms in these processes, or even—as suggested by Nowak-Wegrzyn and Berin[31]—a phenotypic fluidity between FPIES and IgE-mediated food allergy.

The study's major strengths reside in the high number of included patients, their prospective follow-up, and the high number of OFCs performed, which help elucidate the clinical characteristics and prognosis in adults. However, a high percentage of patients were diagnosed by clinical history, without a confirmatory OFC, which could reflect an overdiagnosis of the condition. In addition, patients were selected from a single hospital, which limits the diversity of the sample and the generalizability of the results. Moreover, the number of patients with FPIES triggered by some foods was too small to establish conclusions. Other limitations include the retrospective nature of some data, such as previous episodes before diagnosis. Although OFCs were regularly scheduled, most patients with a positive OFC refused another challenge test, so time of remission may be not exact.

In conclusion, adult FPIES presents some clinical differences compared with pediatric FPIES, such as the absence of vomiting in some patients, less severe acute episodes, and infrequent development of tolerance to the offending foods. Our results would support a reformulation of diagnostic criteria in adults; the major criterion of repetitive vomiting may need to be changed to abdominal pain and vomiting or diarrhea; however, more studies are needed to confirm this proposal. In addition, adult FPIES shows a clear predominance in women, perhaps due to hormonal factors, though we could not prove this. Adults with FPIES also have a higher-than-average prevalence of gastrointestinal pathologies. OFC is the gold standard for diagnosis and is essential in patients with the multiple-food FPIES phenotype to rule out other gastrointestinal diseases. More studies are necessary to confirm our findings and to further refine our understanding of the characteristics of adults with FPIES.

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