

## Food protein-induced enterocolitis syndrome in an adult population from Spain

García Paz V<sup>1</sup>, Carballeira Anca I<sup>1</sup>, Romero Sánchez L<sup>2</sup>, Otero Alonso A<sup>3</sup>, González Torres L<sup>4</sup>, Vila Sexto L<sup>4</sup>

<sup>1</sup>Department of Allergy and Clinical Immunology. Complejo Hospitalario Universitario A Coruña, A Coruña, Spain.

<sup>2</sup>Department of Allergy and Clinical Immunology. Complejo Hospitalario Universitario de Vigo, Vigo, Spain.

<sup>3</sup>Department of Allergy and Clinical Immunology. Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain.

<sup>4</sup>Pediatric Allergy Unit. Department of Pediatrics. Complejo Hospitalario Universitario A Coruña, A Coruña, Spain.

### Correspondence:

Vanesa García-Paz

Department of Allergy and Clinical Immunology.

Complejo Hospitalario Universitario A Coruña (CHUAC)

Street As Xubias s/n

15009. A Coruña, Spain

E-mail: [vanesa.garcia.paz@sergas.es](mailto:vanesa.garcia.paz@sergas.es)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0835

**Key words:** FPIES. Food protein-induced enterocolitis syndrome. Adults. Food allergy. Seafood.

**Palabras clave:** FPIES. Síndrome de enterocolitis inducido por proteína alimentaria. Adultos. Alergia alimentaria. Pescado

Acute food protein-induced enterocolitis (FPIES) is a non-IgE mediated gastrointestinal food hypersensitivity, characterized by profuse vomiting 1-4 hours after ingestion of the offending food, that may be accompanied by pallor, lethargy, hypotension and hypothermia [1]. Although classically considered a pediatric disorder, since 2012 several reports in adult population have been published [2-8].

Our aim was to describe the clinical features of acute FPIES in Spanish adult patients, comparing our findings with those previously published on adult and pediatric populations.

We performed a retrospective chart review of patients referred to our outpatient allergy unit from 2017 to 2020, with clinical manifestations compatible with FPIES.

Patients underwent skin prick tests (SPT) with commercial extracts (ALK, Abelló, Spain), prick by prick with fresh food and total and specific IgE (ImmunoCAP, Thermofisher) determination.

Every 2-3 years, to evaluate tolerance to the offending food, SPT and open food challenges (OFC) were performed. OFC was carried on over two days: on the first day, 30% of a food portion was offered and if there was no reaction, on the 2nd day the patient was asked to have the complete portion. Patients remained under observation during 4 hours afterwards. In case of clinical manifestations, orodispersible ondansetron was administered.

The study met the approval of the Galician Medical Research Ethics Committee (registration code 2021/115).

From the 28 adults included, 21 were women and 7 men, with mean age of 39.82 years (17-65 years). Only one 17-year-old adolescent was included.

Thirteen patients presented allergic rhinoconjunctivitis to airborne allergens and one was egg and milk allergic during childhood.

Mean age at first reaction was 32.07 years (15-60). Average number of reactions before achieving the diagnosis was 5.79 (3 to 10).

All patients presented with repetitive vomiting, 1 to 4h after food ingestion. Twenty-five associated abdominal pain and developed diarrhea during the following 24 hours. Sixteen patients presented pallor and lethargy. Mean latency time between food ingestion and the beginning of symptoms was 137.14 minutes (60-240).

Most frequently involved foods were seafood (11-bivalves, 3-crustaceans) followed by fish (2-hake, 1-salmon, 1-sole).

Only 2 patients developed symptoms after eating foods from different groups: fish and bivalves.

One patient presented serum specific IgE to cow's milk (1.09 kU/L) and other patient positive SPT to salmon and clams.

On follow up, none of the seven patients who agreed to undergo OPF tolerated the offending food. They had been avoiding it for at least 5 years. One of the patients who reacted to boiled egg, tolerated its baked version.

Demographic and clinical data are summarized in Table 1.

Although vomiting was the most frequent form of presentation in our series, abdominal pain has been referred by most authors as the main symptom of adult FPIES [4-6] in contrast to children. Since in those cases, adult patients would not meet the proposed diagnostic criteria [9], Vazquez-Ortiz and Infante [10] have recently proposed considering abdominal pain instead of vomiting as the major criteria of acute FPIES in adults.

In agreement with previous reports [4-8], we found predominance of female adult patients while in pediatric FPIES, more than half of affected children are boys [1].

Given the lack of specificity of clinical manifestations of FPIES and the absence of diagnostic biomarkers, diagnosis delay is common [5,7,8,11,12]. In adults, Li et al [8] reported a median of 10 years from symptom onset to diagnosis, similar to the 8-year delay published by Gonzalez- Delgado et al [5]. Our patients suffered 3 to 10 reactions before the diagnosis of FPIES was achieved.

We found that seafood was the main responsible food involved, as described previously in series from Australia, Spain and Canada [4-8]. Regarding Spanish population, we found that mollusks, specifically bivalves, were involved in most cases, in agreement with Crespo et al [7]. The second most frequently responsible food in our population was fish, as previously reported for Spanish adults [5,7]; in Canada, dairy products [6] and in Australia [4], egg and fish, represented the second responsible foods after seafood, respectively. In children, cow's milk is the main food causing FPIES worldwide [1] but for solid foods, geographical differences have been found [11-14]. More studies in adults are needed to establish if geographical origin influences the predominance of a particular solid food as well.

In our series, only 2 patients (7%) reacted to 2 different food groups, fish and bivalves in both cases, a percentage lower than the 20% reported by González-Delgado et al [9], the 16% by Tan and Smith [4] and the 30% by Du et al [6], and similar to the 10% reported by Crespo et al [7]. Fish-seafood (mollusks and crustaceans) was the most common association found in those studies.

Even if FPIES is not IgE-mediated, affected children have been reported to have increased rates of atopic manifestations [1,11]. There are discrepancies regarding atopic comorbidities in adults suffering from FPIES. We found that half of our patients presented an atopic background. Higher percentages have been reported by González-Delgado et al [5] and Tan and Smith [4]. On the contrary, only 3 out of 19 adult patients presented a history of atopy in the series published by Li et al [8].

As Spanish and Italian children [1], adults show none or low percentages of atypical FPIES [4-7]. Only two patients of the twenty-eight included in the present study, showed detectable food specific IgE.

Time interval to achieve tolerance to the offending food varies depending on the food involved in children. FPIES induced by solid foods, especially fish, seems to have a more protracted course than FPIES induced by cow's milk or rice [1]. In adults we lack data on the natural course of FPIES, although, as we observed, most reports suggest a more prolonged evolution of FPIES in adults than in children [5,7]

In summary, adult FPIES is a not so rare disorder with clinical and epidemiological differences with pediatric FPIES. Seafood is the most frequently involved food. More studies are needed to understand the natural history of the disease in this cohort of patients.

The authors declare no conflicts of interest and we have not obtained any type of financing to carry out this work.

Accepted Article

## References

1. Vila Sexto L. Latest insights on food protein–induced enterocolitis syndrome: An emerging medical condition. *J Investig Allergol Clin Immunol*. 2018;28(1):13-23.
2. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. *J Allergy Clin Immunol*. 2012;130(5):1199-2000.
3. Zubrinich C, Hew M, O’Hehir R. Egg provoked food protein-induced enterocolitis-like syndrome in an adult. *Clinical Case Reports*. 2016;4(9):899-901.
4. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. *Journal of Allergy and Clinical Immunology: In Practice*. 2014;2(3):355-7.
5. González-Delgado P, Caparrós E, Moreno V, Cueva B, Fernández J. Food protein-induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood. *J Allergy Clin Immunol Pract*. 2019;7(2):670-2.
6. Du Y, Nowak-Węgrzyn A, Vadas P. FPIES in adults. *Annals of Allergy, Asthma and Immunology*. 2018;121(6):736–8.
7. Crespo J, Skrabski F, Pérez-Pallise ME, De Castro-Martínez FJ, Zubeldia JM, Infante S. Relevant features of adult-onset food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol Pract*. 2021 Apr;9(4):1759-60.
8. Li DH, Wong-Pack A, Macikunas AL, Kim H. Adults with possible food protein-induced enterocolitis syndrome with crustacean ingestion. *Allergy Asthma Clin Immunol*. 2020 Nov 11;16(1):99.

9. 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(4):1111-26
10. Vazquez-Ortiz M, Infante S. Diagnostic criteria for food protein-induced enterocolitis síndrome. Can do we better? *Ann Allergy Asthma Immunol*. 2021; 126:458-9.
11. Vila L, García V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food proteineinduced enterocolitis syndrome in Spanish children. *Journal of Allergy and Clinical Immunology: In Practice*. 2015;3(4):621–3.
12. 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(4):343-9.
13. Miceli Sopo S, 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 phenotype. *Clin Exp Allergy*. 2012 Aug;42(8):1257-65.
14. Mehr S, Frith K, Barnes EH, Campbell DE, FPIES Study Group. Food protein-induced enterocolitis syndrome in Australia: A population-based study, 2012-2014. *J Allergy Clin Immunol*. 2017 Nov;140(5):1323-30.

Table. Demographic and clinical characteristics of adult patients suffering from food protein-induced enterocolitis.

Characteristics	Value
Sex, n (%)	
Men	7(25)
Women	21 (75)
Age at first reaction (y), median (IQ 25-75)	32.07 (15-60)
Age at diagnosis (y), median (IQ 25-75)	39.82 (17-65)
Delay to diagnosis (y), median	7,75
Number of reactions prior to diagnosis, median (IQ 25-75)	5.79 (3- >10)
Symptoms, n (%)	
Vomiting	28 (100)
Abdominal pain	25 (89)
Diarrhea	25 (89)
Pallor	16 (57)
Lethargy	16 (57)
Latency period, minutes; median (IQ 25-75)	137.14 (60-240)
Food involved n (%)	
Bivalves	11 (39)
Crustacean	3 (10,7)
Fish	4 (14,8)
Egg	3 (10,7)
Cow's milk	1 (3,5)
Banana	1 (3,5)
Peanut	1 (3,5)
Vealmeat	1 (3,5)
Food groups involved, n (%)	
1	26 (92,8)
2 (fish and seafood)	2 (7)
Atopy, n (%)	
Rhinoconjunctivitis	13 (46,4%)
Grass pollen	5 (17,8)
Mites	11 (39)
Food Allergy (egg and CM)	1 (3,5%)