

Food Protein-Induced Enterocolitis Syndrome in Monochorial Monoamniotic twins

Abreu-Ramírez MG MD , García Gutiérrez I MD ,
Seoane-Reula ME MD PhD , Infante S MD PhD

PII: S1081-1206(21)00353-7
DOI: <https://doi.org/10.1016/j.anai.2021.05.006>
Reference: ANAI 3599



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

Received date: 4 February 2021
Revised date: 28 April 2021
Accepted date: 7 May 2021

Please cite this article as: Abreu-Ramírez MG MD , García Gutiérrez I MD , Seoane-Reula ME MD PhD , Infante S MD PhD , Food Protein-Induced Enterocolitis Syndrome in Monochorial Monoamniotic twins, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.05.006>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Food Protein-Induced Enterocolitis Syndrome in Monochorial Monoamniotic twins

Abreu-Ramírez MG, MD¹, García-Gutiérrez I, MD¹, Seoane-Reula ME, MD PhD^{2,3,*}
sonsoles.infante@salud.madrid.org and Infante S, MD PhD^{1,3}

¹Paediatric Allergy Unit. Hospital General Universitario Gregorio Marañón, Madrid, Spain.

²Section of Paediatric Immunology. Hospital General Universitario Gregorio Marañón, Madrid, Spain.

³Gregorio Marañón Health Research Institute (IiSGM), Madrid, Spain.

***Corresponding author:** Sonsoles Infante MD, PhD. O'Donnell St. 48, Paediatric Allergy Unit. Hospital General Universitario Gregorio Marañón, 28009 Madrid, Spain. Telephone number: +34 629069509

Keywords

Gluten allergy; Gluten-fpies; Food Protein-Induced Enterocolitis Syndrome; Fpies; Non-ige-Mediated Food Allergy.

Abbreviations/Acronyms:

CM: cow's milk

FPIES: food protein-induced enterocolitis syndrome

OFC: oral food challenge

sIgE: serum specific IgE

Food protein-induced enterocolitis syndrome (FPIES) is considered a non-IgE mediated food allergy that typically presents in infancy. It is characterized by gastrointestinal symptoms, mainly protracted and delayed vomiting¹. Globally, the most commonly reported FPIES triggers are Cow's Milk (CM), soy, and grains (including rice and oats)^{1,2}. However, common food triggers differ between countries; these variations may

be due to several factors including geography, racial/ethnic differences, ages of patients, FPIES phenotype, and probably genetic and/or epigenetic factors³. FPIES have been barely reported in siblings⁴, it does not appear to be a strong familial association, and very few data are available regarding twins with FPIES.⁵⁻⁶

We report an unusual case of FPIES in monochorial-monoamniotic female twins. They were born at 32 weeks and 1 day of gestational age by cesarean; both girls had atopic dermatitis and transient hypogammaglobulinemia of infancy (significant of IgA and relative of IgM) that resolved after 6 months, with a quantitative study of lymphocyte population within normal limits.

They received exclusive breastfeeding until 8 months (6 months of corrected age) when they started the weaning process with gluten-free cereals and fruits, with good tolerance. At 9 months old, after eating a multigrain porridge (wheat, corn, rice, oats, barley, and rye) both twins developed, 2 hours after the intake, protracted vomiting (6 vomits) accompanied with marked paleness and lethargy; the symptoms resolved within 4 hours and they did not require emergency assistance. Gluten was removed from their diet and they remained asymptomatic. They continued eating gluten-free cereals. One month later, their parents decided to reintroduce gluten-cereals into the kids' diet. The second time the twins ate the same porridge, they developed repeated vomiting, paleness and lethargy. Symptoms started one hour and a half after the ingestion and resolved within a couple of hours. An allergology study was carried out. Skin prick test (SPT) were performed with commercial extracts to wheat, barley, rye, and oats. Serum specific IgE (sIgE) was measured with the ImmunoCAP® system (ThermoFisher Scientific, Uppsala, Sweden) with negative results. Serum detection of tissue anti-transglutaminase (tTG) IgA and IgG, and deamidated gliadin peptide antibody (DGP) IgG were negative. Gluten-FPIES was suspected 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 identified. A gluten-free diet was indicated, no accidental exposures occurred, and other food groups (egg, cow's milk, fish, fruits, meats) were introduced into the girls' diet with good tolerance. They remained asymptomatic and both twins showed healthy general conditions and proper growth indicators. One year later, the allergology study was repeated. The SPT remained negative and an oral food challenge (OFC) with the porridge involved in the reaction was performed. The OFC was carried out in two non-consecutive days, following our protocol⁷ (Figure 1). Both girls tolerated the normal serving size per age without developing symptoms.

FPIES is considered a rare disease, however, it seems not as rare as it is thought but underdiagnosed. The prevalence studies reported a cumulative incidence range between 0.015% and 0.7%^{4,8}. Unlike what happens with IgE-mediated allergy, FPIES does not seem to have a strong familial association. Mehr et al⁴ reported a prevalence of FPIES in 7% of the siblings included in their study but very little data are available in the literature regarding twins with FPIES and the degree of concordance of the disease. Watanabe et al⁵, reported a case of CM-FPIES in monozygotic twin neonates. Feeding was initiated on day 1 with a commercial cow's milk protein-based formula; on day 4th, both newborns started with, bloody stools, abdominal distension, and bilious vomiting; feeding was stopped, and the symptoms disappeared. When the formula was reintroduced, vomiting recurred in both neonates. Since then, they were fed hydrolyzed casein-based formula remaining asymptomatic. CM was successfully reintroduced to their diet at 15 months of age. Shoda T et al⁶ reported two pairs of twins (identical and fraternal) with FPIES. The twins were born a term and fed breast milk and supplemental

formula. The identical twins developed vomiting and bloody stool simultaneously when they were a week old. The fraternal twins developed prolonged vomiting and loose stools at different times (7 and 10 weeks respectively). The clinical symptoms and laboratory findings of the four patients were highly suggestive of FPIES. SPT with CM and sIgE for CM were negative in all four cases. All reported cases in twins have a common trigger: CM. However, our patients presented symptoms with gluten-cereals and remained asymptomatic with a gluten-free diet. They showed similar symptoms, including their onset and clinical courses of disease like the identical twins reported by Shoda⁶ also had negative skin prick test responses and undetectable sIgE to the suspected food at the time of their initial diagnosis like the majority of patients with FPIES. Environmental influences shared by twins may have contributed to the similarity of their clinical features, in addition to their genetic homogeneity. This genetic similarity could probably condition alterations in the immune system, both innate and adaptative^{9,10}.

The age of development of tolerance in patients with FPIES varies by type of food trigger and country of origin. The average reported age of tolerance to grains is 35 months¹. In this case, the girls developed tolerance at 21 months of age. This could be explained because the ideal timing of OFC to determine resolution can vary considerably by the type of food trigger and the country of origin. Unfortunately, since all gluten-containing cereals were removed from their diet, we cannot find out which was the main responsible trigger for this unusual case of gluten-FPIES in monochoorial-monoamniotic twins.

Conflicts of Competing Interest:

The authors declare that they have no conflicts of interest.

Funding

The authors declare that no funding was received for the present study.

References

1. Nowak-Węgrzyn A, Chehade M, Groetch ME, 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):1111-1126.e4.
2. 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 Apr;122(4):407-411.
3. Bartnikas LM, Nowak-Węgrzyn A, Schultz F, Phipatanakul W, Bingemann TA. The Evolution of FPIES: From a Diagnosis That Did Not Exist to a Condition in Need of Answers. *Ann Allergy Asthma Immunol*. 2021 Jan 11: S1081-1206(21)00001-6.
4. 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;140(5):1323-1330.
5. Watanabe M, Tamaki K, Saji T, Nakamura H. Milk induced enterocolitis in monozygotic twin neonates. *Indian Pediatr*. 2009; 46:901-902.
6. Shoda T, Isozaki A, Kawano Y. Food protein-induced gastrointestinal syndromes in identical and fraternal twins. *Allergol Int*. 2011; 60:103–108
7. Infante S, Marco-Martín G, Zubeldia JM, Fuentes-Aparicio V, Alvarez-Perea A, Cabrera-Freitag P, Morales-Cabeza C, Zapatero L. Oral Food Challenge in Food Protein-Induced Enterocolitis Syndrome by Fish: Is There Any Room for Improvement? *Int Arch Allergy Immunol*. 2019;179(3):215-220.
8. Alonso SB, Ezquiaga JG, Berzal PT, et al. Food protein-induced enterocolitis syndrome: Increased prevalence of this great unknown-results of the PREVALE study. *J Allergy Clin Immunol*. 2019;143(1):430-433.
9. Goswami R, Blazquez AB, Kosoy R, Rahman A, Nowak-Węgrzyn A, Berin MC. Systemic innate immune activation in food protein-induced enterocolitis syndrome (FPIES). *J Allergy Clin Immunol*. 2017;139:1885-1896.e9.
10. Mehr S, Lee E, Hsu P, Anderson D, de Jong E, Bosco A, et al. Innate immune activation occurs in acute food protein-induced enterocolitis syndrome reactions. *J Allergy Clin Immunol*. 2019;144:600-602.e2.

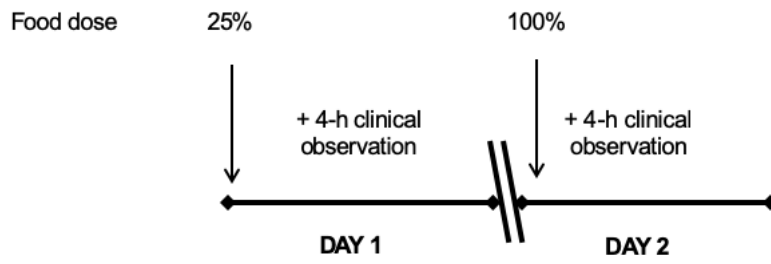


Figure 1. Protocol used in Oral Food Challenge. Source: adapted from Infante et al⁸.