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BRIEF COMMUNICATION

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Food protein-induced enterocolitis syndrome by fish: Not necessarily a restricted diet

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Abstract

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated gastrointestinal food hypersensitivity usually due to cow's milk or soy. Recent researches show that fish is 1 of the most important triggers of FPIES in the Mediterranean countries. Due to the risk of multiple-food FPIES, avoiding foods in the same category or that often occur together may be reasonable. The aim of this study was to evaluate the evolution and follow-up of FPIES related to fish over a period of 20 years. We describe the clinical features of our population, discuss different approaches to oral food challenges, and analyze the possibility of introducing the culprit fish or other nonrelated fish to avoid unnecessary restricted diets.

KEYWORDS
fish, food allergy, food protein-induced enterocolitis syndrome

1 | INTRODUCTION

Food protein-induced enterocolitis syndrome (FPIES) is an uncommon non-IgE-mediated gastrointestinal food hypersensitivity that typically appears in the first year of life. FPIES symptoms consist on recurrent delayed vomiting, lethargy, pallor, diarrhea, hypotension and may progress to a state of dehydration and hypovolemic shock. The clinical features repeat every single time the child eats the culprit food, and it is totally resolved once these proteins are removed from the diet.[1,2] Although several reports have been published in the past few years, there is still a lack of knowledge about this syndrome, its epidemiology, and its clinical characteristics[3-6] FPIES is thought to be a cell-mediated disorder but is uncertain about the role of specific IgE in this pathology. It has been speculated that there might be a local IgE production in the intestinal mucosa that participates in reaction to the food but would not reach the blood stream.[7]

The most frequent offending foods are cow's milk and soy. Among the solid foods, rice is 1 of the most causative foods but it varies depending on the geographic area. Recent data show that fish is 1 of the most important triggers of FPIES in the Mediterranean countries.[8-11]

We sought to evaluate the evolution and follow-up of FPIES related to fish in our Paediatric Unit over a period of 20 years. We herein describe the clinical features of our population to improve the knowledge and management of these children.

2 | PATIENTS AND METHODS

A retrospective study was performed over a period of 20 years. We included all children diagnosed with FPIES by fish at our Paediatric Allergy Unit from January 1996 to March 2017. Diagnosis was based on Sicherer's criteria.[1] A detailed clinical history was performed. The offending fish, age and symptoms at debut, coexistence of other atopic diseases, FPIES to other foods, and IgE-mediated fish sensitization were registered.

Abbreviations: FPIES, Food protein-induced enterocolitis syndrome; OFC, Oral food challenge; SPT, Skin prick test; TGF-β, Transforming growth factor β; TNF-α, Tumor necrosis factor α.

Skin prick test (SPT) were performed with commercial extracts to fish, and fish serum-specific IgE was measured by ImmunoCAP® System. In those cases where an oral food challenge (OFC) was indicated, this was the children who had been asymptomatic for at least 12 months, it was performed with the culprit fish or other fish, to verify if tolerance to the offending fish had been achieved or to verify tolerance to another kind of fish.

The OFC was performed in 2 different ways. Until 2015, our OFC consisted in giving several doses over 30 minutes. During the last 2 years, we performed the OFC in 2 nonconsecutive days; the first day, we gave the children a unique dose of little less of 50% of the serving size per age. If the fish was tolerated, that means they remained asymptomatic for the next 48 hours, a new OFC with the normal serving size per age was performed. In those patients with a history of severe reactions, the OFC was performed in 3 days. All the patients were in observation for at least 4 hours after each OFC.

During the follow-up, we recorded those children that achieved total tolerance, which means they overcame their FPIES; those that only achieve tolerance to some kind of fish (partial tolerance) and children that did not tolerate any.

This study was approved by our local Institutional Review Board, and all the parents gave the corresponding inform consent.

3 | RESULTS

Patient's characteristics are summarized in Table 1. Eighty children were enrolled in this study: 36 female (45%) and 44 male (55%) with a median age of debut of 10 months (IQR 9-11.75 months). The first patient was recruited in January 1996 and the last 1 in March 2017. The median age of our patients was 7.6 years (IQR 4.07-11.93 years).

Hake (*Merluccius merluccius*) (87.5%), megrim (*Lepidorhombus boscii*) (31.25%), and sole (*Solea solea*) (23.75%) were the fish most frequently involved. Forty-five of our patients (56.25%) reacted to 1 unique fish, 23 (28.75%) to 2 different fish, and twelve (15%) to 3 or more different fish. On average, the number of reactions prior to diagnosis was 4 (range 1-10).

Symptoms at the debut were mainly vomiting (97.5%) or vomiting with diarrhea (30%), which usually appeared in a mean time of 126.3 minutes (SD 112.5 minutes) since the ingestion of the culprit fish. Severe symptoms such as hypotension, hypoperfusion, or lethargy were not infrequent at the debut (16.25%), and 20% of our population needed emergency assistance care at least once.

Skin prick test with commercial extract of hake and serum-specific IgE was positive in 3 patients (3.75%).

In 60 of 80 patients (75%), 173 oral food challenges were performed. Forty-five patients achieved tolerance to some kind of fish (75.03%): 25 (41.7%) overcame their FPIES and 20 (33.33%) tolerated another type of fish, mostly canned tuna and swordfish, but not the offending 1. Fifteen of 60 patients challenged (25%) did not tolerate any fish during OFC.

Most patients (n = 46, 76.7%) were first challenged with culprit fish: 11 (23.9%) tolerated at this first attempt (median age, IQR 3, 2.3-4) and 7 (15.2%) tolerate culprit fish some years later (median age, IQR 5, 3-5). OFC with an alternative fish were attempted in 32 patients: in 20 of them (median age, IQR 4,3-7.5) challenge was negative and 7 patients overcame their FPIES after a period of alternative fish intake. 7 of the 35 children that first reacted with the offending fish did not undergo a new OFC (Figure 1).

Almost half of 173 challenges were performed with hake (45.66%), followed by canned tuna (17.92%) and swordfish (11.56%). Most of

TABLE 1 Clinical characteristics of our population

Characteristics	Population	Percentage (%)
Gender	n = 80	
Male	44	55
Female	36	45
Age at 1st reaction (months) (median, IQR)	10 (9-11.75)	
Allergic disorders	29/80	36.25
Atopic dermatitis	19	23.75
Rhinoconjunctivitis	14	17.5
Asthma	14	17.5
IgE-mediated food allergy	23/80	28.75
Egg	10	43.5
Nuts	6	26.1
Fruits/Vegetables	6	26.1
Milk	4	17.39
Coexistence of other FPIES	9/80	11.25
Milk	3	33.3
Shellfish	3	33.3
Egg	1	11.1
Rice	1	11.1
Fruits/Vegetables	1	11.1
Offending fish	n = 80	
Hake	70	87.5
Megrim	25	31.25
Sole	19	23.75
Positive IgE to the offending fish	3	3.75
Single-fish FPIES	n = 45	56.25
Multiple-fish FPIES	n = 35	43.75
2	23	28.75
≥3	12	15
No. of episodes before diagnosis		
Mean	4	
Range	1-10	
No. of patients with multiple episodes	73/80	91.25
2 episodes	14	17.5
3 episodes	24	30
4 episodes	17	21.25
5 episodes	10	12.5
>5 episodes	8	10
Emergency care assistance	16	20

challenges performed with hake were positive (62,03%), while in those performed with canned tuna or swordfish, positive challenges were observed in 22.58% and 15%, respectively (Figure 2). Symptoms at OFC were similar to symptoms at the debut.

In our population, the probability of not presenting a reaction during OFC was 4 times higher in those who received alternative fish than in those who received culprit fish (OR = 4.0, IC 95% 1.2-13.3).

Median age of alternative fish tolerance was 3 years (IQR 2.25-3), while culprit fish challenges were negative at 5 years of age (median, IQR 3-6), although no statistical differences were found.

Only 4 of the 35 children with multiple-fish FPIES did not achieve tolerance to any type of fish.

4 | DISCUSSION

Food protein-induced enterocolitis syndrome used to be an uncommon disease. However, in the past decade the number of patients diagnosed has increased and so does the clinical series reported.[12]

Diagnosis of FPIES is based on clinical history and, if necessary, results of an OFC. Most patients have negative skin prick test results

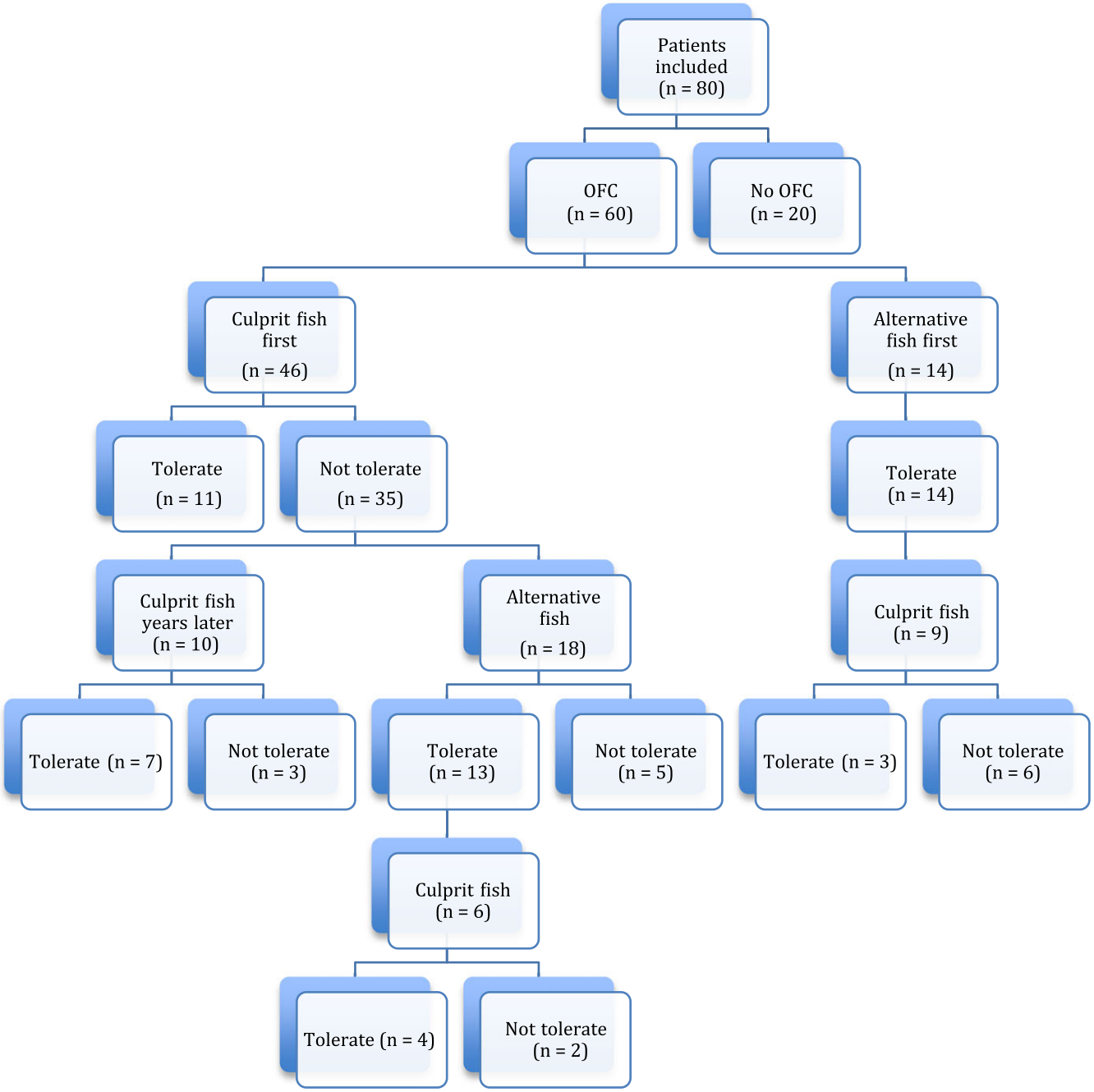

FIGURE 1 Flow chart of oral food challenges performed in our population [Colour figure can be viewed at wileyonlinelibrary.com]

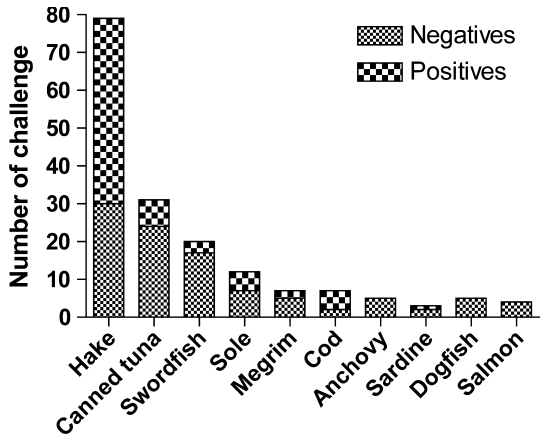

FIGURE 2 Oral food challenges results by fish. Graph distinguishes positive and negative results

and undetectable food-specific IgE antibodies, although 4-30% of children have, or will have, food-specific IgE to the food causing FPIES over time.[13] In our population, only 3 out of the 80 children (3.75%) had serum-specific-IgE positive to fish. This is considerably lower rate compared to FPIES due to other solid foods.[1,14]

In our population, fish is, by far, the solid food most implicated in FPIES.[8,10,15] We think, according to with Katz et al[3] and Sopo et al[9] that there are various FPIES phenotypes around the world and that could explain why different trigger foods are involved.

The age of onset of FPIES appears to be influenced by the time when the food proteins are introduced into an infant's diet[16] although there are some cases of FPIES of adult onset.[17,18] In our population, the median age of debut was 10 months, matching with the introduction of the fish into the diet.

Due to the risk of multiple-food FPIES, avoiding foods in the same category or that often occur together may be reasonable.[19] Nevertheless, in our population of FPIES caused by fish, many of them achieved tolerance to some fish different from the causative 1. We propose to test alternative fish before testing the fish that caused the previous reaction to avoid restrictive diets.

The best tolerated fish in our population were canned tuna and swordfish. Curiously, they are also the best tolerated by children with IgE-mediated allergy to fish. This finding supports the idea that perhaps local specific IgE, produced in the intestinal mucosa, participates in reaction to the food.

In our study, all the children who received first an alternative fish tolerated it. The median age of alternative fish tolerance was earlier than the median age of tolerance to the offending fish.

The International Consensus Guidelines for the Diagnosis and Management of Food Protein-Induced Enterocolitis Syndrome recommend to administer the challenge food at a dose of 0.06-0.6 g, usually 0.3 g of the food protein per kilogram of body weight in 3 equal doses over 30 minutes.[20]

In our population, from the very first children diagnosed with FPIES by fish until now, we have modified our OFC protocols. During the last years, the most useful 1 has been to split the normal serving size in 2 or 3 days. Our children, who succeeded the first day of the OFC, tolerated without any problems the whole meal. And those who did not, that means, the children who developed symptoms during the OFC, these were milder. So, our protocol for OFC showed to be safe.

As FPIES symptoms are delayed, we think that giving several doses could be counterproductive because when the children start to have symptoms they have already eaten more than what they should.

In our experience, performing the OFC in 2/3 nonconsecutive days was safer, than giving several doses every 30 minutes. Children diagnosis with fish FPIES should be tested with an alternative 1 to avoid unnecessary restricted diets.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES

1. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced enterocolitis syndrome. *J Pediatr*. 1998;133:214-219.
2. Leonard SA, Nowak-Wegryzn A. Manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome. *Pediatr Ann*. 2013;42:135-140.
3. Katz Y, Goldberg MR, Rajuan N, et al. The prevalence and natural course of food protein-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population-based study. *J Allergy Clin Immunol*. 2011;127:647-653.
4. Miyazaba T, Itabashi K, Imai T. Retrospective multicenter survey on food-related symptoms suggestive of cow's milk allergy in NICU neonates. *Allergology International*. 2013;62:85-90.
5. Nowak-Wegrzyn A, Muraro A. Food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2009;9:371-377.
6. Mane SK, Bahna SL. Clinical manifestations of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2014;14:217-221.
7. Caubet J-C, Nowak-Wegryzn A. Current understanding of the immune mechanisms of food protein-induced enterocolitis syndrome. *Exp Rev Clin Immunol*. 2011;7:317-327.
8. Zapatero Remón L, Alonso Lebrero E, Martín Fernández E, Martinez Molero MI. Food protein-induced enterocolitis syndrome caused by fish. *Allergol et Immunopathol*. 2005;33:312-316.
9. Sopo SM, 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 phenotypes. *Clin Exp Allergy*. 2012;42:1257-1265.

10. Vila L, García V, Rial MJ, Novoa E, Cacharron T. Fish is a major trigger of solid food protein-induced enterocolitis syndrome in Spanish children. *J Allergy Clin Immunol Pract*. 2015;3:621-623.
11. Gonzalez-Delgado P, Caprrós E, Moreno MV, et al. Clinical and immunological characteristics of a pediatric population with food protein-induced enterocolitis syndrome (FPIES) to fish. *Pediatr Allergy Immunol*. 2016;27:269-275.
12. Nowak-Wegryzn A, Jarocka-Cyrta E, Moschione Castro APB. Food protein-induced enterocolitis syndrome. *J Investig Allergol Clin Immunol*. 2017;27:1-18.
13. Nowak-Wegryzn, et al. Non-IgE-mediated gastrointestinal food allergy. *J Allergy Clin immunol*. 2015;135:1114-1124.
14. Nomura I, Morita H, Ohya Y, Saito H, Matsumoto K. Non-IgE-mediated gastrointestinal food allergies: distinct differences in clinical phenotype between Western countries and Japan. *Curr Allergy Asthma Rep*. 2012;12:297-303.
15. Ruiz-Garcia M, Díez CE, García SS, del Río PR, Ibañez MD. Diagnosis and natural history of food-protein induced enterocolitis syndrome in children from a tertiary hospital in central Spain. *J Investig Allergol Clin Immunol*. 2014;24:354-356.
16. Mehr S, Frith K, Campbell DE. Epidemiology of food protein-induced enterocolitis syndrome. *Curr Opin Allergy Clin Immunol*. 2014;14:208-216.
17. Fernandes BN, Boyle RJ, Gore C, Simpson A, Custovic A. Food protein-induced enterocolitis syndrome can occur in adults. *J Allergy Clin Immunol*. 2012;130:1199-1200.
18. Tan JA, Smith WB. Non-IgE-mediated gastrointestinal food hypersensitivity syndrome in adults. *J Allergy Clin Immunol Pract* 2014;2:355-357.
19. Leornard S, Nowak-Wegryzn A. Manifestations, diagnosis, and management of food protein-induced enterocolitis syndrome. *Curr Opin Pediatr*. 2012;24:739-745.
20. Nowak-Wegryzn A, 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;139:1111-1126.

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