

Fish is a major trigger of solid food protein–induced enterocolitis syndrome in Spanish children

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Clinical Implications

- Fish is the solid food most frequently involved in food protein–induced enterocolitis syndrome (FPIES) in Spanish children. Most patients tolerate types of fish other than the one eliciting FPIES. Fish-induced FPIES is more persistent over time than other solid-induced FPIES.

TO THE EDITOR:

Food protein–induced enterocolitis syndrome (FPIES) is a rare type of non–IgE-mediated gastrointestinal food hypersensitivity that usually appears during the first year of life. The most common triggers are cows' milk and soy.^{1,2}

We aimed to describe the clinical features of FPIES induced by solid foods in pediatric patients evaluated in our daily practice.

We performed a retrospective analysis (2009–2014) of data obtained from the clinical charts of children referred to our pediatric allergy unit with gastrointestinal symptoms after solid food ingestion.

The study sample comprised 21 children (12 girls and 9 boys), who fulfilled Powell's criteria for FPIES, which were updated by Sicherer et al.³ Clinical data are summarized in detail in Table 1. Patients underwent skin prick test and serum-specific IgE determination with the offending and related foods (ImmunoCAP, ThermoScientific, Spain).

All the children experienced clinical manifestations compatible with FPIES, and the diagnosis was made based on clinical symptoms. Oral food challenge (OFC) was performed after the first visit to identify the culprit food only in cases where several foods were involved. Patients were followed up every 12 to 18 months, when OFC with the offending food was performed to assess whether or not the patient had developed tolerance.

All patients presented with repetitive vomiting 60 to 180 minutes after ingestion. Of the 21 patients, 14 presented with associated lethargy (66.6%), and 11 patients with associated pallor (52%). Seven patients (35%) had diarrhea. Only 2 patients developed severe symptoms, which required treatment with intravenous fluids. Median age at diagnosis was 10 months (range, 4 months to 10 years).

Seventeen patients reacted during their first exposure to the suspected food, and 4 patients during their second one. The patients experienced a median of 2 reactions (range, 1 to 6) before the diagnosis of FPIES was established.

Fish was the most frequently implicated food, which affected 17 patients. Hake was responsible for 14 cases, monkfish for 6, and flatfish (sole and megrim) for 4. In 3 cases, grain was responsible for the syndrome (rice and corn, rice and oat, and wheat).

FPIES was caused by banana in 2 patients and by peach in 1 patient.

Of the 21 patients, 3 (14.2%) reacted to more than 1 food type (hake and banana in 2 cases and grains and cow's milk in 1 case).

Once persistence of FPIES was confirmed (at diagnosis and during follow-up), OFC was performed with grains or fish other than those that had already elicited FPIES to avoid unnecessary restrictive diets. The children's family decided the type and number of foods to be used in the challenge, according to their dietary habits. For example, if the patients reacted to hake and their family ate monkfish on a regular basis, this would be the first fish to be tested in the OFC. Thirteen patients agreed to undergo OFC with types of fish other than the one responsible for FPIES, and 8 of them showed tolerance to at least another type of fish.

The children who reacted to fish were older at the time of the first reaction (median, 12 months; range, 9 months to 14 years) than children affected by other solid foods (median, 6 months; range, 4 to 24 months).

FPIES was outgrown in 5 cases where fish was responsible, in the 3 cases caused by fruit, and in the case caused by rice and corn. The median age of tolerance to fish was 4 years (range, 1 to 17 years); the median age of tolerance to other solid foods was 3 years (range, 1 to 4 years).

Four patients reported an allergic background: 1 patient had allergic rhinitis to dust mites and grass pollen, 1 had IgE-mediated cow's milk allergy, and 2 children presented IgE-mediated egg allergy. None of the patients had a family history of atopy.

All skin prick test results were negative, and serum food-specific IgE to the food involved in FPIES was undetectable in all cases. Our observations show fish to be the main trigger of FPIES caused by solid food in Spanish children. This finding has been reported elsewhere.^{4,5} Sopo et al⁶ showed that in Italy fish was the main trigger for FPIES caused by solids. Interestingly, in other parts of the world, such as in the USA, grains were involved in most cases of FPIES caused by solids.⁷ These differences are probably related to different food consumption habits and to the age-specific foods that are introduced into the infant's diet. In Spain, hake and flat fish (sole and megrim) account for most cases of FPIES caused by fish.⁵ These fish are first introduced into the diet of Spanish infants at the age of 9 to 10 months, whereas in the USA, fish is usually introduced after the 12th month. Moreover, although shellfish is considered to be one of the most allergenic foods, none of the patients we report had FPIES caused by shellfish, probably because shellfish is very unlikely to be included in the diet of Spanish children younger than 12 months.

Fish-induced FPIES was more persistent in our study population than FPIES caused by other solid foods. Five of the 17 patients with fish FPIES were diagnosed recently, and OFC has not yet been performed to confirm whether or not they have developed tolerance. Only 4 of the 12 remaining patients achieved tolerance. The oldest patients with persistent FPIES were aged 17 years (patient number 5) and 14 years (patient number 17). Patient 5 developed acute FPIES after ingesting hake for the first time at the age of 12 months, and her parents decided to avoid all types of fish. However, she tried anchovies accidentally

TABLE I. Clinical characteristics and offending foods of patients with solid food protein-induced enterocolitis syndrome

Patient	Age at first reaction	Age at diagnosis	Sex	SPT/IgE	Food	Symptom	Time to onset (min)	Number of reactions	Age of tolerance (y)/food	Breastfeeding (mo)	Tolerance to other related food/age
1	5 mo	3 y	Female	—/—	Banana, hake*	V, D	180	1: banana 1: hake	No	7	Other fruits/6 mo No other fish
2	8 mo	3 y	Female	—/—	Hake*	V	60	1	No	Not breastfed	ND
3	9 mo	4 y	Female	—/—	Small hake, monkfish*	V, L, P	180	1: small hake 1: monkfish	4/Small hake, monkfish	Not breastfed	ND
4	9 mo	3 y	Female	—/—	Banana, hake*	V, L, P	180	1: hake	3/Banana, hake	12	Megrim/9 mo
5	9 mo	5 y	Male	—/—	Monkfish, gilthead sea bream*	V, L, P	120	1: monkfish 1: gilthead sea bream	No	11	ND
6	9 mo	6 y	Male	—/—	Hake, megrim*	V, L	120	1: hake 1: megrim	No	Not breastfed	Salmon, tuna, swordfish/12 mo
7	9 mo	3 y	Female	—/—	Hake, small hake, monkfish, megrim*	V, D, L, P	180	1: hake 1: small hake 1: monkfish 1: megrim	3/Hake, small hake, monkfish, megrim	1	ND
8	10 mo	17 mo	Male	—/—	Hake, sole*	V, L, P	180	1: hake 1: sole	No	Not breastfed	No
9	10 mo	2 y	Male	—/—	Hake*	V, L, P	180	1	No	15	Megrim/12 mo
10	12 mo	17 y	Female	—/—	Hake*	V, D, L, P	90	>6	No	3	Anchovies/4 y
11	12 mo	7 y	Male	—/—	Hake, monkfish, tuna, sole, swordfish*	V, D, L, P	180	5 (1 reaction with each one)	7/Hake, monkfish, tuna fish, sole, sword fish	Not breastfed	No
12	12 mo	4 y	Female	—/—	Monkfish, sea bass, mackerel, gilthead sea bream*	V, L	60	5 (1 reaction with each one)	No	15	Hake, cod/12 mo
13	12 mo	20 mo	Female	—/—	Hake	V, L	120	3	No	4	No
14	12 mo	1 y	Male	—/—	Hake, monkfish*	V, D	60	1: hake 1: monkfish	No	12	No
15	13 mo	4 y	Male	—/—	Hake*	V	120	1	No	Not breastfed	Tuna/18 mo
16	24 mo	7 y	Male	—/—	Hake	V, D	120	1	7/Hake	Not breastfed	Megrim, sole, cod, tuna, swordfish, salmon, monkfish/2 y
17	10 y	14 y	Female	—/—	Salmon	V	60	1	No	2	White fish, swordfish, tuna/4 y
18	4 mo	15 mo	Female	—/—	Rice, oats*	V, L, P	60	1	No	15	Wheat, corn, barley, rye/5 mo
19	5 mo	3 y	Male	—/—	Rice, corn*	V, L, P	60	1	3/Rice, corn	5	Wheat, oats, barley, rye/6 mo
20	8 mo	4 y	Female	—/—	Wheat*	V, D	120	1	No	Not breastfed	Rice, oats, barley, rye, corn/8 mo
21	24 mo	4 y	Female	—/—	Peach	V, L, P	60	2	4/Peach	Not breastfed	Other rosaceae fruits/2 y

SPT, Skin prick test; V, vomiting; D, diarrhea; L, lethargy; P, pallor; ND, not done.

*Patients reacting the first time to the offending food that was introduced into their diet.

when she was 4 years old and experienced no adverse reaction. Patient 17 developed acute FPIES with salmon at the age of 10 years, although she had been exposed to it several times before. She agreed to undergo OFC with different fish species, to which she showed good tolerance.

Tolerance to other fish was confirmed by OFC in 8 of the 13 patients. In our opinion, the benefits of OFC with other fish outweigh the risk of an adverse reaction during the test, because most patients would avoid unnecessarily restricted diets. Interestingly, these patients seem to tolerate blue fish better than white fish.

FPIES was caused by rice in only 2 cases. In one case, the patient was co-sensitized to oat, and in the other, to corn. To our knowledge, this is the first study to report FPIES caused by rice and corn.

Only 4 patients reported an allergic background, but none of them reported a family history of atopy. Zapatero et al⁴ also reported a low incidence of atopy in the family history in Spain, in contrast with data from other authors.^{1,6} A theory supporting the existence of various phenotypes of FPIES has been proposed^{6,8} and could explain the differences observed for the types of food involved, differences in the prevalence of atopy in the family history, and the wide spectrum and severity of the clinical manifestations.

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REFERENCES

1. Caubet JC, Ford LS, Sickles L, Jarvinen KM, Sicherer SH, Sampson HA, et al. Clinical features and resolution of food protein-induced enterocolitis syndrome: 10-year experience. *J Allergy Clin Immunol* 2014;134:382-9.
2. Ruffner M, Ruymann K, Barni S, Cianferoni A, Brown-Whitehorn T, Spergel J. Food protein-induced enterocolitis syndrome: insights from review of a large referral population. *J Allergy Clin Immunol Pract* 2013;1:343-9.
3. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein induced enterocolitis syndrome. *J Pediatr* 1998;133:214-9.
4. Zapatero L, Alonso E, Martin E, Marintez MI. Food protein-induced enterocolitis syndrome caused by fish. *Allergol Immunopathol* 2005;33:312-6.
5. Ruiz-García M, Escudero Díez S, Sanchez García S, Rodríguez del Río P, Ibañez MD. Diagnosis and natural history of food protein-induced enterocolitis syndrome in children from a tertiary hospital in central Spain. *J Invest Allergol Clin Immunol* 2014;24:352-70.
6. Miceli Sopo S, Giorgio V, Dello Iacono I, Novembre E, Mori F, Onesimo R. A multicenter retrospective study of 66 Italian children with food protein-induced enterocolitis syndrome: different management for different phenotypes. *Clin Exp Allergy* 2012;42:1257-65.
7. Nowak-Węgrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; 111:829-35.
8. Katz Y, Goldberg MR, Rajuan N, Cohen A, Leshno M. The prevalence and natural course of food-induced enterocolitis syndrome to cow's milk: a large-scale, prospective population based study. *J Allergy Clin Immunol* 2011;127: 647-53.

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