

Food protein-induced Enterocolitis Syndrome Caused by Fish

L. Zapatero Remón, E. Alonso Lebrero, E. Martín Fernández and M.I. Martínez Molero

Section of Pediatric Allergy. Hospital Materno Infantil Gregorio Marañón, Madrid, Spain.

ABSTRACT

Introduction: Food protein-induced enterocolitis syndrome (FPIES) occurs in infants. Typical symptoms include profuse vomiting and/or diarrhea several hours after ingestion of a given food. The disorder is a non-IgE mediated food hypersensitivity. The most frequently involved foods are milk and soy, but some cases of FPIES induced by solid foods have been described. We report 14 patients with FPIES due to fish protein.

Material and methods: History and physical examination, skin prick test (SPT) with fish allergens and *Anisakis simplex*, prick-by-prick test with implicated fish and determination of specific IgE antibodies against fish were performed. In eight children atopy patch test (APT) were also performed. In nine patients an open oral food challenge with the implicated fish was carried out.

Results: There were six boys and eight girls, aged from 9 to 12 months at diagnosis, with between two and six reactions to the offending fish proteins before the diagnosis was established. Four patients had a previous history of atopy. Presenting symptoms included diarrhea in two patients, profuse vomiting in six patients, and recurrent vomiting and subsequent diarrhea in three patients. In addition to these symptoms, associated septic appearance, apathy and lethargy were present in the remaining three patients.

Onset of symptoms occurred a few minutes after fish ingestion in two patients and from 60 minutes to 6 hours in the 12 remaining patients. SPT to fish were negative in all patients. Serum food-specific IgE antibodies were negative in all patients except one. APT was positive in three patients. Open oral challenge (OC) was performed in nine infants and was positive in all. The patients were followed-up for between 1 and 7 years after diagnosis, and follow-up OC tests were performed after fish had been eliminated from the patients' diet for 3-4 years. Four patients became clinically tolerant to the causal food. Three patients currently tolerate only one type of fish (swordfish).

Conclusions: We report 14 patients with FPIES caused by fish protein. The symptoms suggest a form of cell-mediated, non-IgE mediated food hypersensitivity. The gold standard for diagnosis is OC, although caution should be exercised in infants with several reactions or a recent diagnosis. After a period of elimination of the causal food from the diet, tolerance can develop.

Key words: Enterocolitis. Food allergy. Fish. Non-IgE-mediated food allergy.

Correspondence:

L. Zapatero Remón MD PhD
Avda. Doctor García Tapia, 157 portal E, 4.ªA.
28030 Madrid
E-mail: lzremon@terra.es

INTRODUCTION

Food protein induced enterocolitis syndrome (FPIES), typically appears from the first month of life, usually induced by cow's milk and or soy protein. It was first described by Gryboski in 1967¹, and its main symptoms consist on vomiting ensues, diarrhea, failure to thrive in infant and may progress to acidemia and shock. Symptoms resolve after the responsible protein is removed from the diet, and recur after the reintroduction of the protein, generally with-

in 2 hours, with symptoms that may lead to lethargy, dehydration, hypotension and metabolic acidosis^{2,3}.

There are an increase number of reports pointing of additional causatives solid food such as rice^{2,4,5}, poultry, egg, grains, vegetables and peanut^{2,6,7}, that could trigger this syndrome. There is only one case report of FPIES induced by fish⁸, even though this food is often clinically suspected in pediatric patients by allergist. The disorder is a form of cell-mediated, non-immunoglobulin E (IgE) antibody-associated food hypersensitivity. Recent studies suggest that tumor necrosis factor α (TNF- α) from T cells upon milk stimulation is involved in the pathophysiology of FPIES⁹. A relative lack of expression of transforming growth factor- β (TGF- β) may also be implicated¹⁰.

Our group has studied 14 infants with FPIES due to dietary fish protein. In this study we report the clinical characteristics of these patients and their clinical course.

MATERIAL AND METHODS

We reviewed the medical history of those patients sended to our Allergy Department referring gastrointestinal symptoms after ingestion of fish in which hypersensitivity IgE mediated was to ruled out.

The patients underwent a detailed clinical and nutritional history, physical examination, Skin Prick Test (SPT) for food allergens, Atopy Patch Test (APT), serum specific IgE antibodies against fish, and an open oral food challenge.

SPT were performed with commercial extracts to fish (Leti Laboratories), and *Anisakis simplex* (IPI Laboratories), and prick by prick with the suspicious fish (hake, sole or cork float), positive (histamine) and negative (Glycerol saline) were included. SPT were considered positive if the mean wheal diameter was at least 3 mm greater than the saline control.

Serum fish-specific IgE antibodies were measured by the CAP SystemTM (Pharmacia-Uppsala, Sweden), being the lower limit of detection 0, 35 KU/L.

The APT was performed in 8 children using the same extracts used for SPT and cooked fish (boiled). We used CuratestTM adhesive strips on the back, and kept the occlusion for 48 hours. The APT was read 30 minutes after the removal of the cups, and after 96 hours. The APT reading were based on the assessment criteria recommended by ICDRG¹¹.

The diagnosis of FPIES was based on clinical criteria and in 9 patients on physician supervised oral food challenges after written informed consent was obtained. The open oral challenge was performed initially with the eighth portion of a normal serving size amount per age, and was gradually increased by 2 every 30 minutes to a full serve. The patients remained under physician supervision for three hours, regardless of the outcome of the challenge.

RESULTS

The patient's clinical data are shown in table I.

We report 14 patients (6 males and 8 females), aged between 9-12 months at the time of diagnosis.

Table I
Clinical features of patients with fish protein-induced enterocolitis syndrome

N.º	Age at first reaction	Sex	SPT/Fish-IgE	APT	Fish	Symptom	Duration	Time to Onset	Number of reactions
1	12	F	—/—	ND	S	D	6 h	90 m	4
2	10	F	—/—	—	SH	V	6 h	90 m	5
3	12	F	—/—	—	H, S, CF	V	6 h	60 m	5
4	9	M	—/—	+	H, SH	V, D	24 h	120 m	6
5	10	M	—/—	—	H, SH	V	1 h	5-10 m	U
6	9	M	—/—	ND	CF, SH	D	48 h	6 h	3
7	12	M	—/—	ND	H, CF	V	U	U	3
8	10	F	—/0,40	—	H, S	V, D	48 h	120 m	3
9	11	M	—/—	ND	H, S	V, D	24 h	60 m	2
10	11	M	—/—	ND	H, S	V, L	U	120 m	3
11	12	F	—/—	+	S	V	4 h	120 m	>6
12	12	F	—/—	+	H, S, CF	V	3 h	5-10 m	5
13	9	F	—/—	ND	H, CF	V, L	U	120 m	U
14	9	F	—/—	—	H	V, L	6 h	120 m	3

Age in months; M: male; F: female; SPT: Skin Prick Test; APT: Atopy Patch Test; S: sole; H: hake; SH: small hake; CF: cork float; D: diarrhea; V: vomiting; L: lethargy; U: uncertain; h: hours; m: minutes.

Four patients had previous history of atopy (asthma in 4 cases, atopic dermatitis in 2 and one patient presented recurrent urticaria not related to food). Three patients referred family history of atopy. One patient's father had a clinical anamnesis consistent with FPIES induced by fish in his early childhood. The involved fish were hake, sole and cork float; 10 of them (71 %) had symptoms with more than one fish. Symptoms begun a few minutes after ingestion of fish in 2 cases, and between 60 minutes to 6 hours in 12 remaining patients. Symptoms persisted 3 to 48 hours.

Six patients had 2 to 3 reactions to the offending fish's proteins before the diagnosis was established, 5 patients 4-6 episodes and 1 had 6 incidents.

The presenting symptoms included diarrhea in 2 cases, profuse vomiting in 6, 3 infants had recurrent vomiting and subsequently diarrhea. The remaining 3 patients associated septic appearance, apathy and lethargy, to the previous symptoms described.

SPT with commercial extracts to fish and prick-prick with boiled fish, were negative in all cases. APT was positive in 3 patients. Serum food-specific IgE antibodies to the responsible fishes were negative in all cases, except patient n.º 8, who had positive serum-specific IgE antibodies to hake (0,40 KU/L).

Oral food diagnostic challenge were performed in 9 infants, being positive in all of them (table II). Two patients developed symptoms after the first dose, and in 4, symptoms took place after the whole serving was given. Three patients required emergency treatment, with intravenous fluids and corticosteroids, for a few hours. One of them remained hospitalized for 24 hours. The rest 6 patients overcame symptoms and improved clinically just with oral hydration. The remaining 5 infants did not undergo the oral chal-

lenge, because they referred various evocative episodes of FPIES.

Blood test and stool culture was performed in 3 patients after positive oral challenge. Neutrophilia was not found and the stool culture were negative.

One patient suffered celiac disease, and 2 infants had previous history of egg allergy IgE mediated. Once FPIES induced by fish diagnosis was achieved, one patient developed twice, vomiting and diarrhea, 2 hours after melon ingestion. SPT as well as serum specific IgE antibodies to melon were negative.

Follow-up

We monitored patient's clinical evolution 1-7 years after diagnosis. After an elimination diet of 3-4 year, we undertook follow-up oral challenge. Four infants became clinically tolerant to the causal food. Three patients currently tolerate one single fish (swordfish).

Two patients continued fish elimination diet over 5 years, and their parents do not wish to have them re-challenged at the present time.

About the 5 remaining patients, 2 had a positive re-challenge with hake in last visit, so they will continue diet; 2 infants had a recent diagnosis, and finally, patient 8, who removed fish's protein of diet 3 years ago, has developed recently a sensitization to melon that suggest FPIES by melon, so we would prefer to wait for the re-challenge.

DISCUSSION

FPIES is a severe syndrome of vomiting and diarrhea typically caused by cow's milk or soy protein in infants. The disorder is probably cell-mediated and occurs with negative allergy skin prick test and the absence of serum allergen-specific IgE antibodies².

The prevalence of FPIES in the general pediatric population is unknown but it is considered to be a rare form of gastrointestinal food hypersensitivity.

We report the first series of infants with FPIES caused by fish proteins. The involved fishes were: hake, sole and cork float, usually consumed by children in our country. Ten patients (71 %) had previous history of reaction to more than one fish. None children reacted to cow's milk, 2 infants presented egg allergy IgE mediated, and one patient had vomiting and diarrhea after melon ingestion.

Pathology related to foods is contributed by its consumption pattern; Spain holds the second place amongst European Union's fish consumers.¹² In

Table II
Result of Challenges

N.º	Quantity	Time to Onset	Symptoms	Treatment	Duration
1	One piece	90 m	V	Steroids, ER	> 6 h
2	One piece	5 h	V	Home	2-3 h
3	1/8 piece	30 m	V, L	Steroids, ER	> 6 h
4	One piece	3 h	V	Home	2-3 h
5	1/8 piece	30 m	V	TR, Home	3-4 h
6	1/4 piece	3 h	D	TR, Home	24 h
8	1/4 piece	2 h	V, L	Steroids, ER	24 h
9	1/2 piece	2 h	V	TR, Home	3-4 h
11	One piece	3 h	V	Home	3-4 h

V: vomiting; L: lethargy; ER: emergency room; TR: test room; m: minutes; h: hours.

Spain, fish is usually introduced in children feeding before the first year of life.

Our patients had a median of 4 reactions (2 to 6), before the diagnosis was achieved. This coincides with Nowak-Węgrzyn⁷ series of patients, with a median of 2 reactions (range 2 to 5) before diagnosis. Delayed diagnosis is particularly common in these patients, probably because of the uncommon nature of the disorder, the lack of a confirmatory specific diagnostic test, and the unspecificity of the symptoms that similar to episodes of infectious gastroenteritis. The time course of reactions can also confound the diagnosis. Young infants with FPIES to cow's milk or soy which are exposed to these proteins on a daily basis, typically manifest chronic symptoms. In FPIES caused by solids, the presentations tended to be more severe, because the context of intermittent exposures to the dietary food proteins in slightly older infants.

Our report confirmed previous observations that measurements of food allergen-specific IgE antibodies (SPT or serum levels) are typically negative^{2,11}. Some authors have point out that the development of specific IgE antibodies in FPIES induced by milk or soy, seems to be a sign of poor prognosis for tolerance². Only one of our patients had detectable IgE for hake (0, 40 KU/L).

There are increasing reports of FPIES induced by food other than cow's milk and soy. Nowak-Węgrzyn et al⁷ reported 14 patients with FPIES induced by grains, vegetables and poultry; 5 of them had only sensitization to solid food and the 9 remaining patients also had food hypersensitivity to milk and/or soy. Levy and Danon¹⁴ reported 6 patients with FPIES induced by poultry, legumes and soy, associating FPIES by milk in 3 of them. We want to point out that in our 14 patient's series, no one had previous history of FPIES provoked by cow's milk. We think this fact could have a hand in monosensitization to fish reported in 11 of our 14 patients, quite the opposite to most previous reports which described sensitization to more than one solid food, such as in Nowak-Węgrzyn et al⁷ report, who described that 78 % of patients reacted to more than one food protein.

At diagnosis, all patients aged between 9 to 12 months, coinciding with the median age of diet fish introduction, such as we have commented previously, and clearly distinguished of FPIES due to milk or soy that triggers at an early age. To achieve a correct diagnosis, is necessary to consider the age distribution pattern related with the consumption of diverse food.

Three of our patients, had positive fish APT, without previous history of atopic dermatitis. Hypotheti-

cally, the APT, used with variable clinical utility for atopic dermatitis^{15,16} or eosinophilic gastroenteritis¹⁷, may be of use in the diagnosis of gastrointestinal allergy without evidence of IgE¹⁸, but it has not been sufficiently evaluated in this disorder.

We performed blood testing to 3 of the patients. The polymorphonuclear leukocyte count of the 3 evaluated patients was normal, even though, we consider these results warily, because of the lack of previous cell counts and the limited number of samples.

Powell¹⁹ suggested specific criteria for the diagnosis of milk or soy enterocolitis based on oral challenge. However, this challenge may be dangerous, so that, a confirmatory challenge would not be needed when the typical symptoms occur after ingestion of the food (particularly more than once) and there are no alternative explanations for the symptoms. Therefore the need for an oral food challenge to confirm the diagnosis must be determined on clinical grounds. Otherwise, this modality is used to monitor development of tolerance. Now a days, the better management for this disease is the dietary avoidance of the implicated food.

In patients follow up, 4 infants (28.5 %) became clinically tolerant after a 3-4 year-period elimination diet. Three patients currently tolerate one single fish (swordfish). Five patients continued fish elimination diet (for having a recent diagnosis in 2 infants, because their parents do not desire re-challenge yet in 2 patients, and for having a recent sensitization to another food in 1 infant). The remaining 2 patients had a positive re-challenge with hake in last visit, so they will continue diet.

In Nowak-Węgrzyn⁷ series of 14 patients, 4 became tolerant to the causal food and 5 had new sensitizations. In our study, only one of 14 patients had a new sensitization (to melon), although 2 of them had previous egg IgE-mediated allergy. Only one patient of 6 achieved tolerance in Levy et al¹⁴ report. Vitoria et al⁸ described 3 children with cow's milk protein intolerance and associated enteropathy related to fish, rice and chicken respectively. In patient with FPIES induced by fish, after a period of fish dietary elimination, a normal intestinal biopsy was obtained. Afterwards, an oral food fish challenge was performed, being positive, and a second intestinal biopsy was carry out, demonstrating atrophy of jejunal mucosa.

More research is needed to determine the best course of dietary management, develop laboratory test to avoid the need for oral food challenges, address prevention, and to determine specific treatment modalities.

REFERENCES

1. Gryboski J. Gastrointestinal milk allergy in infancy. *Pediatrics*. 1967;40:354-62.
2. Sicherer SH, Eigenmann PA, Sampson HA. Clinical features of food protein-induced syndrome. *J Pediatr*. 1998;133:214-9.
3. Sicherer SH. Food protein-induced enterocolitis syndrome: clinical perspectives. *J Pediatr Gastroenterol Nutr*. 2000;30:45-9.
4. Borchers SD, Li BUK, Friedman RA, McClung HJ. Rice-induced anaphylactoid reaction. *J Pediatr Gastroenterol Nutr*. 1992;15:321-4.
5. Cavataio F, Carroccio A, Montalto G, Iacomo G. Isolated rice intolerance: clinical and immunologic characteristics in four infants. *J Pediatr*. 1996;128:558-60.
6. Vandenplas Y, Edelman R, Sacre R. Chicken-induced anaphylactoid reaction and colitis. *J Pediatr Gastroenterol Nutr*. 1994;19:240-1.
7. Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics*. 2003;111:829-35.
8. Vitoria JC, Camarero C, Sojo A, Ruiz A, Rodríguez-Soriano T. Enteropathy related to fish, rice, and chicken. *Arch Dis Child*. 1982;57:44-8.
9. Benlounes N, Candalh C, Matarazzo P, Dupont C, Heyman M. The time-course of milk antigen induced TNF- α secretion differs according to the clinical symptoms in children with cow's milk allergy. *J Allergy Clin Immunol*. 1999;104:863-9.
10. Chung HL, Hwang JB, Park JJ, Kim SG. Expression of transforming growth factor β 1, transforming growth factor type I and II receptors, and TNF- α in the mucosa of the small intestine in infants with food protein-induced enterocolitis syndrome. *J Allergy Clin Immunol*. 2002;109:150-4.
11. Wahlberg JE. Patch testing. In: Rycroft RJG, Menné T, Frosch PJ, Benezra C, editors. *Contact Dermatitis*. Berlin: Springer-Verlag; 1992. p. 239-68.
12. Martín MF, Rico MA, Alonso E, Martorell A. Alergia a pescados. In: *Alergia a alimentos. Comité de reacciones adversas a alimentos de la SEAIC*. Ed. Médicas S.L. 2004, p. 89-105.
13. Burks AWW, Casteel HB, Fiedorek SC, Williams LW, Pumphrey CL. Prospective oral food challenge study of two soybean protein isolates in patients with possible milk or soy protein enterocolitis. *Pediatr Allergy Immunol*. 1994;5:40-5.
14. Levy Y, Danon YL. Food protein-induced enterocolitis syndrome-not only due to cow's milk and soy. *Pediatr Allergy Immunol*. 2003;14:325-9.
15. Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol*. 1996;97:9-15.
16. Perackis K, Celik-Bilgili S, Staden U, Mehl A, Niggemann B. Influence of age on the outcome of the atopy patch test with food in children with atopic dermatitis. *J Allergy Clin Immunol*. 2003;112:625-7.
17. Spergel JM, Beausoleil JL, Mascarenhas M, Liacouras CA. The use of skin prick test and patch test to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*. 2002;109:363-8.
18. De Boissieu D, Wagué JC, Dupont C. The atopy patch test for detection of cow's milk allergy with digestive symptoms. *J Pediatr*. 2003;142:203-5.
19. Powell G. Food protein-induced enterocolitis of infancy: differential diagnosis and management. *Compr Ther*. 1986;12:28-37.