Clinical Communications

Food protein–induced enterocolitis-like syndrome in a population of adolescents and adults caused by seafood

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Clinical Implications

- A similar syndrome to food protein–induced enterocolitis commonly described in infants, may be observed in adults specially after seafood ingestion. Symptoms are commonly persistent and in most cases the entity is probably underdiagnosed.

TO THE EDITOR:

Research interest in food protein–induced enterocolitis syndrome (FPIES) has increased in recent years, as evidenced by the high number of publications on the topic. These primarily focus on the pediatric population, whereas there are very few reports in adults.

We describe the clinical features and follow-up of 25 adolescents and adults who experienced exclusively gastrointestinal symptoms, resembling FPIES in infants, after ingesting seafood.

We conducted a prospective follow-up study over a 10-year period (2007-2016) in patients 14 years and older who presented to our allergy section and met the following inclusion criteria:

- Ingestion of seafood (finned fish, crustacean, and mollusk shellfish) elicited exclusively gastrointestinal symptoms (vomiting, acute severe abdominal pain, and/or diarrhea) within 1 to 4 hours.
- Avoidance of the offending food prevented reoccurrence of the reaction.
- Patients related at least 3 different episodes with the same food.

We performed skin prick tests with commercial extracts (Leti; Barcelona, Spain) and prick-prick with fresh food, as commercial extracts of shellfish sometimes produced false negatives.[1] Serum-specific IgE was measured by the ImmunoCAP fluorescent enzyme immunoassay (ThermoFisher Scientific, Phadia, Uppsala, Sweden).

Patients underwent periodic oral food challenge (OFC) with the implicated food every 18-24 months, to confirm diagnosis or check tolerance, except for those who had experienced 2 or more episodes in the previous 12 months with the incriminated food or other related foods. Procedures were performed in a hospital setting, according to Sicherer guidelines.[2]

We obtained a complete blood count with differential before the OFC and 6 hours later if it was positive. We considered the OFC to be positive when symptoms were reproduced, with vomiting or abdominal pain accompanied by pallor, lethargy, diarrhea, or hypothermia.

The local ethics committee approved the study, and patients provided their informed consent before inclusion.

We included 25 patients with exclusively gastrointestinal symptoms after the ingestion of seafood. Clinical data are summarized in Tables I and II. Twenty-two subjects were female and 3 male. The median age at the initial presentation of symptoms was 28 years (25% to 75% interquartile range [IQR], 20.5-38 years). All patients had previously tolerated the foods implicated in the reactions.

The diagnosis was established after a median of 8 reactions (IQR, 5.5-10). The median delay between the first reaction and diagnosis was 8 years (IQR, 3-13).

All patients reported severe abdominal pain, 19 (76%) had vomiting, and 16 (64%) diarrhea, which in 1 case was bloody. Seven patients described more severe symptoms (hypothermia and lethargy) requiring medical care, and 1 lost consciousness. Skin tests and specific IgE detection were negative in all patients. Symptoms were induced by crustaceans in 15 patients (60%), fish in 12 patients (48%), and cephalopods and bivalves in 5

TABLE I. Demographic and clinical characteristics of the population with food protein-induced enterocolitis-like syndrome (n = 25)

Characteristic	Value
Sex, n (%)	
Men	3 (12)
Women	22 (88)
Age at first reaction (y), median (IQ_{25-75})	28 (18.5-38)
Delay to diagnosis (y), median (IQ_{25-75})	8 (3-13)
Symptoms, n (%)	
Abdominal pain	25 (100)
Vomiting	19 (76)
Diarrhea	16 (64)
Hypothermia, lethargy	7 (28)
Loss of consciousness	1 (4)
N episodes, median (IQ_{25-75})	8 (5.5-10)
Latency period (min), median (IQ_{25-75})	120 (60-120)
Duration of symptoms (h), median (IQ_{25-75})	8 (5.7-10.5)
Food implicated, n (%)	
Crustacean	15 (60)
Fish	12 (48)
Cephalopods	5 (20)
Bivalves	5 (20)
N food groups implicated	
1	15 (60)
≥2	10 (40)
Atopy, n (%)	
Rhinoconjunctivitis	18 (72)
Asthma	4 (16)
Atopic dermatitis	3 (12)
Positive skin test to aeroallergens, n (%)	
Yes	18 (72)
No	7 (28)
Mites	11 (61.11)
Pollen	5 (27.77)
Danders	5 (27.77)

IQ, Interquartile range; *n (%)*, absolute frequency (relative frequency).

TABLE II. Descriptive analysis of adolescents and adults with food protein-induced enterocolitis-like syndrome caused by seafood

No.	Sex	Age at first reaction (y)	Age at last reaction (y)	Age at presentation	Diagnosis delay (y)	Food	Symptoms	No. of episodes	Latency period (min)	Duration of symptoms (h)	SPT/sIgE	OFC	Tolerance age (y)	Atopy
1	F	38	44	46	8	Bivalves	P, V, D, H	8	160	12	_	Clam: Positive P, V, D, H	No	Yes
2	F	25	40	42	17	Cephalopods	P, V, D	9	90	10	_	Squid: positive P, V, D	No	Yes
3	F	28	35	37	9	Fish	P, D, H	10	160	8	_	Tuna: Positive P, D, H Anchovy: positive P, D, H	No	Yes
4	F	21	21	23	2	Cephalopods	P, V, D	4	60	5	_	Squid: negative	Yes(23)	Yes
5	F	38	39	40	2	Bivalves, Tuna	P, D	4	240	6	_	<12 mo	No	Yes
6	F	25	44	46	21	Crustaceans	P, V, H, L	10	120	8	_	Shrimp: negative	Yes (46)	No
7	F	14	22	24	10	Fish, Crustaceans, Bivalves	P, V, D	10	90	12	_	Nd	No	Yes
8	F	16	18	19	3	Fish	P, D	8	120	12	_	<12 mo	No	Yes
9	F	35	37	38	3	Bivalves, Crustaceans	P, D	8	180	12	_	<12 mo	?	Yes
10	F	29	30	32	3	Fish, Crustaceans, Cephalopods	P, V	10	60	6	_	Nd	?	Yes
11	F	15	36	36	11	Crustacean	P, D	9	60	3	_	<12 mo	No	Yes
12	M	45	44	46	1	Fish	P, D	7	60	4	_	Hake: negative	Yes (47)	No
13	F	17	18	19	2	Fish, Crustaceans	P, V	10	120	4	_	Hake: positive P, V, L, H Shrimp: positive P, V, L, H	No	Yes
14	M	29	40	44	15	Crustaceans, Cephalopods	P, V	10	60	4	_	Nd	?	No
15	M	14	44	47	33	Crustacean	P, V, H	10	120	12	_	Nd	?	Yes
16	F	20	43	45	25	Crustacean	P, V, D, L, H	10	120	12	_	Nd	_	No
17	F	28	31	31	3	Crustacean, Blue whiting, Sardine	P, V	8	60	4	_	<12 mo	No	Yes
18	F	48	52	52	4	Fish	P, V, D, L	15	120	48	_	<12 mo	No	No
19	F	38	43	47	9	Barnacles, Clams	P, V, D	4	120	6	_	Nd	No	Yes
20	F	14	45	46	33	Fish, Crustaceans	P, V, H	10	120	6	_	<12 mo	No	No
21	F	30	37	38	8	Crustaceans	P, V, D	8	60	6	_	<12 mo	No	No
22	F	33	40	41	8	Crustaceans	P, V	5	90	10	_	<12 mo	No	Yes
23	F	46	50	52	6	Crustaceans, Cephalopods	P, V	5	90	10	_	Shrimp: negative Squid: negative	Yes (54)	Yes
24	F	48	53	54	6	Tuna, Anchovies	P, V, D	6	60	6	_	<12 mo	No	Yes
25	F	27	29	29	2	Tuna	P, V, D	5	120	8	_	<12 mo	No	Yes

D, Diarrhea; *F*, female; *H*, hypothermia; *L*, lethargy; *Nd*, not performed; *M*, male; *OFC*, oral food challenge; *P*, abdominal pain; *SPT/sIgE*, skin prick tests and specific IgE to the implicated food were performed in the first visit to our allergy section; *V*, vomiting; *<12 mo*, OFC was not performed when 2 or more reactions occurred in the last 12 months with the incriminated food or other related foods.

Fish, Bivalves, Cephalopods or Crustaceans: these terms were used if more than 2 species of the respective group produced symptoms. Species are specified when fewer than 2 foods of the class produced symptoms. Duration of symptoms refers to persistence of symptoms during the reactions.

patients each. Ten patients (40%) experienced symptoms with more than 1 group of foods.

In our cases of fish food protein−induced enterocolitis-like syndrome, most patients reported having symptoms with some species of fish (tuna, hake, anchovy, sardines) and tolerating others. In the case of crustaceans and mollusk, patients avoided all species, because of previous reactions with different related species.

We carried out 11 OFCs with the implicated food in 8 patients. Six patients refused OFC, whereas it was not considered necessary in 11 patients, who had recent reactions. Four patients developed tolerance; 3 of these achieved tolerance after a mean period of 3 years, whereas the remaining patient achieved it 21 years later. Since then, they have all eaten the food and other related foods of the same group, regularly. Symptoms persisted in 14 patients, some of whom had a long history (30+ years) of adverse reactions to foods. The absolute neutrophil count measured after positive challenge showed a median increase of 1050 cells/mm^3. Seventy-two patients had an atopic background with symptoms of allergic rhinitis in 18 patients, asthma in 4, and eczema in 3.

FPIES is considered a non−IgE-mediated reaction to foods that manifests in childhood as repetitive emesis, pallor, and lethargy, occurring 1 to 4 hours after ingestion of the offending food and occasionally followed by diarrhea.[2] Although traditionally considered a pediatric disorder, a few reports have recently been published in adults, with seafood standing out as the most common food eliciting a reaction.

In 2012, Fernandes et al[3] reported the case of a 53-year-old man who presented with vomiting, diarrhea, pallor, and hypotension after eating scallops. In 2014, Tan and Smith[4] published a retrospective study in 31 patients who presented gastrointestinal food hypersensitivity predominantly after ingestion of fish, crustaceans, and egg. In 2016, Zubrinich et al[5] published a case report with egg-induced FPIES; the same year Gleich et al[6] also published a retrospective study to identify shrimp tropomyosin−derived T-cell epitopes, finding that 21% of their shrimp-sensitive patients suffered exclusively delayed gastroenterological symptoms but had negligible IgE antibodies to shrimp.

The symptoms of FPIES usually resolve within 24 hours. In our series, the median symptom duration was 8 hours; however, 1 patient complained of abdominal pain for over 48 hours.

Although childhood FPIES is considered a self-limited disorder with a favorable evolution,[7] most of our patients had long histories of symptoms persistence, confirmed by OFC or accidental ingestion. At least a third of the patients presented symptoms for periods longer than 6 years and only a few achieved tolerance. The median number of episodes before diagnosis was 8; most patients avoided the causative food and did not seek medical care. This fact, together with the negativity of skin tests and specific IgE, plus the lack of the typical involvement of the skin or respiratory tract, suggests that this entity is underdiagnosed and that the prevalence is probably much higher.

Most patients had an atopic background (72%), a fact also reported by Tan and Smith,[4] although this finding may be prone to bias, as many patients were referred to our clinic for evaluation of other allergic conditions such as rhinitis and asthma and food hypersensitivity was diagnosed only after careful anamnesis.

The pathophysiology of FPIES is not well understood, although it is classically accepted as a cell-mediated disorder with involvement of specific T lymphocytes, monocytes, and cytokines.[8] The high percentage of atopic patients could suggest local production of IgE that would participate in the development of symptoms.

Otherwise, the factors inducing intolerance to previously unoffending foods are unknown, as are the reasons for the high prevalence in females, also reported by Tan and Smith.[4] Hormonal factors, together with the pattern of seafood ingestion, could contribute to the loss of tolerance.

We report a series of 25 patients older than 14 years of age with exclusive gastrointestinal symptoms appearing 1 to 4 hours after seafood ingestion and resembling FPIES. However, we found some differences with respect to childhood FPIES: clinical manifestations were not as dramatic,[9] with only 7 patients requiring emergency care. All patients had abdominal pain, but only 76% had vomiting and 64% diarrhea. These findings are similar to those reported in adults by Tan and Smith.[4] Thus, vomiting, the main criterion for diagnosing FPIES,[7] was absent in a fourth of our patients. Assuming that this is in fact the same entity, our results suggest that the same criteria may not apply to the adult population. Rather, abdominal pain combined with either vomiting or diarrhea would be the primary clinical signs, whereas hypothermia or lethargy would be clinical features supporting the diagnosis. In conclusion, larger studies are needed to better understand this entity in adult patients, evaluate its prevalence and pathophysiology, and assess whether it is indeed consistent with the syndrome described in childhood.

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