

Allergic reactions to *anisakis simplex* parasitizing seafood

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Background: The ingestion of Anisakidae ssp larvae parasitized fish can cause anisakiasis. Allergic reactions after ingestion of safely cooked but parasitized fish have been reported.

Methods: Twenty-three patients who suffered allergic reactions after seafood ingestion, with negative skin tests were studied. *Anisakis simplex* sensitization was assessed by skin prick test and/or specific serum Immunoglobulin E (IgE). Total serum IgE and specific IgE against the implicated seafood and *Ascaris lumbricoides* were also determined.

Results: Manifestations of *Anisakis simplex* allergy were urticaria/angioedema (18/23) patients and anaphylaxis (5/23). Gastric symptoms were also observed (3/23). Sea fish and shellfish were implicated. Raw and cooked seafood ingestion caused reactions. Total serum IgE ranged from 13 to 7200 KU/L. Specific IgE to *Anisakis simplex* was positive (>0.35 KU/L) in all patients, and skin tests were positive in 20. Serum-specific IgE and skin tests to the involved seafoods were negative in every patient. Serum-specific IgE to *Ascaris lumbricoides* was negative in 13 patients. No association between total IgE and the eosinophil count ($r < 0.1$) was observed, but there was some association between total IgE and specific IgE to *Anisakis simplex* ($r = 0.58$).

Conclusion: *Anisakis simplex* sensitization is the cause of allergic reactions after seafood ingestion. It is important to pay attention to this new "food allergy" to diagnose correctly the etiology of adverse food reactions.

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INTRODUCTION

Anisakis simplex is a nematode of the Anisakidae family, Ascaridoidea superfamily, Ascaridida order that parasitizes, in its adult stage, sea mammals (whales, seals, dolphins, and sea lions). It can, however have several intermediary hosts. Any fish or cephalopod can be parasitized by *Anisakis simplex*. The more frequently parasitized species are codfish, hake, sardine, anchovy, salmon, red mullet, tuna, mackerel, horse mackerel, and squid.¹ The larvae are ingested by sea fish or cephalopods where they develop the third larval stage. The ingestion of Anisakidae ssp third-stage larvae can

cause the human disease known as anisakiasis. The human being acquires the larvae by eating raw or undercooked seafood (smoked fish, salted seafood, pickled or similarly prepared sea fish) or cephalopods that contain the third-stage larvae of *Anisakis simplex*.^{2,3}

After ingestion, *Anisakis* larvae can be invasive, penetrating host stomach or intestinal wall. Acute anisakiasis is probably caused by allergic reactions type I and/or III in the digestive tract mucus with abdominal pain and eosinophilic infiltration.⁴ The chronic anisakiasis form results from the invasion that causes abscess or eosinophilic granulomas. This form can mimic appendicitis, gastroduodenal ulcer, eosinophilic colitis, inflammatory bowel disease, and intestinal obstruction. Some rare cases of anisakiasis affecting lung, spleen, pancreas, and liver have been reported.⁵

Although anisakiasis is not as common in Europe as in Japan,^{2,3} changes in European eating habits have caused an increase in cases reported in Europe, including Spain.^{6–8}

The best treatment for anisakiasis is prophylaxis. The larvae do not resist a temperature higher than 60 °C for 10 minutes, or lower than –20 °C for 24 hours. Nevertheless, the ingestion of safely cooked sea fish, without viable larvae, has been reported in 1990 as a cause of urticaria.⁹ The development of serologic tests for antibodies to *Anisakis simplex* are useful tools for the study of allergic reactions to this parasite and for diagnosis of anisakiasis.¹⁰

There are other reports of patients with allergic reactions after seafood ingestion with negative skin test to fish or shellfish, and positive serum-specific IgE or positive skin tests to *Anisakis simplex*.^{11–14}

We report 23 cases of immediate hypersensitivity to *Anisakis simplex* studying their characteristics and providing our experience in the recognition of this new form of "food allergy." The reactions reported resulted from ingesting the intermediary host.

METHODS AND PATIENTS

Patients

Inclusion criteria were symptoms suggesting allergy such as urticaria, angioedema, and/or anaphylaxis (more than two organs involved in a life-threatening reaction) less than three hours after the ingestion of seafood, with negative skin tests to the seafood involved in the reaction. Sensitization to *Anisakis simplex* was demonstrated by positive skin prick test and/or positive serum-specific immunoglobulin E (IgE) to *Anisakis simplex* extract (CAP system; Pharmacia, Uppsala, Sweden).

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Some patients could identified a “little worm” in their raw seafood. Twenty-three patients were included in the study.

Fiberoptic gastroscopy was performed in three patients who had gastrointestinal manifestations also. Positive personal history of atopy was established when other atopic diseases such as atopic dermatitis, asthma, or rhinoconjunctivitis, had been previously observed by the patients, or they showed positive results to a battery of also allergens and food allergens.

Skin Tests

Skin prick tests with the implicated seafood extracts were performed on the volar side of the forearm according to the sub-committee on skin tests of the European Academy of Allergy and Clinical Immunology.¹⁵ *Anisakis simplex* extract (1 mg/mL) was obtained from International Pharmaceutical Im-

munology, I.P.I. (Madrid, Spain). Histamine chlorohydrate (10 mg/mL) and normal saline solution were used as positive and negative controls, respectively. The maximum wheal diameter and its orthogonal perpendicular were measured 15 minutes after the skin prick, and the mean of both diameters was taken as the test size. A mean wheal diameter at least 3 mm larger than that produced by the negative control was considered positive.¹⁵

“In vitro” Tests

Total serum IgE was assessed by MEIA-IMX system (Abbot Diagnostics, Chicago, Illinois) according to the manufacturer’s instructions.

Serum-specific IgE was determined against the implicated seafood, *Anisakis simplex*, and *Ascaris lumbricoides* by CAP system (Pharmacia Diagnostics, Upsala, Sweden). Results

over 0.35 KU/L were considered as positive.

Statistical Analysis

The geometric means of total IgE and specific IgE to *Anisakis simplex* were calculated. The association between specific IgE to *Anisakis simplex* and total IgE values; and between total and specific IgE, and blood eosinophils/mm³, was assessed by Pearson correlation test.

RESULTS

The results are described in Table 1. The mean age of our patients was 47 years (range 18 to 72 years). There were nine men and fourteen women. A personal history of atopy was found in six of them. Clinical manifestations of *Anisakis simplex* allergy were orofacial angioedema in three patients, generalized urticaria and angioedema in ten,

Table 1. Characteristics of the Patients, Symptoms, Skin Tests, Eosinophil Counts, and Serologic Findings

Age, yr	Sex	Symptoms*	Seafood Intake	Seafood Skin Test	Anisakis Skin Test	IgE to Anisakis	IgE to Ascaris†	Total IgE, KU/L	Atopy	Eosinophils/mm ³
44	m	U/Ae	CF/CSH	—	+	C4/31.3 KU/L	C0	94	NO	109
62	m	U/Ae	RF/CF	—	+	C4/47.4 KU/L	C2	742	NO	200
55	m	U/Ae	RF/CF	—	+	C5/86.0 KU/L	C3	449	NO	232
45	f	U/Ae	CF	—	+	C3/5.46 KU/L	C0	135	NO	390
32	f	U/Gastr	CSH	—	—	C3/11.4 KU/L	C0	410	YES	158
65	f	Ae	RF/CF	—	—	C2/1.69 KU/L	C0	1007	NO	203
49	f	U/Gastr	RF/CF	—	+	C6/>100 KU/L	C4	7200	NO	220
18	f	U	RF	—	+	C3/6.64 KU/L	C0	282	YES	188
59	f	U	CF	—	+	C5/50.3 KU/L	C2	429	YES	202
20	m	U/Ae	CSH	—	+	C3/7.97 KU/L	C1	113	YES	162
38	m	ANPHX	RF/CF	—	+	C6/>100 KU/L	C4	606	NO	180
25	m	U/Ae	CF/CSH	—	+	C4/29.8 KU/L	C0	117	NO	88
60	f	ANPHX	CF‡	—	+	C5/67.0 KU/L	C2	200	NO	190
49	f	U	RF	—	—	C1/0.55 KU/L	C0	13	NO	10
68	m	Ae	CF	—	+	C3/13.7 KU/L	C0	98	NO	91
28	f	U/Ae	RF	—	+	C3/8.54 KU/L	C0	80	YES	210
47	f	ANPHX	CF	—	+	C3/10.4 KU/L	C0	234	YES	531
29	f	U/Ae	CF	—	+	C5/63.8 KU/L	C2	723	NO	630
72	m	Ae	CSH	—	+	C3/13.2 KU/L	C0	190	NO	290
51	m	U/Ae	CF	—	+	C3/16.2 KU/L	C0	166	NO	320
62	f	U/Ae	RF	—	+	C3/14.3 KU/L	C1	306	NO	300
52	f	ANPHX	RF	—	+	C4/46.3 KU/L	C2	233	NO	100
47	f	ANPHX/Gastr	RF	—	+	C2/3.20 KU/L	C0	14	NO	250

* U: urticaria, Ae: angioedema, ANPHX: anaphylaxis, Gastr: gastric symptoms, CF: cooked fish, RF: raw fish, and CSH: cooked shellfish.

† C0 < 0.35 KU/L, C1 = 0.35–0.70 KU/L, C2 = 0.70–3.5 KU/L, C3 = 3.5–17.5 KU/L, C4 = 17.5–50 KU/L, C5 = 50–100 KU/L, and C6 > 100 KU/L.

‡ In this patient, cooked fish was previously frozen for three days. Raw fish in all patients was anchovy in vinegar sauce. Cooked fishes were salmon, hake, red mullet, and sardine.

generalized urticaria in five, and systemic anaphylaxis in five. Gastric symptoms were also observed in three persons.

Several patients had tolerated the implicated seafood between the different allergic episodes. Sea fish were implicated in 18 patients. Shellfish were the cause of reactions in five patients. Raw or undercooked seafood was the cause of the reaction in 11 patients and cooked seafood in 18. A patient ate the cooked fish that caused illness after having frozen it for 48 hours. The most frequently involved raw fish was anchovy in vinegar sauce (frequently eaten in Spain). The cooked fish were salmon, hake, red mullet, and sardine.

The peripheral blood eosinophil count ranged from 10 to 689 cell/mm³ (mean: 228 and SD: 139). Total serum IgE ranged from 13 to 7200 KU/L (geometric mean: 250.25 KU/L). There was no observed significant association between levels of total IgE and the eosinophil count ($r < 0.1$).

Serum-specific IgE to *Anisakis simplex* was positive (>0.35 KU/L) in all patients. Its levels ranged from 0.55 to 100 KU/L (geometric mean: 17.022 KU/L).

There was some association between levels of total IgE and the levels of specific IgE to *Anisakis simplex*. ($r > 0.58$).

The skin prick test to *Anisakis simplex* was positive in 20/23 patients.

Serum-specific IgE levels to fish and seafood; and skin prick tests to them were negative in all patients. Serum-specific IgE to *Ascaris lumbricoides* was positive in ten patients and negative in 13 patients.

Fiberoptic gastroscopy was performed in three patients with digestive symptoms added to allergic symptoms. Two of them had normal findings and the other had a linear erosion in gastric mucosa that disappeared by the time of repeat gastroscopy after 24 hours without treatment.

A matched series of 23 people who usually ate raw and cooked fish or shellfish without any problem were skin tested with *Anisakis simplex* ex-

tract and tested by in vitro techniques for identification of specific IgE to *Anisakis simplex*. All had negative skin prick tests only one had a positive specific IgE to *Anisakis simplex*, (0.69 KU/L). We considered this patient as sensitized without symptoms.

DISCUSSION

Nematodes frequently parasitize sea fish. Anisakidae family members look like a white worm with length from 1 to 3 cm, and 1 mm diameter, their larvae can parasitize a great variety of sea fish and cephalopods.^{2,3} Human beings can be parasitized by *Anisakis simplex* accidentally.^{2,3}

In our experience, there were patients who had very suggestive symptoms of allergy to seafood (anaphylaxis, urticaria, angioedema, or some other symptoms after seafood ingestion) but without evidence of specific IgE to the implicated food (negative skin tests and negative serum specific IgE).

Paradoxically these seafoods have been well tolerated sometimes between the allergic episodes. Our study indicates that these symptoms could be caused by *Anisakis simplex* parasitization of the seafood. Thermostability of allergens of *Anisakis simplex* has been previously confirmed and explains the clinical manifestations after ingestion of cooked or frozen seafood. Heated and deep-frozen extracts of *Anisakis simplex* can detect specific IgE by skin testing and in vitro techniques.¹¹⁻¹⁴

The existence of allergic symptoms after seafood ingestion with negative skin tests to them, and positive skin tests and/or positive serum-specific IgE to *Anisakis simplex* extract corroborates *Anisakis simplex* allergy as the cause of the reactions.¹¹⁻¹⁴

Obviously the evidence for this hypothesis is circumstantial. It is based on the sensitization that we have demonstrated, on the knowledge that some species of fish and seafoods are frequently contaminated with *Anisakis* species, and on the relation of the reaction to the ingestion of fish and seafood. A double-blind, placebo-con-

trolled food challenge with parasitized seafood was thought unethical. A double-blind placebo-controlled food challenge with noninfecting extract could be a possible ethical solution.

Our patients have not had typical characteristics of food allergy with respect to atopy and age.¹⁶ Food allergy is more frequent in younger people and there is usually a personal history of atopy; however, the mean age of our patients is older (47 years), and few (only 6) have had personal histories of atopy, which agrees with previous reports.^{11,12,14}

Anisakis simplex can cause severe symptoms of allergy, including marked anaphylaxis. The most frequent clinical manifestation of *Anisakis simplex* allergy is urticaria with or without facial angioedema. Gastric symptoms were also observed in three patients. This is different from previous reports where more patients had gastric symptoms in addition to the other allergic symptoms.¹¹

In our study, the peripheral blood eosinophil count usually remained at or below the normal range. Blood eosinophils are often increased in other parasitic diseases but our work agrees with other reports about *Anisakis simplex* allergy^{11,12} where eosinophils were also within the normal or low range; this could be due to recruitment of the eosinophils to the inflammatory tissues.¹⁷

Total serum IgE ranged from 13 to 7200 KU/L (geometric mean: 250.25 KU/L). The total IgE showed a marked variability with ten patients with values <200 KU/L; eight patients with values ranging from 200 to 700 KU/L; and five patients with values >700 KU/L, one with 7200 KU/L. This variability in our results is different from other reports where patients have often had high levels of total serum IgE.^{11,14}

The patient with the extremely high IgE was a woman with intense urticaria and gastric symptoms after ingesting raw or cooked sea fish. A fiberoptic gastroscopy for possible parasitic invasion was negative.

The erosion of the gastric mucosa in the other patient was considered a local

reaction after contact with live *Anisakis simplex* larvae because the reaction occurred after ingestion of raw fish (anchovy in vinegar sauce).

Fiberoptic gastroscopy could be useful in patients with allergic reactions after raw or undercooked seafood ingestion who have severe gastric symptoms so to act to prevent penetration of live larvae into the gastric mucosa. We believe these patients are developing a systemic IgE-mediated reaction (caused by their sensitization to *Anisakis simplex*) and a local gastric reaction that could be also IgE mediated.⁴ This local reaction (and their gastric symptoms) could indicate when the larvae are trying to fix and penetrate the gastric mucosa.

Some authors have suggested the existence of cross reactivity between *Anisakis simplex* and other Ascaridida order worms such as *Ascaris lumbricoides*.¹¹ In our study, more than 50% of patients had no evidence of cross reactivity because they (13/20) had negative specific IgE to *Ascaris lumbricoides*. This difference could be due to fewer patients in other reports, or to different distribution of *Ascaris lumbricoides* in their geographic areas, or to the fact that the causative allergen of *Anisakis simplex* allergy is not present in sufficient quantity in these other worms, or to the presence of more than one allergen causing *Anisakis simplex* hypersensitivity.

Seafoods from European fishing grounds are strongly parasitized by nematodes, including early 80% of blue whiting fish (*Micromesistius poutassou*), and 45% of hakes (*Merluccius merluccius*).¹⁸ Our study demonstrates, as described in other reports, that in some cases the ingestion of frozen or cooked seafood (recommended for prophylaxis of Anisakiasis) does not protect against IgE-mediated symptoms due to *Anisakis simplex* allergy.^{9,11,14}

All our controls had negative skin prick tests and only one had a positive specific IgE to *Anisakis simplex* (0.69 KU/L). We considered this patient sensitized without symptoms. We consider that *Anisakis simplex*, like other

food allergens, can sensitize some people without symptoms. In previous reports a great number of controls did not elicit any reaction.¹³

We report 23 patients with allergic reactions after seafood ingestion due to *Anisakis simplex* allergy, including severe anaphylaxis. We recommended a diet without seafood.

Anisakis simplex allergy should be suspected in patients with allergic reactions after seafood ingestion, especially if the same seafood has been tolerated on other occasions and if specific IgE to the involved seafood has not been possible to demonstrate either by skin nor in vitro tests. Clinical history and demonstration of IgE to this parasite confirmed the diagnosis. The nonseafood diet controlled the symptoms of our patients. *Anisakis simplex* allergy may permit accurate diagnosis and effective treatment of many previously undiagnosed or idiopathic reactions.

Further studies are needed to assess the allergenicity of *Anisakis simplex* and its cross reactivity with other nematodes. It is important to pay attention to this new food allergy and to invasive anisakiasis in order to encourage possible governmental control of human consumption of nematode-parasitized seafood.

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REFERENCES

1. Cheng TC. Parasitologia General. Madrid; Superfamilia Heterocheiloidea, 1978;649–51.
2. Ishikura H, Kikuchi K, Nagasawa K, et al. Anisakidae and anisakidosis. Progr Clin Parasitol 1994;3:43–101.
3. Van Thiel PH, Kuipers FC, Roskam RTH. A nematode parasitic to herring causing acute abdominal syndromes in man. Trop Geogr Med 1960;2:97–113.
4. Asaishi K, Nishino C, Totsuka M, et al. Studies on the etiologic mechanism of anisakiasis. (1) Immunological reac-

tions of digestive tract induced by anisakis larvae. Gastroenterol Jpn 1980; 15(2):128–34.

5. Sakanari JA, Mckerrow JH. Anisakiasis. Clin Microbiol Rev 1989;2: 278–84.
6. Mudry J, Lefevre P, Dei-Cas E, et al. Anisakiae Humaine: 5 cas dans le nord de la France. Gastroenterol Clin Biol 1986;10:83–7.
7. Lucas SB, Cruse JB, Lewis AAM. Anisakiasis in the United Kingdom. Lancet 1985;1:843–4.
8. Mira Gutierrez J, Garcia Martos P, Hilarrio Madrid LM, Rodriguez Iglesias MA. Anisakiasis, una patologia emergente en nuestro medio. Rev Clin Esp 1995;195:51–4.
9. Kasuya S, Hamano H, Izumi S. Mackerel-induced urticaria and anisakis. Lancet 1990;335:665.
10. Desowitz RS, Raybourne RB, Ishikura H, Kliks MM. The radioallergosorbent test (RAST) for serological diagnosis of human anisakiasis. Trans R Soc Trop Med Hyg 1985;79:256–9.
11. Audicana MT, Fernandez de Corres L, Muñoz D et al. Anisakis simplex: una nueva fuente de antígenos “alimentarios.” Estudio de sensibilización a otros parásitos del orden ascarididae. Rev Esp Alergol Immunol Clin 1995; 10:325–31.
12. Audicana MT, Fernandez de Corres L, Muñoz D, et al. Anisakis simplex a new sea-food allergen. Allergy 1995; 50(Suppl 26):127.
13. Audicana T, et al. Recurrent anaphylaxis caused by Anisakis simplex parasitizing fish. J Allergy Clin Immunol 1995;96:558–60.
14. Del Pozo MD, Moneo I, Fernandez de Corres L, et al. Laboratory findings in *Anisakis simplex* allergy. J Allergy Clin Immunol 1996;97:977–84.
15. Dreborg S, ed. Skin tests used in type I allergy testing. Position paper. Allergy 1989;44(Suppl 10):1–59.
16. Sastre Dominguez J, Cuesta J, Diaz MA, et al. Alergia a alimentos. In: Sociedad Española de Alergología e Inmunología Clínica, and Laboratory ABELLO Eds “Alergológica: Factores epidemiológicos clínicos y socioeconómicos de las enfermedades alérgicas en España”. Madrid 1995:163–185.
17. Jones RE, Deardorff TL, Kayes SG. Anisakis simplex: histopathological changes in experimentally infected CBA/mice. Exp Parasitol 1990;70: 305–13.

-
18. Pereira Buena, JM. Algunos aspectos de la epidemiología y prevención de la anisakiasis. Revisión de biología del parásito; anisakiasis, diagnóstico, tratamiento, estudio de prevalencia de parasitación de las especies de pescado

de consumo en nuestro país y normativa sanitaria. Junta de Castilla y León (Government of Castile, Spain). Eds. Consejería de de Sanidad y Bienestar Social. Valladolid, 1992,1–56.

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RELATIONSHIP OF COMMUNICATION PATTERNS TO PATIENT AND PHYSICIAN SATISFACTION

The authors analyzed audiotapes of routine followup visits of adult patients with ongoing medical problems to determine communication patterns of 127 physicians with 537 patients. Patients and physicians completed questionnaires that included indications of satisfaction with the visit. The physicians included 35 residents and 60 physicians board certified in internal medicine.

Five communication patterns accounted for 95% of visits and 99% of physicians. The narrowly biomedical pattern, which accounted for 32% of visits and was used at least once by 68% of physicians, was notable for very little physician (2%) and patient (5%) talk devoted to psychosocial topics and high percentage of biomedical information given by physicians (27%) and patients (70%). An expanded biomedical pattern, which accounted for 33% of visits and was used at least once by 61% of physicians, had more moderate levels of biomedical and psychosocial exchange. The biopsychosocial pattern, evident in 20% of visits and used by 42% of physicians, had a balance between biomedical and psychosocial exchange although physicians' communication was still predominantly biomedical (23% compared with 11% psychosocial talk). A psychosocial pattern (7% of visits, 19% of physicians) was dominated by psychosocial exchange; physician talk was 20% psychosocial and 19% biomedical while patients' talk was 55% psychosocial and 25% biomedical. A consumerist pattern (8% of visits, used at least once by 23% of physicians) suggested use of the physician as consultant who answered questions rather than one who asked them and had the highest frequency of information transmission by the physician (43%) and low levels of psychosocial and social exchange.

The average length of the medical visit was 21 minutes (range 2.8 to 73.8 minutes). Narrowly biomedical visits averaged 20.5 minutes; expanded biomedical visits, 21.8 minutes; biopsychosocial visits, 19.3 minutes; psychosocial visits 22.9 minutes; consumerist visits, 21.9 minutes.

Biomedically focused visits were used more often with patients who were more sick, older, and of lower income and were used more often by younger, male physicians. Physician satisfaction was lowest for the narrowly biomedical pattern and highest for the consumerist pattern; patient satisfaction was highest for the psychosocial pattern.

It is not entirely clear what relevance these primary care followup visit data may have to allergy consultation visits, but it is noteworthy that patient-centered visits during which psychosocial issues were addressed were not more time-consuming than more biomedically oriented visits. Shorter appointments might reduce the time devoted to psychosocial issues. This would reduce patient satisfaction and might reduce physician satisfaction.

—RMS

Roter DL, Stewart M, Putnam SM, et al. Communication patterns of primary care physicians. *JAMA* 1997;277:350–6.