

Occupational disease due to *Anisakis simplex* in fish handlers

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ABSTRACT

Background: *Anisakis* is a marine nematode. Its larvae can be found encysted in several species, both in the abdominal cavity and in the adjacent musculature. The most commonly affected commercial species are hake, whiting, cod, and mackerel. The prevalence in fish varies according to the fishing area and the size of the host.

Materials and methods: Until now only three species have been confirmed to be involved in human anisakiasis, the most common ones being *A. simplex sensu stricto* (s.s.) and *A. pegreffii*, and anecdotally, *A. physeteris*. Infestation in humans occurs when they eat raw or undercooked parasitized fish or cephalopods (pickled, cold-smoked, salted, semi-preserved, prepared in certain Asian styles like sushi or sashimi, ceviche).

Results: The majority of anisakiasis cases have been described by Japanese authors. However, over the last few years there has been an increase in the number of cases reported in other countries including Italy and Spain. It is estimated that its incidence in the European Union is 0.32/100,000, and in the Basque Country (Spain), this parasite is responsible for 10% of anaphylaxis cases and 32% of urticaria cases in adults aged 40–60 years, around 300 cases/year. *Anisakis*-related disease in the work environment (occupational disease) is less common.

Conclusions: We present three cases of the occupational disease in Spain due to a type I hypersensitivity to *Anisakis simplex* in individuals who handle fish (one fishmonger, one supermarket employee, and one chef).

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Key words: *Anisakis*, occupational disease, type I hypersensitivity, acute urticaria, protein contact dermatitis

INTRODUCTION

Anisakis is a marine nematode. Its larvae can be found encysted in several species, both in the abdominal cavity and in the adjacent musculature. Large marine mammals (cetaceans and pinnipeds) are the natural definitive host, and the parasite matures to its adult stage in the gastrointestinal tract, from where its unembryonated eggs are released in the host's faeces. The eggs then embryonate in the marine environment and the larvae mature in encapsulated phases (L1-2/L3), at a variable speed depending on the water temperature (4 to 8 days if between 13 and 18 °C, 57 to 82 days

if below 5 °C) [1], until they begin the “free-swimming” L3 phase, in which they are still encapsulated, but can infect microcrustaceans, crustaceans, fish, and cephalopods. Copepods (microcrustaceans) and euphausiids (crustaceans – krill) act as intermediate hosts, and fish (teleosts) and cephalopods (squid in particular) are paratenic hosts, that is, while the larvae are transmitted through predation between fish and squid, they remain in L3, and if they are ingested by definitive hosts, they mature into L4 and the adult phase. If ingested by humans who have eaten infected fish, the larvae will only develop as far as stage L4 (Fig. 1) [2].

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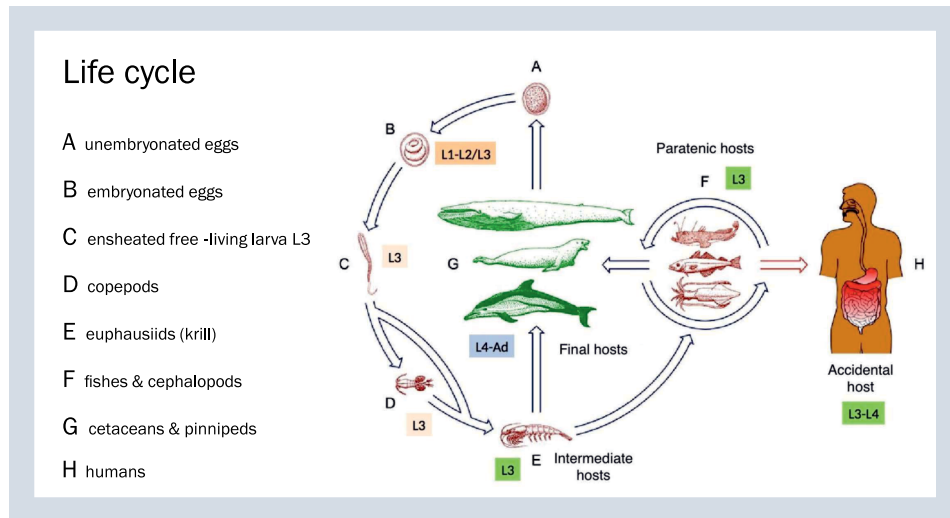


Figure 1. Life cycle of *Anisakis* spp. Source: By courtesy of F.M. Ubeira. Parasitology Laboratory. Santiago de Compostela University, Spain [2]

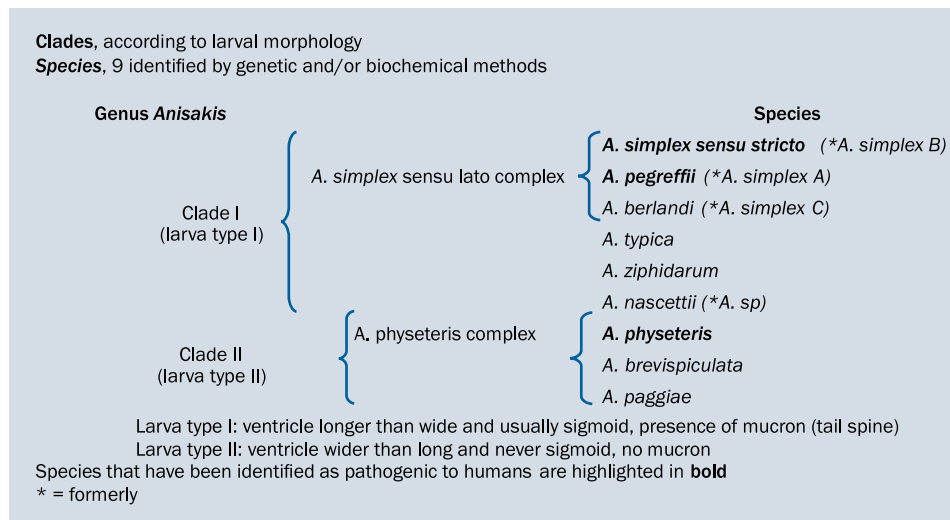


Figure 2. The different species of *Anisakis*. Source: Prepared by the authors, based on Bao Domínguez M, Thesis [9] and Iglesias R et al. [10]

GEOGRAPHICAL DISTRIBUTION

Anisakis are found from the Arctic Circle (66° 33' 46" N) to 50° S, the species varying depending on the latitude. *Anisakis simplex sensu stricto* (s.s.) is found between the Arctic Circle and 35° N, except for the Mediterranean Sea, where the prevalent species is *A. pegreffii*, also found between 35° N and 50° S latitude [3].

The most commonly affected commercial species are hake, whiting, cod, and mackerel, but the parasite has also been identified in a large variety of fish such as sole, john dory, sea bream, horse mackerel, herring, blue whiting, sardine, anchovy, haddock, monkfish, salmon, conger, and turbot, and in cephalopods, such as squid, octopus and cuttlefish [4–7]. We should also point out that studies confirm that the preva-

lence in fish varies according to the fishing area and the size of the host, with larger fish having more infestations [7, 8].

The different species identified are listed in Figure 2 [9, 10]; it is difficult or even impossible to differentiate the larval morphology based on microscopy alone.

PATHOGENESIS

Until now only three species have been confirmed to be involved in human anisakiasis, the most common ones being *A. simplex* s.s. and *A. pegreffii*, and, anecdotally, *A. physeteris*. The geographic distribution of *A. simplex* s.s. and *A. pegreffii*, the species that are responsible for almost all cases of the disease described in humans, is presented in Figure 3 [10].

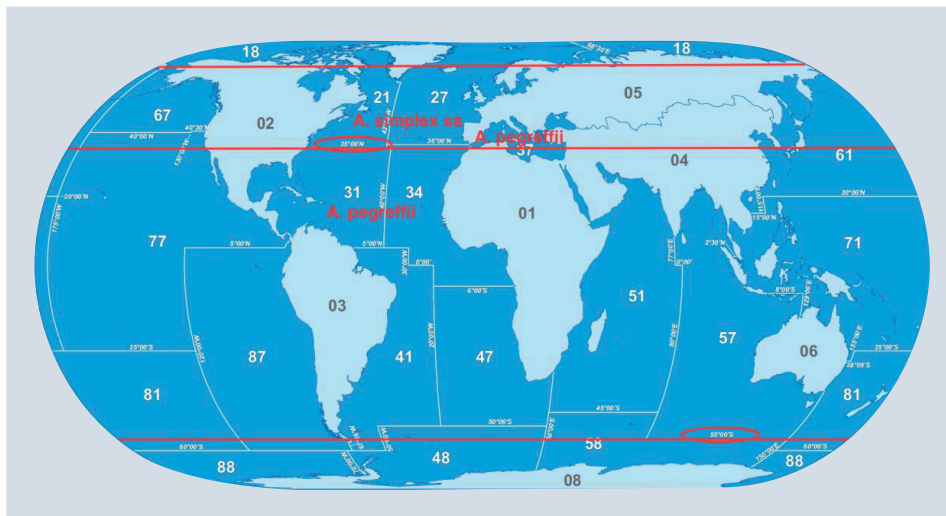


Figure 3. Distribution of *Anisakis* spp. Source: Prepared by the authors, based on FAO Fisheries map and Iglesias R et al. [10]

Infestation in humans occurs when they eat raw or undercooked parasitized fish or cephalopods, that is, those prepared with culinary techniques that do not kill the larvae. Thus, products that are pickled, cold-smoked, salted, semi-preserved, prepared in certain Asian styles (e.g. sushi, sashimi), or products such as ceviche, are responsible for practically all associated infections.

The first case of human infection by a species of the Anisakidae family was reported in the Netherlands by Van Thiel in 1960. The author described the presence of a marine nematode in the centre of an eosinophilic intestinal phlegmon from a patient suffering from acute abdominal pain, as a “very unusual finding.” Later the nematode was identified as *Anisakis* spp., a common parasite of marine fishes and mammals, and the human parasitosis was named anisakiasis. Since then, the majority of anisakiasis cases have been described by Japanese authors, reflecting the frequent consumption of raw fish in that country [11].

However, over the last few years there has been an increase in the number of cases reported in other countries including Italy [8, 12] and Spain [6, 13].

The parasitic disease is caused by larvae in the gastrointestinal tract following the ingestion of infected fish, in which the larvae are still alive and can hook onto the walls of the gastrointestinal tract. This parasitic infection may present in two ways:

- non-invasive or luminal form: the parasite attaches to the stomach wall causing gastritis or even perforation, and in some cases migrating to the small intestine causing symptoms of enteritis, intestinal obstruction, or malabsorption syndrome;
- invasive form: the larvae attach to and penetrate the intestinal mucosa and occasionally invade other organs (pancreas, liver, lungs) causing more severe symptoms.

The most common symptoms are those of intestinal inflammation: abdominal pain, nausea, vomiting, diarrhoea, and sometimes fever. Endoscopy is the most effective diagnostic technique and can also be used therapeutically. It can also be helpful to perform total IgE serology testing, which is elevated in acute parasitic infection and decreases gradually, or *Anisakis*-specific IgE which increases in the first days of reinfection and remains high for months. Abdominal ultrasound or computed tomography can raise suspicion of the disease in cases of very active parasitic infection.

Involvement of the respiratory tract has also been described but is rare. One report describes “two patients that provide evidence for occupational asthma caused by *A. simplex*, based on *in vivo* and *in vitro* tests for *Anisakis*-specific IgE” [14].

Anisakiasis is a well-known, common, frequently-described disease. It is estimated that its incidence [15] in the European Union is 0.32/100 000, and in the Basque Country [16], this parasite is responsible for 10% of anaphylaxis cases and 32% of urticaria cases in adults aged 40–60 years, around 300 cases/year. *Anisakis*-related disease in the work environment (occupational disease) is less common.

We present three cases of occupational disease due to a type I hypersensitivity to *Anisakis simplex* in individuals who handle fish (one fishmonger, one supermarket employee, and one chef).

CASE REPORTS

CASE 1

The first case was a 47-year-old woman, who had been working as a fishmonger for 27 years. She had a history of sensitivity to cobalt, nickel, and hair dyes, and had smoked 8 cigarettes per day for 25 years.

Table 1. Complete battery of foods (Abelló and Allergy Therapeutics laboratories)*

Egg and egg proteins (white, yolk, ovalbumin, ovomucoid)
Cow's milk and allergenic proteins (alpha-lactalbumin, beta-lactoglobulin, casein)
Nuts and cereals (peanut, almond, walnut, hazelnut, pine nut, chestnut, sunflower seeds, wheat, rye, barley, oat, cacao)
Wheat gluten, legumes (soya, haricot bean, lentils, chick-peas)
Meats (rabbit, pork, chicken, turkey)
Fish and seafood (mixture of white fish, mixture of oily fish, mackerel, tuna, cod, hake, sole, salmon, prawn, crab)
Vegetables (potato, tomato, peas, carrot, onion, spinach, celery)
Fruits (peach, apple, cherry, orange, strawberry, banana)
Spices (cumin, aniseed, bay leaf, black pepper, white pepper, curry, nutmeg, saffron, parsley, mustard, sesame)

*Controls: ALK Abelló laboratory: positive – histamine hydrochloride 10 mg/mL; negative – glycerinated saline

She reported a 1-year-history of pruritus and wheals, occurring predominantly on the upper limbs while at work, with remission of symptoms at weekends, during holidays, and while off work due to illness.

A skin prick test was performed with a complete battery of food allergens (Table 1), with negative results. Prick test (ALK Abelló laboratory) was negative to latex and positive to *Anisakis simplex* (12 × 15 mm papule; positive if ≥ 3 mm). She had a positive result of 11 × 12 mm to histamine hydrochloride and a negative response to glycerinated saline.

In vitro testing for specific IgE to *Anisakis simplex* (UniCAP; Pharmacia) was clearly positive with a result of 48 KU/L (positive if > 0.35 KU/L).

The diagnosis was compatible with recurrent acute urticaria due to type I hypersensitivity to *Anisakis simplex*.

CASE 2

The second case was a 38-year-old woman with no relevant past personal or family medical diseases. She was a non-smoker, with no alcohol or drug abuse. She had been working in a supermarket for 10 years, specifically, in the delicatessen, butcher's, and fish sections.

The patient reported that in the previous 6 weeks she had had two acute outbreaks of wheals with intense pruritus, on both occasions when she was working in the fish section.

In the first episode she had pruritic wheals on the hands and various parts of the body. Symptoms improved 6 hours after treatment with oral antihistamines and corticosteroids.

Twelve days later, also while working in the fish section, she had a second episode of widespread wheals and intense pruritus. She was given 5 days of oral antihistamines and corticosteroids. The patient reported that she could not link the symptoms with ingestion of any foodstuff, and that she did not have any symptoms when working in the butcher or delicatessen sections. She was not taking any medications.

A complete food skin prick test was performed (Table 1), which was negative. Prick test was also negative to latex and to additives used in the meat industry (Table 2). A prick by prick test for cereals used in minced meat was also negative.

Table 2. Battery of additives used in the meat industry

Sodium nitrite E250
Ascorbic acid E300
BHA E320
BHT E321
Sodium benzoate E211
Xanthan gum E415
Carrageenan E407
Carboxymethyl cellulose (cellulose gum) E466
Dicalcium diphosphate E450 (vi)
Monosodium glutamate E621
Lactose
Aspartame E951

Skin prick test was positive to *Anisakis simplex* (ALK Abelló laboratory), causing a 6 × 7 mm papule (positive if ≥ 3 mm); the response to histamine was 7 × 9 mm and to glycerinated saline, was negative.

In vitro tests detected a mildly positive response for *Anisakis simplex*-specific IgE (UniCAP; Pharmacia) of 0.6 KU/L (positive if > 0.35 KU/L).

The diagnosis was compatible with acute urticaria due to type I hypersensitivity to *Anisakis simplex*.

CASE 3

The third case was a 37-year-old man, who had been working as a chef in a restaurant for 7 years. He had a history of seasonal rhinitis and had smoked 20 cigarettes per day for 18 years.

In the past 6 months he had had pruritic microvesicular lesions on both hands with interphalangeal and palmar fissures.

He reported that at work he handled fish, cephalopods (mainly cuttlefish) and crustaceans (prawns), and that his symptoms improved when he was not working.

Skin prick tests with the complete battery of foods (Table 1) were performed, with negative results. Prick test to latex was also negative.

Prick test to *Anisakis simplex* (ALK Abelló laboratory) was positive with a 7 × 8 mm papule (positive if > 3 mm),

a 9 × 10 mm response to histamine, and a negative response to glycerinated saline.

In vitro testing gave the following results: elevated total IgE of 279 UI/L (high if > 150 UI/L). The results obtained from quantification of specific IgE to *Anisakis simplex* (UniCAP; Pharmacia) were positive at 0.8 KU/L (positive if > 0.35 KU/L).

The diagnosis was compatible with protein contact dermatitis due to type I hypersensitivity to *Anisakis simplex*.

In six healthy control patients a prick test was performed with the complete battery of foods, meat additives, latex, and *Anisakis simplex*, all of which were negative.

DISCUSSION

The spectrum of allergic reactions to *Anisakis simplex* is wide and includes rhinitis, conjunctivitis, asthma, urticaria/angioedema, allergic contact dermatitis, and anaphylactic shock [4, 13, 14, 17].

The condition may be caused through the consumption of infected fish, or from occupational contact. The sectors most affected by *Anisakis*-related diseases are fishermen/women, fishmongers, and chefs: in general, anyone whose work involves catching, cleaning, handling, selling, or preparing contaminated fish [13, 18].

Purello-D'Ambrosio et al. 2000 [18] conducted a study on sensitisation in fishermen and fishmongers, of 28 individuals studied, four had a positive prick test to *Anisakis simplex*.

The cases we have discussed in this paper are all cases of occupational diseases secondary to *Anisakis simplex* including two cases of acute urticaria and one case of protein dermatitis, all of which are attributable to type I hypersensitivity to *Anisakis simplex*. These findings are in line with the results obtained by Conde-Salazar et al., 2002 [19]; Barbuzza et al., 2009 [20], and Vicente Pardo, 2016 [5].

The diagnosis of the cases was based on the occupational history, the clinical presentation, the allergen exposure pattern (at work vs. off work), and the additional tests including both *in vivo* skin prick tests and *in vitro* tests quantifying *Anisakis simplex*-specific IgE levels.

Recently-developed molecular testing methods may be used to identify cross-reactivity between the protein from *Anisakis* and other allergenic sources such as crustaceans. When a patient is diagnosed with hypersensitivity to *Anisakis*, a molecular test determines the exact protein to which they are sensitised and may therefore be useful for predicting the potential development of reactions to allergens that show cross-reactivity [21, 22].

Prevention should encompass tasks undertaken when fishing (gutting is performed on board the fishing boat), and in the subsequent handling of the product prior to (wholesalers

and during (retailers) its sale to the final consumer, and, lastly, during food preparation. Thus, rapid gutting, correct freezing (see Food and Drug Administration [FDA] recommendations) and adequate cooking of fish are the most pertinent steps to avoid parasitic infection in the end consumer.

Regarding the prevention and treatment of the occupational disease we have looked at, the best options to reduce exposure are barrier methods that protect the mucous membranes and exposed skin in individuals who carry out the tasks mentioned above, along with the provision of prior information and training.

The FDA recommendations [23] for parasite destruction by freezing (3-402.11) are:

- (A) Except as specified in (B) of this section, before service or sale in READY-TO-EAT form, raw, raw-marinated, partially cooked, or marinated-partially cooked FISH shall be:
 - (1) Frozen and stored at a temperature of -20°C (-4°F) or below for a minimum of 168 hours (7 days) in a freezer;
 - (2) Frozen at -35°C (-31°F) or below until solid and stored at -35°C (-31°F) or below for a minimum of 15 hours; or
 - (3) Frozen at -35°C (-31°F) or below until solid and stored at -20°C (-4°F) or below for a minimum of 24 hours.
- (B) Paragraph (A) of this section does not apply to:
 - (1) MOLLUSCAN SHELLFISH;
 - (2) A scallop product consisting only of the shucked adductor muscle;
 - (3) Tuna of the species *Thunnus alalunga*, *Thunnus albacares* (Yellowfin tuna), *Thunnus atlanticus*, *Thunnus maccoyii* (Bluefin tuna, Southern), *Thunnus obesus* (Bigeye tuna), or *Thunnus thynnus* (Bluefin tuna, Northern); or
 - (4) Aquacultured FISH, such as salmon, that:
 - (a) If raised in open water, are raised in net-pens, or
 - (b) Are raised in land-based operations such as ponds or tanks, and
 - (c) Are fed formulated feed, such as pellets, that contains no live parasites infective to the aquacultured FISH;
 - (5) FISH eggs that have been removed from the skein and rinsed.

CONCLUSIONS

Health conditions caused by *Anisakis* are highly relevant for consumers of fish and represent a significant public health issue. It should also be borne in mind that exposure to *Anisakis* can cause an occupational disease in individuals who handle fish (particularly fishermen/women, fishmongers, supermarket workers, and chefs).

Preventative measures should be strengthened to avoid or minimise the health effects that exposure to *Anisakis* can cause, both in the general population and in those exposed in their work environment.

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