



Review

Anisakis allergy in human



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ABSTRACT

Several case reports show allergy and anaphylactic reactions to the fish parasite *Anisakis* in the domestic and occupational setting. Compared with other well-studied parasitic diseases, fish-borne parasitic zoonoses do not get enough attention, especially because these zoonoses have been limited for the most part to populations living in middle-income countries. Human fishery product-borne parasitic diseases caused by nematodes result in infection following ingestion of viable parasites, or as allergic reactions against parasite antigens. With the globalization of the seafood industry, the risk of humans acquiring anisakiasis in developed countries appears to be underestimated. The risk of infection with *Anisakis simplex* and related parasites of fish has been recognized for some time, but it is now emerging that indigestion of material from dead parasites in food also present a danger. The resulting allergic reactions range from rapid onset and potentially lethal anaphylactic reaction to chronic, debilitating conditions. This review discusses the importance of infection with *Anisakis simplex* and potential of allergy in human.

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1. Introduction

In the world, food allergy is increasing at a faster rate than any other allergic disorder (Gupta, Sheikh, Strachan, & Anderson, 2007). The prevalence of food allergy in Europe is uncertain (Janjić et al., 2015; Baltić et al., 2015). Using food challenges as a criterion for diagnoses, the prevalence of food allergy in Europe has been estimated to be between 3 and 4%, both in children and adults. About 75% of allergic reactions among children in Europe are due to eggs, peanut, cows' milk, fish and various nuts (EFSA, 2014, pp. 127–136). Gastrointestinal worms represent a huge global burden of disease, with more than 2.5 billion people infected (WHO, 2012; Baltić et al., 2013). Traditionally, these parasites are much more prevalent in developing than developed countries (Baltić, 1990a).

The most significant freshwater fish zoonotic nematodes which occur in Serbia are *Eustrongylides* spp., of which the most important species is *Eustrongylides excises* (Bjelic-Cabrilo et al., 2013). In humans who have consumed raw or undercooked fish, *Eustrongylides* spp. have produced gastritis and intestinal perforation (Mitchell, Overstreet, & Goodwin, 2009). Human infections with *Eustrongylides* spp. occur after ingestion of raw or poorly cooked

fish meat, since fishes act as intermediate and paratenic hosts in the development of their lifecycles. The pathogenicity to humans can be different to and, most times, more conspicuous than that observed in birds, the natural definitive hosts for this species (Barros, Tortelly, Pinto, & Gomes, 2004). *Eustrongylides* spp. have been reported in various freshwater fish in Japan, Iran, Papua New Guinea, Canada, Bangladesh etc (Köse, 2010). Health statistical yearbook of Republic of Serbia (2016) showed data for non-communicable diseases (males and females). This book included chronic diseases, like cardiovascular diseases, malignant tumors, diabetes, obstructive lung disease, injury and poisoning, mental health disorders and other chronic diseases dominate for decades in our national pathology. Information about food and fish parasites allergies are not presented, because this cases are rare, and no large research in this area.

Anisakiasis (or anisakidosis) and is often associated with acute gastrointestinal symptoms such as abdominal pain, diarrhea, nausea and vomiting. However, patients range from being asymptomatic to requiring emergency room care. In addition, IgE mediated allergic reactions to a range of allergenic proteins are often reported. Some of these allergens, tropomyosin and paramyosin, demonstrate strong molecular and immunological cross-reactivity to other invertebrates, including crustaceans and mites, but are only distantly related to trematodes and cestodes. Since 1960 when

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anisakiasis was first described, thousands of cases have been reported from Japan and hundreds from Europe as well as from other parts of the world (Audicana, Ansotegui, de Corres, & Kennedy, 2002; Nieuwenhuizen & Lopata, 2013).

2. Anisakis in humans

The country with the highest prevalence of *Anisakis* infections in human is Japan (Baird, Gasser, Jabbar, & Lopata, 2014). Infected sushi and sashimi (national dishes of raw fish) are a significant source of human infection, with 2000–3000 cases of anisakiasis being reported annually (Yorimitsu et al., 2013). In Italy, where marinated or raw fish is a culinary tradition in some region, the actual incidence of anisakiasis is believed to be grossly underestimated in human due to a high prevalence of parasitized in the Mediterranean region. The globalization of provincial cuisine, development of better diagnostic tools and greater awareness has led to more frequent reporting of anisakiasis in those countries as well as in other countries like Korea, Australia, China, Croatia and the United States of America (Arizono, Yamada, Tegoshi, & Yoshikawa, 2012; Pravettoni, Primavesi, & Piantanida, 2012). In Norway, only few cases of human anisakiasis have been recorded in association with the intake of raw or only lightly processed fresh marine fish (Borges, Cunha, Santos, Monteiro-Neto, & Santos, 2012; Chávez, González, Oliva, & Valdivia, 2012). In 2014 year, the first case of anisakiasis presenting as a bowel obstruction in child in Croatia (Jurić, Pogorelić, Despot, & Mrklić, 2013) and the first anisakis detected in an endocervical adenocarcinoma in a German-American female from the United States of America (Ramanan, Blumberg, Mathison, & Pritt, 2013).

The main sources of *A. simplex* were the spotted chub mackerel (*Scomber japonicus*) and Japanese flying squid (*Todarodes pacificus*) (Nagasawa, 1990). In Western Europe, herring (*Clupea harengus*) is the main species involved (Audicana et al., 2002), although cases with other species that were insufficiently cooked have also been reported. In Spain, most cases were related to the consumption of pickled anchovies (*Engraulis encrasicolus*) and raw sardines (*Sardina pilchardus*) (Audicana et al., 2002).

Anisakis species have a complex life cycle involving a number of hosts; their adult stages live embedded in the mucosa of the stomach of marine mammals (whale, seal or dolphin). Adult females produce unembryonated eggs which are expelled through the faeces of the hosts. Embryonations take place in seawater and first-stage larvae (L1) are formed in the eggs. Later on they hatch into the second stage (L2) and these free-swimming larvae are ingested by krill and crustaceans. In these intermediate hosts, they mature into the third stage (L3) which is further transferred to other hosts such as fish and cephalopods, still in the L3 larvae form. When the infected fish or cephalopods are subsequently eaten by marine mammals, the larvae develop into adult worms in the final hosts, thus completing their complex lifecycle (Lin, 2015). The generalized anisakis life cycle is shown in Fig. 1.

Humans are accidental hosts and become infected upon consumption of raw or under-processed marine fish and cephalopods contaminated with the third stage larvae. The parasites cannot survive in human hosts and usually become regurgitated or expelled or dead in a few days or weeks. Usually within a few hours after ingestion, the burrowing of the worm into the intestinal wall and subsequent death results in an acute and transient infection manifested by such symptoms as abdominal pain, nausea, vomiting, and/or diarrhea (Audicana & Kennedy, 2008). The condition may sometimes mimic several other gastrointestinal disorders such as gastric ulcer and acute appendicitis. At the same time, the parasite can trigger an immune response and provoke clinical manifestations of allergy in some sensitized patients, and this

borderline disease with simultaneous clinical manifestations of infection and allergy is termed “gastroallergic anisakiasis”. If the larva passes further into the bowel or large intestine, it may lead to eosinophilic granulomatous response after 1–2 weeks and cause more chronic symptoms (Audicana & Kennedy, 2008).

Regarding the *Anisakis* allergy, there has been an interesting debate on whether live or dead larva is necessary to induce the reaction (Audicana et al., 2002; Daschner, Cuéllar, & Rodero, 2012). Several heat- and pepsin-resistant *Anisakis* allergens have been shown to remain active even after cooking or digestion. Therefore, the intake of dead parasite or even residues in contaminated fishery products might cause allergic symptoms. Additionally, inhalation of or contact with *A. simplex* allergens has been reported to cause occupational allergies in fishery and aquaculture workers, fish-mongers and cooks etc. (Nieuwenhuizen et al., 2005; Nieuwenhuizen & Lopata, 2013; Armentia et al., 1998). On the other hand, it has been reported that allergic sensitivity to *A. simplex* is initiated by an active infection with live parasite (Alonso-Gómez et al., 2004). According to some studies on oral challenges with thermally treated *Anisakis* larvae, the patients did not show any allergic or gastric symptoms during or after the challenge. It is generally accepted that an active infection associated with viable larva is required to induce allergic symptoms in the majority of cases (Pravettoni et al., 2012).

Because the symptoms of anisakiasis are non-specific, the disease is often misdiagnosed. For example, in a single study, over 60% of the cases were diagnosed preoperatively as appendicitis, acute abdomen, gastric cancer or Crohn's disease (EFSA, 2010). The clinical diagnosis is usually performed through endoscopy or radiological examination, whereas various immunologic assays have been used for indirect diagnosis, including the skin-prick test, complement fixation test (CFT), immunofluorescent-antibody test (IFAT), immunodiffusion test (IDT), immunoelectrophoretic assays, enzyme-linked immunosorbent assay (ELISA), and radio-allergosorbent test (RAST). Interpretation of the serological tests may be difficult because anisakiasis patients' sera cross-react with antigens from closely related nematode species (e.g. *Ascaris* and *Toxocara* species) and because sera from unaffected individuals may contain specific antibodies which can give false-positive results against *Anisakis* antigens. Of all serodiagnostic assays, the RAST is the most sensitive and specific (EFSA, 2010).

3. Allergic responses in human and *Anisakis* allergens

Human infections with nematodes and other helminthes are typically associated with tissue eosinophilia and elevated levels of IgE, signs that may also occur in patients showing type I hypersensitivity against certain antigens. Tropomyosin, a highly conserved protein in the muscle and skin of many invertebrates, is a well recognized potent allergen since the molecular structure of certain regions of invertebrate tropomyosin differs considerably from the corresponding stretches of the vertebrate (human) type (Sereda, Hartmann, & Lucius, 2008). Paradoxically, both epidemiological studies and experimental animal models imply that chronic infections with some helminthes may protect against, or at least alleviate allergic reactions (Falcone & Pritchard, 2005; Trujillo-Vargas et al., 2007; van den Biggelaar et al., 2004; Wohlleben et al., 2004). This again suggests that the basic elements for allergic reactions are present but clinical reactivity is down regulated (Jackson et al., 2006; Mangan, van Rooijen, McKenzie, & Fallon, 2006; Turner et al., 2005; van den Biggelaar et al., 2000; Wilson et al., 2005). However, since neither adult nor larval anisakids are natural human parasites, no mutual adaptation has evolved and, consequently, possible modulating or immune down regulation are absent. Moreover, due to the similarity of

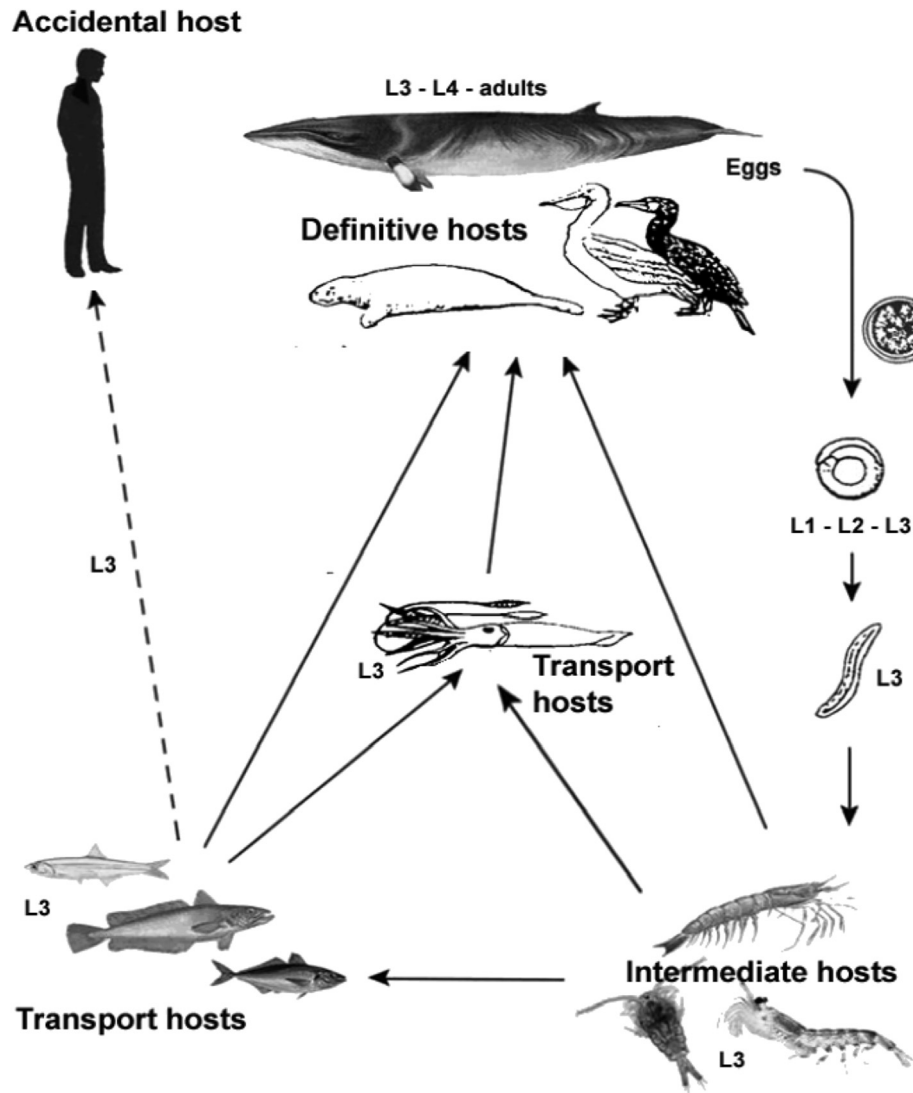


Fig. 1. Life cycle of *Anisakis simplex* (Levsen & Lunestad, 2010; modified from; Mattiucci et al., 1997).

invertebrate tropomyosins, the specifically generated IgE antibodies directed against *Anisakis* larvae, cross-react widely, particularly among seafood allergens and other allergens such as shrimp and house dust mite, respectively (Reese, Ayuso, & Lehrer, 1999).

The *Anisakis*-associated allergic response has only been identified as associated with *A. simplex*. The helminths do not usually induce allergic responses in humans, *Anisakis* often do. Clinical signs include urticaria and gastrointestinal response (Baltić, 1990a). Also, acute allergic reaction can be seen with minor gastrointestinal problem (Baird et al., 2014). Acute urticaria and angioedema affects 20% of the population at some time in their lives, particularly in young adults (Kaplan, 1992) and although usually self-limiting and not life threatening, the condition is nevertheless unpleasant as a result of the intense itching, inability to sleep and even disfigurement when angioedema is present. Angioedema is associated with urticaria in 30% of cases, and is potentially life threatening because of the risk of oedema of the glottis. Anaphylaxis is a rapid-onset and dangerous syndrome characterized by urticaria, angioedema, severe respiratory and gastrointestinal symptoms, collapse and shock. The first signs of an allergic reaction usually appear within 60–120 min after ingestion of infected fish but can take up to 6 h (Audicana et al., 2002).

Currently 12 allergens have been identified in *A. simplex* (Table 1). Patients may be exposed primarily to somatic antigens from dead larvae in food, excretory–secretory (ES) antigens when there is expulsion or surgical removal of the intact larvae, or both, in cases where the larva penetrates the tissue, is killed by the host, and subsequently degenerates inside the host (Baltić, 1990b). Many allergens of *Anisakis* are heat- and/or pepsin-resistant (Caballero & Moneo, 2002) and most of them are present in ES products. The major allergens of *Anisakis* (recognized by more than 50% of patients analyzed) are considered to be Ani s 1 and Ani s 7 20, although in one study Ani s 5 was recognized by 49% of patients (41/84). The 24 kDa Ani s 1 is recognized by 67–87% of patients with gastroallergic anisakiasis and is not detected by asymptomatic individuals (Shimakura et al., 2004).

Infection of human subjects with the *A. simplex* leads to the production of high levels of specific antibodies. High amounts of specific IgE levels explain why some patients experience severe anaphylactic reactions after parasitized fish ingestion (Audicana et al., 1995).

The most important prevention method is to raise the awareness of consumers and producers about the existence of anisakis worms in fish and to recommend avoiding the consumption of raw

Table 1
Allergens of *Anisakis simplex* (Baird et al., 2014).

Allergen	Molecular weight (kDa)	Nematode antigen	Protein	Reactivity in sensitized patients
Ani s 1	24	ES	Kunitz-type trypsin inhibitor	85%
Ani s 2	97	Somatic	Paramyosin	88%
Ani s 3	41	Somatic	Tropomyosin	Unknown
Ani s 4	9	ES	Cystatin	27%
Ani s 5	15	ES	SXP/RAL protein	25%–49%
Ani s 6	7	ES	Serpin	18%
Ani s 7	139	ES	Glycoprotein	83%–100%
Ani s 8	15	ES	SXP/RAL protein	25%
Ani s 9	14	ES	SXP/RAL protein	13%
Ani s 10	22	Unknown	Unknown	39%
Ani s 11	55	Unknown	Unknown	47%
Ani s 11-li	Unknown	Unknown	Unknown	Unknown
Ani s 12	Unknown	Unknown	Unknown	57%

or poorly cooked, marinated, or salted marine fish or squid. *Anisakis* larvae can be easily killed by adequate cooking at temperatures $>60^{\circ}\text{C}$ or freezing, but most probably not by salting and marinating. The US Food and Drug Administration (FDA) recommends that all shellfish and fish intended for raw consumption should be blast frozen to -35°C or below for 15 h or be regularly frozen to -20°C or below for seven days. Australia, Canada, some countries in EU including UK also have similar national food safety guidelines (EFSA, 2010; Baltić, Kilibarda, & Dimitrijević, 2009).

4. Conclusion

With the new international codes regarding food safety, risk assessment methodologies are being seen as the scientific process to address public health, globally. Both epidemiological and risk assessment approaches are dependent upon an evaluation of the occurrence and survival of the transmissive stage of the parasite in question. For many parasitic infections transmitted through the environment, exposure assessment is perhaps the most difficult parameter to measure. The understanding of this variable is dependent not only upon the detection of organisms in the environment, but also on an understanding of the occurrence, transport, survival and fate through various matrices. Here, sensitive, robust and reproducible detection, viability, typing and subtyping methods, with suitability for the matrix in question, will be the arbiters. Only by developing such methods we can attempt to determine the impact of the parasite zoonosis transmitted by food, and their public health significance. Food-borne anisakiasis should be considered as an emerging health risk for people who consume large quantities of fish known to be paratenic host for *Anisakis* spp.

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