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Procedia Food Science 5 (2015) 101 – 104

Procedia Food Science

International 58th Meat Industry Conference "Meat Safety and Quality: Where it goes?"

# Anisakis infection and allergy in humans

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**Abstract**

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 low- and middle-income countries in Europe. Human fishery product-borne parasitic diseases caused by nematodes are the results of 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. For allergy, the only implicated parasite in fishery products is the nematode *Anisakis simplex*.


Peer-review under responsibility of scientific committee of The 58th International Meat Industry Conference (MeatCon2015)

*Keywords:* Anisakis; allergy; human; fish; food-borne parasite

## 1. Introduction

The prevalence of food allergy in Europe is uncertain[1]. Using food challenges as a criterion for 61 diagnoses, the prevalence of food allergy in Europe has been estimated to be between 3 and 4%. About 75% of allergic reactions among children in Europe are due to eggs, peanut, cows' milk, fish and various nuts[2]. Gastrointestinal worms represent a huge global burden of disease, with more than 2.5 bilion people infected[3,4]. Traditionally, these parasites are much more prevalent in developing than developed countries[5].

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Peer-review under responsibility of scientific committee of The 58th International Meat Industry Conference (MeatCon2015)
doi:10.1016/j.profoo.2015.09.028

The infection known as anisakiasis (or anisakidosis) is often associated with acute gastrointestinal symptoms such as abdominal pain, diarrhoea, 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 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[6].

## 2. Anisakis in humans

The country with the highest prevalence of Anisakis infections in humans is Japan[7]. 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[8]. In Italy, where marinated or raw fish is a culinary tradition in some region, the actual incidence of anisakiasis is belived to be grossly underestimated in human due to the high prevalence of parasitized fish in the Mediterranean region[9]. 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[10,11]. In Norway, only a few cases of human anisakiasis have been recorded in association with the intake of raw or only lightly processed fresh marine fish[12,13]. In 2014, the first case of anisakiasis presenting as a bowel obstruction in a child in Croatia[14] and the first anisakid detected in an endocervical adenocarcinoma in a German-American female from the United States of America[15] were reported.

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. The condition may sometimes mimic several other gastrointestinal disorders such as gastric ulcer and acute appendicitis[16].

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[17]. 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[17].

## 3. Allergic responses in human and anisakis allergens

While helminths do not usually induce allergic responses in humans, anisakids often do. Clinical signs include urticaria and gastrointestinal response[16]. Also, acute allergic reaction can be seen with minor gastrointestinal problem[7]. Acute urticaria and angioedema affects 20% of the population at some time in their lives, particularly in young adults[18]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 rapidonset 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 minutes after ingestion of infected fish but can take up to six hours[6].

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[16]. Many allergens of Anisakis are heat- and/or pepsin-resistant[19] and most of them are present in ES products. The major allergens of Anisakis (recognised by more than 50% of patients analysed) are considered to be Ani s 1 and Ani s 7[20], although in one study Ani s 5 was recognised by 49% of patients (41/84). The 24 kDa Ani s 1 is recognised by 67–87% of patients with gastroallergic anisakiasis and is not detected by asymptomatic individuals[21].

Table 1. Allergens of *Anisakis simplex*[7].

| Allergen | Molecular weight (kDa) | Nematode antigen | Protein | Reactivity in sensitised 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% |

Legend: ES-protein from excretory–secretory products.

The most important prevention method is to raise the awareness of consumers and producers about the existence of anisakid worms in fish and to recommend avoiding the consumption of raw or poorly cooked, marinated, or salted marine fish or squid. Anisakid larvae can be easily killed by adequate cooking at temperatures > 60°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 hours or be regularly frozen to -20°C or below for seven days[22]. Other countries in the EU, UK, Australia and Canada also have similar national food safety guidelines[17,23].

## Acknowledgement

This paper was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia, Project TR 31011.

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