Anisakiasis in Europe: emerging, neglected, misdiagnosed, or all of the above?

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Abstract

Supported by the intensified migration and transport of people and foodstuffs, expansion of culinary trends that rely on raw and lightly thermally processed seafood, more sustainable management of aquatic resources, primarily marine mammals in terms of their conservation, and the development of more sensitive diagnostic tools, the rate of fish-borne parasitosis cases has increased worldwide in recent decades. Judging from a recent ranking, anisakiasis is one of the most important zoonoses in Europe from the public health perspective. The infective third-stage larva of the nematode *Anisakis* spp. is contracted by consumption of insufficiently thermally processed fish and cephalopods, evoking gastric, intestinal, ectopic or (gastro) allergic clinical type of disease in humans. Moreover, based on the widespread anti-*Anisakis* seroprevalence in the asymptomatic healthy population, a fifth form of the disease has been proposed. In contrast to the ubiquitous nature of the larvae in paratenic hosts (e.g. fish and cephalopods), the epidemiological status in European countries is very diverse, mostly unknown and strongly underestimated. Therefore, this article highlights the most important recent assessments of anisakiasis clinical cases at the EU level, with a short overview of the biological characteristics of this nematode.

Keywords: *Anisakis* spp.; *zoonosis; nematode; fish; cephalopods*

Introduction

With a rapidly growing human population, the existing vegetable and animal production is facing the challenge of satisfying the increasing need for protein. In the context of exploitation and production of high-quality, easily digestible protein and low fat, as well as value added and functional foods (Shaviklo, 2015), fisheries and aquaculture are considered the most important providers. Regulated implementation of best practices in fisheries and the development of sustainable aquaculture have helped the latter to surpass wild fisheries, by reaching 53.1% in 2015, alleviating the pressures from exploitation of natural resources (FAO, 2014; 2016).

However, the increasing worldwide perception about benefits of seafood consumption typical to the Mediterranean diet, compared to red meat deemed a risk

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factor for pathologies such as cancer and cardiovascular diseases (Shamsi, 2019), has consequently increased the need to more closely scrutinise the potential risk of transmitting fish-borne parasites (FBP) from seafood to consumers. The exposure of the human population to such a risk is still vaguely known (Bao et al., 2017), although this is crucial for the implementation of risk management measures, especially in areas where fishing and aquaculture are among the primary activities of the local population.

Although there is an extensive range of helminth parasites in fish, only a moderate number of species is capable of causing food-borne diseases in humans (WHO, 1995). From the public health stance, the number of fish-borne parasitoses (FBP) is still underestimated, although according to palaeoparasitology, this is not an emerging issue (Fornaciari and Gaeta, 2014). It has been speculated that in the Chilean Chinchorro culture, dating back 9,000 years and whose mummification of the dead is considered the oldest example in human history, the fish cestode *Diphyllobothrium pacificum* (Trematoda, Dyphillobothridae) was related to cases of anaemia, given the Chinchorro's predominantly seafood diet, according to skull analysis (Arriaza and Standen, 2009). This cestode has been also identified from mummies from the Inca period originating from the Atacama Desert (Santoro et al., 2003). Similarly, eggs of the fish trematode *Clonorchis sinensis* (Trematoda, Chlonorchidae) have been found in coprolites from corpses of Korean and Chinese Ming, Western Han and Chu dynasties, suggesting its prevalence over the last 2300 years (Fornaciari and Gaeta, 2014).

In contemporary Europe, the EFSA Panel on Biological Hazards (BIOHAZ) published its scientific opinion on the risk assessment of parasites in fishery products, highlighting fishery-borne parasitic diseases caused by cestodes, trematodes and nematodes that infect humans following ingestion of viable parasites, or as allergic reactions against parasite antigens (EFSA, 2010). Interestingly, the analysis have mostly focused on the infective third-stage larvae (L3) of the nematode *Anisakis simplex*, and status and bottlenecks concerning the etiology and pathogenesis of anisakiasis and anisakidosis; *i.e.* the former entity related to human infection by species of genus *Anisakis*, and the latter by members of Anisakidae family.

Similarly, anisakids were the main, though not exclusive focus of the EU-driven initiative PARASITE (http://parasite-project.eu/index), developed within the Framework Program 7. The project involved EU and non-EU experts who provided detailed epidemiological studies on zoonotic parasites in European fish stocks, a comprehensive quantitative risk analysis and several innovative technologies to mitigate the impact of zoonotic parasites along the seafood value chain (Levsen et al., 2018). Another EU network of experts with a broader perspective encompassing the most important EU food-borne parasites (https://www.euro-fbp.org) developed a list prioritising parasite species based on multi-criteria decision analyses (MCDA). This MCDA resulted in a disease risk ranking based on multiple aspects that compose the particular risk, using modified criteria suggested by FAO/ WHO (2014) (Bouwknegt et al., 2018). *Anisakis*, a single prioritised fish-borne parasite in the study, was scored as seventh at the EU-wide level after *Echinococcus multilocularis*, *Toxoplasma gondii*, *Trichinella spiralis*, *E. granulosus*, *Cryptosporidium* spp., and *Trichinella* spp. other than *T. spiralis*. Broken down by European regions, it was the fifth most important parasite in Northern, tenth in Western, seventh in Eastern, forth in South-Western and sixth in South-Eastern Europe.

Given that once exotic culinary dishes based on raw or lightly processed seafood, e.g. Japanese sushi and sashimi, Caribbean ceviche, Mediterranean carpaccio, Hollandaise maatjes, Norwegian gravlax, Spanish boquerones en vinagre, Hawaiian lomi lomi, Thai koi pla, pla ra, pla som and som fak, Philippinese kinilaw, sabaw and sukba, have followed the migration of the native population traditionally preparing such meals, and has translocated intercontinental distances, they have since become established within new areas with no or negligible prevalence of the particular FBP. Consequently, this shifted the epidemiological status of these parasites, from endemic areas towards sporadic "allochthonous" outbreaks where the pathogen has not been previously reported. Eiras et al. (2018) reviewed reported cases of fish-borne nematodiases among returned travellers over the past 25 years, retrieving a total of 100 cases of fish-borne nematode infections reported in returned travellers in 22 countries around the world, including seven EU countries (Austria, England, France, Germany, Italy, Spain and the Netherlands). The most frequent nematode appeared to be *Gnathostoma* sp. (Spirurida, Gnathostomatidae) (46 cases), whereas only six reported cases were attributed to *Anisakis simplex*. The former has the two most important species of public health concern; *G. spinigerum* endemic to Northeast to Southeast Asia, especially Thailand and Japan (Miyazaki, 1960), and *G. binucleatum*, endemic to Latin America (Mexico, Ecuador and Peru) (Nawa et al., 2015), both infecting humans through the consumption of live, raw or poorly cooked fish, snakes, frogs and some mammals parasitized by third-stage infective larvae (Akahane et al., 1998).

Given its neglected and emerging character, and the increasing tendency of consumption of lightly processed seafood in the region, the aim of this short overview is to present the recent epidemiological status of *Anisakis* clinical reports in European countries, excluding allergic hypersensitisation cases, except when relevant for the understanding of the former.

Anisakiasis etiology

The causative agent is the third-stage infective larva (L3) of *Anisakis simplex* sensu stricto (s. s.) and *A. pegreffii* parasitizing visceral cavity and lateral

Figure 1: Infective third stage larvae (L3) of *Anisakis pegreffii* (Nematoda, Anisakidae) isolated from the visceral cavity of blue whiting (*Micromesistius poutassou*) caught off the Central East Adriatic Sea coast (FAO European fishing zone 37.2.1) observed under the stereomicroscope, held in autoclaved filtered seawater in a Petri dish.

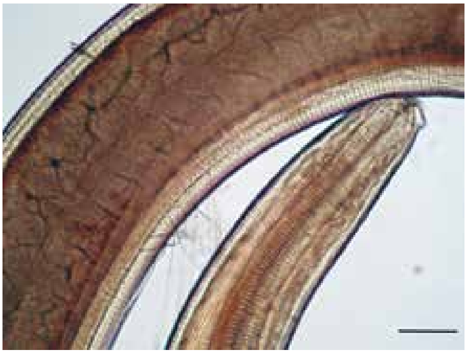

Figure 2: Mid-body showing developing intestine (upper left corner) and oral part showing long oesophagus of the *Anisakis pegreffii* third-stage larva (L3) observed under the light microscope (scale bar: 200 μm).

Figure 3: High magnification of the anal part of *Anisakis pegreffii* larva that recently moulted into the fourth-stage larva (L4), therefore is lacking characteristic mucron tail (scale bar: 25 μm).

muscles of fish and mantle cavity of cephalopods (Figure 1-2). Although both species have a worldwide geographical distribution due to the worldwide migration of their final hosts, marine mammals (Blažeković et al., 2015), at the level of EU waters, the former is more abundant in the North Atlantic, while the latter in the East Mediterranean and adjacent seas. Their sympatric area of admixture is the Alboran Sea (West Mediterranean), although hybrid genotypes can be found as far as in the Adriatic (Mladineo et al., 2017). Such distribution reflects the fact that *A. simplex* s. s. is mostly contracted in Spain and in Northern EU countries, while *A. pegreffii* is a more frequent pathogen in Italy and Croatia.

Additionally, there are seven other *Anisakis* species, but to date their involvement in human infection has not been confirmed by molecular tools, as purely morphological identification of L3 is insufficient for taxonomically correct assignment (Mattiucci et al., 2018).

Nonetheless, EFSA (2010) proclaimed that no marine fishing grounds could be considered free of *A. simplex* larvae in respect to wild-caught fish, while in farmed fish, a rare L3 occurrence has been noted in Atlantic salmon (*Salmo salar*) (Levsen and Maage, 2016) and sea bass (*Dicentrarchus labrax*) (Cammillieri et al., 2018).

The *Anisakis* spp. life cycle

The nematode uses the food-chain to infect the final host, which encompass a number of cetaceans belonging to *Balenopteridae*, *Delphinidae* and *Phocoenidae* within whose gastric chambers forth-stage larvae (L4) (Figure 3) arrive through feeding. Here, the larvae moult into adults of separate sex, which then reproduce and expel eggs that are released by the marine mammals. Within the egg, the first-stage larva (L1) moults into the second-stage larva (L2), or exits the egg and infects the intermediate host, becoming an early L3 larva. A wide range of planktonic euphausiids act as the larval vehicle towards the first paratenic host; fish and cephalopods. L3 larvae (Figure 4) ingested by the paratenic host penetrates through the stomach and intestinal wall, attaching to the surface of visceral

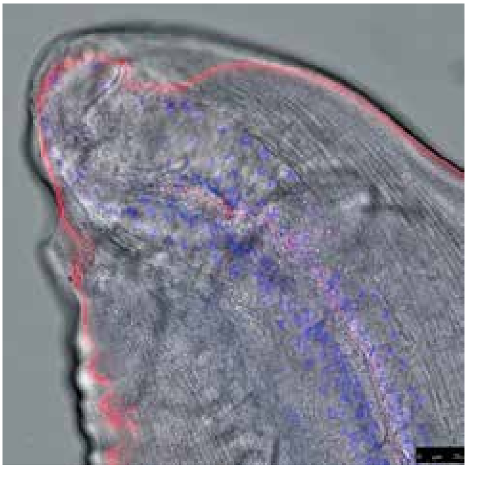

Figure 4: Oral part of the *Anisakis pegreffii* third-stage larva (L3) under confocal microscope showing DAPI (4,6-diamidino-2-phenylindole)-labelled oesophageal cell nuclei (blue) and immunohistochemical localisation of ß-tubulin in cuticle (red, labelled by monoclonal antitubulin-Cy3 antibody).

organs. Larvae have shown a preference for a particular organ (Mladineo and Poljak, 2014), while migration into the lateral muscles occurs both *intravitam* and *postmortem* in fish (Šimat et al., 2015; Cipriani et al., 2016). When the first paratenic host is ingested by a larger fish or cephalopod, the L3 within its viscera shifts to the second paratenic host. Accidentally, the first paratenic host can be eaten by humans in the form of a thermally lightly or unprocessed dish, setting off anisakiasis or anisakidosis, although L3 can also survive in humans for a limited time. The first or second paratenic host is eventually eaten by the final marine mammalian host, closing this indirect life cycle.

Epidemiology in Europe

There are four specific forms recognised today, depending on the site of larval penetration and the accompanying pathology; gastric, intestinal, ectopic and gastro-allergic (Hochberg and Hamer, 2010). In respect to the latter, *Anisakis* is the sole fish-borne parasite implicated in allergic reactions in terrestrial vertebrates, including humans. It is still not clear whether infection by live larva triggers sensitisation in humans that after each subsequent ingestion of anisakid antigens provokes different forms of allergic reaction, or whether even the non-viable larvae can provoke the same (Moneo et al., 2017). The allergic reaction to anisakid antigens has also been regarded as a professional pathology occurring in the fish-processing industry (Barbuzza et al., 2009; Mazzucco et al., 2012; Nieuwenhuizen and Lopata, 2014), among fishermen and fishmongers (Purello-D’Ambrosio et al., 2000), and even among employees in poultry facilities administering feed containing fishmeal (Armentia et al., 1998). Moneo et al. (2017) recently suggest that the seroprevalence of anti-*Anisakis* IgE in the clinically asymptomatic population should be recognised as a fifth form of anisakiasis, which is crucial from the epidemiological point of view, as the circulating anti-*Anisakis* IgE could react at any time with new antigen contact.

The epidemiological situation in respect to clinical cases in Europe is vague, though the global understanding is that the disease is usually misdiagnosed and highly underestimated. EFSA (2010) reported on the incidence of the disease in Spain, the Netherlands and Germany, although such numbers are likely to be underestimated today. For example, two recent and extreme case studies reported that over 200 and 140 larvae were extracted by endoscopy in a Spanish (Jurado-Palomo et al., 2010) and Portuguese patient (Baptista-Fernandes et al., 2017), respectively. Bao et al. (2017) conducted the first quantitative risk analysis of *Anisakis* infection in Spain, estimating that some 7700-8320 cases are left unreported, in contrast to the actually reported cases per 100,000 inhabitants per year, ranging from 3.87 to 19.2 cases per 100,000 inhabitants per year.

A recent systematic review of epidemiology of food-borne nematodiasis in the EU in the period 2000–2016 reported a total of 236 indigenous clinical cases of anisakiasis, mostly in Spain (158 or 66.9%) and Italy (67 or 28.4%) (Serrano-Moliner et al., 2018). However, these numbers seem to underestimate the real EU status of the disease, as Cavallero et al. (2018) retrieved only from Italian hospital discharge records in total 370 clinical cases obtained from 2005 to 2015. Of these, 40% showed allergic manifestations, of which the half exhibited anaphylactic reactions. Among patients, 80.3% lived near the coast, and 51.1% originated from southern Italy (Apulia). Women prevailed (51.1%), patient mean age was 46.7 years, although the highest frequency occurred between 40–49 years (21.4%). The mean length of hospital stay was 5.7 days and 62.7% of patients showed a lower educational level. This is in agreement with a previous Italian study of *Anisakis* sensitisation rates, which showed marked geographic differences (range 0.4-12.7%), indicating that the highest number of cases were reported along the Adriatic and Tyrrhenian coasts. The study suggested that the consumption of homemade marinated anchovies, as an age-old tradition, accounts for such distribution. Moreover, analysing the impact of immigration on the prevalence of *Anisakis* hypersensitivity showed that immigration from southern Italy or non-EU countries caused sensitisation of approximately 60% subjects in Milan and Turin (AAITO-IFIACI, 2011). Another retrospective epidemiological study in Italy that covered over two decades of literature reports found only 73 cases, the majority of which were detected by endoscopy (51.4%) and laparotomy (48.6%) (Guardone et al., 2018). The site of the parasite was mainly the intestine (42.5%), followed by stomach (43.8%), oesophagus (1.4%) and different ectopic sites (12.3%), whereas the source of infection was raw or undercooked anchovies (65.7%).

In contrast, however, a recent retrospective study spanning the period 2010–2014 estimated that the incidence of anisakids in French hospitals amounted to 37 positively identified clinical cases. Authors extrapolated this to 0.62 cases/month or 7.4 cases/year, mainly affecting individuals of an average age of 42 years (11-69) and predominantly women (Yera et al., 2018). Interestingly, they indicated that compared to a previous report (e.g. 21 cases in three years; Hubert et al., 1989) this represented a decrease in anisakidosis, most likely related to stricter adherence to EU regulation (2004) and promotional media campaigns.

Clinical cases in Austria and Belgium were reported from travellers returning from the USA and Chile, respectively (Verhamme and Ramboer, 1988; Auer et al., 2007), though there are no recent data.

In Croatia, only two case reports focused on anisakiasis; the first using molecular tools to identify L3 in archival paraffin-embedded sections of the sigmoid colon of a woman deceased from another etiology (Mladineo et al., 2016). The second reported the pathology in a 14-year boy three days after the consumption of raw fish (sushi), exhibiting oedema and eosinophilic infiltration in the appendix and increased anti-*Anisakis* IgE titre (Jurić et al., 2013). However, no infective larvae were isolated from the patient, although laparotomy and biopsy were performed early after the onset of symptoms. More importantly, the authors failed to report the specific method of *Anisakis* serodiagnosis, as it has been acknowledged that most assays tend to overestimate the Ig titre, except for the gold standard, indirect ELISA. In the healthy asymptomatic Dalmatian population, the seroprevalence of anti-*Anisakis* IgE has been evaluated by indirect ELISA based on recombinant antigens Ani s 1 and Ani s 7 (Mladineo et al., 2014). It was found to be 2% overall (inland, urban and island population), with the highest prevalence occurring in the island population (3.5%, Fisher's exact 95% CI 1.42-6.45). Expectedly, it prevailed among individuals who consumed raw fish or had daily fish consumption of homemade origin, or had professional, artisanal or hobby contact with fisheries or the fish industry.

Case reports or epidemiological data for other EU countries is lacking or is not publicly available.

Other anisakids

These include species belonging to the genera *Pseudoterranova* and *Contracaecum*. *Pseudoterranova decipiens* (previously named *Phocanema decipiens*) has only been implicated in a single human case reported in Europe (Cavallero et al., 2016). Namely, in Italy in 2015, a colonoscopy administered after the occurrence of nonspecific clinical symptom detected the nematode penetrating the ascending colon in a woman. Molecular identification inferred by cytochrome c 2 (cox2) mitochondrial locus revealed *Pseudoterranova decipiens* sensu stricto as the causative agent.

In contrast, *C. osculatum* has to date been implicated in a human case only in Australia (Shamsi and Butcher, 2011).

Conclusions

Except in cases of acute allergic reaction to *Anisakis* spp., there is a scarce availability and traceability of official records concerning other clinical types of anisakiasis in EU. This in particular can be attributed to the mostly mild gastrointestinal symptoms exhibited during the limited course of the disease, which do not necessitate more than a visit to the general practitioner. Only extreme cases characterised by ingestion of large number of larvae, or particularly pathogenic larvae, where endoscopy or a surgical approach such as laparoscopy is exerted in hospitals, are reported and available for analysis. Therefore, the resulting data that could be collected among EU countries vary, being insufficiently robust to create a meaningful epidemiological analysis. The best example of this is observed in Croatia, where apparently 2% of Dalmatian population is seropositive to specific *Anisakis* antigens, with only two clinical cases reported. More public and professional campaigns are needed to explain the risk of *Anisakis* infection to both consumers and medical experts.

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Anisakijaza u Europi: emergentna, zapostavljena, pogrešno dijagnosticirana, ili sve od navedenoga?

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Učestalost parazitoza koje se prenose ribom je posljednjih desetljeća porasla širom svijeta, potpomognuta pojačanom migracijom i prijevozom ljudi i hrane, širenjem kulinarskog trenda koji se osniva na sirovoj i termički nedovoljno obrađenoj morskoj hrani, održivijim upravljanjem vodenim resursima, poglavito morskim sisavcima u smislu njihove zaštite, kao i razvojem osjetljivijih dijagnostičkih alata. Sudeći prema nedavnoj europskoj rang-listi, s gledišta javnog zdravstva, jedna od najznačajnijih zoonoza je anisakijaza. Infektivna ličinka trećeg stadija oblića *Anisakis* spp. se prenosi konzumacijom nedovoljno termički obrađene ribe i glavonožaca, uzrokujući želučani, crijevni, ektopični i (želučano) alergijski klinički oblik bolesti u ljudi. Dodatno, temeljem široko rasprostranjene seroprevalencije anti-*Anisakis* antitijela u asimptomatične i zdrave populacije, nedavno je predložen i peti oblik bolesti. U suprotnosti s ubikvitarnosti ličinki u parateničnom domaćinu (ribe i glavonošci), epidemiološko stanje anisakijaze u Europi je vrlo raznoliko, većinom nepoznato i vrlo podcijenjeno. U tu svrhu ovaj rad naglašava najznačajnije nedavne procjene kliničkih slučajeva anisakijaze na razini Europe, dajući i kratki pregled bioloških osobitosti oblića.

Ključne riječi: *Anisakis* spp., *zoonoze*, *oblići*, *riba*, *glavonošci*