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1. On parasites and fishes

Fishes commonly harbor many parasites [1,2], some of them can be transmitted to humans, leading to various diseases such as diphyllobothriosis, anisakidosis, *larva migrans* syndrome due to *Gnathostoma* spp. or *Spirometra* spp., liver or intestinal flukes infections and others [3]. However, only diphyllobothriosis and anisakidosis are endemic in Western countries. Anisakid nematodes, which are the most widely distributed [4], are well-known from fishermen as they can be easily seen with the naked eye in the intestines or the peritoneal cavity of freshly caught infected fish. The narrow larvae of this roundworm measure about 2 cm long and are often present by dozens. Additionally, human anisakidosis does not go unnoticed, since it induces acute stomach pain within few hours after ingestion of raw fish. Evisceration of fishes rapidly after fishing avoid migration of the larvae in the muscles of the dead fish [5]. However, in some conditions larvae can migrate before capture of the fish [6]. For this reason, freezing fishes destined be consumed raw is the most suitable prevention measure. By contrast, infection of fish with diphyllobothriid is more difficult to notice. First, the plerocercoid larvae of the cestode parasites are usually located in the muscle tissue of the fish, thus early eviscerating cannot get rid of it. Secondly, human infection is asymptomatic during weeks after consumption of the infected meal. It can remain so, or sometimes results in mild and non-specific gastrointestinal symptoms (diffuse abdominal discomfort, diarrhea or constipation) [7]. Thus, except when proglottids are released with feces, the disease is rarely suspected. Rare complications, e.g. intestinal obstruction or erratic migration [8], can occur, mainly in cases of massive infestation (the historically described megaloblastic anemia due capture of vitamin B12 by the parasite is practically exceptional nowadays and was more likely due to hostile life conditions in Europe after war).

These parasites are broad tapeworms, which have a complex life cycle with various definitive hosts over the world (various marine or terrestrial mammals, birds and even reptiles), depending on the genus and species [9]. Overall 16 species from three genera (*Adenocephalus, Diphyllobothrium* and *Dibothriocephalus*), have been recorded from humans [9-12], but only six species are commonly diagnosed in humans, namely *Adenocephalus pacificus*, *Diphyllobothrium balaenopterae*,

Dibothriocephalus dendriticus, *Dibothriocephalus latus*, *Dibothriocephalus nihonkaiensis* (previously named *Diphyllobothrium pacificum*, *Diplogonoporus balaenopterae*, *Diphyllobothrium dendriticum*, *Diphyllobothrium latum* and *Diphyllobothrium nihonkaiense,* respectively) and *Diphyllobothrium stemmacephalum* [9]. The recent taxonomic change which has occurred in 2017, consecutive to the work of Waeschenbach et al., allowed to differentiate species with marine definitive hosts (*Diphyllobothrium* genus) from species with terrestrial definitive hosts (*Dibothriocephalus* genus) [9]. Although diphyllobothrioses are zoonoses, *D. latus* and *D. nihonkaiensis* to a lesser degree, infect mainly humans as definitive hosts [9].

2. What's new with diphyllobothriosis?

Diphyllobothriosis is the most common fish-borne cestodiasis with an estimated 20 million people infected worldwide [8]. In Europe, a survey reported that several dozen cases were reported each year in Finland and Sweden in the 1990's [13], but globally, the incidence of human diphyllobothriosis has decreased over the last 20 years in northern and eastern Europe [8]. *Dibothriocephalus latus,* the endemic species in Europe, parasitizes freshwater fish (mainly pikes and perches), and has been detected in as much as 25% of perches in Como Lake (Italy) in a recent study [14]. *D. latus* infection tends to be considered a re-emerging disease in Switzerland due to the consumption of raw or marinated fish prepared as tartare, carpaccio or gravelax, but there are no signs that it is similar in France or Italy. However, the absence of notification makes epidemiological estimates difficult [15].

Infections due to allochthonous species (*D. nihonkaiensis, Diph. balaenopterae, A. pacificus*) have been occasionally documented in Europe [12,15-17], and very recently a series of 7 cases of *D. nihonkaiensis* infection was reported to be acquired in France, or at the very least, in Europe [18], while this parasite species is not endemic in this area. These seven cases were diagnosed over a short period (about 2 years), in a limited area (East part of Brittany, France), contrasting with the absence of cases of diphyllobothriosis during many years. All patients were customers of Japanese restaurants or consumers of sushis, and none of them had traveled to the Northern Pacific area where *D. nihonkaiensis* is highly prevalent [7,16], clearly indicating that infection was acquired through imported

fish, namely Pacific salmon which is both an intermediate host of this parasite and a commonly-used fish for sushi preparation. *Dibothriocephalus nihonkaiensis* is reported with an increased frequency in Japan, where it accounts for an estimated 100 to 200 cases of autochthonous infection per year, as well as for travelers' infections [18].

These findings underline that modification of food habits due to the increasingly popular and fashionable consumption of raw fish and particularly of Japanese sushi, can rapidly modify the epidemiology of parasite infections at a time of globalized fish market. Indeed, geographic distribution of parasites can be easily influenced by worldwide transport of fresh fish on ice, towards geographical areas from which diphyllobothriosis was not detected previously, or where another species was endemic, raising the question of potential transmission to susceptible intermediate hosts or even to wild definitive hosts present in the local environment. At a time when eating habits and climate are changing, tracing sources of infection is important to prevent potential implantation of parasites in new areas. Of course, this would imply that the parasite larvae would adapt to other copepod and fish species than their original intermediate hosts, but this has been previously seen with the newly-described infection of rainbow trout (*Oncorhynchus mykiss*) with *D. dendriticus* plerocercoids in Chile [20].

Even though diphyllobothriosis is not a life-threatening human disease, it is necessary to achieve accurate diagnosis. Diphyllobothriideans cannot be identified at species-level morphologically, but this is not required because all species are treated in the same way. However, molecular identification is crucial to update epidemiological data and to track the geographic distributions of species in Europe or other low endemic countries, where diphyllobothriosis could re-emerge. Kuchta et al. previously addressed the same question, when cases of infection with *A. pacificus* were diagnosed in Spain, probably due to imported fish from South America [12]. Regarding the recent French cases, it would be of interest to know where imported salmons came from exactly, as the pathogen exists not only in Japan, but also in Korea, Northern Eastern China, Northern Eastern Russia and North Pacific coast of Northern America [19], and if they were delivered to other European countries. Whether Atlantic

salmon farms of Northern Europe could be contaminated with *D. nihonkaiensis*, although very unlikely, is another question which could be investigated, and requires life cycle adaptation, as stated above. In any case, it is very astonishing that only *D. nihonkaiensis* infection seems to increase, as one would imagine that Atlantic salmon is also used with increasing frequency for sushi preparation, and it is known to be commonly infected with autochthonous species (*D. dendriticus* and others).

3. Diagnosis and treatment: an easy track

Diagnosis of diphyllobothriosis relies on morphological analysis of proglottids of worm fragments emitted with stools: they are trapezoidal, with a central uterine pore and a rosette-shaped uterus. Eggs can be found by microscopic examination of stools. They are ovoid, operculate, with a thin tainted shell, and unembryonated at emission. Length of eggs can vary depending on the species [8]. However, morphological characteristics do not allow to identify the parasite at species level, but only as Diphyllobothriid. For species identification, sequencing of a mitochondrial marker like the *cox1* gene is needed [16].

Diphyllobothriosis is easily cured with a single oral dose of praziquantel. Sensitivity to treatment seems variable depending on the species, but a 10 mg/kg administration is usually sufficient [8]. Elimination of the parasite should be controlled 3 to 4 weeks after treatment by microscopic examination of stools for ova, and in case of treatment failure a 25-50 mg/kg dose can be administered. Praziquantel has only few side effects and its only contraindications are concomitant ocular cysticercosis and co-treatment with rifampicine. If necessary, diphyllobothriosis can be also treated with niclosamide (2 g regimen for adults and 50 mg/kg for children under 6-year old) [8]. However, niclosamide is less frequently available, and administration should be divided into 2 intakes 1 hour apart, with no food uptake up to 3 hours after the last dose, which is quite laborious compared to praziquantel. To date, no clear drug resistance of Diphyllobothriid tapeworms has been described.

4. Prevention: don't forget the basics!

Beyond all the epidemiological considerations, it is remarkable that the European regulation (EC, no 853/2004) requiring freezing fish destined to raw consumption is obviously not applied by all food

providers. This simple measure has contributed to reduce the prevalence of infection in Northern Europe where it was highly endemic, however, this is not currently applied in Japan [19]. Whether true amateurs of sushi esteem it decreases the taste properties of the product might be considered, and could explain a lack of observance of sushi providers. Anyway, they should be reminded to follow the European regulation, which is very clear. Additionally, warnings regarding fish-borne parasites should be provided to the consumers of raw fish, and information concerning means of prevention should be disseminated to avoid a burst of cases in endemic and non-endemic countries. Finally, continuous medical education programs should include the topic of fish-borne parasites to help general practitioners diagnosing these infections.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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