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Review Article

Opisthorchiids, Heterophyids and Aquaculture: A Brief Review

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Abstract

Fish borne zoonotic trematodes (FZTs) affect millions of people worldwide especially in Asian countries and are of considerable economic importance because of their various degrees of morbidity and economic losses. They are normally transmitted to the definitive host by consumption of raw or improperly cooked fish harbouring viable metacercariae. The life cycle is complex which requires two intermediate hosts (snails & fish) and one definitive host (human). Interestingly, they can also complete their life cycle in the hosts other than the humans (reservoir hosts) which play a great role to maintain the infection in the environment. Diagnosis is mainly done by demonstration of eggs and adult parasites from infected definitive or reservoir host and recently, it is complemented by molecular techniques. These trematodes are mostly prevalent in the countries with traditional aquaculture practices. So, proper aquaculture practices should be followed and the production of parasite free fish for human consumption should be a key objective for the aquaculture industry. This review summarizes the global status, life cycle pattern, pathology, diagnosis and also some recommendations for prevention and control of the fish borne zoonoses.

Keywords: Aquaculture; Fish; Metacercariae; Opisthorchiidae; Heterophyidae; Zoonoses

Introduction

There are many helminths which are transmitted to humans from lower vertebrates and vice versa. Out of many helminths including trematodes (*Opisthorchis* spp., *Clonorchis sinensis*, minute intestinal flukes), cestodes (*Diphyllobothrium* spp., *Spirometra* spp.), nematodes (*Gnathostoma* spp., Anisakids); fish-borne zoonotic trematodes (FZTs) represent an important group of human parasites (Dorny et al., 2009; Lima dos Santos & Howgate, 2011). FZTs are found within four families, i.e. Opisthorchiidae, Heterophyidae, Nanophyetidae and Echinostomatidae (Class: Trematoda Rudolphi, 1808; phylum: Platyhelminths Genenbaur, 1859). However, the trematodes of the family Heterophyidae (*Haplorchis taichui*, *H. pumilio*, *Heterophyes nocens*, *H. continua*, *Metagonimus yokogawai*, *M. takashii* etc.) and Opisthorchiidae (*Clonorchis sinensis*, *Opisthorchis viverrini*, *O. felineus* etc.) are of common occurrence in East and Southeast Asia (Sohn & Chai, 2005). Liver flukes, *Opisthorchis* spp. & *C. sinensis* are very important trematodes with a high impact on human health in many countries (WHO, 2011). Heterophyids are small intestinal trematodes that infect susceptible hosts and responsible for significant morbidity, food safety and quality problems (Toledo et al., 2006). Fish borne trematodes have a complex life cycle with two intermediate hosts and one definitive host. Larval stages may occur in either invertebrate or vertebrate hosts. The first intermediate host is always snail which plays very important role in the development of life cycle stages like sporocyst, rediae, and cercariae. Fish act as a second intermediate host and transmit infection to the susceptible hosts. The life cycle stages allow them to withstand external conditions like excreta, soil, and water and use different intermediate, definitive and reservoir hosts including humans to complete their life cycle (Chai et al., 2005). The reservoir hosts can act as a source of infection for definitive and intermediate hosts. These adaptive features of intermediate stages of parasites enable a wide variety of transmission modes to the hosts including human. People get infected with FZTs if they eat raw or undercooked freshwater and sometimes brackish water fish containing active metacercariae (Keiser & Utzinger, 2009). The presence of the snail, fish and mammalian host (including man) is essential to transmission, and this combination must be sustainable for the parasite to remain endemic in a region.

Global status

Food-borne trematodoses are one major group of the neglected tropical diseases (NTDs) worldwide with more than 40 million people infected (WHO, 2011) and 750 million (10% of the world's total population) are under the risk (Keiser & Utzinger, 2009). According to Keiser & Utzinger (2005), about 600 million and 80 million people are at risk for infection with *C. sinensis* and *Opisthorchis* spp., respectively. For *C. sinensis*, 35 million people are already estimated to be infected. (Lun et al., 2005; IARC, 2012). In southeastern Asia, more than 90 million people are at risk of infection, and at least 10 million people are estimated to be infected by *O. viverrini* (Andrews et al., 2008). These zoonotic trematodes are mostly prevalent in the East Asian countries because of traditional feeding habits and aquaculture practices. But, few human reports are also available from the countries other than Asia. The distribution and human case reports of the trematodes of Opisthorchiidae and Heterophyidae are presented in Table No.1.

Aquaculture and Fish borne Zoonotic Trematodes

Over the past three decades, the aquaculture sector has developed to become as one of the fastest growing food producing sectors in the world and it has been estimated that more than 80% of global aquaculture products for human consumption is produced in fresh water (Hastein et al., 2006). As the human population continues to grow, there is an ever growing demand to increase production by utilizing water resources such as ponds, canals, cages, reservoirs, lakes, rivers, etc. (Phan et al., 2010) for cultivation of aquatic species to get animal protein, particularly in the tropics (Davies et al., 2006). However, the aquaculture practices throughout the Asia are almost similar (Guo, 2001). Manure from the animal husbandry (domestic pig, poultry etc.) and human night soil is used to fertilize ponds. The byproducts of fish are often fed to dogs, cats or pigs. The recirculation of waste material including human and animal manure is conducive for the life cycle of FZTs. Eggs of trematodes are released in faeces of their definitive hosts into the pond, where snails and fishes are available as the first and the second intermediate hosts respectively. Thus, culture practices using excreta from final hosts as manure in ponds can enhance the persistence of FZTs (Lima dos Santos & Howgate, 2011). Moreover, the exponential increase in aquaculture is suggested to be the major cause of the emergence of FZTs in East and Southeast Asia (Keiser & Utzinger, 2005). The fish species in the carp poly-culture, which belongs to the family of Cyprinidae, are considered to be the most suitable intermediate hosts for FZTs (WHO, 1995; Sukontanson et al., 1999). More than 100 species of freshwater fish have been shown to be naturally infected with *C. sinensis* and more than 35 species with *Opisthorchis* spp. (Adam et al., 1997). As aquaculture practices are similar throughout all of Asia; these practices may directly impact on the prevalence and persistence of FZTs (WHO, 2011).

Life cycle of Fish borne trematodes

The transmission of the parasite to the fresh-water snail host (first intermediate host) is related to the defecating habits of the definitive hosts (human) and other fish-eating mammals (Dog, Cat etc.) resulting in contamination of water by the faeces containing the eggs of flukes during the rainy season (Mas-Coma & Bargues, 1997). Pigs and poultry are penned alongside the ponds and their excreta are used directly as manures. Cattle, dogs, cats and other animals, not necessarily domestic, which are reservoir hosts for the parasites may live in the vicinity of fish farms and their excreta too can enter the ponds. All the human and animal fecal material contributes to the maintenance of high numbers of trematode eggs. The freshly passed eggs are mainly eaten by freshwater snails, mostly of the genus *Bithynia* spp. Young snails (1-3 month-old) are more susceptible than older snails (Chanawong & Waikagul, 1991). In the snail, miracidium hatch in the intestine or rectum and penetrate the rectal wall to reach perirectal tissues and develop as sporocyst (Rim, 1982) within 4 hrs of infection (Yamaguti, 1975). Rediae are liberated from sporocyst 16 days after infection (Komiya, 1966). Cercariae are released into water bodies from rediae as free swimming stage where they penetrate the scale and skin of the fish, lose their tail, and encyst (metacercariae) chiefly in muscles (Vichasri et al., 1982) and head of the fish (Tesana et al., 1985). When infected fish is ingested by a suitable definitive or reservoir host, the metacercariae excyst in the duodenum, and mature or migrate through the common bile duct to the intrahepatic bile ducts, where they mature in 3-4 weeks (Kaewkes, 2003). The metacercariae grow to the adult stage in about 4 weeks after infection (Rim, 1986) and eggs are released into water through human and animal fecal material (Phan et al., 2010). The presence of snails and cultivated cyprinids in the water combined with the traditional habit of consuming raw fish complete the FZTs life cycle so that humans are infected (Figure 1).

Transmission and public health importance

Transmission of fish-borne trematodes is greatly dependent on behavioral patterns determined by food habits, socio-economic and cultural conditions in endemic areas. These trematodes can be transmitted to humans through consumption of improperly cooked fish or raw fish containing the infective metacercarial stage of the parasite (Ziegler et al., 2011). In some places, human has the habit of eating raw, pickled, or insufficiently cooked fish (Sripa et al., 2010). Further, fresh water or brackish-water fish are consumed as sushi and sashimi in some countries like Japan. Travelers dining in local restaurants or street shops of such countries can be expected to have much higher risks of infections with various parasites (Nawa et al., 2005). The public health importance of these species is due to their wide geographical distribution, high prevalence and severe morbidity (MacLean et al., 2006; Lima dos Santos & Howgate, 2011). They have long been known to cause serious disease in certain areas of the world. The incidence of the diseases may also increase if poor sanitation habits persist and no effective control measures are put in practice (Phan et al., 2011).

Infection pattern

Human infection follows by the consumption of raw or improperly cooked fresh water fishes, containing metacercariae (Kumchoo et al., 2003). Since the source of infection may be the same, mixed infections often occur in some patients (Chai et al., 2005). These trematodes may affect the liver, small intestine, and other organs producing disease of different intensities viz. mild to debilitating (Nguyen et al., 2009). Generally, infections by liver flukes are asymptomatic, but high levels of infection and chronic infection cause damage to the bile duct epithelium, eliciting gastrointestinal problems and damage to the liver and possibly cholangiocarcinoma (Lun et al., 2005). However, the degree of pathogenicity and clinical involvement depends largely on the number of parasites and the duration of infection. If the infection is intensified by continued exposure, the pathological process may extend to the bile ducts, gall-bladder and result in cirrhosis (IARC, 1994). The liver flukes, *C. sinensis* and *Opisthorchis* spp., are reported to be the major causative agents of bile duct cancer (Sithithaworn et al., 2012). Due to the strong association of liver fluke infections and cholangiocarcinoma, *C. sinensis* and *O. viverrini* have been rated as Class-1 carcinogens by the International Agency for Research on Cancer (WHO, 2011). The minute intestinal flukes may cause inflammation, ulceration, haemorrhage, persistent diarrhoea and other enteropathic conditions leading to malabsorption and protein loss (WHO, 1995). Intestinal flukes can cause serious pathologic changes in the heart, brain, and spinal cord (Toledo et al., 2006).

Diagnosis

As trematodes have multiple life stages, one needs to identify the parasite at any of the stages like egg, metacercariae and adult parasite to diagnose and suggest remedial measures. In parasitology, diagnosis is mainly done on the basis of demonstration of eggs in a faecal sample. But, eggs of Opisthorchiids such as *C. sinensis*, *Opisthorchis* spp. and a range of species within the family Heterophyidae have almost similar morphology, and identification of parasite based only on light microscopy is problematic (Districh et al., 1992). So, it is often difficult to distinguish between such morphologically similar trematodes, particularly for the eggs and larval stages, using standard methods (Wongsawad et al., 2009). To address this issue, molecular techniques are at present considered to be the most reliable, as they dot not only identify the species of the parasite but also detect the variants in same species (Harris & Crandall, 2000). Specific DNA probes/primers have been developed to detect trematodes in the human stool (Wongratanacheewin et al., 2002) and in fish (Parvathi et al., 2008). PCR targeting ribosomal DNA has been investigated to discriminate *O. viverrini*, *C. sinensis*, *H. taichui*, and *H. pumilio* in the mixed infection (Sato et al., 2009). Cytochrome oxidase I (COI) sequence marker has been also introduced to separate *O. viverrini* and *H. taichui* (Thaenkham et al., 2007). Internal transcribed spacer (ITS) regions to determine life cycle stages of Heterophyid trematodes (Skov et al., 2009) and multi locus enzyme electrophoresis (MEE) has been performed to determine genetic markers of *O. viverrini* (Saijuntha et al., 2006). Multiplex PCR has been successfully developed to discriminate *C. sinensis* and *O. viverrini* based on mitochondrial genes in mixed infection (Le et al., 2006). A second internal transcribed spacer region (ITS2) has also been used as a genetic marker for identification of several trematodes (Iwagami et al., 2000).

Discussion

Fish borne zoonotic trematodoses remain a public health problem worldwide and are recognized as emerging zoonotic diseases affecting millions of people. These diseases are mostly prevalent in the countries where fish consumption is high especially in south East Asian countries where transmission of the diseases is enhanced by poor hygiene, vectorial abundance and animal reservoirs. These diseases are transmissible to human beings by eating raw or partially cooked fish. Many factors contribute to the high prevalence of the infection, including lack of education, improper diagnosis due to non-specific clinical symptoms, poverty, malnutrition, lack of food inspection and poor sanitation.

Amongst these FZTs, liver flukes (*C. sinensis*, *O. viverrini*, *O. felineus*) and intestinal flukes (*H. taichui*, *H. pumilio*, *M. yokogawai*, *M. takashii* etc.) are the most neglected tropical disease agents (WHO, 2011). Amongst many fishborne parasitic diseases, more than 70 species of trematodes belonging to the family Opisthorchiidae and Heterophyidae are known to be zoonotic (WHO, 2011). They cause significant public health problems worldwide, especially in Asian countries (WHO, 2004; Keiser & Utzinger, 2005) and are recognized as an important group of emerging and re-emerging human pathogens especially to populations living in low and middle-income group of people in different countries (Chai et al., 2005).

Fish harbouring such trematodes are, therefore, significant from public health point of view, especially in Asian countries (Keiser & Utzinger, 2005). The strong cultural preferences in many countries, particularly in Asia, for eating raw or insufficiently cooked infected fish are believed to be the greatest risk factor for human infection. Coupled with this, globalization of the food supply, increased international travel, increase in the population of highly susceptible persons, and change in culinary habits are some factors associated with the increased diagnosis of fish borne parasitic diseases worldwide (Dorny et al., 2009). Increased incidences of fish borne parasitic diseases are also due to the development of new and improved diagnosis, increase in raw fish consumption and production due to development of aquaculture (Lima dos Santos & Howgate, 2011). All these factors affect economics in terms of loss of productivity, and health care costs as well as food safety issues (Roberts et al., 1994; WHO, 2004).

In the past, the risk of human infection with these parasites was considered to be limited to distinct geographic regions because of parasites' adaptations to specific definitive hosts, selection of intermediate hosts and particular environmental conditions. However, these barriers are slowly being breached—first by international travel developing into a major industry, and second, by rapid, refrigerated food transport which became available to an unprecedented degree at the end of the 20th century (Orlandi et al., 2002). Assurance of the safety and quality of the products is, therefore vital from public health point of view. But, due to inadequate systems for routine diagnosis and monitoring or for the reporting for many of the zoonotic parasites, the incidence of human disease and parasite occurrence in fish is underestimated.

Future prospects for control and prevention

As farmed raised fish is the main protein source for domestic consumption and an essential product for exporting to other countries, the production of parasite free fish should be a key objective for the aquaculture industry. The control measures should be focused to interrupt the life cycle of the trematodes. Treatment of manure should be done before using as a fertilizer in the aquaculture or commercial food stuff should be used which may reduce the transmission of eggs to the snails. Proper interventions can be made to control the intermediate as well as reservoir hosts and strategic deworming should be done in all the final hosts to break the life cycle. In the endemic areas, mass education is necessary to change the habits related to raw and undercooked fish consumption among the population. PCR-based molecular methods can be applied to check the infection in the definitive as well as intermediate hosts because of their pronounced advantages including simplicity, sensitivity, and their applicability to all life-stages. There is a need for research to understand the complete life cycle pattern and to develop the diagnostic techniques for control of the infections at the transmission level.

Species	*Country/region*	*Human infection*	*First reporter*
Heterophyes heterophyes	Egypt, India	Yes	von Siebold in 1852 (Ransom, 1920)
Heterophyes nocens	Japan, Korea	Yes	Onji and Nishio (1916)
Heterophyes dispar	Egypt, Korea, Middle East	Yes	Looss (1902)
Heterophyes aequalis	Egypt, Middle East	Yes	Looss (1902)
Heterophyes pleomorphis	Uganda	No	Bwangamoi and Ojok (1977)
Twelve other species (subspecies)[c]	--	No	--

Table 1: Reports of important zoonotic Opisthorchiids and Heterophyids in different countries.

A. Imported human cases were reported in Korea (Eom et al., 1985a, Eom et al., 1985b, Chai et al., 1986a, Chai et al., 1986b).
B. Imported human cases were reported in Japan (Kagei et al., 1980)(Eom et al., 1985a, Chai et al., 1986b).
C. H. dispar limatus was synonymized with H. dispar (Witenberg, 1929). The validity of H. elliptica has been questioned (Waikagul and Pearson, 1989).H. aegyptiaca, H. fraternus, H. persicus, H. heterophyes sentus, H. inops, and H. palidus, were synonymized with H. heterophyes (Witenberg, 1929). H. katsuradai was synonymized with H. nocens (Witenberg, 1929). H. superspinata (syn. H. bitorquatus) and H. chini have been transferred to another genus Alloheterophyes (Pearson, 1999).

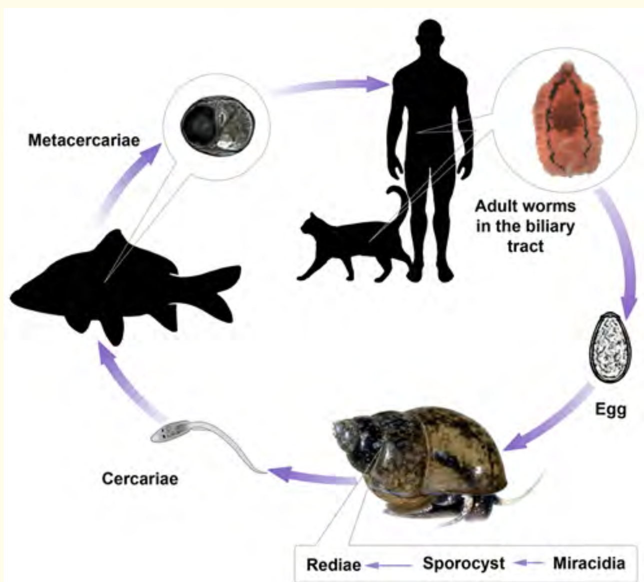

Figure 1: Life cycle of Opisthorchis felineus (Nikita I. Ershov *et al.* 2019).

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