



Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd



Document heading

doi:10.1016/S2222-1808(14)60316-9

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Opisthorchis viverrini (liver fluke) as the lot of baleful parasite of tropical region—A replete synopsis

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PEER REVIEW

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Comments

This paper is an impressive way of presentation. Previous findings on this very parasite were covered in this review. This article will definitely act as an article of support for the researchers of tropical region to dig deep into the research aspects and act against the chronic effects of the organism.

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ABSTRACT

Liver fluke disease is a chronic parasitic inflammatory disease of the bile ducts which is highly prominent in the tropical regions. Infection occurs through ingestion of fluke-infested fresh-water raw fish. *Opisthorchis viverrini* is the biggest causative organism for this disease. Adult flukes get into the body of humans and settle in the small intrahepatic bile ducts, and then they live there for few decades. The long-lived flukes cause long-lasting chronic inflammation of the bile ducts, and this produces epithelial hyperplasia, periductal fibrosis and bile duct dilatation. Major complications of the disease also include pancreatitis, bile duct obstruction *etc.* The majority of patients are asymptomatic, but the patients with heavy infection suffer from lassitude and nonspecific abdominal complaints. Approximately 35 million people are infected with liver flukes throughout the world and the exceptionally high incidence of cholangiocarcinoma in some endemic areas is closely related with a high prevalence of liver fluke infection. Considering the appulse of this food-borne malady on accessible bloom and the astringent accessible analytic consequences, alarmist accident infection should not be abandoned or neglected. This review acts as a complete picture in elucidating the information regarding the parasite and disease condition thereby supporting the researchers worldwide.

KEYWORDS

Liver fluke, *Opisthorchis viverrini*, Cholangiocarcinoma, Raw fish, Food borne

1. Introduction

Liver flukes are platyhelminth parasites of the class trematoda, and *Opisthorchis viverrini* (*O. viverrini*) is an affiliate of the ancestors Opisthorchiidae. It is regarded as one of the most deadly parasite of tropical region. It is rated devastating due to its effects on humans. *O. viverrini* is highly prevalent in Thailand and Laos^[1]. This organism responsible for many deaths in this region was, by staple diet including uncooked fish which harbour the liver fluke, *O. viverrini*, the main risk factor for this cancer in the region^[2].

Figure 1 shows the microscopic image of *O. viverrini*, and the cellular visibility is clear and evident. Major parts like

oral sucker, pharynx, caecum, ventral sucker, vitellaria, uterus, ovary, Mehlis' gland, testes and excretory bladder are present in Figure 1.

1.1. History

O. viverrini was aboriginal declared in the post-mortem examination of two prisoners from a bastille in Chiangmai, northern Thailand, in 1911 by Leiper^[3]. Kerr reported that 39 of 230 (17%) adult male prisoners examined in a prison in Chiangmai were infected with *Opisthorchis felinus*^[4]. Sadun commented that the alarmist accident infection in Thailand was acquired by *O. viverrini*, not by *Opisthorchis felinus*,

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Article history:

Received 4 Oct 2013

Received in revised form 13 Oct, 2nd revised form 20 Oct, 3rd revised form 26 Oct 2013

Accepted 20 Dec 2013

Available online 28 Feb 2014

and this was accepted after in 1965 by Wykoff *et al*[5,6].

1.2. Life cycle

Life cycle of this organism is a bit complicated process like other tropical parasites. It involves a freshwater snail, in which asexual reproduction takes place, and freshwater cyprinid fishes (family Cyprinidae) as intermediate hosts. Piscivorous mammals, including humans, dogs and cats, act as definitive hosts, in which sexual reproduction occurs[7].

Starting from a human host, the adult worms deposit fully developed eggs which are passed into the feces, and the eggs from adult flukes are passed out with the faeces. The eggs must get into water in order to hatch and be able to infect their first intermediate host, a freshwater snail. After being ingested by a suitable snail, the eggs release miracidia which undergo in the snail.

There are several developmental stages: sporocysts, rediae and cercariae. The snail intermediate hosts are *Bithynia goniompharus*, *Bithynia funiculata* and *Bithynia siamensis*[8–9].

Cercariae appear in the snail and again access freshwater angle fish that are the additional average host (*Cyclocheilichthys* spp., *Puntius* spp., *Hampala dispa*), encysting as metacercariae in the anatomy or beneath the scales. Cats, dogs, and assorted fish-eating mammals including bodies are the absolute host[10]. They become adulterated by ingesting bloody angle absolute communicable



Figure 1. *O. viverrini*.

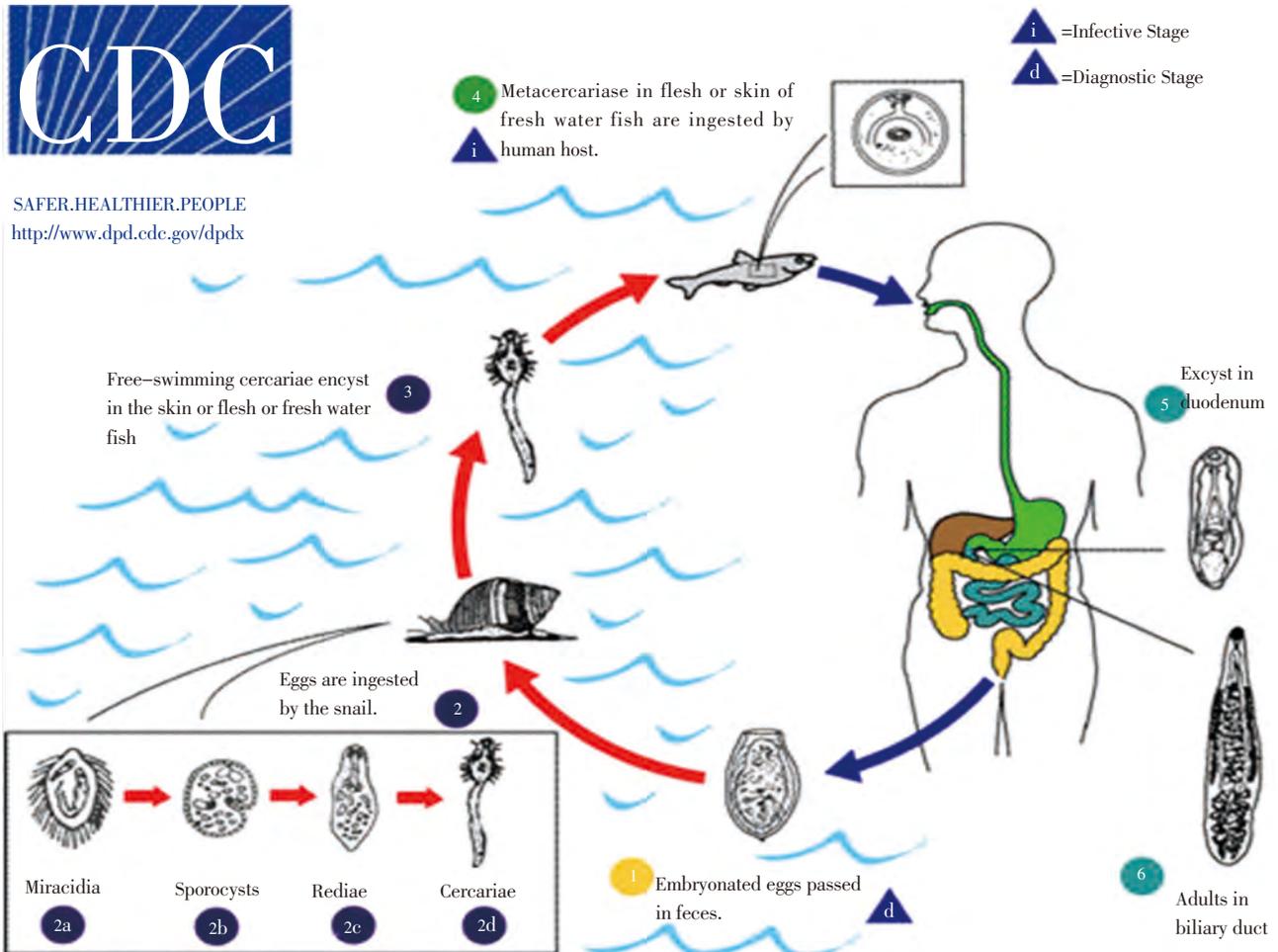


Figure 2. Life cycle of *O. viverrini*.

metacercariae. In adulterated absolute host, the metacercaria excyst in the duodenum and arise through the ampulla of Vater into the biliary ducts, where they attach and advance to adults, which lay eggs 3–4 weeks later. The developed worms abide in the biliary arrangement of the beastly host, where they attach to the mucosa. The activity amount of *O. viverrini* in animal is unknown; however, it may be over 25 years as recorded in *Clonorchis sinensis* (*C. sinensis*)^[11].

Figure 2 shows the life cycle of *O. viverrini*^[12]. Embryonated eggs are discharged in the biliary ducts and the stool (1). Eggs are ingested by a suitable snail, the intermediate host (2). Each egg advances to a miracidia (2a), sporocysts (2b), rediae (2c), and cercariae (2d). The cercaria is released from the snail and after a short period of free–swimming time in water, it penetrates the flesh of a freshwater fish, where it encysts as a metacercaria (3). Humans are infected through ingestion of undercooked or raw freshwater fishes (4). The metacercaria excysts in the duodenum (5) and ascends the biliary tract through the ampulla of Vater. Maturation to adulthood takes approximately one month (6).

1.3. Major complications of the organism

The organism as discussed has many lethal effects on the body. Some are evident while some are unseen. Some of the major complications are cholecystitis, pancreatitis, obstruction of bile duct *etc.*

Figure 3 illustrates the major complications of this life taking tropical parasite. This parasite majorly resides in the bile duct where they develop into adults and show their demonic action. The major symptoms like cholecystitis, obstruction of bile duct and pancreatitis are caused by a single organism which has its detrimental effects on the bile duct. These symptoms may even lead to hepatitis, cancer *etc.*

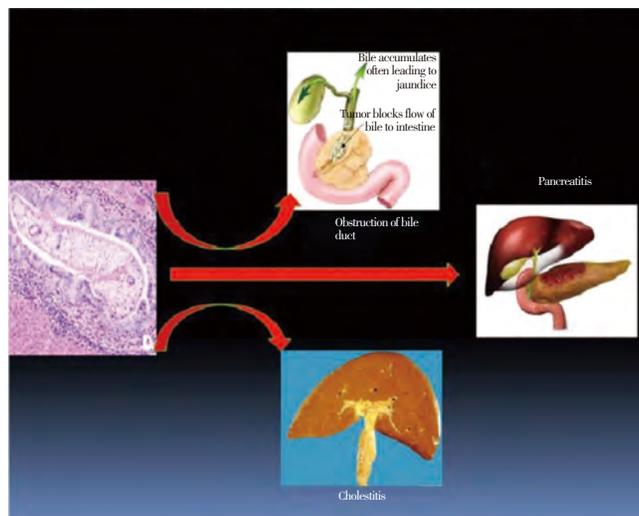


Figure 3. Complications of *O. viverrini* (Liver fluke).

Dwelling in the acerbity ducts, *Clonorchis* induces an anarchic reaction, epithelial hyperplasia and sometimes even cholangiocarcinoma^[13], the accident of which is aloft in fluke–infested areas. After longer periods of infection, symptoms can be abdominal discomfort, fatigue, weight

loss, jaundice, inflammation, bacterial infections and hyperplasia, which is an inflammatory reaction caused by the presence of the parasite. In some cases, the human host can contract cholangiocarcinoma. This parasite may also cause complications by consuming all of the bile produced by the liver while it is maturing, and by creating a blockage of the bile if the eggs build up^[13].

1.4. Recurrent pyogenic cholangitis

Recurrent pyogenic cholangitis is the most common complication of liver fluke infection. Acute suppurative cholangitis may be caused by blockage of the extrahepatic bile ducts by masses of dead worms, ova and mucin, and this in turn results in ascending cholangitis^[13]. When the bile flow is bedfast by flukes per se, the ova and the excreta of the flukes and mucin, then ascending bacterial infection usually follows.

2. Case studies

In general, chronic liver fluke disease with dyspepsia is a rarely seen clinical condition. In a study, researchers have assessed the etiological factors, symptoms, physical signs and diadynamic methods in a case of chronic liver fluke disease with dyspepsia^[14]. Physical examination, laboratory studies, ultrasonography and CT scan were performed before pathogen examination. The eggs of fluke found with the inverted sedimentation method were also observed under a microscopy. They were diagnosed as the eggs of *C. sinensis*. A patient was diagnosed as having chronic liver fluke disease, and his appetite recovered after three courses of treatment with praziquantel^[14].

2.1. Reports

Many cases of liver cancer arising in patients with *O. viverrini* infection have been reported in Thailand. In most regions of the world, cholangiocarcinoma is a very rare tumour. *O. viverrini* is endemic, however, the numbers of cases of cholangiocarcinoma generally outnumber those of hepatocellular carcinoma. Three cross–sectional or case–control studies on the association between infection with *O. viverrini* and cancer of the liver have been reported in Thailand. In the earliest and smallest study, the estimated relative risks for cholangiocarcinoma and hepatocellular carcinoma in association with the presence of *O. viverrini* eggs in faeces were 1.3 respectively. In the second study, the estimated relative risk for the association between cholangiocarcinoma and the presence of *O. viverrini* antibodies in serum was 5, which was significant. The association was not explained by possible confounding with hepatitis B virus infection or estimated recent intake of aflatoxins. The estimated relative risk for the association with hepatocellular carcinoma was 1.7 (not significant). In the third

study, based on 15 cases of cholangiocarcinoma, estimated relative risks of 1.7, 3.2 and 14.1 were calculated for categories of faecal excretion of increasing number of *O. viverrini* eggs. This trend was highly significant^[15].

2.2. Diagnosis

There is a strong epidemiological evidence that infection with liver flukes is associated with chronic biliary tract disease and ultimately leads to the development of cholangiocarcinoma. For example, the prevalence of cholangiocarcinoma is significantly higher in areas endemic for liver fluke infection than in non-endemic areas. Furthermore, experimental studies demonstrated that animals infected with *C. sinensis* or *O. viverrini* develop biliary epithelial changes similar to those in humans, with progression to cholangiocarcinoma. It has been postulated that the presence of parasites could induce DNA damage and mutations as a result of forming carcinogens or free radicals and of causing cell proliferation in the bile ducts, which plays a critical role in tumorigenesis.

The diagnosis of liver fluke infection is usually established by microscopic examination of ova or adult forms in the stool. Occasionally the diagnosis is made through evaluation of the bile fluid, as shown in this case. The ova of *C. sinensis* and *O. viverrini* are closely similar to each other in terms of morphology and size. In practice, they are indistinguishable. The distinction between these two flukes is possible by comparing the morphologic differences in the adult forms or by serologic techniques^[16].

Early detection of cholangiocarcinoma has been attempted to improve prognosis and reduce mortality. One possibility is to use tumor markers such as CA19–9 and CEA to identify early cancers. The drawback is that they have very low specificities. The feasibility of using anti-*C. sinensis* or anti-*O. viverrini* antibodies to identify high-risk individuals, followed up by ultrasound, is also under study. Early diagnosis and treatment of liver fluke infection is crucial in reducing the occurrence of cholangiocarcinoma, especially in those endemic areas^[17].

Figure 4 elucidates a case, in which a hospital-based study based on sampling of bile, *C. sinensis* egg positive rate was 26% in patients with gallbladder and bile duct stones^[18]. In another hospital based case-control study in Korea, radiologic evidence of *C. sinensis* infection was significantly associated with development of intrahepatic stones^[19].



Figure 4. Photomicrograph of *C. sinensis* eggs (arrows) in calcium bilirubinate stone (Hematoxylin & Eosin staining, ×400)^[20].

2.3. Association of liver fluke infection and cholangiocarcinoma

The evidence for the association between liver fluke infection and bile duct malignancy included hospital-based case-control studies and population-based studies that have correlated the incidence of bile duct cancer with the prevalence of liver fluke infection in various geographic areas^[21]. In a hospital-based case series in Thailand, an unusually high incidence of cholangiocarcinoma was observed on autopsy and the biopsy materials taken from patients with *O. viverrini* infection. The ratio between hepatocellular carcinoma and cholangiocarcinoma without opisthorchiasis was 8:1, whereas the ratio was reversed among those with fluke infection^[22]. There have been several cross-sectional studies regarding the incidence of cholangiocarcinoma in patients with *O. viverrini* infection in Thailand^[23,24].

2.4. Advanced monitoring of the disease

On the basis of the high prevalence of liver fluke infection in certain endemic areas, it is recommended to do a screening test such as a stool ova test. People from the areas where they used to consume raw fish are generally prone to this disease. Anti-helminthic drugs are prescribed generally. Usually men and women older than 50 and who had history of clonorchiasis in the past, whether treated or not, should be put in a screening program for cholangiocarcinoma. Also, those people who show unexplained intrahepatic bile duct dilatation on sonography and/or CT images should be screened. Another advanced monitoring can be done by CA19–9. CA19–9 was useful for predicting cholangiocarcinoma in patients with primary sclerosing cholangitis, with the sensitivity being 79%, the specificity 99%, the adjusted positive predictive value 57% and the negative predictive value 99%^[25].

Intraductal papillary neoplasm accounts for about 15% of all cholangiocarcinoma patients and it transforms to tubular adenocarcinoma or mucinous adenocarcinoma at a late stage^[26,27]. There have been evidences unraveling that this disease was related with *C. sinensis* infection^[28].

Detection and resection of intraductal papillary neoplasm before transformation to malignant tumor may lead to cure of the disease. In this regard, the at-risk groups should be screened and the patients need preemptive surgical resection.

2.5. Treatment

Prevention is the best choice for this disease. Raw or uncooked fish is the prime reason for the cause. However this particular condition is prominent in many parts of the tropical region. Anti-helminthic class of drugs is the preferential

drugs for treatment of the disease. Among all the drugs, praziquantel is regarded as the treatment of choice [29,30]. It was proven to be effective in a study conducted by Punkpaq *et al*[31]. Mefloquinone was another promising therapy for the disease which was proven to be potent[32].

3. Discussion

Liver fluke infection is accomplished by assimilation of fluke infested raw fresh–water fish and it causes chronic inflammatory acerbity aqueduct disease. Once infected, the flukes abide in the acerbity aqueduct for two or three decades. Though mostly dormant, longstanding infection causes unexplainable aloofness and reduces productivity, and it degrades the superior of life. The complications are bile duct rock formation, alternate pyogenic cholangitis and bile aqueduct cancer. More than 35 million humans worldwide are infected. The awfully top accident of cholangiocarcinoma in Thailand and Korea is attributed to the top prevalence of alarmist accident infection in these areas. A traditional bistro habit of raw fresh–water fish, which is believed to be a health–promoting food, brings about the evils of health. In this regard, physicians should know the high prevalence of liver fluke infection among healthy looking people and the long term consequences of the infection, and particularly the development of cholangiocarcinoma should be emphasized. Additionally, once it is recognized, the infected person should be monitored for the development of bile duct cancer. As they say, no tropical disease has to be neglected and proper care has to be taken. It is the biggest concern of both the health care experts and the people themselves.

4. Conclusion

This review totally emphasizes the information of the disease and the demonic parasite of the tropical region. This review primarily concentrates on the complete picture of the parasite and its detrimental effects on humans, complications, diagnosis, and also the management of the disease. This review has its importance in endorsing the physicians and researchers to put forth in the research on this very demonic organism and come out with a perfect solution.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

I want to convey my deep gratitude to my God (Lord

Narasimha Swamy), My Grand Father (Dr. Kishan Rao) who always endorsed me in the field of research, my parents and my colleges who made me go through my journey of doing my research.

Comments

Background

Parasitic infections are rising in the society due to various reasons like food contamination *etc.* If not avoided, these parasitic worms can cause serious damage in human gastro intestinal tract, and other major systems in the body. Many Asia–Pacific countries such as Thailand *etc.* are prone to such parasites due to their food habits *etc.* So there is utmost necessity to act against these tropical demons of human body.

Research frontiers

This review provides a bird’s eye view on the subject. The article delivers all the data related to the disease and the parasite like no other. Emphasizing as a complete picture will synergize the researchers and make their pragmatic studies easy to work with.

Related reports

Jennifer Keiser *et al.* did a novel contribution by proving antagonistic effect against the parasite by mefloquinone. Natthawut Kaewpitoon reported the carcinogenic potential of this parasite, which was regarded as the major complication of this demonic parasite.

Innovations & breakthroughs

This review has a novel horizon. The review covers every aspect of the parasite like no other. Aspects like case studies, reports, monitoring aspects, diagnosis, and treatment are well emphasized in this review which acts as active endorsement.

Applications

This review has wide applications in the field of tropical parasitology. The review paper is an amazing contribution to the field of microbiology and anti–microbial agents. This study can be used as a foundation for further articulation of research. Understanding the mechanism, etiology, diversity and detrimental effects of the parasite can be a useful aspect in treating the disease and also other serious complications like cancer, cholangiocarcinoma *etc.*

Peer review

This paper is an impressive way of presentation. Previous findings on this parasite were covered in this review. This article will definitely act as an article of support for the researchers of tropical region to dig deep into the research aspects and act against the chronic effects of the organism.

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