Parasitology International 61 (2012) 17–24

Contents lists available at ScienceDirect

Parasitology International

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

Clonorchis sinensis and clonorchiasis, an update

Sung-Tae Hong [a,*], Yueyi Fang [b]

[a] Department of Parasitology and Tropical Medicine, Institute of Endemic Diseases, Seoul National University College of Medicine, Seoul 110-799, Republic of Korea
[b] Guangdong Center for Disease Control and Prevention, Guangzhou, China

ARTICLE INFO

Available online 30 June 2011

Keywords:
Clonorchis sinensis
Clonorchiasis
Biocarcinogen

ABSTRACT

Clonorchis sinensis is the most common human liver fluke in East Asia. Several studies proved its carcinogenesis in humans and it was reclassified as a group 1 biological carcinogen in 2009. It is still actively transmitted in endemic areas of Korea, China, Russia, and Vietnam. Currently it is estimated that more than 200 million people are at risk of infection, 15–20 million people are infected and 1.5–2 million show symptoms or complications. Several molecules and genes of the fluke have been identified and characterized. Studies on its oncogenesis and omics-based findings have been especially encouraging. Diagnosis of its infection depends mainly on detection of eggs in feces but other methods have been developed. ELISA using crude extract antigen is now popular for its diagnosis. Diagnosis by detecting DNAs from eggs in feces has been developed using PCR, real-time PCR, and LAMP, which have been found sensitive and specific. Imaging diagnosis has been studied in depth and is widely used. Any evidence of clonorchiasis, such as eggs, DNAs, or images, may lead to recommendations of chemotherapy in endemic areas. Praziquantel is the major chemotherapeutic agent for clonorchiasis and recently tribendimidine was found effective and is now under investigation as a promising chemotherapeutic alternative. Sustainable control programs which include mass chemotherapy with praziquantel and education for prevention of re-infection may reduce its morbidity and eliminate its infections in endemic areas.

1. Introduction

Clonorchis sinensis Looss, 1907 is a commonly found human liver fluke of the family Opisthorchiidae. The liver fluke is widely distributed in East Asia and it is heavily endemic in some localities [1]. Although the first human case of *C. sinensis* infection in China was reported in 1878, archeological evidence in Hubei suggested that human infections can be traced back at least 2300 years [2]. Several surveys in China found that the disease was endemic over a much broader geographical area, covering 23 provinces/autonomous regions/municipalities [3]. Other endemic areas are bordering China, such as Korea, East Russia, Taiwan, and Vietnam.

The disease condition by *C. sinensis* infection is called clonorchiasis. The fluke and the human body have adapted well to each other, and most of the infected humans feel minimal subjective symptoms. Only cases of heavy infection or those with complications feel epigastric pain, loose stool, fever, loss of appetite, and general malaise. That is the reason why the fluke has survived in humans and why it is neglected by doctors, health policy authorities, and even infected individuals. However, clonorchiasis is a major and current health problem in most endemic areas. Clonorchiasis is included in control programs of neglected tropical diseases by WHO.

C. sinensis is known to cause cholangiocarcinoma in humans. Since there has been significant scientific evidence of serious complications, it was reclassified as one of group 1 biocarcinogens by the International Agency of Cancer Research in 2009 [4].

This paper reviews recent publications on *C. sinensis* or clonorchiasis to update and summarize scientific developments on this fluke.

2. Biology and life history

The fluke *C. sinensis* is a leaf-shaped slender digenetic trematode, 15–20 mm long and 3–4 mm wide (Fig. 1). It requires 3 different hosts for completion of its life cycle; snails, fish, and mammals. Freshwater snails of *Parafossarulus* sp., *Alocinma* sp., and *Bithynia* sp. are its first intermediate hosts. The snails eat *C. sinensis* eggs in water and miracidia hatch in the body of snails. The miracidium grows to a sporocyst, but a sporocyst develops into 20–50 rediae and a redia produces nearly 50 cercariae. Finally 1000–2500 cercariae from an infected snail are shed into water. The cercariae swim actively to find the second intermediate host [5]. Larval stages in the snails reproduce asexually during summer only. Larval development in snails as determined experimentally occurs in 95 days [6]. Many cyprinid fish are known as second intermediate hosts. When the cercariae meet the second intermediate hosts, they invade the mucous skin of the fish and become encysted metacercariae in the muscle. Maturation of the metacercariae requires 30–45 days as determined by an experimental challenge [6]. The metacercariae are globular and measure 130–

* Corresponding author.
E-mail address: hst@snu.ac.kr (S.-T. Hong).

1383-5769/$ – see front matter
doi:10.1016/j.parint.2011.06.007

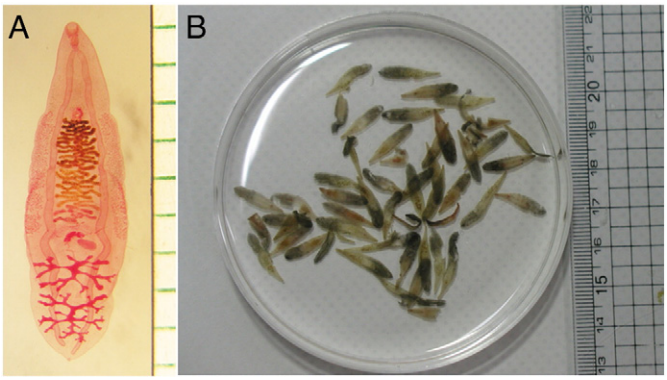

Fig. 1. Adult worms of *Clonorchis sinensis*. (A) Mature worm, acetocarmine stained. (B) Dead worms collected from an infected man after praziquantel medication in Korea.

160 μm in diameter. The larvae can survive in fish muscle for one year until the next summer. When mammals including humans ingest the fish host, the metacercariae excyst in the fish in the duodenum within a few minutes [7] and rapidly migrate into the biliary tree. When the larvae reach the intrahepatic bile duct, they maturate into adults. Adult flukes may live more than 26 years in humans [8]. One worm produces around 2500–3000 eggs every day by sexual reproduction [5]. The eggs flow down to the intestine with bile and pass out via feces and reach water to continue the life cycle.

3. Epidemiology

The distribution of clonorchiasis is determined by the distribution of snails. Humans are infected by eating raw freshwater fish. Fishing and eating of raw fish is a popular and old tradition that has remained habitual and stubborn for thousands of years in endemic areas. The eating habit has resulted in persistent transmission of the liver fluke to humans [9–11].

Adult males are more highly and heavily infected in most endemic areas [10]. This finding reflects the behavioral pattern of fishing and alcohol consumption. Since the life span of *C. sinensis* is around 30 years, infection accumulates through life of humans [11]. Regarding accumulated infection, infection rate and burden, as measured by number of eggs per gram of feces (EPGs), has been recorded as increasing with age and in males [10–13]. In Korea and China, the infection rate and EPGs increased by age from 10 to 40 or 50 years to a peak but decreased in later years in endemic areas. However, most of the recent infected population show light infection with low EPGs by chemotherapy, and the peak has moved to individuals in their 60s [13].

The increasing infection rate and EPGs by age represent two phenomena. One is that the human body is easily re-infected and super-infected. Most susceptible mammals acquire little protective immunity for further infection during present infection or after treatment. Rats, mice, and rabbits are known to be resistant to re-infection and super-infection [14,15]. This is a reason why heavy burden of infection is common in humans in endemic areas. The other one is the drop of infection rate and EPGs after the peak. Because of accumulated infection, people in endemic areas have shown increasing rates and burdens by age, but the rates and burdens have decreased after a peak in their 40s to 60s. The peak infection rate was recorded in their 40s in a heavy endemic area in China where egg positive rate was 40%–70% [12], but it moved to 60s in Korea where the rate was 10%–30% [13]. The major difference between the two study areas was its endemicity. Hong [11] suggested the possibility that the drop of infection rate and burden after the peak age may be an outcome of early death of infected people due to serious complications. Infection of *C. sinensis* is accumulated since immunity of human hosts is not protective to re-infection and super-infection. This life-long accumulation induces more complications among an infected and aged population in endemic areas.

Based on the second national survey on parasitic diseases between 2001 and 2004 in China, the overall *C. sinensis* infection rate of the surveyed population was 0.58% [3]. More surveys at known endemic areas in China examined a total of 217,829 persons, 27 known endemic provinces, and found 5230 (2.4%) positives for eggs of *C. sinensis*[16]. Guangdong had the highest infection rate (16.4%) among provinces, followed by Guangxi (9.8%), and no human cases of *C. sinensis* infection were found in 8 provinces or autonomous regions (Fig. 2). Based on the survey, the number of infected people was estimated at 12.5 million in China [16]. In addition to this estimation, a recent report on clonorchiasis control revealed that a heavy endemic area was widely distributed in Heilongjiang Province along the river basin of Songhuajiang, Mudanjiang, and Heilongjiang, Northeast China [12]. One small survey also found an 18.9% egg positive rate in a village of Liaoning Province, Northeast China [17]. The real population figures of clonorchiasis in China may be over 12.5 million because of distribution of focal hidden endemic foci.

In China, occasional food contamination (e.g. cross-food contamination) was found to be a main risk factor [16]. In addition, other risk factors include a low educational level of local residents and a lack of appropriate sanitation. For example, it is common that in some endemic regions in particular Guangdong and Guangxi, simple lavatories (e.g. no sanitary treatment) are built adjacent to fish ponds. The snails and fish are contaminated in the pond water by human excrement containing *C. sinensis* eggs [16]. Freshwater aquaculture has rapidly expanded with a resulting increase in fish contamination that has resulted from a lack of quarantine measures for fish products [18]. Although clonorchiasis is heavily endemic in several localities, no systematic control measures have been conducted and thus its endemicity is maintained for a long time in many endemic areas in China.

In Korea, the last national survey on the status of intestinal helminthiasis in 2004 recorded a 2.9% egg positive rate of *C. sinensis* in the general population [19]. In endemic areas of course, higher rates of over 10% have been reported in provinces or river basins (Fig. 3) [13]. The data estimate 1.3 million people for clonorchiasis in Korea.

In Russia, the Amur River basin is a known endemic area of clonorchiasis [20]. The river basin is very wide and; at least 1 million people are estimated to be infected in Russia.

In Vietnam, several kinds of fish-borne trematodes infect humans [21]. Of them, 2 liver flukes, *C. sinensis* and *Opisthorchis viverrini*, are distributed in Vietnam. *C. sinensis* is endemic in northern Vietnam, and one million people are estimated to be infected [22].

In Taiwan, clonorchiasis was heavy endemic in 3 localities in southern Taiwan [1]. However, there have been no recent publications that report the status of clonorchiasis, therefore it is difficult to estimate the number of infected people in Taiwan.

Summarizing those recent status reports, it is globally estimated that more than 200 million people are at risk of its infection, 15–20 million people are infected, and 1.5–2 millions have symptoms or signs of *C. sinensis* infection because 10% of them are heavy infected with complications.

4. Pathology and oncogenesis

Infected intrahepatic or extrahepatic bile ducts undergo severe pathological changes [10,11]. The changes are adenomatous hyperplasia of the biliary epithelium, mucin-secreting metaplasia, ductal dilatation, periductal inflammation and fibrosis, and dysplasia or neoplasia of biliary cells (Fig. 4). Most of the pathological changes have been resolved after treatment; however, not complete [11].

The intraductal papillary neoplasm of the bile duct induced by *C. sinensis* was found to be the pancreaticobiliary type and a precursor lesion of cholangiocarcinoma (CCA) [23]. The study suggested a