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REVIEW

Human *Angiostrongylus cantonensis*: an update

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Abstract *Angiostrongylus cantonensis* was first discovered in 1935 and has become an important emerging pathogen causing human angiostrongyliasis. Major outbreaks of human angiostrongyliasis have been reported in endemic regions. Thousands of cases of human angiostrongyliasis have been documented worldwide. *A. cantonensis* has spread from its traditional endemic regions of the Pacific islands and Southeast Asia to the American continent including the USA, Caribbean islands and Brazil. Humans acquire *A. cantonensis* by consumption of raw or undercooked intermediate snail hosts or paratenic hosts. The main clinical manifestations of human angiostrongyliasis are eosinophilic meningitis and ocular angiostrongyliasis. The treatment of this disease includes supportive treatment, corticosteroid therapy, and combined therapy with corticosteroids and anthelminthics. The most effective method for prevention is to persuade people not to eat raw or undercooked intermediate and paratenic hosts.

Introduction

Angiostrongylus cantonensis, a lung nematode, was first discovered in rats in Guangzhou (Canton), China in 1935 by Chen [1], and has now been found in many regions around the world [2]. *A. cantonensis* is recognized as an emerging zoonotic pathogen that has caused hundreds of cases of human angiostrongyliasis worldwide since human *A. cantonensis* infection was first reported in Taiwan in 1945. In the past decades, major outbreaks were reported in endemic regions, especially in mainland China. So far, more than 2,800 cases have been recorded worldwide [2]. This worm not only threatens people living in endemic regions, but also is a big health concern for those entering these endemic zones.

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Life cycle

Life cycle completion of *A. cantonensis* requires both definitive hosts and intermediate hosts (Fig. 1). Rats, as definitive hosts, are infected with *A. cantonensis* after ingesting third-stage larvae. The larvae migrate to the central nervous system (CNS), where they become the fourth and fifth-stage larvae via two molts, and finally develop to adult worms [3]. However, the worms undergo sexual maturity and lay eggs in pulmonary arteries. Eggs hatch into first-stage larvae, which migrate up the bronchial tree, are swallowed and are excreted out with the feces [4]. The larvae in feces are swallowed by intermediate snail hosts and develop after two molts into third-stage (infective) larvae, which can be transmitted to paratenic (transport) hosts such as shrimps, land crabs, frog, lizard and predacious land planarians [5–9], if they ingest infected intermediate hosts. Humans are not natural definitive hosts of *A. cantonensis* but acquire *A. cantonensis* by eating either intermediate or paratenic hosts containing infective larvae (Fig. 1). The worm couldn't complete its life cycle in humans but remains in the central nervous system (CNS) thus causing eosinophilic meningitis or moves to the eye chamber causing ocular angiostrongyliasis.

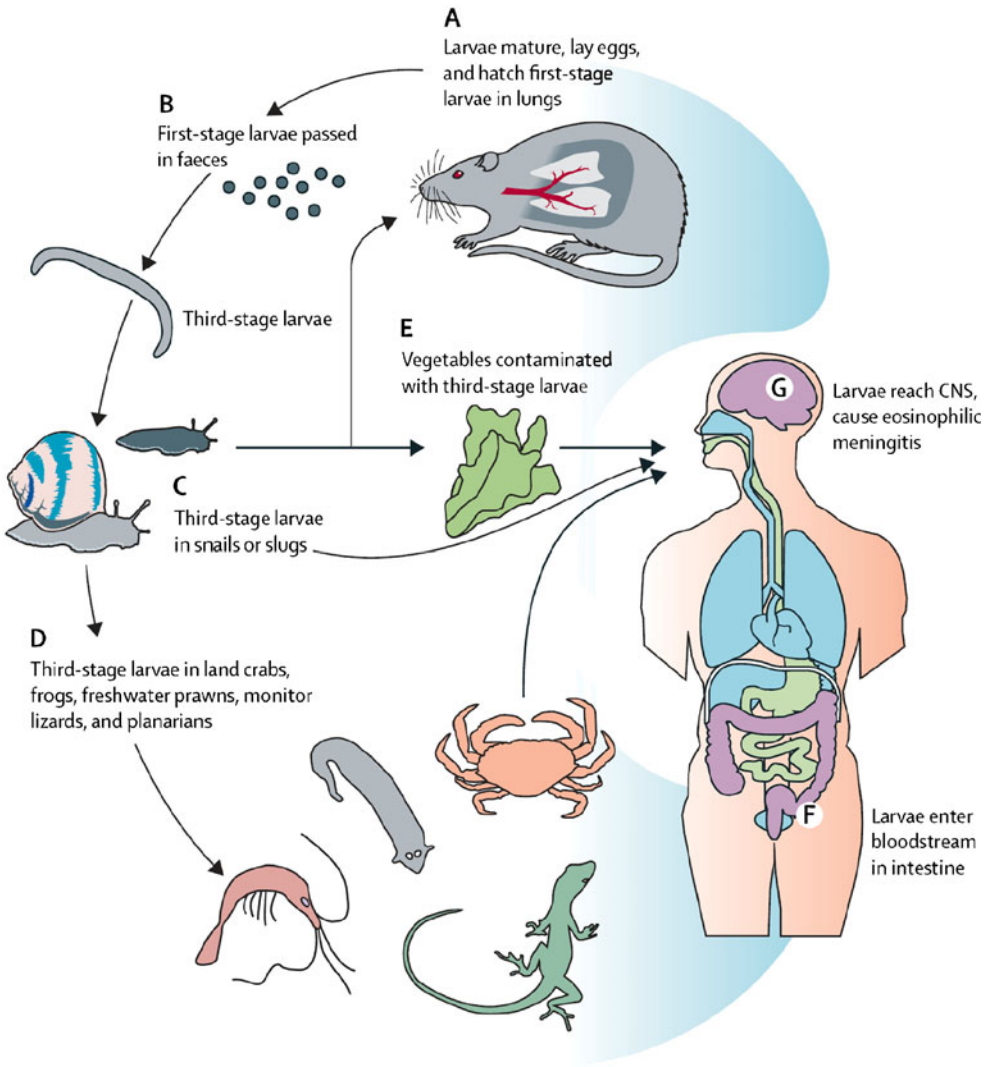

Fig. 1 The life cycle of *Angiostrongylus cantonensis*. The adult worms develop to sexual maturity and lay eggs in the pulmonary arteries (**a**). The eggs are hatched into first-stage larvae (the juveniles), which are swallowed and are excreted out with the feces (**b**). The larvae in feces are swallowed by intermediate host mollusks (snails or slugs) and develop into third-stage (infective) larvae (**c**). The third-stage larvae are then transmitted to the paratenic hosts such as shrimps, land crabs, predacious land planarians and monitor lizards (**d**). Humans occasionally acquire *A. cantonensis* when they eat snails and slugs, and sometimes land crabs, frogs, freshwater shrimps, monitor lizards, or vegetables, which contain the infective larvae (**e**). The larvae are digested from tissues and enter the blood-stream in the intestine (**f**). The larvae finally reach the central nervous system (CNS) and cause eosinophilic meningitis (**g**) or move to the eye chamber and cause ocular angiostrongyliasis. (Adapted from Wang et al. [2])

Molecular biological characteristics

The molecular characteristics of this nematode are incompletely known. The genome of *A. cantonensis* has not been sequenced, but some studies have been done regarding the genes and proteins of this parasite. A cDNA library of *A. cantonensis* fourth-stage larvae which were isolated from the brain of artificial infected mice was constructed and 1,200 clones have been sequenced. The fourth larvae are similar to that found in the patients who were infected with this parasite. Bioinformatics assay revealed 378 cDNA clusters of which 168 contained open reading frames encoding proteins containing an average of 238 amino acids. Characterization of these encoded proteins by gene ontology analysis showed enrichment in proteins with binding and catalytic activity [10]. In addition, a total of 1,277 expressed sequence tags (ESTs) of *A. cantonensis* were randomly downloaded from NCBI and analyzed. According to function, the identified 695 ESTs could be grouped into 13 categories [11]. In addition, some proteins such as cystatin [12], galectin [13], and γ-butyrobetaine hydroxylase [14] of *A. cantonensis* have been cloned and expressed, and their functions have been assayed.

Clinical features

The incubation of human angiostrongyliasis ranges from one day to several months [4]. The most common clinical presentations of this disease are eosinophilic meningitis and ocular angiostrongyliasis. However, a rare and extremely fatal encephalitic angiostrongyliasis was also reported in some cases [15]. The main symptoms for adult patients with eosinophilic meningitis are headache, neck stiff, paresthesias, vomiting and nausea (reviewed in Wang et al. [2]). Aggregated data from Thailand, Taiwan, mainland China, and the USA showed that 95% of patients suffered from headache, 46% had mild neck stiffness, 44% suffered from persistent paresthesia, 38% had vomiting and

28% had nausea. In addition, these symptoms could be accompanied by face or limb paralysis, photophobia, and diplopia. Continuous high intracranial pressure and corresponding damage to the brain and lung may precipitate unconsciousness, coma, and even death in severe cases [16]. However, the symptoms of children differ greatly from those of adults. Stiff neck and paresthesias are observed less frequently in children, but a high occurrence of nausea and vomiting is found, with 82% of pediatric patients having nausea and vomiting. The incidences of fever (up to 80%), somnolence (82%), constipation (76%) and abdominal pain (34.2%) are relatively higher in children than among adults.

Epidemiology

Human *A. cantonensis* infection

Human *A. cantonensis* infection has attracted increasing public attention worldwide due to outbreaks, and also because more and more sporadic cases are being reported in Western travelers in recent years. By 2008, over 2,800 cases of human angiostrongyliasis had been documented in approximately 30 countries [2]. However, there are, no doubt, many more cases, unreported due to lack of awareness of this parasite within the medical community. During the period 2008–2010, an additional 77 cases were reported (Table 1).

Human angiostrongyliasis occurs sporadically or in outbreaks with cases ranging from several to hundreds in endemic regions. A high incidence of human angiotrongyliasis is observed in Thailand. A number of major outbreaks of human *A. cantonensis* infection have been reported in mainland China in recent years (Table 2). However, as endemic areas have widened and international travel has increased, there is a trend in which more and more Western travelers returning from endemic areas are being identified with *A. cantonensis* infection.

Angiostrongylus cantonensis is mainly endemic in the Pacific islands and Southeast Asia where most cases of human angiostrongyliasis have occurred [35]. Presently, however, *A. cantonesis* has spread from its traditional endemic regions to the Americas including the USA, the Caribbean islands and Brazil, where foci for *A. cantonensis* have been discovered and a number of cases have been reported [36–38]. Moreover, sporadic cases have been reported in travelers after returning from Pacific Islands and Caribbean islands [37].

Table 1 Cases of human angiostrongyliasis reported worldwide since 2008

Regions	Cases	References
China	65	[17, 18]
Thailand	8	[19, 20]
India	1	[21]
French	1	[22]
Germany	1	[23]
Jamaica	1	[24]

Table 2 The outbreaks of human angiostrongliasis have been reported in mainland China since 1997

Years	Regions	Cases	References
1997	Zhejiang	65	[25]
1999	Heilongjiang	2	[26]
1999	Liaoning	3	[26]
2002	Fujian	8	[27]
2002	Fujian	13	[28]
2002	Fujian	8	[29]
2003–2005	Yunnan	28	[30]
2004	Zhejiang	3	[31]
2005–2006	Yunnan	31	[32]
2006	Beijing	160	[33]
2007	Guangdong	6	[34]
2006–2008	Guangdong	32	[17]
2007–2008	Yunnan	33	[18]

Sources for human infection

Humans acquire *A. cantonensis* by consumption of raw or undercooked intermediate hosts or paratenic hosts. The main dietary sources for human infection vary by geographic location and dietary custom. In China, *Pomacea canaliculata* and *Achatina fulica* are main vectors for human infection [39]. *P. canalicutus*, native to South America, was introduced to Taiwan and the mainland of China in the 1980s. *P. canalicutus* has replaced the African giant snail, *Achatina fulica*, as a major intermediate host and has become the main source of human infection both in Taiwan and mainland China. The dietary habit of eating raw or undercooked snails (*Pila* spp.) is the main primary route of infection in Thailand [9]. Eating third-stage larvae contaminated vegetables is also an occasional transmission pathway. Contaminated vegetables have been implicated in an outbreak in Jamaica [37] and vegetable juice was involved in an outbreak in Taiwan [40]. The consumption of raw frog is also a sporadic route for infection [41, 42]. Monitor lizard is a main source of infection in India and Sri Lanka [7]. Freshwater shrimps, fish and crabs are suspected sources of infection in the Pacific Islands [43].

The prevalence of *A. cantonensis* in China

China has become one of the major countries where cases of human angiostrongyliasis increased significantly in the

past decade. Therefore, much more efforts have been made to investigate the prevalence of *A. cantonensis* in this country. So far, *A. cantonensis*–endemic foci have been discovered in seven provinces in mainland China [44] (Fig. 2). A retrospective study of published prevalence of *A. cantonensis* in mainland China revealed that 22 of 32 species of wild mollusk species (69%) are infected with the parasite [45]. *A. fulica* has been recorded with the highest rate and intensity of infections, followed by slugs (*Vaginulus* spp.) and *P. canaliculata*. The rates and intensities of infections in terrestrial snails and slugs are higher than in freshwater mollusks. This was confirmed by a recent national survey conducted in China [44]. *P. canaliculata* and *A. fulica* were found in 11 and six provinces, respectively. Out of 11,709 *P. canaliculata* snails examined 6.8% were infected with *A. cantonensis*. Of 3,549 *A. fulica* snails examined, 13.4% were infected with *A. cantonensis*. The infection prevalence among terrestrial snails was 0.3%. A total of 5,370 terrestrial slugs were dissected, revealing an infection prevalence of 6.5%. The prevalence among the other freshwater snails was 0.05%. However, a recent study demonstrated that *P. canaliculata* had an average infection rate of 21%, significantly higher than that of *A. fulica* (10%) in Shenzhen, Guangdong province [17]. *P. canaliculata* has replaced *A. fulica* playing an important role in the epidemiology of *A. cantonensis* in recent outbreaks of human angiostrongyliasis [45].

The retrospective study also revealed that 11 of 15 wild rodent species in mainland China are infected with *A. cantonensis* [45]. *Rattus norvegicus* is the most frequently identified host with a generally higher prevalence and intensity of infection compared with other rodents. This was consistent with a national survey that found 32 of 711 rats infected with *A. cantonensis* (31 *R. norvegicus* and one *R. flavipectus*). Interestingly, *A. cantonensis* was also found in nonhuman primate, equine and canine species. *A. cantonensis* was discovered in paratenic host frog species (*Hylarana guentheri*, *Rana limnocharis*, and *Rana plancyi*) and toads (*Bufo melanostictus*), but has not yet been identified in freshwater shrimp, fish, crabs, or planaria in published studies [45]. *A. cantonensis* was not found in any of 652 paratenic hosts collected during a national survey that included frogs, shrimps, crabs, toads and fish [44].

Diagnosis

Human angiostrongyliasis is confirmed by detection of *A. cantonesis* in patients. However, the detection rate is frequently low [46, 47]. The diagnosis is, therefore, primarily based on clinical symptoms and medical history. The typical clinical manifestation of human angiostrongyliasis is eosinophilic meningitis. However, other causes for this clinical presentation must be considered [48]. Medical history of eating intermediate or paratenic hosts of *A. cantonensis* is critical for diagnosis. The detection of eosinophils and brain lesions are also helpful for diagnosis. Eosinophils account for a large portion of white cell counts in blood and CSF in *A.*

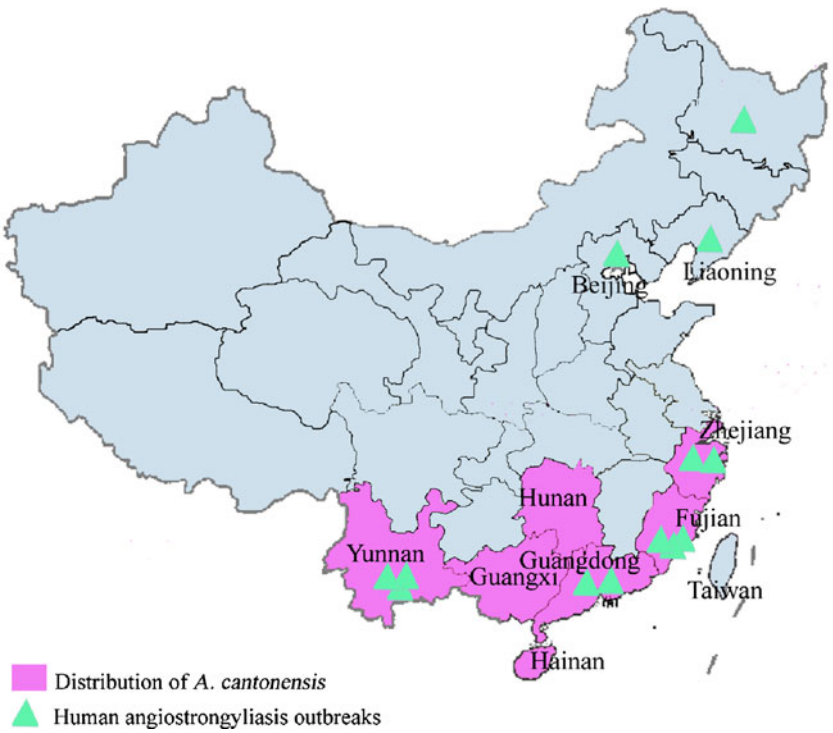

Fig. 2 The distribution of *Angiostrongylus cantonensis* and its outbreaks in China. The endemic regions of *A. cantonensis* are marked in *purple* and those with outbreaks of human *A. cantonensis* are marked with *green triangles*

cantonensis infections [47, 49]. MRI and CT have been used to detect damage in brain for differential diagnosis of *A. cantonensis* from other parasites [50–52].

To effectively diagnose and manage *A. cantonensis* infection, serological tests such as enzyme-linked immunosorbent assay (ELISA) have been developed to detect the antigens of or antibodies against *A. cantonensis* in serum or cerebrospinal fluid. The detection of circulating antigens in serum or CSF provides a rapid confirmation of infection. Monoclonal antibodies (mAbs) against parasite-specific antigens detect circulating antigen with relatively high specificity and reasonably good sensitivity (reviewed in Eamsobhana et al. [53]). Recently, several mAbs against the excretory/secretory (ES) proteins have been developed [54]. The mAbs against an ES protein of 55 kDa have the highest specificity and sensitivity. The detection rate of antigen in the sera of angiostrongyliasis patients was 100% and cross-reactions to normal sera or the sera of patients with other parasitic infection, such as clonochiasis, fasiolopsiasis, ancylostomiasis, anisakiasis or schistosomiasis were not found [55]. In addition, antigens from *A. cantonensis* can also be detected in sera by immuno-PCR [56]. Human antibodies to *A. cantonensis* may be generated after infection. Several specific *A. cantonensis* antigens such as 29 kD, 31 kD, 32 kD and 66 kD have been identified for immunodiagnosis of the presence of such antibodies [57–59].

Treatment

Human angiostrongyliasis displays two main forms of clinical presentation: eosinophilic meningitis and ocular angiostrongyliasis. For eosinophilic meningitis, effective supportive treatments are repeated lumbar puncture and analgesics [46, 47]. Corticosteroid therapy has been effective in human angiostrongyliasis [60]. Anthelminthics, such as albendazole and mebendazole, have been used to treat this disease in attempts to more effectively relieve symptoms and reduce their duration. The mean duration of headache was reduced significantly by using albendazole alone [61]. The combination of corticosteroids and anthelminthics has been commonly used for treatment of human angiostrongyliasis ([62], and also see review in Wang et al. [2]). Currently, some Chinese herbal medicines display efficacy for treating angiostrongyliasis in animal studies but have not been used in humans [63–67]. Surgery is required to remove worms from the eyes of patients with ocular angiostrongyliasis.

Prevention and control

Because of its worldwide distribution, it is impossible to eliminate *A. cantonensis* from the environment. However, it is possible to avoid or reduce human infection by blocking the transmission pathway of this parasite. The simple method is to persuade people not to eat raw or undercooked intermediate and paratenic hosts in endemic regions. Epidemiological surveys indicate that most cases of human angiostrongyliasis would be avoided in this way. Also some rare cases caused by eating contaminated vegetables can be avoided by effective washing. However, the difficulty for prevention is that most people have no or limited knowledge of the worm and are totally unaware of the danger of consuming it. Therefore, one of the most effective measures would be the spread of knowledge regarding *A. cantonensis* and its potential for damage to the health of the general population, especially in remote and poor areas of endemic regions. Another approach is persuading people to abandon their habit of eating raw snails and paratenic hosts. Travelers heading to endemic regions must know the dangers of eating raw mollusks and raw vegetables with unknown sources and should avoid these foods. For physicians in both non-endemic and endemic regions, it is necessary to be aware of the existence of these worms, their symptoms and modes of transmission to suspect and diagnose *A. cantonensis* infection in humans promptly.

Conclusion

Although advances in molecular level have been achieved in many human parasites, the molecular and biochemical characteristics of this worm were rarely reported due to short of investigation in the past two decades. Sporadic cases and outbreaks of human angiostrongliasis have been reported worldwide in recent years. Some new diagnoses have been developed based on ES proteins. More and more epidemiological information have been revealed in endemic regions especially in China. Effective treatments have been developed for human angiostrongyliasis. However, the most effective way to protect against human angiostrongyliasis is to impede the transmission of *A. cantonensis* to humans.

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