World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v16.i6.698

World J Gastroenterol 2010 February 14; 16(6): 698-702
ISSN 1007-9327 (print)

REVIEW

Capillaria hepatica in China

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Received: October 11, 2009 Revised: December 9, 2009
Accepted: December 16, 2009
Published online: February 14, 2010

Abstract

Capillaria hepatica (*C. hepatica*) is a parasitic nematode causing hepatic capillariasis in numerous mammals. Ecologic studies showed that the first hosts of *C. hepatica* were rodents, among which rats had relatively high infection rates, which explains why *C. hepatica* spreads globally. Anatomical studies showed that the liver was the principal site of colonization by these parasites and physical damage tended to occur. Although *C. hepatica* might lead to serious liver disorders, relevant clinical reports were rare, because of the non-specific nature of clinical symptoms, leading to misdiagnosis. This review mainly focuses on the biological characteristics and epidemiology of *C. hepatica* in China and histopathologic changes in the liver, with expectation of gaining a better understanding of the disease and seeking more effective treatment.

Key words: *Capillaria hepatica*; Enoplida infections; Liver diseases; Host-parasite interactions; Diagnosis; Treatment

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Li CD, Yang HL, Wang Y. *Capillaria hepatica* in China. *World J Gastroenterol* 2010; 16(6): 698-702 Available from: URL: http://www.wjgnet.com/1007-9327/full/v16/i6/698.htm DOI: http://dx.doi.org/10.3748/wjg.v16.i6.698

INTRODUCTION

Capillaria hepatica (*C. hepatica*) is a nematode parasite of wild rodents and other mammals and has worldwide distribution[1-8]. Adult worms colonize the liver of the host[6,9-11]. They can cause hepatica capillariasis, a serious liver disorder, which may be found both in humans and animals[11-14]. These parasites could be accidentally transmitted to humans by ingestion of embryonated eggs. Up to the year 2000, 37 cases of human infections had been documented[15]. However, there are few reports of the pathology of the infection, which results in serious effects in subjects because of the special anatomic area in which *C. hepatica* congregates. Clinical symptoms of hepatica capillariasis were non-specific with manifestations of persistent fever, hepatomegaly, eosinophilia and, more seriously, death.

MORPHOLOGY AND BIOLOGICAL FEATURES

Morphology

A typical adult *C. hepatica* takes the shape of a slender nematode, with the anterior part of the body narrow, and the posterior part gradually swelling. The females measure about 53-78 mm × 0.11-0.20 mm, but males are approximately 24-37 mm × 0.07-0.10 mm. The esophagus is long, occupying half of the body of the female and a third of the male body. The cauda of *C. hepatica* bears a copulatory spicule and sheath. The eggs of *C. hepatica* resemble those of *Trichuris trichiura*, but differ in size. The *C. hepatica* egg is about 48-66 μm × 28-36 μm, and numerous minipores can be seen in the outer shell[16].

Biological features

C. hepatica parasites live in liver parenchyma, where they

Table 1 Three cases of hepatica capillariasis in China

Reporter	Date	Area in China	Diagnostic basis
Bing-Kun Xu[27]	1979	Guangdong Province	*Capillaria hepatica* (*C. hepatica*) detected by liver biopsy
Xi-Meng Lin[28]	2003	Tangzhuang, Xinxiang City	Persistent fever (40℃), hepatomegaly eosinophilia, and adult *C. hepatica* detected by liver biopsy
Jia-Nin Huang[29]	2003	Fuzhou City, Fujian Province	Persistent fever, anemia, hepatomegaly, eosinophilia, and eggs detected by liver biopsy

Table 2 Infection rate in distinct areas with different rodent species

Reporter	Date	Area in China	Investigated species	Infection rate (%)
Zhou *et al*[33]	1990	Wuhan City, Hubei Province	Norway rat	61.90
			Rattus flavipectus	61.90
			Mus musculus	19.10
Liu *et al*[40]	1997	Shandong Province	Various rodent species including those of rodent-shaped animals	27.36 (Norway rat dominant)
Zhou *et al*[34]	1998	Kunming City, Yunnan Province	Norway rat	66.67
			Yellow breasted rat	65.13
			Mus musculus	21.11
Yuan *et al*[36]	1998	Ningde City, Fujian Province	Chestnut rat	55.56
			Norway rat	66.67
			Rattus flavipectus	44.33
			Rattus losea	38.94
			Rattus confucianus	30.00
Xue *et al*[37]	1998	Fuqing City, Fujian Province	*Rattus flavipectus*	13.11
			Norway rat	12.34
			Shrew	5.29
			Mus musculus	4.59
Zhang *et al*[35]	2002	Jiangle Location, Fujian Province	Norway rat	46.15
			Rattus flavipectus	66.67
Shen *et al*[39]	2003	Dali City, Yunnan Province	Commensal Mus	76.83
			Norway rat	77.01
			Rattus flavipectus	77.46
			Wild Mus	4.47
			Rattus rattus sladerni	38.81
Lin *et al*[41]	2007	Henan Province	Norway rat	25.83
			Rattus flavipectus	12.90
			Mus musculus	10.00
Tung *et al*[38]	2009	Taichung	Various species of rodents	49.50

become biologically mature, then lay eggs in this site. Eggs are immature when produced in the first 4 wk, and these eggs will develop into larvae under favorable conditions of appropriate temperature and moisture. When embryonated, eggs can be ingested by a predator, their larvae then hatch and invade the intestinal mucosa, transporting themselves *via* the mesenteric vein and portal vein to the liver. The first ecdysis takes place 3-4 d after their arrival in the liver, followed by the second, third (5-7 d) and fourth (9-16 d) larval stages. In the fourth stage, sexual differentiation starts. After sexual differentiation (male, 18 d; female, 20 d), they will experience their final ecdysis and become fifth-stage larvae. The life-span of the female lasts about 59 d, with 40 d for males[17]. It is worthy of note that eggs produced by females in the liver are metabolically active for a prolonged period of time, but remain immature. The host which has ingested these immature eggs displays a "spurious infection". In contrast, "true infection" occurs when the host ingests embryonated eggs, which will result in the production of larvae that can invade the intestine wall and lead to hepatica capillariasis.

EPIDEMIOLOGY IN CHINA

Epidemiology in the human population

Reports of the 37 cases of hepatica capillariasis indicate they were scattered predominantly in Japan, India, America, Canada, Brazil, Germany, Italy, Korea and Czechoslovakia[15,18-26]. While only 3 cases of "true infection" had been confirmed in China[27-29], those few cases found in China do not necessarily encompass the overall actual morbidity, as the final diagnosis would have to rely on biopsy or necropsy[30,31], so both the rate of misdiagnosis and missed diagnosis could be higher. Table 1 shows the 3 cases with detailed clinical symptoms.

Epidemiology in the animal population

The chief hosts of *C. hepatica* are various rodents, including more than 70 species, and the principal hosts include *Tamias striatus*, squirrel, mole, shrew, opossum, weasel and skunk[32]. In mainland China, the total infection rate of hepatica capillariasis in rodent species ranges widely. Table 2 highlights the infection rate in distinct areas with different rodent species[33-41].

PATHOLOGY OF HEPATICA CAPILLARIASIS

C. hepatica primarily invade the sinus hepaticus, where they experience maturation and egg-laying. Both the worms and their eggs cause focal chronic inflammation in the liver, and around these worms and eggs appear diverse inflammatory cells, including macrophages, eosinophils, and some multinucleate giant cells. Inflammatory infiltration may persist until the final formation of encapsulation or calcification of dead worms. After the focal parasitic necroinflammatory lesions, septal fibrosis occurs. Although the pathological course of the formation of fibrosis has not been well established, it was speculated that the slow and continuous release of disintegrated products from encapsulated parasitic lesions activated the Kupffer cells, which then promoted the development of fibrosis in the liver[42]. Whether there is a relationship between the focal parasitic hepatic lesions and septal fibrosis remain to be resolved. In the experiment of Gomes *et al*[12], rats were first infected with 600 embryonated eggs, and then injected with a corticoid and *C. hepatica* antigen. After treatment, focal inflammation ceased, but there was no evident alteration in the formation of septal fibrosis. These findings indicated that, although focal lesions and septal fibrosis were both caused by *C. hepatica* infection, they played different roles in the pathological course of the infection. Further studies should be conducted to explore the pathological course of hepatic fibrosis.

DIAGNOSIS

Hepatica capillariasis is an exceptionally rare infection in humans with non-specific clinical manifestations, and frequent misdiagnoses have been made[43]. More importantly, the main difficulties interfering with correct diagnosis were related to the unique biological characteristics of the parasite. Apart from those cases of "spurious infection", both worms and eggs could not be detected in the peripheral blood and stools of infected hosts, so routine laboratory tests of blood and stools invariably showed negative results. Although liver biopsy was a precise and quick method in confirming *C. hepatica* infection, it was not the most appropriate one, as biopsy was a traumatic diagnostic approach. With introduction of immuno-techniques, the detection of *C. hepatica* became more convenient and efficient. Assis and colleagues[12] employed an indirect immunofluorescence test to diagnose hepatica capillariasis successfully. Huang *et al*[44] developed a diagnostic test for experimental rat hepatica capillariasis using an enzyme-linked immunosorbent assay, with high sensitivity and specificity, which was specific for *C. hepatica* infection. The tests described above have been considered practical, reliable and sensitive. A sensitive immunological test is useful for particular clinical situations, but it is essential to take account of the epidemiological surveys in local areas, which may help lead to a more comprehensive diagnosis.

The differential diagnosis should include accidental tissue infection by nematodes, including *Toxocara cati*, *Toxocara canis*, *Fasciola hepatica*, and *Schistosoma japonicum*, hepatitis B virus, hepatitis C virus and visceral larva migrants[45-48].

TREATMENT

Pereira *et al*[30] reported a case of hepatica capillariasis in Brazil where the male subject with massive *C. hepatica* infection survived after treatment with prednisone, disophenol, and pyrantel tartrate. Thanks to marked eosinophilia in the peripheral blood and hepatic lesions, the patient underwent initial therapy with prednisone (60 mg/d) for a session of 10 d and sequential maintenance by 10 mg every other 10 d. To kill the parasites, or at least to prevent the production of eggs, the patient was treated with disophenol (2-6-diiodo-4-nitrophenol) intramuscularly in a single dose of 7.5 mg/kg body weight and with pyrantel tartrate orally in a single dose of 30 mg/kg body weight. Three years after the treatment, a needle biopsy of the liver, showed sparse portal fibrosis but it was otherwise normal, and the patient remained well during an 8-year follow-up. Also, medication with albendazole was generally effective[31].

Other than chemical treatment, partial hepatectomy or some distinct surgical intervention proved therapeutically effective in animal experiments in rats. The results revealed morphologically that the fibrosis was unaffected, but its relative quantity within the microscopic field appeared significantly decreased, as a consequence of the increased liver tissue mass following regeneration[49].

RESEARCH ACHIEVEMENTS

While prevalence of *C. hepatica* is dominant in rodents, other mammalian species showed slight resistance to this infection even in laboratory conditions. Yang *et al*[50] examined the predisposition to *C. hepatica* between rats and cats by injecting each animal with embryonated eggs at high density. The long-term investigation revealed that every rat became infected with *C. hepatica*, while, as was expected, the liver biopsy from cats showed negative results. To further confirm whether there were some differences between rats and mice in the course of the formation of hepatic fibrosis, Andrade *et al*[13] infected both rats and mice with embryonated eggs, and he found that, although rats and mice both had the same pathological changes in the first stage, there were distinct features in the development of hepatic fibrosis. Researching into the immunological mechanisms of hepatica capillariasis, Kim *et al*[51] measured cytokine mRNA expression in mice spleen cells and mesenteric lymph node cells. In the earlier stages, expression of T-helper, Th1 and Th2, cells were at a high level, as well as the expression of immunoglobulin G1 and G2. Expression in functional cells in the spleen was relatively higher than in mesenteric lymph node cells, which indicated that the spleen was the main location of the

response to the infection rather than the mesenteric lymph node. With the density of egg production, expression of interferon-γ became stronger, suggesting that it had significant importance in the defense against infection.

CONCLUSION

C. hepatica can cause a serious liver disorder in its hosts including humans and animals. More simple and accurate diagnostic methods and more effective treatment measures need to be further developed. A better understanding of *C. hepatica* and hepatica capillariasis would help humans to better combat the disease.

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S- Editor Tian L **L- Editor** Cant MR **E- Editor** Lin YP