Capillaria hepatica in China

Chao-Ding Li, Hui-Lin Yang, Ying Wang

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]. They can cause hepatica capillariasis, a serious liver disorder, which may be found both in humans and animals[10-12]. 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[13]. 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[10].

Biological features

C. hepatica parasites live in liver parenchyma, where they...
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\(^{[33-41]}\).

---

### Table 1 Three cases of hepatica capillariasis in China

| Reporter          | Date | Area in China           | Diagnostic basis                                                                 |
|-------------------|------|-------------------------|----------------------------------------------------------------------------------|
| Bing-Kun Xu\(^{[25]}\) | 1979 | Guangdong Province      | *Capillaria hepatica* (C. hepatica) detected by liver biopsy                    |
| Xi-Meng Lin\(^{[24]}\) | 2003 | Tangzhuang, Xinxian City | Persistent fever (40°C), hepatomegaly eosinophilia, and adult C. hepatica detected by liver biopsy |
| Jia-Nin Huang\(^{[26]}\) | 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, Rattus flavipectus, Mus musculus                | 61.90             |
| Liu et al\(^{[40]}\) | 1997 | Shandong Province                 | Various rodent species including those of rodent-shaped animals (Norway rat dominant) | 27.36             |
| Zhou et al\(^{[36]}\) | 1998 | Kunming City, Yunnan Province     | Norway rat, Yellow breasted rat, Rattus flavipectus, Mus musculus | 66.67             |
| Yuan et al\(^{[34]}\) | 1998 | Ningde City, Fujian Province      | Chestnut rat, Norwegian rat, Rattus flavipectus, Rattus lutea, Rattus confucianus | 55.56             |
| Xue et al\(^{[37]}\) | 1998 | Fuzhong City, Fujian Province     | Norway rat, Shrew, Mus musculus                             | 12.34             |
| Zhang et al\(^{[39]}\) | 2002 | Jiance Location, Fujian Province  | Norway rat, Rattus flavipectus, Mus musculus                | 46.15             |
| Shen et al\(^{[38]}\) | 2003 | Dali City, Yunnan Province        | Commercial Mus, Norway rat, Rattus flavipectus             | 76.83             |
| Lin et al\(^{[41]}\) | 2007 | Henan Province                    | Norway rat, Rattus flavipectus, Mus musculus, Shrew, Rattus rattus sladerni | 38.11             |
| Tung et al\(^{[38]}\) | 2009 | Taichung                         | Norway rat, Rattus flavipectus, Mus musculus                | 12.90             |

---

Li CD et al. *Capillaria hepatica* in China | WJG | www.wjgnet.com | 699 | February 14, 2010 | Volume 16 | Issue 6 |
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[49]. 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*[51], 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[49]. 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[13] employed an indirect immunofluorescence test to diagnose hepatica capillariasis successfully. Huang *et al*[40] 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 canis, Toxocara cati, Fasciola hepatica, and Schistosoma japonicum*, hepatitis B virus, hepatitis C virus and visceral larva migrans[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-diodo-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[11].

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[39].

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*[46] 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*[40] 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.

REFERENCES

1. Stidworthy MF, Lewis JC, Masters NJ, Boardman SI, Hopper JS, de Linan FJ, Redrobe SP, Sayers G. Capillaria hepatica in primates in zoological collections in the British Isles. *Vet Rec* 2009; 164: 66
2. Resendes AR, Amaral AF, Rodrigues A, Almeria S. Capillaria hepatica: a cause of hepatic lesions and septal fibrosis in rats. *J Vet Sci* 2004; 5: 207-213
3. Carvalho-Costa FA, Silva AG, de Souza AH, Moreira CJ, de Souza DL, Valverde JG, Jaeger LH, Martins PF, de Meneses VF, Araújo A, Bôia MN. Pseudoparasitism by Calodium hepaticum (syn. Capillaria hepatica) in house mice (Mus musculus) in the Azores archipelago. *Vet Parasitol* 2009; 160: 340-343
4. Quadros RM, Pilati C, Marques SM, Mazzolli M, Benedet RC. Capillaria hepatica in Puma concolor: first report in Brazil. *J Zoo Wildl Med* 2009; 40: 586-587
5. Pizzato R, Gordon JC, Flach EJ, Routh AD, Clark B, Boardman WS. Capillaria hepatica (syn Calodium hepaticum) in primates in a zoo pathological collection in the UK. *Vet Rec* 2008; 163: 690-691
6. Tesana S, Puapairoj A, Saeseow O. Granulomatous, hepatolittiasis and hepatomegaly caused by Capillaria hepatica infection: first case report of Thailand. *Southeast Asian J Trop Med Public Health* 2007; 38: 636-640
7. Reperant LA, Deplazes P. Cluster of Capillaria hepatica infections in non-commensal rodents from the canton of Geneva, Switzerland. *Parasitol Res* 2005; 96: 340-342
8. Redrobe SP, Patterson-Kane JC. Calodium hepaticum (syn. Capillaria hepatica) in captive rodents in a zoological garden. *J Comp Pathol* 2005; 133: 73-76
9. Mowat V, Turton J, Stewart J, Lui KC, Pilling AM. Histopathological features of Capillaria hepatica infection in laboratory rabbits. *Toxicol Pathol* 2009; 37: 661-666
10. Jeong WI, Do SH, Hong IH, Ji AR, Park JK, Ki MR, Park SC, Jeong KS. Macrophages, myofibroblasts and mast cells in a rat liver infected with Capillaria hepatica. *J Vet Sci* 2008; 9: 211-213
11. Oliveira L, de Souza MM, Andrade ZA. Capillaria hepatica-induced hepatic fibrosis in rats: paradoxical effect of repeated infections. *Rev Soc Bras Med Trop* 2004; 37: 123-127
12. Gomes AT, Cunha LM, Bastos CG, Medrado BF, Assis BC, Andrade ZA. Capillaria hepatica in rats: focal parasitic hepatic lesions and septal fibrosis run independent courses. *Mem Inst Oswaldo Cruz* 2006; 101: 895-898
13. Andrade SB, Andrade ZA. Experimental hepatic fibrosis due to Capillaria hepatica infection (differential features presented by rats and mice). *Mem Inst Oswaldo Cruz* 2004; 99: 399-406
14. Ferreira LA, Andrade ZA. Capillaria hepatica: a cause of septal fibrosis of the liver. *Mem Inst Oswaldo Cruz* 1993; 88: 441-447
15. Juncker-Voss M, Prosl H, Lussy H, Enzenberg U, Auer H, Nowotny N. Serological detection of Capillaria hepatica by indirect immunofluorescence assay. *J Clin Microbiol* 2000; 38: 431-433
16. Hamir AN, Rupprecht CE. Hepatic capillariasis (Capillaria hepatica) in porcupines (Erethizon dorsatum) in Pennsylvania. *J Vet Diagn Invest* 2000; 12: 463-465
17. Wright KA. Observation on the life cycle of Capillaria hepatica (Bancroft, 1893) with a description of the adult. *Can J Zool* 1961; 39: 167-182
18. Govil H, Desai M. Capillaria hepatica parasitism. *Indian J Pediatr* 1996; 63: 698-700
19. Choe G, Lee HS, Soo JK, Chyi JY, Lee SH, Eom KS, Chi JG. Hepatic capillariasis: first case report in the Republic of Korea. *Am J Trop Med Hyg* 1993; 48: 610-625
20. Cislaghi F, Radice C. Infection by Capillaria hepatica. First case report in Italy. *Helv Paediatr Acta* 1970; 25: 647-654
21. Slaís J, Słętra J. Solitary liver granulomas in man caused by Capillaria hepatica (Bancroft, 1893) in Czechoslovakia. *Folia Parasitol* (Praha) 1972; 19: 373-374
22. Pereira VG, França LC. [Human Capillaria hepatica infection. Report of a case treated successfully] *Rev Hosp Clin Fac Sao Paulo* 1981; 36: 31-34
23. Slaís J. The finding and identification of solitary Capillaria hepatica (Bancroft, 1893) in man from Europe. *Folia Parasitol* (Praha) 1973; 20: 149-161
24. Vargas Carreto G, López Martínez H, Victoria Victoria R, Hernández Muñoz G. [Capillaria hepatica. Report of the 2nd case found in the Mexican Republic] *Bol Med Hosp Infant Mex* 1979; 36: 909-917
25. Silverman NH, Katz JS, Levin SE. Capillaria hepatica infestation in a child. *S Afr Med J* 1973; 47: 219-221
26. Fan PC, Chung WC, Chen ER. Capillaria hepatica: a sporious case with a brief review. *Kaohsiung J Med Sci* 2000; 16: 360-367
27. Xu BK, Li DN. General condition on the rare human parasites in China. *Zhongguo Yixue Zazhi* 1979; 59: 286-290
28. Lin XM, Li H, Zhao XD, Lin XD, Li H, Zhao XD, Deng Y. 1 case of capillaria hepatica infection. *Zhonggguo Jishengchongbing Fangzhi Zazhi* 2004; 17: 230
29. Huang JN, Lin JX. The pathological diagnosis of the first case of capillaria hepatica in Fujian province. *Zhonggguo Renshou Gouhanbuang Zazhi* 2004; 20: 556
30. Pereira VG, Mattosinho Franca LC. Successful treatment of Capillaria hepatica infection in an acutey ill adult. *Am J Trop Med Hyg* 1993; 32: 1273-1274
31. Nabi F, Palaha HK, Sekhriar D, Chitalae A. Capillaria hepatica infestation. *Indian Pediatr* 2007; 44: 781-782
32. Solomon GB, Handley CO. Capillaria hepatica (Bancroft, 1893) in Appalachian mammals. *J Parasitol* 1971; 57: 1142-1144
33. Zhou ZL, Wu HY, Mao XP, Fang ZM. Investigate the infection rate of capillaria hepatica on rats. *Zhonggguo Bingyuan Shengwuxue Zazhi* 1991; 4: 225
34. Zhou XM, Zhang GF, Li C, Li FH, Yin ZH, Yang JL, Su P. Investigation on rats infected with Capillaria hepatica in Kunming, *Zhonggguo Renshou Gouhanbuang Zazhi* 1998; 14: 33
35. Zhang LY, Huang JY, Yang FZ. Investigate on rats infected with capillaria hepatica in Jangle. *Zhonggguo Jishengchoubing Fangzhi Zazhi* 2003; 16: 19-20
36. Yuan GL, Li YY, Chen WJ. Investigation on Rattus losea infected with Capillaria hepatica in Ningsde. *Zhonggguo Meijie Shengwuxue Ji* Konyuzi Zazhi 2000; 11: 301-302
37. Xue YS, Wu CH, Huang MS, Li RH. Investigation on rats infected with capillaria hepatica in Fuqing. *Haixia Yufang Yixue Zazhi* 1998; 2: 31-32
38. Tung KC, Hsiao FC, Yang CH, Chou CC, Lee WM, Wang KS, Lai CH. Surveillance of endoparasitic infections and the first report of Physaloptera sp. and Sarcocystis spp. in farm rodents and shrews in central Taiwan. *J Vet Med Sci* 2009; 71: 43-47
39. Shen L, Luo ZY, Li W, Li ZH, Gao C, Yang WB, Li LY, Qian
Li CD et al. *Capillaria hepatica* in China

40 Liu YX, Yang ZQ, Meng XR, Wu QY. Investigation on rats infected with capillaria hepatica in some region of Shandong province. *Dongwuxue Zazhi* 1997; 32: 1-3

41 Lin XM, Xu BL, Zhao XD, Li H, Huang Q, Deng Y, Hao ZY, Zhang AM. Epidemiological investigation on capillaria hepatica infection among little animal in henan province. *Zhongguo Jishengchoubing Fangzhi Zazhi* 2007; 2: 44-46

42 Lemos QT, Magalhães-Santos IF, Andrade ZA. Immunological basis of septal fibrosis of the liver in Capillaria hepatica-infected rats. *Braz J Med Biol Res* 2003; 36: 1201-1207

43 Galvão VA. [Capillaria hepatica: an evaluation of its pathogenic role in man] *Mem Inst Oswaldo Cruz* 1981; 76: 415-433

44 Huang HC, Ling HB, Liang SH, Xing WL, Pan CW. Diagnosis of Experimental rat hepatica capillariasis by ELISA. *Wenzhou Yixueyuan Xuebao* 2001; 31: 299-300, 302

45 Chen H, He YW, Liu WQ, Zhang JH. Rosiglitazone prevents murine hepatic fibrosis induced by *Schistosoma japonicum*. *World J Gastroenterol* 2008; 14: 2905-2911

46 Dobrucali A, Yigitbasi R, Erzin Y, Sunamak O, Polat E, Yakar H. Fasciola hepatica infestation as a very rare cause of extrahepatic cholestasis. *World J Gastroenterol* 2004; 10: 3076-3077

47 Yan KK, Guirgis M, Dinh T, George J, Dev A, Lee A, Zekry A. Treatment responses in Asians and Caucasians with chronic hepatitis C infection. *World J Gastroenterol* 2008; 14: 3416-3420

48 Zheng M, Cai WM, Weng HL, Liu RH. ROC curves in evaluation of serum fibrosis indices for hepatic fibrosis. *World J Gastroenterol* 2002; 8: 1073-1076

49 Santos CC, Onofre-Nunes Z, Andrade ZA. Role of partial hepaetectomy on Capillaria hepatica-induced hepatic fibrosis in rats. *Rev Soc Bras Med Trop* 2007; 40: 495-498

50 Yang FZ, Huang XH, Tu ZP, Zhang YZ. Establishment of an animal model of capillaria hepatica infection among little animal in Henan province. *Zhongguo Jishengchouxue Yu Jishengchoubing Zazhi* 2000; 18: 229-231

51 Kim DK, Joo KH, Chung MS. Changes of cytokine mRNA expression and IgG responses in rats infected with Capillaria hepatica. *Korean J Parasitol* 2007; 45: 95-102

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