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EDITORIAL

Parasites of the liver: A global problem?

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Abstract

Parasitic liver diseases can be caused by trematodes, cestodes, nematodes, and protozoa. This pathology is significant because millions of people in different parts of the world have liver parasites, which can manifest themselves in the development of inflammation, liver cysts, cholecystitis, cholelithiasis, pancreatitis and liver cirrhosis that are often threatening their lives. The International Agency for Research on Cancer considers three species of trematodes, *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*, to be carcinogens. Complex modern examination methods, in some cases including extensive screening of large populations, are required for diagnosing liver parasites. Treatment of parasitic liver diseases is differentiated and can involve a combination of surgical and therapeutic measures. There is no doubt that the clinical and epidemiological scale allows one to regard parasitic liver diseases as a global healthcare problem.

Key Words: Liver; Parasites; Epidemiology; Diagnosis; Clinics; Treatment; Echinococcosis; Opisthorchiasis; Fascioliasis; Schistosomiasis

Core Tip: Parasites in the liver are a common cause of disease with the possible development of cholangitis, cirrhosis and cancer. Diagnosis of liver parasites is difficult. The purpose of this article is to identify the problem from the perspective of its increasing importance, epidemiological aspects, the feasibility of diagnosis and treatment, indicating specific clinical variants of the pathology.

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INTRODUCTION

Parasitic liver diseases can be caused by trematodes, cestodes, nematodes, and protozoa[1]. Among trematodes, members of the families Opisthorchiidae (*Opisthorchis felineus*, *O. viverrini*, and *Clonorchis sinensis*) and Fasciolidae (*Fasciola hepatica* and *F. gigantica*) are especially prominent. Schistosomas (*Schistosoma mansoni, S. japonicum*, *S. intercalatum*, *S. mekongi*) can also infect the liver[2]. For the cestodes *Echinococcus granulosus* and *E. multilocularis*, humans are the intermediate host with hydatid cysts residing mainly in the liver[3]. When infested by nematodes (*Ascaris lumbricoides*, *Strongyloides stercoralis*, *Toxocara canis*, and *Capillaria hepatica*), the liver can be damaged during the migration of larvae, blockage of the hepatobiliary tract, or due to the human immune response to helminths[4]. Among protozoan parasites, one can especially highlight *Entamoeba histolytica* whose invasion can be complicated by amebic liver abscess in 9% of cases[5]. Pathological changes in the liver can also occur in patients with malaria (especially *Plasmodium falciparum* invasion)[6], Chagas disease (*Trypanosoma cruzi*)[7], and visceral leishmaniasis (*Leishmania infantum* and *L. donovani*)[8].

Research into parasitic infestations is highly relevant due to the fact that millions of people in different parts of the world have these infectious diseases or are at risk of being infected[9]. From 15% to 18% of cancer cases of various locations in humans are associated with the presence of viruses, bacteria or parasitic invasions[10]. The International Agency for Research on Cancer (IARC) considers three species of trematodes, *S. haematobium*, *O. viverrine* and *Clonorchis sinensis*, to be responsible for helminth-induced human cancer; they regarded *S. haematobium* and *O. viverrini* as group 1 carcinogens and *C. sinensis*, as a group 2 carcinogen[9,11]. In its 2021 review, European association for the study of the liver indicates that the development cycle of a number of parasites is accompanied by maturation or proliferation in the liver and occurrence of inflammatory changes in liver tissue, which lead to disease development[1]. Currently, the dominant view is that parasitic infestations of the liver are a global health problem and require significant work to improve the diagnostic, therapeutic and preventive measures[12].

ECHINOCOCCOSIS

Echinococcosis can have two main forms of disease: Alveolar echinococcosis (AE) and cystic echinococcosis (CE), caused by *Echinococcus multilocularis* and *Echinococcus granulosus*, respectively. Echinococcosis is a relatively rare disease, the incidence of which does not exceed 200 *per* 100000 population in endemic areas[3]. But the mortality rate from this pathology can reach 90% in untreated patients[13]. Areas highly endemic for CE include western China, central Asia, South America, Mediterranean countries and eastern Africa; contact with dogs and livestock are the main risk factors[14]. The main source of invasion are hunting dogs and farm animals. Man is the intermediate host[1,3].

The period from infection to the onset of clinical manifestations can be several decades[15]. In 70% of patients, the liver is the main target organ, but other organs may also be affected. The first symptoms that appear when the cyst size is more than 10 cm include pain in the right hypochondrium and epigastrium, loss of appetite. Complications of echinococcosis may include liver abscesses, cholangitis, peritonitis and the development of allergic reactions. Contrast-enhanced ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and positron emission tomography with 18F-fluorodeoxy glucose are employed to diagnose echinococcosis[1]. Detection of protein biomarkers and DNA detection by polymerase chain reaction assays can be used for complex diagnostics and differentiation of species belonging to the genus *Echinococcus*[3]. The best method for early diagnosis and mass population screening for CE and AE in endemic areas is ultrasound[16].

Currently, the following treatment options are available for CE: (1) Surgery; (2) Percutaneous treatment; (3) Medical therapy with anthelmintics (benzimidazoles or their combination with praziquantel); and (4) Observation and waiting for the emergence of cysts in an inactive form[17].

OPISTHORCHIASIS

In its report published in 2023, the World Health Organization (WHO) noted that foodborne trematodes were included in the roadmap for the control of parasitic infestations for the period from 2021 to 2030[18]. The prevalence of invasion of three liver flukes, *Clonorchis sinensis*, *O. viverrini*, and *O. felineus*, is very high and associated with significant public health problems in endemic regions[19]. Intermediate hosts of these helminths include freshwater snails and freshwater fish[20]. Adult parasites can live in the bile ducts from 10 to 26 years[21]. The population of people with liver flukes in Southeast Asia and Eastern Europe, according to various estimates, ranges from 17 million[22] to 27 million people[23,24]. About 100 species of fish can cause parasite infections in humans[25,26].

Clinical manifestations of liver flukes are very diverse and include inflammation of the bile ducts and gallbladder walls, sludge formation in bile, periductal fibrosis[27,28]. Subsequent complications include cholangitis, cholecystitis, cholelithiasis, pancreatitis, and liver cirrhosis[27,29]. In Russia, there is a widespread view about the pronounced clinical polymorphism of *O. felineus* invasion[30].

A major medical and social problem for East Asia and Southeast Asia is the ability of liver flukes to determine the occurrence of cholangiocarcinoma, which is confirmed by the IARC opinion[11,31]. A meta-analysis found that cholangitis is registered in patients with trematodes 16 times more often, and those with cholangiocarcinoma, five times more often than in people without parasitosis[32]. In Thailand alone, 20000 people die annually from cholangiocarcinoma associated with opisthorchiasis[20]. In the north of Western Siberia, a close relationship was found between invasion of *O. felineus* and cases of cholangiocarcinoma[33]. In this regard, a number of studies reported that the association between opisthorchiasis and cholangiocarcinoma is a global health problem[2,25,34].

To diagnose liver fluke, detection of eggs in feces[35], immunological methods[27,28], cholangiography, ultrasonography, CT, and MRI are used[36]. In Russia, diagnostics of opisthorchis eggs using microscopy of duodenal bile is widely employed.

Praziquantel still remains the main drug for the etiological treatment of trematodes[37]. Standard recommended doses are 25 mg/kg three times daily for 2-3 days[18].

FASCIOLA HEPATICA AND FASCIOLA GIGANTICA

One of the most clinical important trematode species is fascioliasis. Every year, 2.4 million new cases of this parasitosis are reported in Africa, Europe, Asia, South and Central America[38-40]. Infection occurs through ingestion of food (vegetables or raw liver) containing F. hepatica and F. gigantica. After entering the human body, helminths penetrate the intestinal wall and most often reach the bile ducts and gallbladder[2]. They can cause mechanical damage with focal hemorrhage, inflammatory responses, and necrotic lesions. The pathogenic effect of F. hepatica and F. gigantica is associated primarily with the development of local inflammatory reactions in the bile ducts. Adult forms of parasites can live in the human body for more than 10 years[40].

The dominant clinical manifestations of fascioliasis include gallstone formation. Chronic hepatitis and its complications are relatively rare[41]. To diagnose fascioliasis, parasitological techniques, immunological tests, ultrasound, radioisotope scanning, MRI and CT are used. Deworming is usually carried out using Triclabendazole, the use of which may be associated by the emergence of drug resistance[41].

SCHISTOSOMIASIS

WHO recognizes schistosomiasis as one of the global problems of the planet's population[42]. The number of people infected with schistosomiasis reaches 207 million in Africa, South America, China, Indonesia, the Philippines[43,44]. The intermediate hosts of schistosomiasis are freshwater mollusks. Humans are the final hosts[45]. *S. japonicum*, which can cause rapid progression to liver fibrosis and occasional liver failure[46-48], and *S. haematobium*, which the IARC classifies as a probable human carcinogen[49,50], are considered hepatotropic schistosomes.

Acute schistosomiasis can last 1-2 months and is manifested by fever, skin rash, dry cough, hepatosplenomegaly, leukocytosis, eosinophilia[51-53]. The presence or combination of gastrointestinal and urogenital symptoms (dysuria, hematuria, hemospermia, dyspareunia) may be characteristic of individuals with chronic schistosomiasis. Liver damage in schistosomiasis can lead to the development of hepatic fibrosis in 40% of infected patients[54,55].

For the diagnosis of schistosomiasis, it is recommended to use the determination of specific antibodies in blood serum and antigenic and molecular tests to isolate specific DNA[51]. To identify *Schistosoma spp.* eggs, parasitological examinations of urine or feces samples are performed using the light microscopy method[51], as well as tissue biopsies from the intestine or bladder[56].

Praziquantel is the leading drug in the treatment of schistosomiasis and is prescribed at a dose of 40 mg/kg body weight[57].

CONCLUSION

Modern globalization has led to the fact that population migrations are an integral part of life. A significant proportion of residents of North America and Europe regularly visit the countries of Southeast Asia, Africa and South America during tourist trips. It is important to emphasize the global nature of the problem. More than one hundred countries around the world are endemic for liver parasite infestations, and the total number of infected people is several hundreds of millions. Control over quality and effectiveness of parasitosis treatment is not optimal. The IARC has listed three fluke species (*S. haematobium*, *O. viverrini*, and *Clonorchis cinensis*) as carcinogens. There is no doubt that this situation deserves significant attention and active efforts to be improved. It is necessary to strengthen sanitary educational work among traveling people and improve the qualifications of doctors for timely diagnosis and treatment of parasitosis. International medical organizations must adequately navigate modern information in order to set priorities for healthcare development, which should include the problem related the influence of parasites on public health.

FOOTNOTES

Author contributions: Tsukanov VV, Vasyutin AV and Tonkikh JL contributed to this paper; Tsukanov VV designed the overall concept and outline of the manuscript; Vasyutin AV and Tonkikh JL contributed to the discussion and design of the manuscript; Tsukanov VV, Vasyutin AV and Tonkikh JL contributed to the writing, editing the manuscript, and review of literature.

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