IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Short Communication
May 2020 Vol.:18, Issue:2

Parasitic Disease of the Liver and Biliary Tree - Historical Background and Current Scenario

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ISSN 2349-7203
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Submission: 23 April 2020
Accepted: 01 May 2020
Published: 30 May 2020

Keywords: Clonorchis Sinensis, Opisthorchis viverrini, Fasciola hepatica, Cystic echinococcosis, hemoglobinuria Schistosomiasis, bilharziasis

ABSTRACT

Parasitic involvement of the liver and biliary tree is an important differential diagnosis in patients with jaundices especially those from tropical or subtropical continents. *Entamoeba histolytica*, *Echinococcus granulosus*, *Schistosoma haematobium*, *Leishmania donovani*, and *Plasmodium falciparum* parasites are mainly responsible for causing hepatic complications. Several parasites infest liver or biliary tree, either during their maturation stages or as adult worms. Biliary tree parasites may cause pancreatitis, cholecystitis, biliary tree obstruction, recurrent cholangitis, biliary tree strictures and some may lead to cholangiocarcinoma. Several parasites infest liver or biliary tree, either during their maturation stages or as adult worms. Biliary tree parasites may cause pancreatitis, cholecystitis, biliary tree obstruction, recurrent cholangitis, biliary tree strictures and some may lead to cholangiocarcinoma.

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INTRODUCTION

Amebic liver abscess is the most common extraintestinal manifestation of amoebiasis. (1)

Approximately 50-80% of individuals with fever and constant, aching right upper quadrant pain. In up to 50% of cases, patients present more chronically with protracted diarrhea, weight loss, and abdominal pain. (2)

Infection of the cyst can facilitate the development of the liver abscess and mechanic local complications, such as mass effect on bile ducts and vessels that can induce cholestasis, portal hypertension, and Budd-Chiari syndrome. (3)

Schistosomiasis, also known as snail fever and bilharzia, is a disease caused by parasitic flatworms called schistosomes. (4)

The urinary tract or the intestines may be infected. Symptoms include abdominal pain, diarrhea, bloody stool, or blood in the urine. Those who have been infected for a long time may experience liver damage, kidney failure, infertility, or bladder cancer. (5)

The chronic phase occurs when the worms mature in the bile duct and can cause symptoms of intermittent pain, jaundice, and anemia. (6)

F. hepatica can cause sudden death in both sheep and cattle, due to internal hemorrhaging and liver damage. (7)

Leishmaniasis, which can occur a few months to years after infection, includes fever, damage to the spleen and liver, and anemia. (8)

Drug-induced hepatotoxicity is often thought to be the primary cause of the observed liver injury, and this can be a major concern in anti-malaria drug development. (9)

Around 700 million people, in more than 70 countries, live in areas where the disease is common. In tropical countries; schistosomiasis is second only to malaria among parasitic diseases with the greatest economic impact. Schistosomiasis is listed as a neglected tropical disease. (10)

Schistosomiasis, also known as snail fever and bilharzia, is a disease caused by parasitic flatworms called schistosomes. The urinary tract or the intestines may be

infected. Symptoms include abdominal pain, diarrhea, bloody stool, or blood in the urine. Those who have been infected for a long time may experience liver damage, kidney failure, infertility, or bladder cancer. In children, it may cause poor growth and learning difficulty. (11)

Visceral leishmaniasis (VL), also called kala-azar, is a systemic parasitic infection caused by protozoa of the genus Leishmania.

The parasite primarily infects the cells of the reticuloendothelial system and the disease almost invariably is fatal if left untreated. Patients with VL usually present with prolonged fever, anorexia, and weight loss. (12)

Infection with the intracellular protozoan parasite Leishmania donovani causes a potentially fatal disease wherein macrophages of the viscera including the spleen, liver, and bone marrow become infected, leading to splenomegaly and hepatomegaly. (13)

A proportion of patients present with cyst-related complications that require medical attention promptly. For cysts located in the liver, a cysto-biliary fistula is the most common complication (13% to 37% of cases). (14)

Cystic echinococcosis typically occurs in poor pastoral regions in which sheep or other livestock are raised and in which dogs are kept, for herding or property guarding, in close proximity to households. (15)

Acute liver fluke disease is related to the damage caused by the migration of immature flukes which leads to liver inflammation, hemorrhage, necrosis, and fibrosis. F. tunneling through hepatic tissue. In cattle, infections are often asymptomatic due to the host's encapsulation of the parasite. (16)

Fasciola hepatica is the most common and important liver fluke and has a cosmopolitan distribution in cooler climates. Hepatic fasciolosis is mainly of economic importance in sheep or cattle, but other species may provide a reservoir of infection. (17)

The liver is an important organ involved during the hepatic stage of the malaria parasite's life cycle, where malaria sporozoites develop into merozoites. The merozoites are then released into the circulation and enter the erythrocytic stage.

Common histopathological findings of the liver in P. falciparum malaria include reactive Kupffer cells, retention of haemozoin pigment and minimal PRBC sequestration. (18)

C. Sinensis causes mechanical injury and inflammation at the environs of biliary tree due to fluke activities, metaplasia of mucin-producing cells in the mucosa, progressive periductal fibrosis and hyperplasia of epithelial cells. (19)

Strongyloidiasis is a parasitic infection that typically results in mild symptoms and rarely causes severe or disseminated disease. Seldom encountered in the United States, it is usually only considered when a patient presents with persistent eosinophilia and/or hyperinfection with multiorgan involvement. Little is known regarding the impact that strongyloides has on the progression of cirrhosis. (20)

History of the Liver and Biliary tree parasite

Amoebiasis was first described by Lösh in 1875, in northern Russia. E. dispar, evidence shows there are at least two other species of Entamoeba that look the same in humans: E. moshkovskii and Entamoeba Bangladeshi. The reason these species haven't been differentiated until recently is because of the reliance on appearance. (21) The most dramatic incident in the US was the Chicago World's Fair outbreak in 1933, caused by contaminated drinking water. There were more than a thousand cases, with 98 deaths (22) After an infectious mosquito bite, sporozoites must leave the bite site and find their way to hepatocytes, where liver stage development occurs. The dermis-to-hepatocyte journey (23) *S. haematobium* was the first blood fluke discovered. Theodor Bilharz, a German surgeon working in Cairo, identified the parasite as a causative agent of urinary infection in 1851. (24)

Along with other helminth parasites *Clonorchis Sinensis* and *Opisthorchis viverrini*, S. haematobium was declared as Group 1 (extensively proven) carcinogens by the WHO International Agency for Research on Cancer (IARC) Working Group on the Evaluation of Carcinogenic Risks to Humans in 2009. (25)

Clonorchis sinensis, the Chinese liver fluke, is a liver fluke belonging to the class Trematoda, phylum Platyhelminthes.

It infects fish-eating mammals including humans. In humans, it infects the common bile duct and gall bladder, feeding on bile. It was discovered by a British physician James McConnell at the Medical College Hospital in Calcutta (Kolkata) in 1874. The first description was given by Thomas Spencer Cobbold, who named it Distoma sinense. .The infection, called clonorchiasis, generally appears as jaundice, indigestion, biliary inflammation, bile duct obstruction, even liver cirrhosis, cholangiocarcinoma, and hepatic carcinoma. (26) In 1921, Léon Seurat erected the genus Wuchereria and placed this worm in it as *Wuchereria bancrofti*. (27)

In 1908, while working at the Pasteur Institute in Tunis, Charles Nicolle and Louis Manceaux discovered a protozoan organism in the tissues of a hamster-like rodent known as the gundi, *Ctenodactylus gundi*. (28)

In 1841, Gabriel Valentin found flagellates that today are included in Trypanoplasma in the blood of trout. (29)

In 1903, David Bruce identified the protozoan parasite and the tsetse fly vector of African trypanosomiasis. (30)

Critical Gaps in Knowledge of the Liver and biliary tree Parasites Research

The knowledge gaps in vector bionomics that will be of immediate benefit to current control operations include better estimates of human biting rates and natural infection rates of P. argentipes, with L. donovani, and how these vary spatially, temporally and in response to IRS. (31)

Success with vector control strategies has led to a relative increase in the burden attributable to congenital transmission of *T cruzi.* Congenital *T cruzi* infection is generally asymptomatic and parasitological and serological testing is required for diagnosis. (32)

Immuno-pathogenesis after excystation was similarly well advanced by the use of a novel murine model of amebic colitis. However, it is still challenging to apply these findings to clinical and epidemiological settings. This is mainly because of the lack of a complete infection animal model of amebiasis by oral–fecal infection. (33)

It is believed that these three diseases can eventually be eliminated in mainland China if all the research gaps are abridged in a short period of time. (34)

Major discoveries and Research in Liver and biliary tree Parasites Parasitic liver diseases

Abdominal pain, jaundice and weight loss are commonly manifested, but infections can also lead to bloody stools, muscle pains and fever.

Major discoveries in the area of hepatic parasitology have increased the understanding of pathophysiology of commonly reported manifestations. They have also increased available treatment modalities and management of infected patients. The trematode Clonorchis Sinensis (Chinese or oriental liver fluke) is a pathogen causing liver disease and common in Asia.

In endemic regions, multiple long-standing untreated liver fluke infections have been associated with liver and bile duct cancers, including cholangiocarcinoma. (35)

Entameba histolytica is a causative protozoan for amebiasis and particularly affects developing countries. Symptoms are intestinal (amoebic dysentery, acute rectocolitis, chronic non-dysenteric colitis, ameboma) and extraintestinal (AHA or amebic hepatic abscess, brain abscess, genitourinary and cutaneous disease). (36)

The existence of a pathogenic and non-pathogenic species was confirmed by further research by Sargeaunt and Williams in 1978), William Petri et al in 1987 and Diamond and Clark in 1993. The World Health Organization accepted this hypothesis in 1997. (37)

Malaria, for which female Anopheles mosquito is a vector, is a devastating disease killing 0.6 million humans annually. There are five Plasmodium species that cause human malaria *P. falciparum, P. vivax, P. malariae, P relictum, P. berghii). P. falciparum and P. vivax* infections are the most common. *P. falciparum* infections and the malaria-associated deaths are most prevalent in Africa whereas the same is true about *P. vivax* infections in Southeast Asia and South America. This disease has a very long history because it seems to have a mention in the clay tablets from Mesopotamia, Egyptian remains (3200 and 1304 BC), Indian writings of the Vedic period (1500 to 800 BC), the works of Greek poets and scientists (750-322 BC including Homer, Sophocles, Aristophanes, Hippocrates, Plato, Aristotle), the Chinese medical canon Nei Chin (270 BC) The existence of a hepatic stage prior to the erythrocytic stage in the life cycle of the parasites was discovered by Henry Shortt and Cyril Garnham in 1948. It was Wojciech Krotoski who demonstrated the final stage in the life

cycle (dormant stages in the liver) (38) Alveolar echinococcosis (AE) results in humans infected by the metacestodes of *Echinococcus multilocularis* (EM), mainly through travel and domestic dogs. AE is a major global public health issue (most reported in China, Central Asia, the Middle East and some parts of Europe) (39) The disease can progress to hepatic alveolar echinococcosis (HAE). Another species of the same genus, Echinococcus granulosus (the canid tapeworm), causes in its larval stage, the most serious human disease caused by a larval cestode- Cystic echinococcosis (CE). CE results from accidental infection of humans with larval stages from dogs and sheep (40). A significant progress has been achieved in echinococcosis research in the 20th century recognised in many endemic regions where resources and structures are lacking for effective surveillance and control of these zoonoses threatening humans(41) Hepatic schistosomiasis caused by the blood fluke Schistosoma mansoni is a widespread infection worldwide, most reported in Africa (42). Laboratory Diagnosis Of Liver And Biliary Parasites The symptomatology of malaria vary and resembles many other diseases, laboratory diagnosis will be helpful in support for clinical care. Besides the routine methods the following newer techniques like Fluorescent microscopy, Direct acridine orange staining, and immunological methods like ELISA mostly used. RDTs(Rapid diagnostic tests are based on the detection of antigens derived from malaria patients in lysed blood, using immunochromatographic methods.

The polymerase chain reaction(PCR) is a technique widely used in molecular biology. DNA polymerase is used to amplify a piece of DNA by in vitro enzymatic replication. As PCR progress, the DA thus generated is itself used as template for replication.RT-PCR is one step procedure and hence quick. Besides this Flow cytometry, Mass spectrometry are also currently used in research laboratories.

DNA dot blot hybridization was performed for screening out the Entamoeba (Entamoeba histolytica and Entamoeba dispar) positive samples. The probe used for the purpose was HMe probe (EcoRI+ Hind III) as previously published. (43)

Enzyme immunoassay (EIA) kits for *Entamoeba histolytica* antibody detection as well as EIA kits for antigen detection are commercially available in the United States.

Antibody detection is most useful in patients with extraintestinal disease (i.e., amebic liver abscess) when organisms are not generally found on stool examination. Antigen detection may be useful as an adjunct to microscopic diagnosis in detecting parasites and can

distinguish between pathogenic and nonpathogenic infections. The indirect hemagglutination (IHA) test has been replaced by commercially available EIA test kits for routine serodiagnosis of amebiasis. (44)

Hydatid disease of the liver is still endemic in certain parts of the world. The diagnosis of non-complicated hydatid cyst of the liver depends on clinical suspicion. (45)

Previously surgical treatment has been necessary for management of biliary parasites. However, recently ERCP and endoscopic papillotomy proved to be successful and replaced unnecessary. (46)

Lymphatic filariasis is endemic in India and South-East Asia. Detection of microfilaria is infrequently reported during cytological evaluation of various lesions or body cavity fluids. Microfilariae in cytological smears of few benign and malignant neoplasms have also been reported. (47)

1- Current treatment part of hepatic parasites and 2- CDC and WHO recommendations

Liver - protozoa	Treatment	CDC and WHO recommendations
Babesiosis	Babesiosis normally resolve spontaneously in most healthy individuals, but with patients with an impaired immune system may require treatment such as clindamycin, quinine, and/or other antiparasitic or antibiotic drugs. Clindamycin and quinine are the drugs most commonly used to treat individuals with severe symptoms of babesiosis. (48)	CDC = Most asymptomatic patients do not require treatment for babesiosis infection. For the ill patients the treatment is usually 7-10 days of either: Atovaquone PLUS azithromycin; or Clindamycin PLUS quinine
S. American Trypanosomiasis	Benznidazole is often considered the first-line therapy because of its better tolerability, but both drugs produce significant side effects. Nifurtimox has also been recommended. (49) -	For all cases of acute or reactivated Chaya's disease the antiparasitic treatment. The two drugs used to treat infection with T. cruzi are nifurtimox and benznidazole. Contraindications for treatment include severe hepatic and/or renal disease
Liver - cestode	**Treatment**	**CDC and WHO recommendations**
Echinococcosis	The growth and proliferation of the larva of Echinococcus spp are similar to a slow-growing tumor and difficult to differentiate it from each other. The general approach to the treatment of Echinococcus spp remains to be surgery. Antiparasitic medications cannot kill cysts. (50)	The CDC approach to cystic echinococcosis is to "watch and wait". Chemotherapy with benzimidazoles is preferred and albendazole for small cysts or multiple cysts in several organs as first choice and second choice mebendazole. The third option Percutaneous Aspiration, injection of chemicals and reaspiration (PAIR).

LIVER - TREMATODE	Treatment	CDC and WHO recommendations
Schistosomiasis	The goals of treatment for infection of schistosomiasis are: 1) improvement of sanitation conditions; 2) environmental control to reduce exposure to the snail; 3) education to reduce unsafe water contact; and 4) Mass Drug Administration. The main antiparasitic drug recommended is praziquantel and some antimalarial drugs were found to have some antischistosomal properties, such as the artemisinin, synthetic trioxolanes, and mefloquine.	CDC = It is important the timing of treatment for schistosomiasis with praziquantel. It is most effective against the adult worm and requires the presence of a mature antibody response to the parasite. The dose and duration of praziquantel depends on the species and immune response of the patient

Strongyloidiasis	There are three main goals in the treatment of Strongyloides stercoralis infection: 1) to eliminate the possible autoinfection, the organism must be cleared from the patients completely; 2) treat symptomatic infection; 3) prevent complications associated with asymptomatic infection. The drug of choice to treat uncomplicated infections is oral ivermectin (100µk Kg^{-1} for 2 days). In cases of hyper infection, the minimum time is for 2 weeks. (52)	CDC = The recommended first line of therapy is ivermectin. The dosage and duration depends on the stage; acute and chronic strongyloidiasis versus hyper infection syndrome/disseminated.

BILIARY TREE - PROTOZOA	Treatment	CDC and WHO recommendations
Cryptosporidiosis	AIDS patients are among the highest risk for biliary cryptosporidiosis and the treatment is primarily endoscopic. The organism causes abdominal pain or cholangitis with papillary stenosis. Endoscopic sphincterotomy facilitates drainage and decompression of the biliary tree, and so forth relief. Consider: Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for 14 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, or Paromomycin 500 mg PO four times a day for 14 days–21 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement (53) -	CDC = Nitazoxanide has been approved for individuals with healthy immune system. The effectiveness of the drug in immunosuppressed patients is unclear.
Microsporidiosis	The treatment for microsporidiosis depends on the infecting microsporidiosis species, the immune status of the human host, and the organs involve. The majority of cases of intestinal and biliary microsporidiosis in AIDS patients are caused by Enterocytozoon bieneusi. The treatment goals are: 10 For AIDS patients to initiate or optimize of ART; 2) Albendazole 400 mg BID in adults or 7.5 mg/kg in children for 2-4 weeks in patients with GI, skin, muscle or disseminated microsporidiosis. For intestinal E. Bieneusi infection, oral fumagillin 20 mg TID for 14 days has been used but has potential serious adverse effects (severe thrombocytopenia). (54)	CDC = Recommends to start with ART; albendazole and funagillin have demonstrated a consistant activity. Against microsporidia. Albendazole is recommended for initial therapy of intestinal and disseminated infection. - Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents.

Current Research on Liver and Biliary parasitic diseases

Entameba

Another thorough review by Kantor et al (2018) on E.histolytica outlines the current knowledge regarding *E. histolytica* and *E. dispar* and provides insight into the development of a vaccine. (60)

Clonorchiasis

There is plenty of current research available on C. Sinensis. Worthy of mentioning is an elaborate review paper published by **Tang et al (2016)** in which authors have compiled from 126 references, the current knowledge of C. Sinensis viz. the epidemiology, disease burden, treatment of clonorchiasis, techniques for detecting C. Sinensis infection in humans and intermediate hosts and vaccine development against clonorchiasis. The authors have also described newer data regarding pathogenesis as well as genome, transcriptome and secretome of C. Sinensis. The paper goes a long way in providing perspectives for future studies as well as aiding the development of innovative strategies for the prevention and control of clonorchiasis. (61)

Echinococcosis

Echinococcosis is listed as a neglected parasitic infectious disease in WHO's European region. To raise the awareness of cystic echinococcosis (CE) among general public and policymakers of the European countries to the magnitude of the problem, the HERACLES (Human cystic Echinococcosis ReseArch in CentraL and Eastern societies) collaborative project was designed in 2013 by WHO and Department of Infectious diseases, Italy. The aim of the five-year project was to provide new insights into parasite/host relationship associated with CE. The long-term goal of HERACLES was to translate the research results into affordable and easy-to-use, point-of-care commercial tools (POC-LOC) for use in Eastern European countries (EEC)**.** (62)

In a study by **Apaer et al (2019)**, a subcutaneous infection model of *E.multilocularis* was developed in C57 BL/6 mice, and after 3 months, partial hepatectomy (PHx) was performed. Delayed liver regeneration after PHx was observed in infected model. The authors concluded that this was probably due to immune-mediated suppression of proinflammatory cytokines

during the chronic phase of E. multilocularis infection. This study is claimed as the first to report the impact of E. multilocularis infection on hepatic regeneration process after partial hepatectomy. (63) **Tuxun et al (2018)** have proposed the use of a combination of interleukins IL-23 and IL-5 as a new tool follow-up of patients with AE. The authors propose that this tool could substitute FDG-PET whenever non-available to assess disease progression. The interleukin combination will supposedly serve as a surrogate marker in patients with HAE. (64)

Opisthorchiasis

In a recent research study, **Young et al (2014)** have characterized the draft genome and transcriptomes of O. viverrini elucidated the survival strategies of the fluke within the hostile bile duct and showed the adaptation of the parasite to a lipid-rich diet from bile and/or cholangiocytes. They also reported that O. viverrini and other flukes secrete proteins that directly modulate host cell proliferation. This research opens new avenues the design of new interventions in opisthorchiasis. (65)

Schistosomiasis

Given the tropical burden of S. mansoni infections in the African continent, standardized organometry is now recommended by the World Health Organisation to regional programs for their surveillance efforts towards *S. mansoni* infections **(Kamden et al, 2020)**. Using ultrasonography, **Kamden et al (2020)** conducted a survey on school children having *S.mansoni* infections. from five neighbouring villages of Cameroon. This survey provides normal, standard organometric data for a Cameroonian population. The authors propose that the survey can be extrapolated for assessing hepatic morbidity in neighbouring *S. mansoni* endemic areas or in other countries with comparable settings. (66)

Prevention, transmission, and control of Liver and Biliary parasites

Treatment of amebiasis includes pharmacologic therapy, surgical intervention, and preventive measures, as appropriate. Most individuals with amebiasis may be treated on an outpatient basis. (67)

Visceral leishmaniasis (VL), also known as kala-azar is fatal if left untreated in over 95% of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen

and liver, and anaemia. *Leishmania* parasites are transmitted through the bites of infected female phlebotomine sandflies, which feed on blood to produce eggs. The epidemiology of leishmaniasis depends on the characteristics of the parasite and sandfly species, the local ecological characteristics of the transmission sites, current and past exposure of the human population to the parasite, and human behaviour. A number of herbivorous and omnivorous animals act as intermediate hosts of *Echinococcus*. They become infected by ingesting the parasite eggs in contaminated food and water, and the parasite then develops into larval stages in the viscera.

Cystic echinococcosis (CE) is the larval cystic stage (called echinococcal cysts) of a small taeniid-type tapeworm (*Echinococcus granulosus*) that may cause illness in intermediate hosts, generally herbivorous animals and people who are infected accidentally. (68)

Biliary tree parasites can cause cholecystitis, recurrent cholangitis, biliary obstruction, stone formation and biliary tree strictures. ERCP is an important diagnostic and therapeutic method in these cases. Liver flukes if not diagnosed and managed early, may later lead to cholangiocarcinoma. Schistosomal liver disease is a major problem in endemic areas.

Ultrasonography is an important diagnostic tool and can help in identifying the degree and stage of fibrosis. Antishistosomal drugs if given early may stop the progress of disease. In hydatid disease, the endoscopic management is effective in cases where liver cyst rupture into the biliary tree.

Combined medical treatment with albendazole and praziquantel is effective in all forms of hydatid disease. Percutaneous drainage of liver cyst is effective and should be considered in such patients. New methods of management of hydatid disease may replace surgery in the future. (69)

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